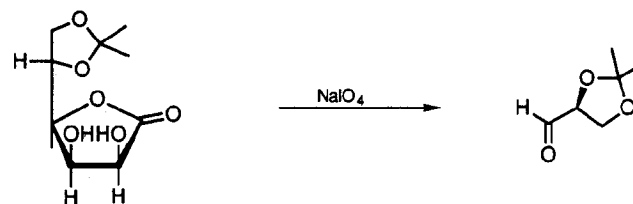


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L-(S)-GLYCERALDEHYDE ACETONIDE
(1,3-Dioxolane-4-carboxaldehyde, 2,2-dimethyl-, (S)-)



Submitted by Christian Hubschwerlen, Jean-Luc Specklin, and J. Higelin.¹

Checked by Todd M. Heidelbaugh and Leo A. Paquette.

1. Procedure

A 500-mL, four-necked, reaction flask, equipped with a mechanical stirrer, thermometer, and glass pH electrode combined with an automatic titrator (Note 1), is charged with sodium (meta)periodate (85.5 g, 0.4 mol) (Note 2) and water (200 mL). The suspension is cooled to 0°C in an ice bath and 3 N sodium hydroxide (about 133 mL, 0.4 mol) is added dropwise at a rate such that the temperature does not exceed 7°C. The final pH of the suspension is 5.5. The cooling bath is removed and finely powdered 5,6-O-isopropylidene-L-gulono-1,4-lactone (Note 3) (43.6 g, 0.2 mol) is added in one portion. The temperature of the mixture is kept below 30°C (Note 4). The pH of the suspension is maintained at 5.5 during the course of the reaction by addition of aqueous 15% sodium carbonate (about 15 mL). The suspension is further stirred at room temperature for 30 min, saturated with sodium chloride (105 g), and filtered by suction using a Büchner funnel. The white solid (Note 5) is washed thoroughly with two, 50-mL portions of brine and the pH of the combined aqueous layers is adjusted to

6.7 with aqueous 15% sodium carbonate before extraction with dichloromethane (6 x 100 mL) (Note 6). The combined organic extracts are dried over magnesium sulfate (25 g). The magnesium sulfate is removed by filtration and washed with two, 50-mL portions of dichloromethane. The organic solutions are combined and slowly concentrated to about 50 mL under reduced pressure (Note 7). The remaining solution is placed in a 100-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a 10-cm vacuum-jacketed, Claisen-Vigreux column (10-mm diameter). With constant stirring by a magnetic stirrer, the solution is further concentrated by distillation under reduced pressure (400 mbar) at 35°C (bath temperature) (Note 8). The temperature of the oil bath is then gradually increased to 80°C and the glyceraldehyde acetonide is distilled between 51°C and 52°C. The distillate is collected in a receiver cooled with an ice-methanol bath (Note 9). Approximately 14.5 g of L-(S)-glyceraldehyde acetonide (56% based on 5,6-O-isopropylidene-L-gulonono-1,4-lactone) is obtained.

2. Notes

1. A 200-mm Radiometer combined glass/reference electrode (Ag/AgCl) was used. To control the pH the submitters used a Radiometer standard pH meter PHM82 coupled to a TTT80 titrator. The end point was set to pH 5.5. If an automatic delivery system is not used the pH range should be kept between 4 and 6 during the oxidation process. Low pH values favor hydrolysis of the acetonide protective group, high pH values lead to epimerization of the aldehyde. The checkers did not use an automatic titrator. The pH was adjusted manually; 1.25 hr was required to bring the solution to pH 5.5.

2. Sodium (meta)periodate (puriss. p.a.) was purchased from Fluka Chemical Corporation and used without any purification.

3. 5,6-O-Isopropylidene-L-gulonono-1,4-lactone was purchased from Fluka Chemical Corporation and used without any purification. It can also be synthesized from ascorbic acid in a two-step procedure.²

4. The temperature of the solution was kept between 20°C and 30°C by occasional cooling with an ice-water bath.

5. The white solid is mainly sodium iodate and sodium chloride.

6. GLC analysis of a sample of the crude, aqueous solution indicates the presence of 95% of the theoretical amount of glyceraldehyde acetonide. This crude, aqueous solution can be used for further chemical transformations,² but was not stored for more than 6 hr at 0°C. GLC analysis of the aqueous layer after dichloromethane extraction still indicates the presence of about 30% of the total amount of glyceraldehyde acetonide in the aqueous solution.

7. The submitters used the following conditions: rotatory evaporator bath temperature: 35°C, cooling water temperature: -5°C; pressure: 500 mbar.

8. In the condenser, the cooling water was replaced by a methanol-ice mixture.

9. (S)-Glyceraldehyde acetonide is an unstable liquid that starts to polymerize on standing even at low temperature. It can be depolymerized by distillation before use. The ¹H NMR spectrum is as follows (CDCl₃) δ : 1.43 and 1.49 (2 s, 2 x 3 H), 4.08-4.21 (2 dd, 2 x 1 H, J = 4.4, 7.6), 4.38 (ddd, 1 H, J = 2, 4.4, 7.6), 9.72 (d, 1 H, J = 2), internal tetramethylsilane standard). The optical rotation is $[\alpha]_D^{20}$ -75.4° (benzene, c 8) [lit. $[\alpha]_D^{20}$ -67.9°/69.7° (benzene, c 8/2.2)^{3,4}].

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Optically pure glyceraldehyde acetonides are widely used in the synthesis of enantiomerically pure compounds (EPC synthesis).⁵ Whereas D-(R)-glyceraldehyde acetonide is easily obtained from the inexpensive D-mannitol,^{6,7} there are only a limited number of practical syntheses of the enantiomeric L-(S)-glyceraldehyde acetonide.^{8,9} Difficulties arise from different sources: 1) availability of the starting material diisopropylidene-L-mannitol; 2) length of the synthesis;¹⁰ 3) nature of the reactants used : mercury acetate, mercaptans, lead tetraacetate, ozone at -78°C, 4) moderate yields.¹¹⁻¹⁴

The procedure reported here is practical, uses readily available, non-toxic starting materials, and can be easily scaled up. No harmful by-products are formed during the synthesis, and sodium iodate, generated during the periodate cleavage, can be recycled into sodium metaperiodate.¹⁵

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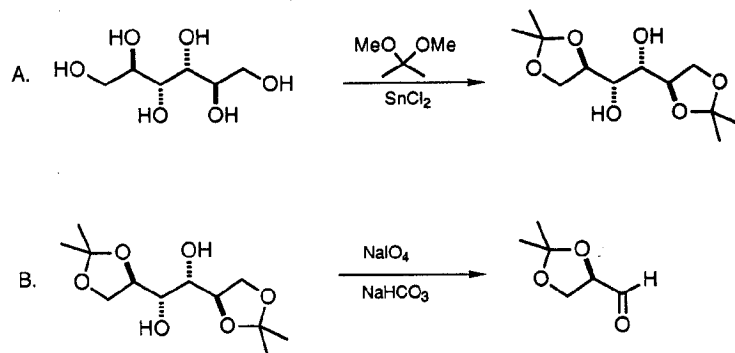
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

L-(S)-Glyceraldehyde acetonide: 1,3-Dioxolane-4-carboxaldehyde, 2,2-dimethyl-, L- (8); 1,3-Dioxolane-4-carboxaldehyde, 2,2-dimethyl-, (S)- (9); (22323-80-4)
Sodium (meta)periodate: Periodic acid, sodium salt (8,9); (7790-28-5)
5,6-O-Isopropylidene-L-gulono-1,4-lactone: L-Gulonic acid, 5,6-O-(1-methylethylidene)-, γ -lactone (11); (94697-68-4)

D-(R)-GLYCERALDEHYDE ACETONIDE
(1,3-Dioxolane-4-carboxaldehyde, 2,2-dimethyl-, (R)-)



Submitted by Christopher R. Schmid and Jerry D. Bryant.¹

Checked by Marc J. McKennon and Albert I. Meyers.

1. Procedure

A. *1,2:5,6-Diisopropylidene-D-mannitol*. A 1-L, three-necked flask equipped with overhead stirrer, heating mantle, and condenser with drying tube is charged with 100 g of D-mannitol (0.549 mol), 240 mL of freshly-distilled 1,2-dimethoxyethane (Note 1), and 160 mL of 2,2-dimethoxypropane (1.3 mol). Stirring is begun and 0.1 g of stannous chloride is added. The remaining neck is capped with a septum and the stirred slurry is heated to reflux. Reflux is maintained until the mixture becomes clear (30-50 min) and is continued for 30 min after clarity is attained. The heating mantle is removed and the solution is cooled below reflux. Pyridine (200 μ L) is added through the septum via syringe. After the solution is cooled to room temperature, it is

transferred to a tared, 1-L, one-necked flask, and the contents are concentrated on a rotary evaporator, beginning at room temperature and increasing the temperature to 95-100°C. The flask contents are held at that temperature until no more evaporate is collected (15-30 min). The semi-solid is then cooled to room temperature, to yield 130-160 g of crude solid product of 50-55% purity (72-80 g, 50-56% yield) as assayed by ¹H NMR against dichloromethane (Note 2).

B. *2,3-O-Isopropylidene-D-glyceraldehyde*. A large, magnetic stir bar is added to the flask that contains the crude solid diacetonide from procedure A above and 700-800 mL of dichloromethane (10 mL/g of diacetonide) is added. The flask is equipped with a condenser and heating mantle, and the slurry is stirred vigorously and heated to reflux until the solids are digested to an even consistency. The mantle is removed, the slurry is allowed to cool below reflux, and Celite (10 g) is added with stirring. The contents are further cooled to room temperature and vacuum-filtered through a pad of Celite on a glass frit filter into a three-necked, 2-L vessel. The flask is rinsed with 50 mL of dichloromethane and the rinse is filtered through the funnel. The 2-L vessel is then equipped with an overhead stirrer, thermometer, and water bath, and stirring is begun at 300-350 rpm. A solution of 30-40 mL of saturated aqueous sodium bicarbonate (0.4 mL/g of diacetonide) is added with stirring, followed by 130-140 g of sodium metaperiodate (2.0 mol equiv), added portionwise over 2-3 min. The resulting mixture is stirred while the internal temperature is maintained below 35°C with water bath cooling. After the solution is stirred for 2 hr, 35-50 g of magnesium sulfate (0.5 g/g of diacetonide) is added and stirring is continued for 20 min. The slurry is vacuum-filtered through a glass frit filter into a 2-L, one-necked, round-bottomed flask. The filter cake is removed, transferred back into the three-necked vessel, 200 mL of dichloromethane is added, and the resulting slurry is stirred for 10 min. The slurry is vacuum-filtered (Note 3) and the filtrate is added to the one-necked flask (Note 4).

The filtrate-containing flask is equipped with a 12"-Vigreux column, distillation head, receiver, and heating mantle, and dichloromethane is removed by distillation (head temperature to 40°C) (Note 5). The residual oil is cooled and transferred to a 250-mL, round-bottomed flask and the flask is equipped with a simple distillation head, cow receiver, and heating mantle. After a brief forerun (2-3 g), product is collected by distillation at 30 mm (65-120°C) into a chilled receiver (5°C) to afford 54-68 g (75-85%) of crude 2,3-O-isopropylidene-D-glyceraldehyde (Note 6). The crude product is transferred to a 100-mL, round-bottomed flask equipped with a 6"-Vigreux column, cow receiver, and heating mantle, and redistilled (Note 7) at 30 mm, collecting the fraction distilling at 67-73°C into a chilled receiver to afford 50-64 g of product (70-80%, 34-45% overall, Note 8).

2. Notes

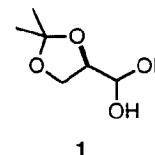
1. Commercial samples of 1,2-dimethoxyethane were found to contain trace impurities that inactivate the stannous chloride catalyst. Simple distillation affords purified solvent.²

2. Samples of about 50 mg are weighed and dissolved in 0.5 mL of (methyl sulfoxide)-d₆ (DMSO-d₆) and 10 µL of dichloromethane is added. A small portion of this solution is then withdrawn and diluted in an NMR tube with DMSO-d₆. ¹H NMR integration parameters are as follows: 32K data points, recycle delay of 5 s, 30° pulse angle. Measurement is against the hydroxyl proton doublet (2 H) at δ 4.63. If the hydroxyl doublet is not satisfactorily resolved, additional dilution is performed.

Physical data for material purified by slurry in dichloromethane followed by recrystallization from butyl ether is as follows: mp 121.8-123.4°C (lit.^{3a} mp 118-120°C); $[\alpha]_D^{23} +1.9^\circ$ (CH₃OH, c 1.74), lit.⁴ $[\alpha]_D^{20} +1.9^\circ$ (CH₃OH, c 2); ¹H NMR (CDCl₃) δ: 1.36 (s, 6 H), 1.42 (s, 6 H), 2.70 (d, 2 H, J = 6.7), 3.75 (approx. t, 2 H, J = 6.2), 3.98

(dd, 2 H, J = 8.4, 5.4), 4.10-4.22 (m, 4 H); ¹³C NMR (CDCl₃) δ: 25.19, 26.72, 66.74, 71.16, 76.22, 109.39; IR (KBr) cm⁻¹: 3400, 3292, 2980, 2933, 2895, 1386, 1372, 1265, 1212, 1070, 859. Anal. Calcd. for C₁₂H₂₂O₆: C, 54.95; H, 8.45. Found: C, 54.80; H, 8.50.

3. In the presence of water, 2,3-O-isopropylidene-D-glyceraldehyde forms the highly water soluble hydrate 1. Failure to dry the reaction and reslurry the filter cake results in loss of about 10% yield.



4. On standing, the filtered solids take on a color characteristic of iodine; the solids can be decomposed by treatment in water with sodium thiosulfate or bisulfite to a negative starch-iodide endpoint.

5. Removal of dichloromethane (CH₂Cl₂) in the final step was performed by the checkers using a rotary evaporator. The pressure was monitored during evaporation and was not allowed to drop below 100 mm. In this fashion the same yield of material was obtained as reported.

6. On standing, both the initially distilled and redistilled material may deposit a small amount of flocculent solid or gel characteristic of polymerized material, which results in some thickening of the product oil.

7. The checkers found that a single distillation of the final product was sufficient to obtain pure material.

8. The physical characteristics are as follows: $[\alpha]_D^{23} +70-80^\circ$ (c 1.0-1.5, benzene, taken immediately upon completion of distillation); ¹H NMR (CDCl₃) δ: 1.40

(s, 3 H), 1.47 (s, 3 H), 4.12 (m, 2 H), 4.36 (m, 1 H), 9.70 (d, 1 H, $J = 1.9$); ^{13}C NMR (CDCl_3) δ : 24.73, 25.84, 65.11, 79.49, 110.79, 201.38; IR (neat) cm^{-1} : 2990, 2940, 2890, 2820, 1730, 1375, 1250, 1215, 1150, 1070, 840. Material obtained from this scale procedure is approximately 90% monomeric; the presence of polymeric material is shown in the ^1H NMR by broad signals at δ 4.7, 3.9 and 1.23.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

2,3-O-Isopropylidene-D-glyceraldehyde has been obtained from D-mannitol by a bis-ketalization/glycol cleavage sequence using a number of ketalizing reagents,³ and either lead tetraacetate^{3h,5} or lead periodate⁶ to effect glycol cleavage. The compound has also been prepared using alternative methodology,⁷ and from other chiral pool sources.⁸ This procedure represents recently disclosed² optimization efforts on previously reported syntheses of 1,2:5,6-diisopropylidene-D-mannitol^{3a} and 2,3-O-isopropylidene-D-glyceraldehyde.^{6h}

A review article reports information regarding the preparation, handling, and storage of this important 3-carbon chiral source.⁹ Our experience with the compound demonstrates that it tends to polymerize and readily adds water to form hydrate **1** in aqueous solution, from which it is extracted with only difficulty. Both hydrated and polymerized aldehyde can contaminate samples and result in lowered optical rotation values, even though no racemization has occurred. The present procedure provides

anhydrous aldehyde, that polymerizes on standing. Polymerized material can be cracked by redistillation (threshold temperature ca. 90°C) at reduced pressure to provide monomer without compromise of enantiomeric integrity; monomeric aldehyde has been obtained routinely in our labs by distillation from still pots that contain substantially polymerized material. Although polymeric material can be stored for months at room temperature in sealed containers and re-cracked to provide monomer with good recovery, refrigerated storage retards polymerization rates and probably extends the useful lifetime of the compound, as polymerized material failed in some instances to re-crack to monomer. Other workers have recommended storage in a frozen benzene matrix,¹⁰ and a report on successful re-cracking of refrigerated polymerized material has appeared.¹¹ We recommend the use of freshly-distilled material in synthetic applications.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2,3-O-Isopropylidene-D-glyceraldehyde: 1,3-Dioxolane-4-carboxyaldehyde, **2,2-dimethyl-, (D)-** (8); 1,3-Dioxolane-4-carboxyaldehyde, **2,2-dimethyl-, (R)-** (9); (15186-48-8)

1,2:5,6-Diisopropylidene-D-mannitol: Mannitol, **1,2:5,6-di-O-isopropylidene-, D-** (8); **D-Mannitol**, **1,2:5,6-bis-O-(1-methylethylidene)-** (9); (1707-77-3)

D-Mannitol (8,9); (69-65-8)

Dimethoxyethane: Ethane, **1,2-dimethoxy-** (8,9); (110-71-4)

2,2-Dimethoxypropane: Acetone, **dimethyl acetal** (8); Propane, **2,2-dimethoxy-** (9); (77-76-9)

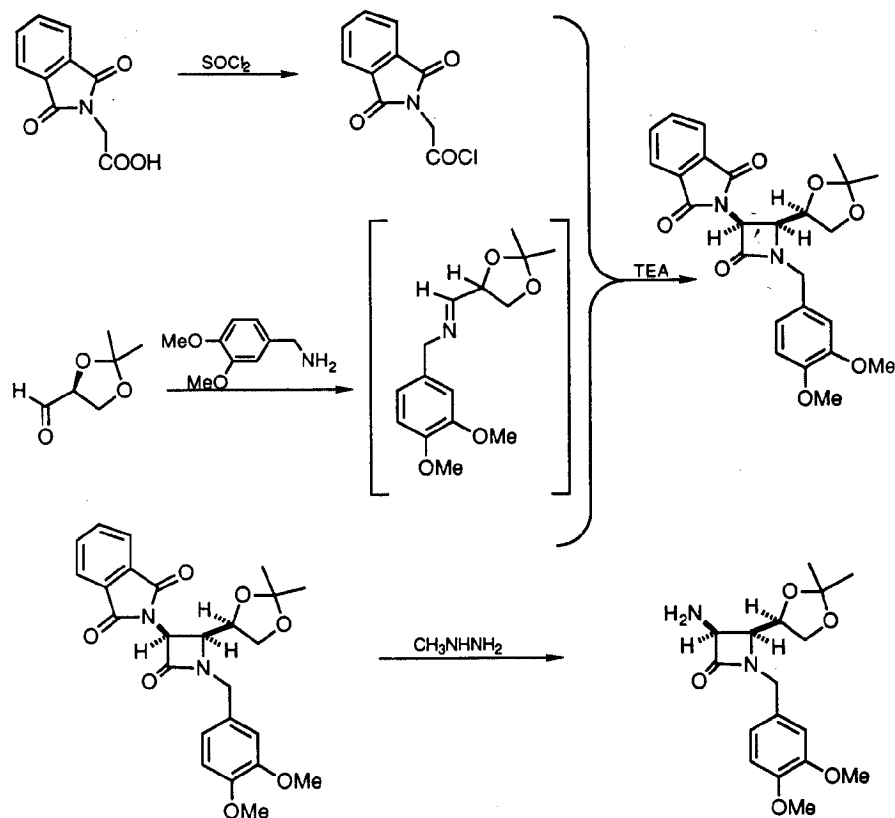
Stannous chloride (Aldrich: Tin(II) chloride): Tin chloride (8,9); (7772-99-8)

Pyridine (8,9); (110-86-1)

Sodium metaperiodate (Aldrich: Sodium periodate): Periodic acid, **sodium salt** (8,9); (7790-28-5)

(3S,4S)-3-AMINO-1-(3,4-DIMETHOXYBENZYL)-4-[(R)-2,2-DIMETHYL-1,3-DIOXOLAN-4-YL]-2-AZETIDINONE

(2-Azetidinone, 3-amino-1-[(3,4-dimethoxyphenyl)methyl]-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-, [3S-[3 α ,4 α (S*)]]-)



Submitted by Christian Hubschwerlen and Jean-Luc Specklin.¹

Checked by Julien G. Doyon and Leo A. Paquette.

1. Procedure

A. Phthalylglycyl chloride. Phthalylglycine (102.5 g, 0.5 mol; Note 1) is placed in a 750-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a reflux condenser (Note 2). Thionyl chloride (109 mL, 1.5 mol, Note 3) is added in one portion and the resulting suspension is stirred at reflux for 18 hr. The reaction mixture is cooled to room temperature before removing excess thionyl chloride under reduced pressure (Note 4). The residue is suspended in ether (100 mL, Note 5) and stirred for 1 hr at 0°C. The crystals are filtered by suction using a Büchner funnel (Note 6), washed with cold ether (50 mL), and dried under vacuum. Approximately 100 g of phthalylglycyl chloride (90% based on phthalylglycine) is obtained (Note 7).

B. (3S,4S)-3-Amino-1-(3,4-dimethoxybenzyl)-4-[(R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-azetidinone. The crude aqueous solution of L-(S)-glyceraldehyde acetonide (estimated content, 190 mmol) prepared in the preceding procedure is placed in a 1000-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar (32 mm) and a 100-mL, pressure-equalizing dropping funnel that is connected to an argon flow line. Dichloromethane (200 mL, Note 5) is added to the aqueous solution and the dropping funnel is charged with a solution of 3,4-dimethoxybenzylamine (31.1 g, 0.186 mol, Note 8) in dichloromethane (50 mL). The flask is flushed with argon and an argon atmosphere is maintained throughout the entire reaction sequence until the final work up. The solution is vigorously stirred and cooled to 10°C with an ice-water bath. The solution of 3,4-dimethoxybenzylamine is added dropwise over 5 min and the mixture is stirred for 20 min then transferred into a 1000-mL separatory funnel. The organic phase is separated and the aqueous layer is extracted with dichloromethane (2 x 100 mL). The combined organic layers are collected in a 1000-mL Erlenmeyer flask and dried over magnesium sulfate under argon. After the magnesium sulfate is removed by filtration and thoroughly washed with three, 100-mL portions of

dichloromethane, the filtrate is placed in a 1000-mL, round-bottomed flask and concentrated to about 100 mL (Note 9). The solution is transferred to a 500-mL, two-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a thermometer, and a 250-mL, pressure-equalizing dropping funnel connected to an argon flow line. The solution is cooled to 0°C (ice-methanol bath) and treated with triethylamine (33.5 mL, 0.24 mol, Note 10). The dropping funnel is filled with a solution of phthalylglycyl chloride (41.5 g, 0.186 mol) in dichloromethane (75 mL). This solution is added dropwise over 45 min. The reaction mixture is stirred for 1 hr at room temperature then transferred to a 1000-mL separatory funnel before sequentially washing with water (2 x 200 mL), cold 2 N hydrochloric acid (100 mL), saturated, aqueous sodium bicarbonate solution (100 mL), and brine (100 mL). The organic phase is dried over a mixture of magnesium sulfate and Fuller's earth (Fluka), filtered, and evaporated under reduced pressure. The resulting yellow syrup (72 g, 0.154 mol, 82% from 3,4-dimethoxybenzylamine, Note 11) is dissolved in 1,2-dichloroethane (200 mL, Note 5), treated with N-methylhydrazine (8.9 mL, 0.170 mol, Note 12) and refluxed for 60-80 min. The resulting suspension is cooled to room temperature and filtered by suction using a Büchner funnel. The crystals are thoroughly washed with two, 100-mL portions of 1,2-dichloroethane and discarded. The combined organic solutions are evaporated to a heavy syrup under reduced pressure. The residue is dissolved in ethyl acetate (400 mL) and sequentially washed with water (2 x 150 mL) and aqueous 10% sodium chloride solution. The organic layer is dried over magnesium sulfate, filtered by suction using a Büchner funnel and evaporated. The resulting crystals are recrystallized from ethyl acetate/hexane (2:1). Approximately 30-32 g of (3S,4S)-3-amino-1-(3,4-dimethoxybenzyl)-4-[(R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-azetidinone are obtained (49-52% from 3,4-dimethoxybenzylamine; 54% from 5,6-O-isopropylidene-L-gulono-1,4-lactone) as pale yellow crystals, mp. 101-103°C (Note 13).

2. Notes

1. Phthalylglycine was purchased from Fluka A.G and used without any purification.
2. The gas released during the reaction should be vented through a calcium chloride trap to the back of an efficient hood.
3. Thionyl chloride of technical grade was distilled prior to use.
4. The submitters used the following conditions: rotatory evaporator; water bath temperature, 60°C; pressure, 120 mm then 60 mm.
5. Diethyl ether, dichloromethane, and dichloroethane puriss p.a. were used as purchased from Fluka A.G.
6. The submitters filtered the suspension under a stream of argon.
7. Phthalylglycyl chloride is a colorless powder. It can be stored for several weeks at room temperature in the absence of moisture and air, mp 85-87°C (lit.² 85-86°C).
8. 3,4-Dimethoxybenzylamine was purchased from Aldrich Chemical Company, Inc., and used without any purification. It is air sensitive and decomposes on standing into a white solid (3,4-dimethoxybenzoic acid). The success of the cycloaddition depends on having stoichiometric quantities of reagents. The quantity of 3,4-dimethoxybenzylamine added (less than one equivalent) is related to the average quantity of glyceraldehyde acetonide present in the crude aqueous solution.
9. The submitters used the following conditions: rotatory evaporator, water bath temperature, 35°C; pressure: 500 mm. The quality of the imine solution is determined in the following way: an aliquot of the dichloromethane solution is further evaporated under reduced pressure and analyzed by ¹H NMR (CDCl₃). The ratio of integral value (height in mm) of the signal of the imine proton at δ 7.8 ppm to the signal of the three aromatic protons at δ 6.85 ppm gives a fairly good idea of the course of the reaction.

The presence of an excess of 3,4-dimethoxybenzylamine in the solution leads to the formation of an insoluble by-product resulting from the reaction of 3,4-dimethoxybenzylamine with phthalimidoacetyl chloride. It renders the final purification more tedious.

10. Triethylamine (puriss. p.a.) was purchased from Fluka A.G. and used without any purification.

11. N-[(2R,3R)-cis-1-(3,4-Dimethoxybenzyl)-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-oxo-3-azetidiny]phthalimide can be purified at this stage by flash column chromatography (dichloromethane/ethyl acetate 9:1) but does not tend to crystallize. The ¹H NMR spectrum is as follows (CDCl₃) δ : 1.23 and 1.35 (2 s, 2 x 3 H), 3.39 (dd, 1 H, J = 6.5, 8.5), 3.66 (dd, 1 H, J = 6.5, 8.5), 3.79 (dd, 1 H, J = 5, 9), 3.89 and 3.91 (2 s, 2 x 3 H), 4.32 and 4.81 (2 x d, 2 x 1 H, J = 15), 4.36 (dt, 1 H, J = 6.5 and 9), 5.30 (d, 1 H, J = 5), 6.82-6.93 (m, 3 H), 7.76-7.90 (m, 4 H).

12. N-Methylhydrazine was purchased from Fluka and was used without any purification. All the operations should be carried out under a well-vented hood since N-methylhydrazine is a carcinogen.

13. An analytically pure sample can be obtained after a further recrystallization from ethyl acetate (mp 106-107°C). The ¹H NMR spectrum is as follows (CDCl₃) δ : 1.36 and 1.45 (2 s, 2 x 3 H), 1.86 (broad s, 2 H), 3.53 (t, 1 H, J = 7.5), 3.70 (dd, 1 H, J = 6, 10), 3.87 (2 s, 2 x 3 H), 4.06 and 4.80 (2 d, 2 x 1 H, J = 18), 4.15-4.30 (m, 3 H), 6.80-6.82 (m, 3 H).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Monocyclic azetidinones are useful building blocks in organic synthesis. Besides the wide use in the syntheses of monobactam antibiotics and nuclear analogues of natural bicyclic β-lactam antibiotics,³ new applications have appeared with the syntheses of unnatural α-amino acids, amino sugars⁴ and inhibitors of elastase.⁵

These building blocks can be obtained either by the Miller cyclization of β-hydroxy-α-amino acids⁶ or by the Staudinger reaction⁷ ([2+2] ketene-imine cycloaddition). The procedure reported here follows the second route and has the advantages of being diastereospecific and to proceed in high yield. For a large scale preparation, the harmful and toxic N-methylhydrazine can be replaced by N,N-dimethyl-1,3-propanediamine.⁸ Further transformations of the key intermediate have been reported elsewhere.^{7a,9}

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Phthalylglycyl chloride: Isoindolineacetyl chloride, 1,3-dioxo- (8); 2H-Isoindole-2-acetyl chloride, 1,3-dihydro-1,3-dioxo- (9); (6780-38-7)

Phthalylglycine: 2-Isoindolineacetic acid, 1,3-dioxo- (8); 2H-Isoindole-2-acetic acid, 1,3-dihydro-1,3-dioxo- (9); (4702-13-0)

Thionyl chloride (8,9); (7719-09-7)

L-(S)-Glyceraldehyde acetonide: 1,3-Dioxolane-4-carboxaldehyde, 2,2-dimethyl-,

L- (8); 1,3-Dioxolane-4-carboxaldehyde, 2,2-dimethyl-, (S)- (9); (22323-80-4)

3,4-Dimethoxybenzylamine: Veratrylamine (8); Benzenemethanamine,

3,4-dimethoxy- (9); (5763-61-1)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

N-Methylhydrazine: Hydrazine, methyl- (8,9); (60-34-4)

5,6-O-Isopropylidene-L-gulono-1,4-lactone: L-Gulonic acid,

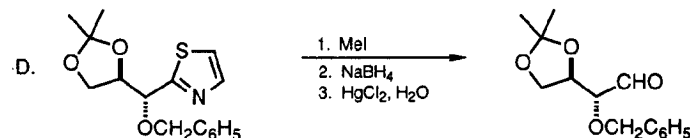
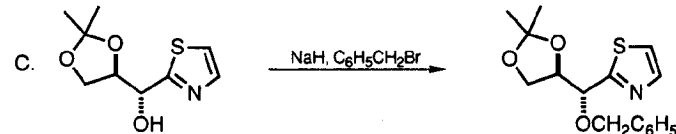
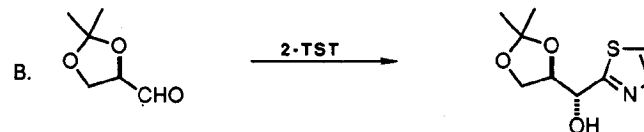
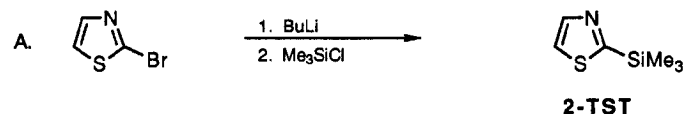
5,6-O-(1-methylethylidene)-, γ -lactone (11); (94697-68-4)

DIASTEREOSELECTIVE HOMOLOGATION OF D-(R)-GLYCERALDEHYDE

ACETONIDE USING 2-(TRIMETHYLSILYL)THIAZOLE:

2-O-BENZYL-3,4-ISOPROPYLIDENE-D-ERYTHROSE

(1,3-Dioxolane-4-acetaldehyde, 2,2-dimethyl-
 α -(phenylmethoxy)-, [R-(R*,R*)]-)



Submitted by Alessandro Dondoni and Pedro Merino.¹

Checked by Gregory P. Brengel and Albert I. Meyers.

1. Procedure

A. *2-(Trimethylsilyl)thiazole (2-TST)*. A 500-mL, four-necked, round-bottomed flask, containing a magnetic stirring bar, is equipped with two, 100-mL, pressure-equalizing dropping funnels and a low-temperature thermometer (Note 1). The dry apparatus is filled with argon and kept under a slightly positive pressure (ca. 100 mm) of this gas for the entire reaction time. The flask is charged with 200 mL of freshly distilled diethyl ether (Note 2) and 111 mL of a 1.5 M solution of butyllithium (0.167 mol) in hexane (Notes 3 and 4). One of the two dropping funnels is charged with 25 g (0.152 mol) of 2-bromothiazole (Note 5) in 50 mL of diethyl ether (Note 2) and the other with 16.5 g (0.152 mol) of chlorotrimethylsilane (Note 6) in 50 mL of diethyl ether (Note 2). The reaction flask is cooled to -78°C in a dry ice-acetone bath. While the solution in the flask is stirred, 2-bromothiazole is added dropwise over a period of 1 hr. After 20 min additional stirring, chlorotrimethylsilane is added dropwise over 30 min and stirring is continued for 1 hr at -78°C. The resulting mixture is then allowed to warm up to room temperature. A saturated aqueous sodium bicarbonate solution (200 mL) is added and the mixture is transferred into a 1-L separatory funnel. After the mixture is shaken, the organic layer is recovered and the aqueous layer is extracted with diethyl ether (200 mL). The combined organic layers are dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure by rotary evaporation with the external bath temperature not higher than 40°C. The residue is distilled from a 100-mL flask at reduced pressure in a Claisen apparatus equipped with a 10-cm Vigreux column (Note 7). The distillation, after a forerun at 40-65°C (15 mm) consisting mainly of bromobutane, gives 20.2 g (85%) of 2-(trimethylsilyl)thiazole as a colorless liquid, bp 88-91°C (16-17 mm) (Note 8).

B. *(1R)-2,3-Di-O-isopropylidene-1-(2-thiazolyl)-D-glycitol*. A 100-mL, three-necked, round-bottomed flask, containing a magnetic stirring bar, is equipped with a

50-mL pressure-equalizing dropping funnel and a low-temperature thermometer (Note 1). The dry apparatus is filled with argon and kept under an inert gas pressure of ca. 100 mm for the entire reaction time. The flask is charged with 2.0 g (0.0154 mol) of D-glyceraldehyde acetonide (Note 9) in 25 mL of dichloromethane (Note 10) and the dropping funnel is filled with 2.4 g (0.0153 mol) of 2-TST in 25 mL of dichloromethane (Note 10). The reaction flask is cooled to 0°C in an ice bath. While the solution is stirred, 2-TST is added dropwise over a period of 15 min. After the reaction is stirred for 12 hr at room temperature, it is complete as shown by TLC (silica, diethyl ether - petroleum ether 1:1). Dichloromethane (ca. 40 mL) is removed under reduced pressure and the residue is treated with tetrabutylammonium fluoride (14 mL of a 1.1 M solution in tetrahydrofuran, 0.0154 mol) (Aldrich Chemical Company, Inc.) Desilylation is complete as shown by TLC (silica, diethyl ether - petroleum ether, 1:1) in 10 min. Volatile material is removed under reduced pressure and the residue is treated with 50-60 mL of water. The mixture is extracted with dichloromethane (3 x 50 mL) and the combined dichloromethane solutions are dried with anhydrous sodium sulfate. The solvent is removed under reduced pressure and the solid residue (3.14 g) is flash chromatographed (silica, diethyl ether - petroleum ether, 3:2) to give 2.85 g (84%) of the alcohol as a white solid, mp 114-116°C (from dichloromethane-hexane) (Note 11).

C. *(1R)-O-Benzyl-2,3-di-O-isopropylidene-1-(2-thiazolyl)-D-glycitol*. A 250-mL, two-necked, round-bottomed flask containing a magnetic stirring bar, is equipped with a 50-mL pressure-equalizing dropping funnel. The dry apparatus is filled with argon and kept under an inert gas pressure of ca. 100 mm greater than the atmosphere until the aqueous work-up (Note 1). The flask is charged with 2.6 g (0.012 mol) of the alcohol (from Step B) in 100 mL of tetrahydrofuran (Note 12) and the dropping funnel is filled with 2.06 g (0.012 mol) of benzyl bromide (Note 13) in 10 mL of tetrahydrofuran (Note 12). Sodium hydride (0.0145 mol, 0.69 g of a 50% dispersion in oil) (Note 14) is

added in portions to the flask and, after gentle reflux for 20 min, the mixture is cooled to room temperature and the solution of benzyl bromide is added dropwise via the addition funnel (10-15 min). Tetrabutylammonium iodide (0.48 g, 0.0013 mol) is added in one portion and the solution is stirred overnight at room temperature (Note 15). The solvent is removed under reduced pressure (water aspirator) and the residue is treated with 50 mL of saturated sodium chloride (NaCl) solution. The mixture is extracted with dichloromethane (3 x 50 mL) (dilution of the aqueous phase with water to avoid emulsions may be necessary) and the combined extracts are dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure using a rotatory evaporator and the residue is flash chromatographed (silica, diethyl ether - petroleum ether 1:1) to give 3.53 g (96% yield) of product as an oil (Note 16).

D. Thiazolyl-to-formyl deblocking. The protected 1-(2-thiazolyl)-D-glycitol (3.5 g, 0.0115 mol) is dissolved in 70 mL of acetonitrile (Note 17), methyl iodide (24.7 g, 0.173 mol, purified by passing through neutral alumina) is added and the resulting mixture is heated to reflux until N-methylation of thiazole is complete (at least 24 hr) as shown by TLC (Notes 15 and 18). The solvent is removed under reduced pressure and the residue (Note 19) is dissolved in at least 70 mL of methanol. The solution is cooled to 0°C in an ice bath and sodium borohydride (0.65 g, 0.0172 mol) is added in portions while the solution is stirred vigorously. After the solution is stirred for 30 min at 0°C, it is treated with 2 mL of acetone, and the solvent is removed under reduced pressure. The residue is treated with a saturated solution of sodium chloride (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined extracts are dried over anhydrous sodium sulfate and the solvent is removed under reduced pressure. The resulting oil (Note 20) is dissolved in acetonitrile (5 mL) and the solution is slowly added to a vigorously stirred solution of mercury chloride (3.7 g, 0.0136 mol) in a 4:1 mixture of acetonitrile - water (50 mL). After being stirred at room temperature for 15 min, the reaction mixture is filtered on a Büchner funnel through Celite and the sticky

inorganic residue is rinsed with diethyl ether. The combined ethereal extracts are added to the filtered solution and the mixture is concentrated to ca. 10 mL by evaporation of the solvent under reduced pressure. The residue is treated with a saturated solution of potassium chloride (KCl) (50 mL), extracted with dichloromethane (3 x 50 mL), and the combined extracts are dried over anhydrous sodium sulfate (Note 21). Removal of volatile material under reduced pressure gives an oil that is flash chromatographed (silica, diethyl ether - petroleum ether 1:1) to afford 1.77 g (62%) of 2-O-benzyl-3,4-isopropylidene-D-erythrose (Note 22).

2. Notes

1. The glass components of the apparatus were dried overnight in a 150°C-oven and allowed to cool in a desiccator over a drying agent before assembly.
2. Diethyl ether was distilled from sodium wire under a nitrogen atmosphere immediately prior to use.
3. A 1.5 M solution of butyllithium in hexane was purchased from Aldrich Chemical Company, Inc. Aliquots were transferred to a 100-mL graduated cylinder, stoppered with a rubber septum using a 15-gauge cannula and argon.
4. The slight excess of butyllithium with respect to chlorotrimethylsilane is used to avoid acid-catalyzed protodesilylation of 2-TST during the work-up operations.
5. 2-Bromothiazole, available from Aldrich Chemical Company, Inc., was distilled prior to use.
6. Chlorotrimethylsilane was obtained from Fluka Chemical Corporation and distilled before use.
7. The Claisen distillation head was filled with glass wool to avoid formation of foam. The checkers found that constant heating of the distillation apparatus with a heat gun greatly facilitates the rate of distillation and minimizes the column holdup.

8. The product showed the following spectroscopic properties: ^1H NMR (80 MHz, CDCl_3 , TMS) δ : 0.40 (s, 9 H), 7.40 (d, 1 H, $J = 3.0$), 8.01 (d, 1 H, $J = 3.0$); ^{13}C NMR (75.5 MHz, CDCl_3 , TMS) δ : -1.20 (q), 121.3 (d), 145.8 (d), 174.3 (s). Other physical properties includes $n_D^{22.5}$ 1.4975 and $d = 0.987$.

9. The aldehyde was freshly distilled material prepared according to the *Organic Syntheses* procedure.²

10. Dichloromethane was freshly distilled under a nitrogen atmosphere from calcium hydride.

11. This product (anti-adduct) was $\geq 95\%$ diastereomerically pure based on comparison of the ^1H NMR spectrum with that of the syn-adduct.³ Physical properties and spectral data are as follows: $[\alpha]_D -1.2^\circ$ to -1.5° (MeOH, c 1.0); ^1H NMR (80 MHz, CDCl_3 - D_2O , TMS) δ : 1.40 (s, 3 H), 1.47 (s, 3 H), 4.0 (m, 2 H), 4.45 (m, 1 H), 5.07 (d, 1 H, $J = 5.1$), 7.30 (d, 1 H, $J = 3.2$), 7.73 (d, 1 H, $J = 3.2$); ^{13}C NMR (75.5 MHz, CDCl_3 , TMS) δ : 25.16 (q), 26.69 (q), 65.38 (t), 71.77 (d), 78.42 (d), 110.54 (s), 120.33 (d), 142.96 (d), 170.95 (s).

12. Tetrahydrofuran was distilled from lithium aluminum hydride under a nitrogen atmosphere immediately prior to use.

13. Benzyl bromide was purchased from Aldrich Chemical Company, Inc., and purified by passing through neutral alumina.

14. Sodium hydride, 60% dispersion in mineral oil from Aldrich Chemical Company, Inc., was used as obtained.

15. The reaction appeared complete by TLC (silica, diethyl ether - petroleum ether, 1:1); R_f alcohol = 0.15, R_f O-benzyl derivative = 0.27.

16. Physical properties and spectral data are as follows: $[\alpha]_D +53.7^\circ$ to $+59.6^\circ$ (CHCl_3 , c 1.66); ^1H NMR (270 MHz, CDCl_3 , TMS) δ : 1.34 (s, 3 H), 1.39 (s, 3 H), 4.02 (dd, 1 H, $J = 4.9, 1.2$), 4.52-4.70 (m, 3 H), 4.83 (d, 1 H, $J = 5.5$), 7.33-7.35 (m, 5 H), 7.39 (d, 1 H, $J = 3.2$), 7.81 (d, 1 H, $J = 3.2$); ^{13}C NMR (75.5 MHz, CDCl_3 , TMS) δ : 25.39 (q),

26.54 (q), 56.31 (t), 72.81 (t), 78.65 (d), 79.09 (d), 110.67 (s), 120.73 (d), 128.74 (d), 128.86 (d), 129.20 (d), 138.0 (s), 143.5 (s) 170.55 (s).

17. Reagent grade acetonitrile from Carlo Erba was used as obtained.

18. The R_f of the N-methylthiazolium salt is zero.

19. A sample of this material obtained in a separate experiment was crystallized from methanol - diethyl ether to give the pure N-methylthiazolium iodide as white crystals, mp 181-183°C (dec); ^1H NMR (80 MHz, CD_3OD , TMS) δ : 1.33 (s, 3 H), 1.51 (s, 3 H), 3.95-4.51 (m, 3 H), 4.17 (s, 3 H), 4.79 (br d, 2 H), 5.36 (d, 1 H, $J = 7.2$), 7.34 (s, 5 H), 8.27 (m, 2 H).

20. A sample of this material obtained in a separate experiment was purified by chromatography (silica, dichloromethane - diethyl ether 85:5) to give the pure thiazolidine as 1:1 mixture of diastereoisomers : oil; ^1H NMR (80 MHz, CDCl_3 , TMS) δ : 1.36 (s, 3 H), 1.42 (s, 3 H), 2.31 (s, 1.5 H), 2.33 (s, 1.5 H), 2.77-3.25 (m, 4 H), 3.66 (m, 1 H), 3.90-4.55 (m, 4 H), 4.77 (s, 2 H), 7.32 (s, 5 H).

21. The solid residue contains mercury salts and should be disposed of by procedures used for heavy metal residues.

22. The product showed the following properties: oil; $[\alpha]_D +36.8^\circ$ to $+37.1^\circ$ (CHCl_3 , c 1.70); IR (film) cm^{-1} : 2720, 1734; ^1H NMR (270 MHz, CDCl_3 , TMS) δ : 1.35 (s, 3 H), 1.43 (s, 3 H), 3.81 (dd, 1 H, $J = 6.8, 2.5$), 3.92 (dd, 1 H, $J = 6.1, 9.6$), 4.07 (dd, 1 H, $J = 9.2, 7.3$), 4.35 (m, 1 H), 4.67 (AB quartet, 2 H, $J = 11.6$), 7.3-7.38 (m, 5 H), 9.70 (d, 1 H, $J = 2.5$); ^{13}C NMR (75.5 MHz, CDCl_3 , TMS) δ : 25.22 (q), 26.55 (q), 66.37 (t), 73.51 (t), 75.22 (d), 83.31 (dd), 110.24 (s), 128.38 (d), 128.75 (d), 137.23 (s), 201.4 (d).

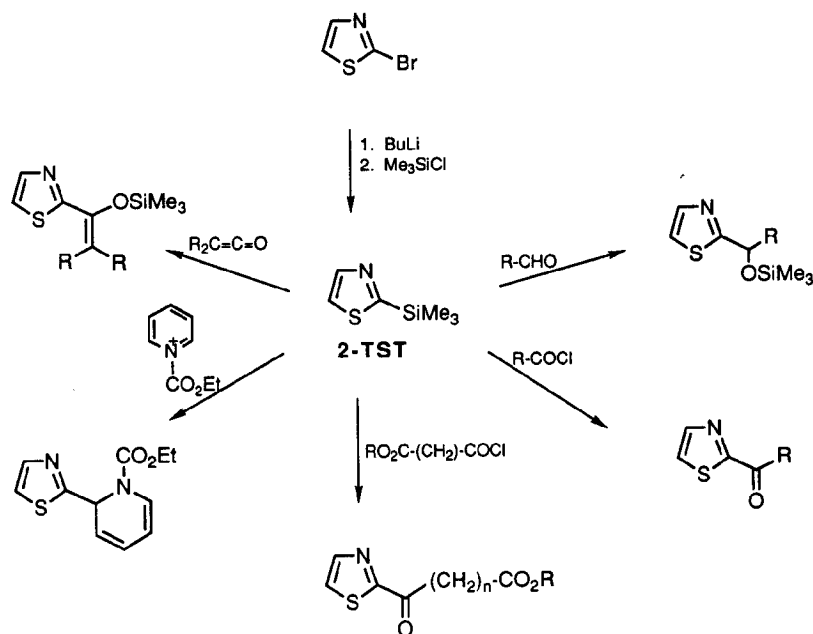
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983. See Note 21.

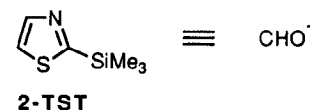
3. Discussion

2-(Trimethylsilyl)thiazole (2-TST)⁴ is used as a stable and convenient substitute for 2-lithiothiazole for introducing various substituents at C-2 of the thiazole ring (Figure 1). Reactions of 2-TST with various carbon electrophiles⁵ occur readily under mild conditions without the need for any catalyst to give the corresponding 2-substituted thiazoles in fair yields. As has been already pointed out,⁵ the multigram preparation of 2-TST from 2-bromothiazole via halogen-metal exchange is much more convenient and practical than the procedure⁶ employing the highly volatile and expensive unsubstituted thiazole.

Figure 1. Synthesis of 2-Substituted Thiazoles from 2-TST



The procedure presented here illustrates the use of 2-TST as a one-carbon homologating reagent of a chiral α,β -dialkoxy aldehyde.^{3,7} The protocol is based on three essential key operations, i.e., the anti-stereoselective addition ($ds \geq 95\%$) of 2-TST to the aldehyde (Step B), the protection of the hydroxy group at the newly formed stereogenic center (Step C), and the liberation of the formyl group from the thiazole ring (Step D). This step involves a sequence of three reactions (N-methylation of the thiazole ring, reduction, and hydrolysis) that occurs under almost neutral conditions and leaves unaltered the asymmetric centers in the chiral compounds. The procedure for the N-methylation appears more practical than an earlier method⁸ employing trimethyloxonium fluoroborate in liquid sulfur dioxide.⁹ Overall, 2-TST appears to serve as an equivalent to the formyl anion synthon. The iterative application of this principle over several consecutive cycles produces a series of homologues of D-glyceraldehyde up to a nine-carbon chain and with an all-*anti* configuration of the vicinal hydroxy groups.³ This linear iterative one-carbon extension technology was successfully applied to L-threose acetonide,³ dialdoses,^{3,10} and α -amino aldehydes.¹¹



Although various compounds are known to act as synthetic equivalents to the formyl anion synthon,¹² the advantages that appear to be associated with the use of 2-TST warrant comment. First, 2-TST is a readily available, relatively cheap, and storable reagent; second, it reacts promptly and stereoselectively with aldehydes under neutral conditions; third, it gives high yields of products that are stable to isolation and purification and nevertheless can be readily transformed into aldehydes.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

2-(Trimethylsilyl)thiazole: Thiazole, 2-(trimethylsilyl)- (10); (79265-30-8)

2-O-Benzyl-3,4-isopropylidene-D-erythrose: 1,3-Dioxolane-4-acetaldehyde, 2,2-dimethyl- α -(phenylmethoxy)-, [R-(R*,R*)]- (11); (103795-12-6)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

2-Bromothiazole: Thiazole, 2-bromo- (8,9); (3034-53-5)

Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

(1R)-2,3-Di-O-isopropylidene-1-(2-thiazolyl)-D-glycitol: 2-Thiazolemethanol, α -(2,2-dimethyl-1,3-dioxolan-4-yl)-, [R-(R*,R*)]- (11); (103795-10-4)

Dichloromethane: Methane, dichloro- (8,9); (75-09-2)

D-Glyceraldehydeacetone: 1,3-Dioxolane-4-carboxaldehyde, 2,2-dimethyl-, D- (8); 1,3-Dioxolane-4-carboxaldehyde, 2,2-dimethyl-, (R)- (9); (15186-48-8)

Tetrabutylammonium fluoride: Ammonium, tetrabutyl-, fluoride (8); 1-Butanaminium, N,N,N-tributyl-, fluoride (9); (429-41-4)

(1R)-O-Benzyl-2,3-di-O-isopropylidene-1-(2-thiazolyl)-D-glycitol: Thiazole, 2-[(2,2-dimethyl-1,3-dioxolan-4-yl)(phenylmethoxy)methyl]-, [R-(R*,R*)]- (11); (103795-11-5)

Benzyl bromide: Toluene, α -bromo- (8); Benzene, (bromomethyl)- (9); (100-39-0)

Sodium hydride: (8,9); (7646-69-7)

Tetrabutylammonium iodide: (8); 1-Butanaminium, N,N,N-tributyl-, iodide (9); (311-28-4)

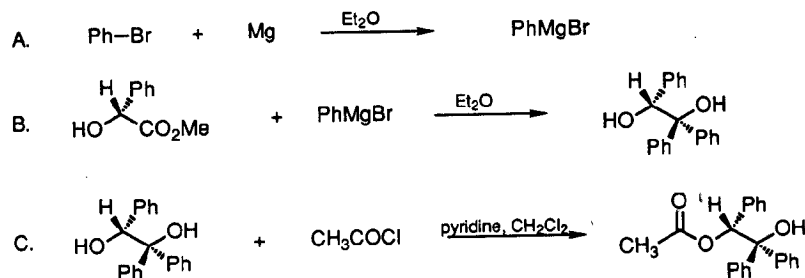
Acetonitrile: (8,9); (75-05-8)

Methyl iodide: Methane, iodo- (8,9); (74-88-4)

Sodium borohydride: Borate (1-); tetrahydro-, sodium (8,9); (16940-66-2)

Mercury(II) chloride: Mercury chloride (8,9); (7487-94-7)

(R)-(+)-2-HYDROXY-1,2,2-TRIPHENYLETHYL ACETATE
(1,2-Ethanediol, 1,1,2-triphenyl-, 2-acetate, (R)-)



Submitted by Manfred Braun, Silke Gräf, and Sabine Herzog.¹

Checked by Joseph Lynch and Ichiro Shinkai.

1. Procedure

A. Preparation of an ether solution of phenylmagnesium bromide (Note 1).

Ether (100 mL) is added to magnesium (Mg) turnings (74.6 g, 3.07 mol) in a dry, 5-L flask equipped with an overhead stirrer, reflux condenser, and addition funnel. Iodine (several crystals) is added and the mixture is stirred for several minutes (the color dissipates). Bromobenzene (9.23 mL, 13.76 g, 87.64 mmol) is added and the mixture is heated with a heat gun to initiate the reaction. A solution of bromobenzene (322.8 mL, 481 g, 3.06 mol) in ether (600 mL) is added dropwise over 2.75 hr, maintaining a gentle reflux. The dark brown mixture is stirred an additional 3 hr at ambient temperature under nitrogen and then cooled in an ice/methanol bath to 0°C.

B. *(R)-(+)-1,1,2-Triphenylethanediol*. A solution of methyl *(R)-(-)-mandelate* (92.3 g, 0.556 mol) (Note 2) in ether (500 mL) (Note 3) is added dropwise to the cold solution of phenylmagnesium bromide prepared in Step A at a rate such that the temperature does not rise above 10°C (1.25 hr required). The mixture is then allowed to stir an additional 2 hr with cooling (final temp 6°C) before heating to reflux. After 3 hr at reflux the solution is allowed to stand overnight at ambient temperature under nitrogen. The solution (*Caution: Contains benzene*) is poured onto 1 kg of ice contained in a 5-L, round-bottomed flask placed in an ice bath and equipped with an overhead stirrer and reflux condenser. A solid mass results that is broken up with a spatula so that it is partly stirrable. Hydrochloric acid (6 N, 516 mL) is added dropwise, while monitoring the pH, to a pH of 3.9. The two-phase, liquid mixture is stirred for 1 hr at ambient temperature. The layers are separated and the aqueous layer is extracted with methylene chloride (CH₂Cl₂) (3 x 250 mL). The combined organic layers are dried (MgSO₄), filtered, and concentrated to a thick caramel-like oil (179 g). Methanol (300 mL) is added causing crystallization and the mixture is heated to reflux to give a clear yellow solution. The solution is allowed to cool to room temperature over several hours. It is then cooled in an ice bath to 0°C and aged for 1 hr. The product is collected on a filter and washed with cold (-10°C) methanol (200 mL). The solid is dried under reduced pressure at 50°C (106.6 g, 66%), mp 123-127°, $[\alpha]_{\text{D}}^{20} +220^\circ$ (95% ethanol, c 1). Liquid chromatographic (LC) analysis shows 96.6% purity with 3.2% benzoin contamination (area %, uncorrected for relative response).

C. *(R)-(+)-2-Hydroxy-1,2,2-triphenylethyl acetate [(R)-HYTRA]*. Acetyl chloride (32.6 mL, 0.458 mol) in CH₂Cl₂ (85 mL) is added dropwise to *R-(+)-triphenylethanediol* (103.04 g, 0.355 mol) and pyridine (46.4 mL, 0.574 mol) in CH₂Cl₂ (860 mL) at 0°C (ice/methanol bath). The rate is controlled so that the temperature does not exceed 5°C. After the addition is complete, the mixture is allowed to warm to ambient temperature and aged for 4 hr. LC assay shows 1% unreacted diol. Water

(430 mL) is added and the mixture is stirred vigorously for 30 min (pH was 3.5). The mixture is concentrated on a rotary evaporator until second phase CH_2Cl_2 is no longer observed in the distillate or in the reaction mixture. Water (100 mL) is used to aid transfer of the solids to a filter, the filter cake is washed with water (600 mL), and air dried (with suction) overnight. The resulting wet cake is transferred to a 3-L flask equipped with an overhead stirrer, a distillation head, and an addition funnel. Toluene (2 L) is added and the azeotrope is removed by atmospheric distillation. After 480 mL of distillate is collected (80 mL of second phase water), 300 mL of toluene is added; an additional 460 mL of distillate is collected and fresh toluene (500 mL) is added. After 100 mL of clear distillate is collected, fresh toluene (200 mL) is added a third time and the mixture is finally distilled to a 1.5-L mark on the flask (a total of 1620 mL of distillate, including 90 mL of second phase water, is collected). The mixture is allowed to cool overnight with stirring and then cooled to 0°C and aged for 2 hr. The product is collected on a filter, washed with toluene (room temperature, 400 mL) and dried under reduced pressure at 60°C for 7 hr (Note 4); 108.91 g (92.3%), mp 249-251°C, $[\alpha]_{\text{D}}^{25} +213^\circ$ (pyridine, *c* 1), $[\alpha]_{\text{D}}^{20} +218^\circ$ (pyridine, *c* 1). LC analysis shows 100.0% pure (Notes 5 and 6).

2. Notes

1. The preparation of phenylmagnesium bromide follows approximately the procedure of Allen, C. F. H.; Converse, S. *Org. Synth., Coll. Vol. I* **1941**, 226.

2. Commercial methyl (R)-(-)-mandelate can be used. The submitters prepared it from (R)-(-)-mandelic acid (BASF AG, D-Ludwigshafen), $[\alpha]_{\text{D}}^{20} -154.9^\circ$ (water, *c* 2): A 2-L, round-bottomed flask equipped with a condenser with a drying tube and a magnetic stirrer is charged with 100 g (0.66 mol) of (R)-(-)-mandelic acid and 500 mL of dry methanol. One milliliter of sulfuric acid is added and the mixture is heated under

reflux for 2 hr. (LC analysis showed a 97:3 ratio of ester to acid which did not change after 2 hr further reflux). The flask is cooled in an ice bath and 50 mL of water and 7 g (83 mmol) of sodium bicarbonate (NaHCO_3) are added under stirring, which is continued until the pH rises to 7.6. The mixture is filtered and concentrated on a rotary evaporator at 50°C. On cooling the two-phase liquid mixture a solid mass is obtained that is broken up with a spatula; water (200 mL) is added and the slurry is stirred for 2 hr. The product is collected on a filter, washed with water and dried under reduced pressure to give 93.0 g (85%) of white solid, mp 56-58°C, $[\alpha]_{\text{D}}^{25} -133^\circ$ (95% ethanol, *c* 1) [lit.² $[\alpha]_{\text{D}}^{25} -128.6^\circ$ (ethanol, *c* 1)].

3. Molten methyl mandelate dissolves readily in diethyl ether.

4. Careful drying is strongly recommended, since methanol is retained tenaciously by crystalline 1,1,2-triphenyl-1,2-ethanediol. Material containing minor amounts of methanol can be used in the following step provided that the acylation is performed with a 50% excess of acetyl chloride.

5. (R)- and (S)-HYTRA are commercially available from Merck AG, D-Darmstadt.

6. The spectral properties are as follows: ^1H NMR (CDCl_3 , 300 MHz) δ : 1.96 (s, 3 H, CH_3); 2.78 (s, 1 H, OH); 6.68 (s, 1 H, PhCH); 7.05-7.40 (m, 13 H, ArH); 7.54-7.57 (m, 2 H, ArH).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

(R)-(+)-1,1,2-Triphenyl-1,2-ethanediol is available from methyl³ and ethyl⁴ (R)-(-)-mandelate by treatment with phenylmagnesium bromide. The synthesis of (R)-(+)-2-hydroxy-1,1,2-triphenylethyl acetate [(R)-HYTRA] has been reported previously by the submitters.^{5,6} (S)-(-)-2-Hydroxy-1,1,2-triphenylethyl acetate is available according to this procedure starting from the enantiomeric methyl (S)-(+)-mandelate or (S)-(+)-mandelic acid, respectively, both of which are commercially available. Doubly deprotonated HYTRA can be used to introduce an acetate moiety into achiral as well as chiral aldehydes in an enantioselective manner.

1. Institut für Organische und Makromolekulare Chemie, Heinrich-Heine Universität, Universitätsstrasse 1, D-40225 Düsseldorf, West Germany.
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Appendix Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(R)-(+)-2-Hydroxy-1,1,2-triphenylethyl acetate: 1,2-Ethanediol, 1,1,2-triphenyl-, 2-acetate, (R)- (11); (95061-47-5)

Phenylmagnesium bromide: Magnesium, bromophenyl- (8,9); (100-58-3)

Bromobenzene: Benzene, bromo- (8,9); (108-86-1)

(R)-(+)-1,1,2-Triphenylethanediol: 1,2-Ethanediol, 1,1,2-triphenyl-, (R)- (11); (95061-46-4)

Methyl (R)-(-)-mandelate or (R)-(-)-methyl mandelate (Aldrich catalog name):

Mandelic acid, methyl ester, (R)- or mandelic acid, methyl ester (R)-(-)- (8);

Benzeneacetic acid, α -hydroxy-, methyl ester, (R)- (9); (20698-91-2)

Acetyl chloride (8,9); (75-36-5)

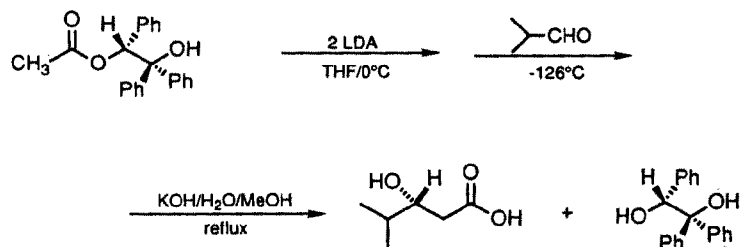
(R)-(-)-Mandelic acid: Mandelic acid, D-(-)- (8); Benzeneacetic acid, α -hydroxy-, (R)- (9); (611-71-2)

STEREOSELECTIVE ALDOL REACTION OF DOUBLY DEPROTONATED

(R)-(+)-2-HYDROXY-1,2,2-TRIPHENYLETHYL ACETATE (HYTRA):

(R)-3-HYDROXY-4-METHYLPENTANOIC ACID

(Pentanoic acid, 3-hydroxy-4-methyl-, (R)-)



Submitted by Manfred Braun and Silke Gräf.¹

Checked by K. Ryan, J. Lynch, and I. Shinkai.

1. Procedure

A 500-mL, two-necked, round-bottomed flask is equipped with a magnetic stirrer, septum, and a connection to a combined vacuum/nitrogen line (Note 1). The air in the flask is replaced by nitrogen by repeated evacuation and flushing with nitrogen, the pressure of which is maintained during the reaction at ca. 70 mm above atmospheric pressure with a mercury bubbler. Dry tetrahydrofuran (100 mL) (Note 2) and 38.4 mL (0.269 mol) of diisopropylamine (Note 3) are injected with syringes through the septum. The mixture is cooled to -78°C by means of a dry ice/acetone bath and treated with stirring with 165 mL (0.264 mol) of a 15% solution of butyllithium in hexane. The dry ice/acetone bath is replaced with an ice bath, and stirring is

continued for 30 min. A 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, septum, and a connection to the combined vacuum/nitrogen line (Note 1) is charged with 40.0 g (0.120 mol) of (R)-(+)-2-hydroxy-1,2,2-triphenylethyl acetate [(R)-HYTRA]. The air in the flask is replaced with nitrogen, and 400 mL of dry tetrahydrofuran is added via a cannula with 1.2 mm inside diameter, whereby the flask is slightly evacuated. The suspension is stirred at -78°C in a dry ice/acetone bath. The ice-cold solution of lithium diisopropylamide, prepared as described above, is added via a cannula under vigorous stirring, whereby the 2-L flask is slightly evacuated. The reaction mixture is stirred at 0°C for 60 min to complete the double deprotonation. A clear orange solution forms that is cooled, below -70°C (dry ice/acetone bath). Thereafter, 900 mL of dry 2-methylbutane (Note 4) is added via a cannula. A thermocouple, connected to a resistance thermometer (Note 5), is introduced via the septum. The reaction flask is plunged into a bath of liquid nitrogen, the depth of immersion being 0.5-1 cm (Note 6). When the temperature of the suspension has reached -128°C a solution of 18.3 mL (0.200 mol) of 2-methylpropanal in 5 mL of dry tetrahydrofuran is added dropwise via syringe through the septum at such a rate that the temperature does not rise above -126°C. Stirring is continued for 90 min at -128°C to -106°C (Note 7). The mixture is treated with 500 mL of a saturated aqueous solution of ammonium chloride and allowed to reach room temperature.

The organic layer is separated and washed twice with a total of 200 mL of water. The aqueous reaction layer is extracted five times with a total of 600 mL of chloroform. The organic extracts are washed twice with a total amount of 250 mL of water. The combined organic layers are dried with magnesium sulfate and evaporated to dryness. The residual solid product is carefully dried under reduced pressure to yield 48-50 g (≥ 100%) (Note 8).

The crude product is transferred to a 2-L, round-bottomed flask equipped with a magnetic stirrer and a condenser. Methanol (1.4 L), water (0.4 L), and 66.6 g of potassium hydroxide are added and the mixture is refluxed for 3 hr. After the solution is cooled to room temperature, the organic solvent is removed on a rotary evaporator. The residual aqueous alkaline suspension is filtered through a suction filter. The solid (Note 9) is washed carefully with 250 mL of water. In a separatory funnel the combined aqueous layers are washed three times with a total of 300 mL of methylene chloride. The aqueous solution is transferred to a 2-L, round-bottomed flask, immersed in an ice bath, and acidified to pH 2.5 by cautious addition of 6 N hydrochloric acid. The mixture is stirred vigorously with a magnetic stirrer, and the pH is controlled carefully to avoid over-acidification. The clear solution is again poured into a separatory funnel, saturated with sodium chloride, and extracted with five 100-mL portions of diethyl ether. The pH of the aqueous layer is controlled and readjusted to pH 2.5 by addition of 6 N hydrochloric acid, if necessary. The combined organic layers are dried with magnesium sulfate and concentrated in a rotary evaporator without heating. The yellow syrupy residue is dried carefully at room temperature under reduced pressure (10^{-3} mm) to yield 9.7-12.4 g (61-78%) (76 mmol; 63%) of (R)-(+)-3-hydroxy-4-methylpentanoic acid in 86-92% optical purity (Note 10), $[\alpha]_{\text{D}}^{20} +32^{\circ}$ to $+37^{\circ}$ (99% chloroform, c 0.11) [lit.² $[\alpha]_{\text{D}}^{20} +40.5^{\circ}$ (chloroform, c 0.0063); lit.³ $[\alpha]_{\text{D}}^{20} +40.14^{\circ}$ (chloroform, c 1.22)].

2. Notes

1. Alternatively, the flask can be closed with a three-way stop-cock to maintain connections to a vacuum pump and to a nitrogen line.

2. Tetrahydrofuran is distilled first from sodium wire and then under nitrogen from lithium aluminum hydride. 2-Methylbutane (purchased from Aldrich Chemical

Company, Inc.) and petroleum ether (low-boiling fraction, bp 30-37°C) are distilled from lithium aluminum hydride under nitrogen. The solvents are stored under nitrogen, and can be taken from the receiving flasks, closed with septums, with syringes or cannulas.

3. Diisopropylamine (Merck AG, D-Darmstadt) is distilled from calcium hydride and stored over molecular sieves (3 Å). Butyllithium (15% solution in hexane) was purchased from Merck AG, D-Darmstadt.

4. Instead of 2-methylbutane, a low-boiling fraction of petroleum ether (bp 30-37°C), but not pure pentane, can be used (cf. Note 2).

5. Because of the inaccuracy of alcohol thermometers it is strongly recommended that one monitor those reactions that are run below -80°C with a resistance thermometer. The submitters used an apparatus purchased from Ebro, D-Ingolstadt.

6. The submitters used a 2-L Dewar cylinder of 20 cm inner depth, covered with aluminum foil. The mixture should be stirred very vigorously to avoid solidification.

7. When the addition of the aldehyde is complete, liquid nitrogen is removed from the Dewar cylinder.

8. ^1H NMR ($\text{CDCl}_3/\text{TMS}/300\text{ MHz}$) δ : 0.82 (d, 3 H, $J = 6.9$, CH_3), 0.83 (d, 3 H, $J = 6.7$, CH_3), 1.53 (m, 1 H, $\text{CH}(\text{CH}_3)_2$), 2.35 (m, 2 H, CH_2), 3.56 (m, 1 H, $\text{CH}(\text{OH})$), 6.72 (s, 1 H, CHPh), 7.11 (m, 10 H, Ar-H), 7.32 (m, 3 H, Ar-H); 7.63 (m, 2 H, Ar-H). $[\alpha]_{\text{D}}^{20} +159^{\circ}$ to 171° (99% chloroform, c 1) mp 178° to 190°C . The optical rotation is influenced by the diastereomeric ratio and by traces of HYTRA, if present. Those traces can be detected by TLC on silica gel ($R_f = 0.2$, chloroform).

9. Colorless, crystalline, optically pure (R)-(+)-1,1,2-triphenyl-1,2-ethanediol can be recovered in >95% yield after recrystallization from methanol as described in

the accompanying procedure (cf. Braun, M.; Gräf, S.; Herzog, S. *Org. Synth.* **1993**, *72*, 32), mp 124°C, $[\alpha]_D^{20} +224^\circ$ (95% aqueous ethanol, c 0.984).

10. The optical purity of 3-hydroxy-4-methylpentanoic acid is determined by shift measurements on the methyl ester. Chemical purity exceeds 98% according to GC. The submitters report consistent ee of 92-94%; the checker's experience is recorded in the procedure.

Waste Disposal Information

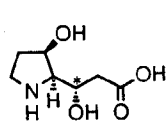
All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

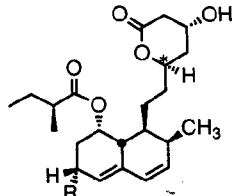
The addition of doubly deprotonated HYTRA to achiral^{4,5} as well as to enantiomerically pure aldehydes⁶ enables one to obtain non-racemic β -hydroxycarboxylic acids. Thus, the method provides a practical solution for the stereoselective aldol addition of α -unsubstituted enolates, a long-standing synthetic problem.⁷ As opposed to some other chiral acetate reagents,⁷ both enantiomers of HYTRA are readily available. Furthermore, the chiral auxiliary reagent, 1,1,2-triphenyl-1,2-ethanediol, can be recovered easily. Aldol additions of HYTRA have been used in syntheses of natural products and biological active compounds, and some of those applications are given in Table I. (The chiral center, introduced by a stereoselective aldol addition with HYTRA, is marked by an asterisk.)

Preparation of (R)-(+)-3-hydroxy-4-methylpentanoic acid has been reported previously by the submitters.⁵ Alternative syntheses of (R)-(+)- or (S)-(-)-3-hydroxy-4-methylpentanoic acid rely on aldol reactions of chiral ketone, ester, or amide enolates,^{2,8-10} and Lewis-acid mediated additions of chiral silyl ketene acetals to isobutyraldehyde.^{3,11} Since both enantiomers of HYTRA are readily available this method enables one to prepare (S)-3-hydroxy-4-methylpentanoic acid as well.

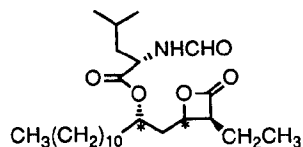
TABLE I
NATURAL PRODUCTS AND BIOLOGICALLY ACTIVE ANALOGUES
PREPARED BY STEREoseLECTIVE ALDOL ADDITION OF DOUBLY
DEPROTONATED (R)- AND (S)-HYTRA



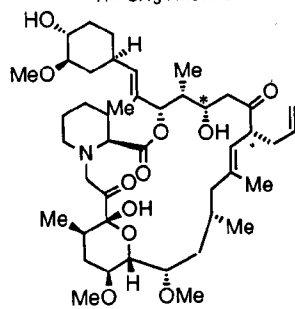
Detoxinine¹²



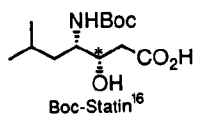
R = H : Compactin¹³
R = CH₃ : Mevinolin¹³



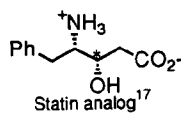
Tetrahydrolipstatin¹⁴
(Pancreatic lipase inhibitor)



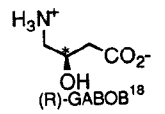
FK 506¹⁵
(Immunosuppressant)



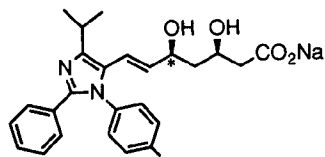
Boc-Statins¹⁶



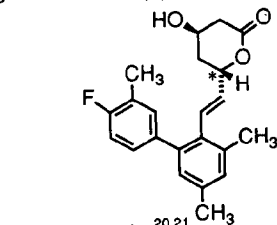
Statin analog¹⁷



(R)-GABOB¹⁸



SDZ 64-406¹⁹
(antihypercholesterolemic agent)



Compactin analog^{20,21}
(antihypercholesterolemic agent)

1. Institut für Organische und Makromolekulare Chemie, Heinrich-Heine Universität, Universitätsstrasse 1, D-40225 Düsseldorf, Germany.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(R)-(+)-2-Hydroxy-1,2,2-triphenylethyl acetate: 1,2-Ethanediol, 1,1,2-triphenyl-, 2-acetate, (R)- (11); (95061-47-5)

(R)-3-Hydroxy-4-methylpentanoic acid: Pentanoic acid, 3-hydroxy-4-methyl-, (R)- (10); (77981-87-4)

Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

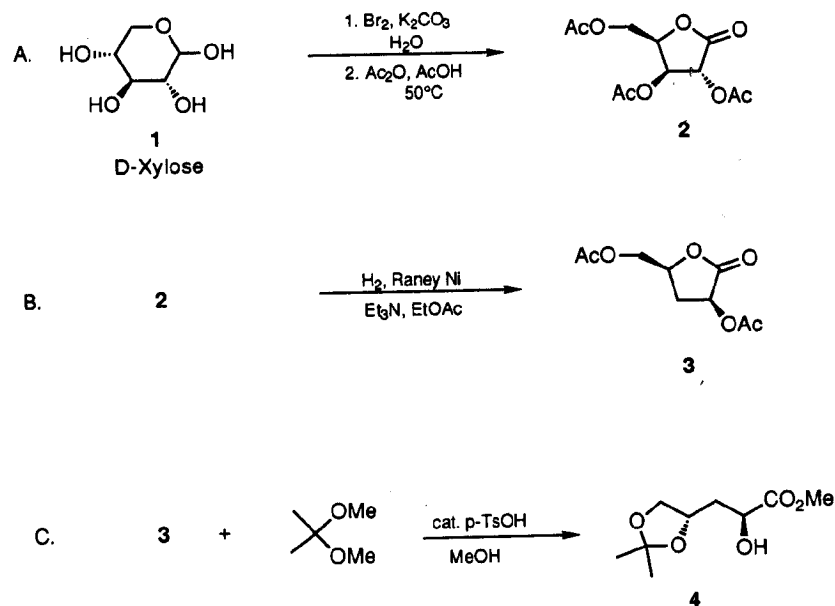
2-Methylbutane: Butane, 2-methyl- (8,9); (78-78-4)

2-Methylpropanal: Isobutyraldehyde (8); Propanal, 2-methyl- (9); (78-84-2)

(R)-(+)-1,1,2-Triphenylethanediol: 1,2-Ethanediol, 1,1,2-triphenyl-, (R)- (11); (95061-46-4)

(2S,4S)-2,4,5-TRIHIDROXYPENTANOIC ACID 4,5-ACETONIDE
METHYL ESTER

(D-erythro-Pentonic acid, 3-deoxy-4,5-O-(1-methylethylidene)-, methyl ester)



Submitted by Ruen Chu Sun and Masami Okabe.¹

Checked by Timothy C. Gahman and Larry E. Overman.

1. Procedure

A. *Tri-O-acetyl-D-xylono-1,4-lactone* 2. a) Bromine oxidation. A 250-mL, three-necked, round-bottomed reaction flask equipped with a magnetic stirrer, thermometer, and an addition funnel is charged with 30.0 g (0.20 mol) of D-xylose and 80 mL of water. After the clear aqueous solution is cooled with an ice-water bath, 34.0 g (0.23 mol) of potassium carbonate is added in portions, keeping the temperature below 20°C. After the mixture is cooled to below 5°C, 12 mL (0.22 mol) of bromine is added dropwise over 90 min, keeping the temperature of the reaction mixture below 10°C (Note 1). The orange solution is stirred at that temperature for 30 min, then at room temperature overnight. The reaction is quenched by careful addition of 88% formic acid (2.5 mL) to afford a colorless solution (Note 2). The solution is concentrated at 50°C on a rotary evaporator and 20 mL of acetic acid is added. The mixture is concentrated again at 50°C to remove any residual water (Note 3).

b) Acetylation. The residual white semi-solid is transferred to a 500-mL, three-necked, round-bottomed reaction flask with the aid of warm acetic acid (40 mL). The flask is equipped with a mechanical stirrer, thermometer, and an addition funnel. After the suspension is warmed to 50°C, 180 mL (1.9 mol) of acetic anhydride is added dropwise over 90 min, keeping the temperature between 50-55°C. After the mixture is stirred at that temperature overnight and then cooled to room temperature, 200 mL of water is added. The mixture is extracted with 200 mL of dichloromethane (CH₂Cl₂). The organic layer is washed with 200 mL of water. The combined aqueous layers are back-extracted with 100 mL of CH₂Cl₂. The combined organic layers are placed in a 1-L Erlenmeyer flask. After the solution is cooled with an ice-water bath, 200 mL of 2 N sodium hydroxide is added and the mixture is stirred for 30 min. The aqueous layer is separated and back-extracted with 50 mL of CH₂Cl₂. The combined organic layers are washed with 200 mL of brine, dried over sodium sulfate, and concentrated under

reduced pressure. The residue (54 g) is suspended in 50 mL of ethyl acetate. To the stirred suspension, 70 mL of hexane is added dropwise. After stirring at room temperature for 1 hr, the mixture is cooled with an ice-water bath for 30 min. The precipitate is filtered and washed with a cold 1:2 ethyl acetate/hexane mixture (2 x 60 mL) to yield 39.3-40.7 g (71.6-74.2%) of **2** as light beige crystals, mp 96-97°C (lit.² mp 94-95°C) (Note 4).

B. Di-O-acetyl-3-deoxy-D-arabino-1,4-lactone 3 (Note 5). A 300-mL, bench-top, high-pressure reactor (Note 6) is charged with 9.83 g (35.8 mmol) of **2**, 1 g of Raney nickel (Note 7), and 65 mL of ethyl acetate. After 7.5 mL (73 mmol) of triethylamine is added, the pressure in the bomb is immediately raised to 1000 psi with hydrogen. After the mixture is *stirred vigorously* (see Note 6) at room temperature (15°C) for 3 hr, the temperature is adjusted to 30°C, and the stirring is continued for 24 hr. The pressure is released, and the bomb is flushed with nitrogen. The catalyst is removed by filtration and washed with ethyl acetate (*Caution! Fire hazard!* See Note 7). The combined filtrate and washes are washed with 75 mL of water. The aqueous layer is back-extracted with 25 mL of ethyl acetate. The combined organic layers are then washed with 75 mL of 1 N hydrochloric acid. The aqueous layer is back-extracted again with 25 mL of ethyl acetate and this extract is combined with the original organic layer. After washing with 75-mL portions of saturated sodium bicarbonate solution, and brine, the organic layer is dried over sodium sulfate and the solvent is removed to give ca. 6.5 g of crude product (Note 8). The crude product is dissolved in 7 mL of warm ethyl acetate. Cooling to room temperature with stirring results in crystallization of **3**. Hexane (13 mL) is added dropwise to the slurry. After the mixture is stirred at room temperature for 1 hr, it is stored in a refrigerator overnight. The precipitate is filtered and washed with a cold 1:4 ethyl acetate/hexane mixture (6 mL) to yield 5.8 g (75%) of **3** as a white solid, mp 68-70°C (lit.² mp 69-71°C) (Note 9).

C. (2S,4S)-2,4,5-Trihydroxypentanoic acid 4,5-acetonide methyl ester 4. A 100-mL, round-bottomed reaction flask equipped with a magnetic stirrer, reflux condenser, and an argon inlet tube is charged with 5.4 g (25 mmol) of the diacetate **3**, 0.5 g (2.5 mmol) of p-toluenesulfonic acid monohydrate, and 5 mL of methanol. After the mixture is refluxed for 3 hr and cooled to room temperature, 18 mL (140 mmol) of 2,2-dimethoxypropane is added. After 3 hr of stirring, sodium acetate (powder, 0.41 g, 5 mmol) is added and the mixture is stirred for 20 min to quench the reaction. Ethyl acetate (50 mL) and saturated sodium bicarbonate solution (50 mL) are added to the reaction mixture. The organic layer is removed and the aqueous layer is back-extracted twice with 25-mL portions of ethyl acetate. The combined organic layers are washed with 25 mL of brine, dried over sodium sulfate, and concentrated to afford 5.5 g of a colorless oil. Distillation through a short path distillation apparatus (with no forerun) gives 4.6 g of **4** (90% yield) as a colorless oil, bp 71-78°C (0.1 mm) (Note 10).

GC analysis of the product on a capillary column shows the diastereomeric purity to be 98.9% (Note 11). Enantiomeric integrity is confirmed after conversion to the corresponding p-phenylbenzoate by HPLC analysis on a chiral column (Note 12).

2. Notes

1. Since the reaction is exothermic at the beginning, one must avoid the accumulation of bromine in the reaction mixture.
2. A negative potassium iodide-starch test is obtained.
3. To remove the last traces of water and acetic acid the checkers found it most convenient to place the residue on a high vacuum line overnight.
4. The elemental analysis and the spectral properties of the product **2** are as follows: Anal. Calcd for C₁₁H₁₄O₈: C, 48.18; H, 5.15. Found: C, 47.97; H, 5.01. IR (KBr) cm⁻¹: 1805, 1792, 1750; ¹H NMR (CDCl₃) δ: 2.13 (s, 3 H), 2.14 (s, 3 H), 2.19 (s,

3 H), 4.27 (dd, 1 H, J = 12.8 and 2.9), 4.39 (dd, 1 H, J = 12.8 and 2.9), 5.00 (dt, 1 H, J = 7.7 and 2.9), 5.62 (t, 1 H, J = 7.8), 5.69 (d, 1 H, J = 7.9).

5. This is a modification of the procedure described by Bock, Lundt, and Pedersen.²

6. The checkers used a Paar model 4022 stirred pressure reactor. Rapid stirring is essential to ensure that hydrogenation takes place more rapidly than elimination; otherwise a number of side reactions, e.g., deoxygenation at C(5), occur. Deoxygenation was observed by the checkers if the stirring rate was less than maximum or if the reactor was filled to a higher level, e.g., when the reaction was conducted on twice the scale described. Using industrial hydrogenation equipment with stirring at 500 rpm, the submitters report that this step can be conducted on a 1-mol scale with identical yield.

7. *Caution! The catalyst is extremely pyrophoric when exposed to the air in a dry condition; it should be kept wet with solvent at all times.* The catalyst (Raney 2800 Grade Active Nickel Catalyst in Water) is purchased from Davison Chemical, and is weighed out while it is wet. The catalyst is washed by suspension in methanol and decanted to remove water. It is further washed with ethyl acetate prior to use. The checkers obtained similar results with Raney nickel (50% slurry in water) catalyst purchased from Aldrich Chemical Company, Inc.

8. The crude diacetate contains a small amount of the epimeric acetate, as detected by NMR (m, 4.88 ppm, CDCl₃), that can be produced by isomerization of 3 with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane (CH₂Cl₂).

9. The elemental analysis and the spectral properties of product 3 are as follows: Anal. Calcd for C₉H₁₂O₆: C, 50.00; H, 5.59. Found: C, 50.11, H, 5.59. IR (KBr) cm⁻¹: 1791, 1745; ¹H NMR (CDCl₃) δ: 2.07 (dt, 1 H, J = 12.8 and 10.3), 2.12 (s, 3 H), 2.18 (s, 3 H), 2.78 (ddd, 1 H, J = 12.8, 8.8, and 6.0), 4.19 (dd, 1 H, J = 12.5 and 5.8), 4.38 (dd, 1 H, J = 12.5 and 3.1), 4.68 (m, 1 H), 5.51 (dd, 1 H, J = 10.3 and 8.8).

10. The elemental analysis and the spectral properties of product 4 are as follows: Anal. Calcd for C₉H₁₆O₅: C, 52.93; H, 7.90. Found: C, 52.83; H, 7.96; [α]_D +3.0° (MeOH, c 1.0): IR (neat) cm⁻¹: 3455, 1742, 1378, 1368; ¹H NMR (CDCl₃) δ: 1.37 (s, 3 H), 1.43 (s, 3 H), 1.81 (ddd, 1 H, J = 13.9, 9.3, and 4.5), 2.11 (ddd, 1 H, J = 13.9, 8.4, and 3.1), 3.01 (d, 1 H, J = 5.9), 3.60 (dd, 1 H, J = 8.2 and 6.8), 3.80 (s, 3 H), 4.11 (dd, 1 H, J = 8.2 and 6.0), 4.32 (m, 1 H), 4.39 (m, 1 H).

11. The retention time of 4 is 5.1 min, and that of the (2R,4S)-isomer is 4.7 min (on an OV-101, 12.5-m capillary column: 100°C to 140°C at 4°C/min). Proton magnetic resonance spectrum of the (2R,4S)-isomer exhibits the following absorptions (CDCl₃) δ: 1.34 (s, 3 H), 1.40 (s, 3 H), 2.05 (t, 2 H, J = 6.1), 3.15 (d, 1 H, J = 3.8), 3.64 (dd, 1 H, J = 8.2 and 6.7), 3.80 (s, 3 H), 4.10 (dd, 1 H, J = 8.2 and 6.1), 4.31 (m, 1 H), 4.35 (m, 1 H).

12. A small amount of 4 is treated with p-phenylbenzoyl chloride (1.2 equiv) and triethylamine (2 equiv) in CH₂Cl₂ at room temperature overnight. After aqueous workup, the crude product is purified by chromatography on silica gel, eluting with 15% ethyl acetate in hexane. The fractions containing the product are combined and concentrated. The residue is dissolved in 5% 2-methyl-1-propanol/heptane (ca. 1 mg/2 mL). The corresponding diastereomeric mixture is prepared via isomerization of 3 with DBU, and the (2R,4R)-isomer (enantiomer) is prepared from L-xylose. HPLC analysis of the solution on Chiralcel OC 250 mm x 5 mm (purchased from Daicel Chemical), eluting with 5% 2-methyl-1-propanol in heptane (1 mL/min), reveals no detectable amount of the enantiomer [0.24% of the (2R,4S)-isomer was detected]. The retention times of the (2S,4S)-, (2R,4R)-, and (2R,4S)-isomers are 33.2, 45.3, and 54.0 min, respectively. Alternatively a Chiralcel OD column can be employed.

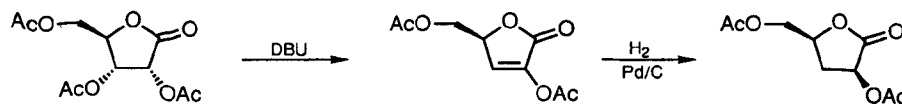
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

The present procedure for the preparation of (2S,4S)-2,4,5-trihydroxypentanoic acid 4,5-acetonide methyl ester is a slight modification of a method previously reported by the submitters.³ The hydrogenation step is based on the method of Bock, Lundt, and Pedersen,² in which the 3-acetoxy group is eliminated and the resulting unsaturated lactone is simultaneously reduced with high stereoselectivity to afford di-O-acetyl-3-deoxy-D-arabino-1,4-lactone. A cleaner reaction was achieved by using Raney-Ni (instead of using palladium on carbon). When platinum catalysts are employed, the corresponding 2,3-dideoxy sugar lactones are obtained.⁴

A two-step sequence to prepare di-O-acetyl-3-deoxy-D-arabino-1,4-lactone from tri-O-acetyl-D-ribono-1,4-lactone has also been reported, but in a low yield of 46% because of the difficulty of controlling the elimination of the 3-acetoxy group, since the 2,3-unsaturated lactone also undergoes further elimination.⁵ Furthermore, partial racemization of the enolizable 2,3-unsaturated lactone could occur during treatment with DBU.⁶



The ready availability of the selectively protected 2,4,5-trihydroxypentanoic acid derivatives of defined stereochemistry, such as (2S,4S)-2,4,5-trihydroxypentanoic acid 4,5-acetonide methyl ester described here, coupled with Mitsunobu inversion,^{3,7} provide chiral synthons with the promise of broad utility.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(2S,4S)-2,4,5-Trihydroxypentanoic acid 4,5-acetonide methyl ester: D-erythro-Pentonic acid, 3-deoxy-4,5-O-(1-methylethylidene)-, methyl ester (12); (134455-80-4)
Tri-O-acetyl-D-xylono-1,4-lactone: D-Xylonic acid, γ -lactone, triacetate (10); (79580-60-2)
D-Xylose (8,9); (58-86-6)
Bromine (8,9); (7726-95-6)

Formic acid (8,9); (64-18-6)

Acetic anhydride (8); Acetic acid anhydride (9); (108-24-7)

Di-O-acetyl-3-deoxy-D-arabino-1,4-lactone: D-threo-Pentoic acid, 3-deoxy- γ -lactone,

2,5-diacetate (10); (79580-65-7)

Raney nickel: Nickel (8,9); (7440-02-0)

Ethyl acetate: Acetic acid, ethyl ester (8,9); (141-78-6)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

p-Toluenesulfonic acid monohydrate (8); Benzenesulfonic acid, 4-methyl-, monohydrate (9); (6192-52-5)

2,2-Dimethoxypropane: Acetone, dimethyl acetal (8); Propane, 2,2-dimethoxy- (9); (77-76-9)

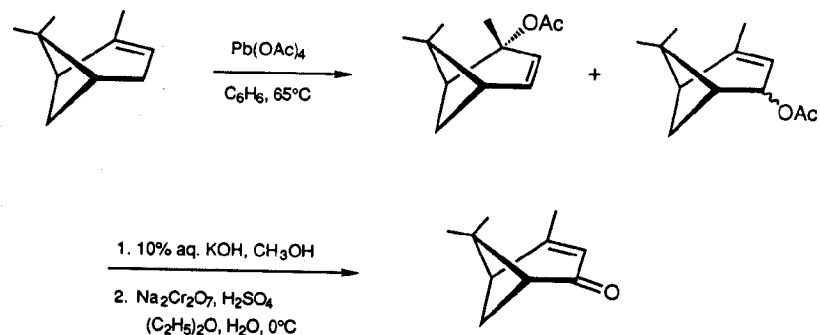
p-Phenylbenzoyl chloride: 4-Biphenylcarbonyl chloride (8); [1,1'-Biphenyl]-4-carbonyl chloride (9); (14002-51-8)

2-Methyl-1-propanol: Isobutyl alcohol (8); 1-Propanol, 2-methyl- (9); (78-83-1)

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU): Pyrimido[1,2-a]azepine, 2,3,4,6,7,8,9,10-octahydro- (8,9); (6674-22-2)

L-Xylose (8,9); (609-06-3)

(1R,5R)-(+)-VERBENONE OF HIGH OPTICAL PURITY
(Bicyclo[3.1.1]hept-3-en-2-one-, 4,6,6-trimethyl-, (1R)-)



Submitted by Mark R. Sivik, Kenneth J. Stanton, and Leo A. Paquette.¹

Checked by Bradley J. Newhouse and Albert I. Meyers.

1. Procedure

(1R)-(+)- α -Pinene (25.0 g, 0.183 mol, $[\alpha]_{\text{D}}^{20} +50.9^\circ$ (neat), 98.6% ee) (Note 1) and 350 mL of dry benzene (Note 2) are placed in a base-washed, 1000-mL Morton flask fitted with a mechanical stirrer, condenser, internal thermometer, and gas inlet. The flask is set in a heating mantle and warmed to 65°C , at which point lead tetraacetate (77.8 g, 0.175 mol) is added via Gooch tubing over 20 min (Note 3). The reaction mixture becomes bright yellow, this color slowly changing to tan after heating at 65°C with stirring for 1 hr. The solution is cooled to room temperature and filtered through a 1-in pad of Celite. The Celite is washed with several 50-mL portions of benzene. To the filtrate is added 300 mL of water, at which point brown-black lead oxide precipitates (Note 4). The two-phase system is swirled vigorously at 10-min

intervals for an hour and then filtered through a 1-in pad of Celite. The layers of the filtrate are separated and the aqueous phase is extracted with three 150-mL portions of ether. The combined organic fractions are dried over magnesium sulfate, filtered, and concentrated by rotary evaporation at room temperature to give a mixture of acetates as a colorless liquid (Note 5).

Without purification, the mixture of acetates is placed in a 250-mL round-bottomed flask and 150 mL of a 10% potassium hydroxide solution in aqueous methanol is introduced at room temperature. After 24 hr of stirring, the brown mixture is poured into a separatory funnel, diluted with 200 mL of water, and extracted with four 150-mL portions of ether. The combined ethereal fractions are dried over anhydrous magnesium sulfate, filtered, and concentrated to give a mixture of alcohols (Note 6) as a light yellow oil.

The mixture of alcohols is placed in a 1000-mL round-bottomed flask, dissolved in 300 mL of ether, and cooled to 0°C. To this solution is added via an addition funnel over a 30-min period a mixture of sodium dichromate dihydrate (27.5 g, 0.092 mol), 100 mL of water, and 10.2 mL of concd sulfuric acid. The mixture is stirred at 0°C for 1 hr, warmed to room temperature where stirring is maintained overnight, diluted with 200 mL of water, and poured into a separatory funnel. The layers are separated and the aqueous phase is extracted with ether (3 x 200 mL). The combined organic layers are washed with saturated sodium bicarbonate solution (200 mL) and brine (200 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give 16.8-17.8 g (61-65%) of verbenone (Note 7). Final purification is achieved by distillation of the oil through a 5-in Vigreux column at reduced pressure (dry ice-acetone cooled receiver); 13.1 g (47%), bp 108-110°C (5 mm) (Note 8).

2. Notes

1. (1R)-(+)- α -Pinene was purchased from the Aldrich Chemical Company, Inc. The optical purity of the starting material is based on the maximum reported rotation for the dextrorotatory enantiomer: $[\alpha]_D^{20} +51.6^\circ$ (neat).² The levoratory form is also available from the same vender in high optical purity.

2. Benzene is reagent grade quality and distilled from sodium/benzophenone ketyl. This solvent is a suspect carcinogen and should be handled in a well-ventilated hood.

3. Lead tetraacetate was purchased from the Sigma Chemical Company. This reagent is highly toxic and should be handled in a well-ventilated hood with gloves.

4. The checkers did not observe a precipitate on this scale, but it was observed on smaller-scale runs.

5. The tertiary acetate is formed initially^{3,4} and constitutes the major component of the mixture that may also contain residual amounts of benzene. Failure to remove all the lead oxide can induce further isomerization to the secondary acetate. To avoid this, a second filtration may be necessary. Although further purification is unnecessary, results in lower yields, and is not recommended, distillation at this point will give 26.8 g (75%) of a colorless oily acetate mixture.

6. Decomposition and lower yields result if this mixture is distilled, since the tertiary isomer loses water on attempted purification.⁵ Both alcohols yield the same ketone in the oxidation step.

7. The undistilled product is sufficiently pure for most purposes.

8. The verbenone is clear on distillation but yellows slightly on exposure to air. This does not affect its quality. Radial chromatography (4-mm plate, 10% ethyl acetate/hexane) of a 1-g sample yielded 900 mg of pure verbenone, $[\alpha]_D^{22.0^\circ}$ (EtOH, c 2.00). Column chromatography (200 g of silica, 10% ethyl acetate hexane)

was used to purify verbenone from the small scale preparation. A 43% overall yield was obtained, $[\alpha]_D^{20} 202.5^\circ$ (EtOH). The optical rotation of high quality verbenone has been reported by several groups as neat samples.^{6,7,8} The percent of enantiomeric excess in the present example is correlated directly to the optical purity of the starting α -pinene.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983. Particular care must be taken in the disposal of waste materials containing lead and chromium compounds.

3. Discussion

In recent years, verbenone has been used with increasing frequency as a convenient "chiral pool" starting material for enantiospecific natural product synthesis⁹ and for the preparation of chiral ligands for transition metals.¹⁰ However, a serious deterrent to the use of verbenone in this capacity is the rather low enantiomeric purity of commercially available material (customarily 55-60% ee). The short sequence outlined here provides a ready and convenient means for obtaining (1R)-(+)-verbenone in high optical purity. Since several firms offer both enantiomers of the α -pinene precursor in high quality (> 98% ee), the present procedure is a direct method for obtaining either essentially pure verbenone enantiomer in reasonable quantities. The possibility of upgrading the optical purity of lower grade α -pinene in advance of its oxidation also exists.²

The reaction sequence is based on the readiness with which α -pinene undergoes oxidation predominantly to the tertiary acetate with $\text{Pb}(\text{OAc})_4$.^{3,4} Dichromate oxidation of the derived alcohol proceeds by way of a second allylic rearrangement to give verbenone without affecting the neighboring stereogenic centers.

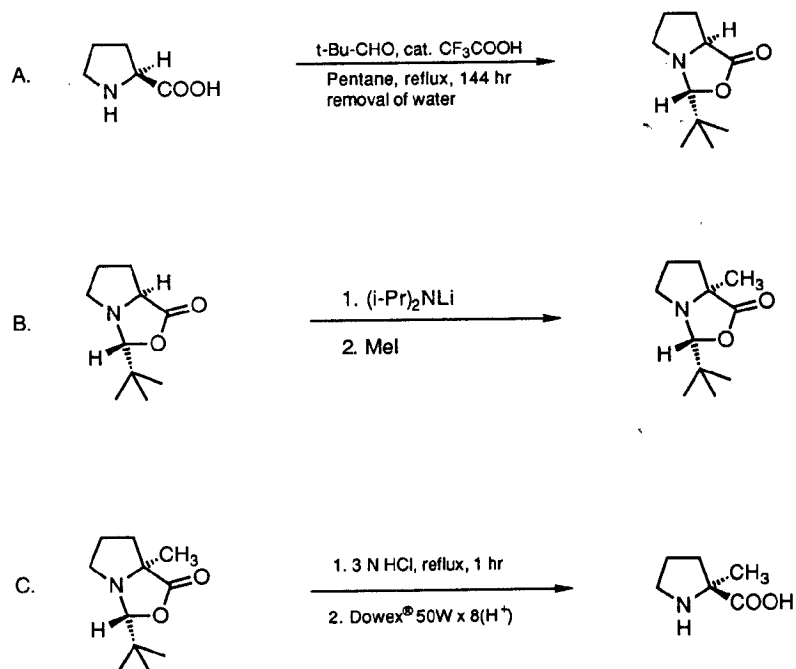
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(1R,5R)-(+)-Verbenone: Bicyclo[3.1.1]hept-3-en-2-one-, 4,6,6-trimethyl-, (1R-cis)- (9); Bicyclo[3.1.1]hept-3-en-2-one-, 4,6,6-trimethyl-, (1R)- (10,11,12); (18309-32-5)
(1R)-(+)- α -Pinene: 2-Pinene, (1R,5R)-(+)- (8); Bicyclo[3.1.1]hept-2-ene, 2,6,6-trimethyl-, (1R)- (9); (7785-70-8)
Benzene (8,9); (71-43-2)
Lead tetraacetate: Acetic acid, lead(4+) salt (8,9); (546-67-8)
Sodium dichromate: Chromic acid, disodium salt, dihydrate (8,9); (7789-12-0)

SYNTHESIS OF (S)-2-METHYLPROLINE:
A GENERAL METHOD FOR THE PREPARATION OF
 α -BRANCHED AMINO ACIDS
(L-Proline, 2-methyl-)



Submitted by A. K. Beck, S. Blank, K. Job, D. Seebach, and Th. Sommerfeld.¹
 Checked by Frank Narjes and Larry E. Overman.

1. Procedure

A. *(2R,5S)*-2-*tert*-Butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one. To a suspension of 40.0 g (0.347 mol) of (S)-proline (Note 1) in 1400 mL of pentane (Note 2) in a 2.5-L, round-bottomed flask are added 225 mL (2.072 mol) of pivalaldehyde (Note 3) and 3.0 mL (38.9 mmol) of trifluoroacetic acid. The mixture is heated at reflux for 72 hr with azeotropic removal of the water formed (Dean-Stark trap). After the addition of another 40.0 mL (0.368 mol) of pivalaldehyde, 1 mL of trifluoroacetic acid (13.0 mmol), and 200 mL of pentane (Note 4), refluxing is continued for an additional 72 hr. Water, 5.4 mL total, is collected. After the reaction mixture is cooled to room temperature, it is filtered under argon (Note 5). The resulting clear solution is concentrated in a 1000-mL flask under reduced pressure. The residue is distilled in a Kugelrohr oven (70°C/0.0005 mm) (Notes 6 and 7) to afford 42.5 - 47.0 g (0.232-0.257 mol, 67-74%) of the desired product as a colorless oil (Notes 8 and 9).

B. *(2R,5S)*-2-*tert*-Butyl-5-methyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one. In a 250-mL, round-bottomed flask equipped with a magnetic stirrer, 18.3 mL (0.131 mol) of diisopropylamine (Note 10) is mixed with 120 mL of dry tetrahydrofuran (THF, Note 11) under argon. At -78°C bath temperature, 88.6 mL of a 1.6 M solution of butyllithium (0.142 mol) in hexane is added and the mixture is allowed to warm to room temperature for 20 min. After the mixture is recooled to -78°C, the lithium diisopropylamide (LDA) solution is added over a period of 20 min (Note 12) to a solution of 20.0 g (0.109 mol) of *(2R,5S)*-2-*tert*-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one in 600 mL of dry THF in a 1-L, round-bottomed flask, precooled to -78°C. Tetrahydrofuran (20 mL) is used to rinse the 250-mL flask. After keeping the resulting solution at -78°C for 45 min, 8.8 mL (0.142 mol) of iodomethane (Note 13) is added over a period of 10 min. The resulting mixture is allowed to warm to 0°C over a period of 3 hr, and 300 mL of a saturated aqueous solution of ammonium chloride is added.

After separation, the organic layer is washed with 300 mL each of saturated aqueous solutions of sodium carbonate and brine. Each aqueous layer is extracted twice with 200 mL of ethyl acetate. The combined organic layers are dried over magnesium sulfate and the solvent is removed in a rotary evaporator at ca. 15 mm. Traces of solvent are removed by drying the residue at 60°C/0.05 mm for 2 hr under an oil pump vacuum to yield 19.8 - 20.5 g (0.100-0.104 mol, 93-95%) of the desired product. It is used directly in the next step (Note 14).

C. *(S)*-2-Methylproline. In a 1-L, round-bottomed flask, 20.1 g (0.102 mol) of (2R,5S)-2-tert-butyl-5-methyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one in 400 mL of 3 N hydrochloric acid (HCl) is heated to reflux for 1 hr. The water is removed under reduced pressure in a rotary evaporator (ca. 15 mm). The dark residue is treated with 400 mL of 3 N HCl and extracted four times with 200 mL each of dichloromethane (CH₂Cl₂). The combined organic layers are washed once with 200 mL of 3 N HCl. The combined aqueous layers are concentrated and dried under reduced pressure in a rotary evaporator at elevated temperature (60°C at 15 mm). The residue is suspended in 50 mL of water and adsorbed on 600 g of Dowex 50W x 8 (H⁺ form) (Note 15) in a 50 x 380-mm column. Water is passed through the column. After 200 mL of effluent, the pH changes to 2; after another 700 mL, the pH of the effluent is 7. The amino acid is then eluted with 3 N aqueous ammonia. After 500 mL of effluent, the developing hot front reaches the outlet. The following 2000 mL are collected and yield 12.0 - 12.3 g of the amino acid, free of inorganic salts, after removal of the water (Notes 16 and 17). The 500 mL of water collected subsequently contains another 0.34 g, yielding altogether 93-98 mmol [85-90% from (2R,5S)-2-tert-butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one] of *(S)*-2-methylproline, $[\alpha]_D^{RT}$ -71.1° to -72.1° (MeOH, c 1.0), mp 248-252°C (dec). The enantiomeric excess (ee) of a sample with a rotation of -72.1° was shown to be 99.0 ± 0.5% by capillary gas chromatographic analysis of a derivative (Note 18) using a chiral column (Note 19) (see Figure 1).

2. Notes

1. *(S)*-Proline was used as commercially available. The submitters obtained *(S)*-proline from Degussa AG (D-Hanau), while the checkers used material from Aldrich Chemical Company, Inc.

2. When higher boiling solvents such as cyclohexane are used, the reaction is complete earlier, but side-products can be detected that are difficult to remove from the reaction mixture and that tend to catalyze decomposition of the desired product.

3. Commercially available material can be used. As pure pivalaldehyde is expensive, the submitters used technical grade as provided by BASF AG (D-Ludwigshafen). The material was washed with water (to remove alcohol impurities) and distilled before use. The checkers used material from Aldrich Chemical Company, Inc., without purification.

4. Pentane has to be replenished since some is lost from the reaction mixture because of its low boiling point and the prolonged heating period.

5. Since the product is extremely sensitive to hydrolysis, contact with air and moisture have to be avoided. Thus, the reaction mixture was filtered through a funnel under a stream of argon.

6. The use of an Aldrich Kugelrohr oven allowed for distillation in a large flask. This is advantageous, since decomposition may ensue above 100°C.² For this reason distillation has to be carried out at as low a pressure as possible. In most cases the submitters used a turbo pump, but application of a normal high vacuum pump with a distillation temperature of 90°C at 0.04 mm is also possible.

7. To recover part of the excess pivalaldehyde, the material that was collected in the cooling trap used with the rotary evaporator and with the Kugelrohr oven can be distilled over a 35-cm Vigreux column; this yielded 150 mL of recovered pivalaldehyde.

8. The spectrum is as follows: ^1H NMR (200 MHz, CDCl_3) δ : 1.55-2.25 (m, 4 H), 2.98 [(m (centered), 2 H)], 3.78 (dd, 1 H, $J = 9, 5$), 4.49 (s, 1 H). Additional analytical data are given in ref. 3.

9. As described in Note 5 above, the product hydrolyzes on contact with moisture (the clear liquid turns milky at the surface). Therefore any transfer of this compound must be carried out under argon and the product must be stored under an inert atmosphere in a refrigerator.

10. Diisopropylamine was distilled over calcium hydride and stored under argon before use.

11. THF was freshly distilled under argon over potassium or sodium/benzophenone.

12. For addition of the LDA solution, either a bowed metal needle or a Teflon cannula (2 mm diameter) can be used. See ref. 4 for a diagram of the set up.

13. Iodomethane was filtered through neutral aluminum oxide (the submitters used Alumina Woelm B, Akt. I) directly before use to remove moisture and decomposition products. (A layer of brown material was found on top of the aluminum oxide when the iodomethane had not been freshly distilled.)

14. A pure sample for determining the analytical data of this bicyclic product was obtained by Kugelrohr distillation (bp 85°C at 0.05 mm). The spectrum is as follows: ^1H NMR (200 MHz, CDCl_3) δ : 0.88 (s, 9 H), 1.36 (s, 3 H), 1.60-1.90 (m, 3 H), 2.10-2.25 (m, 1 H), 2.75-2.90 (m, 1 H), 3.05-3.20 (m, 1 H), 4.24 (s, 1 H). Further data for this compound are available in Ref. 3.

15. Dowex 50W x 8 (Na^+ form), as purchased from Fluka AG or recovered from previous use, is stirred for 30 min with ca. 6 N HCl, washed until nearly neutral, stirred with ca. 6 N ammonium hydroxide, washed with water, then stirred a second time with ca. 6 N HCl and washed until neutral (pH 7). The resin thus obtained is used directly.

16. Though yellow-colored, the 2-methylproline thus obtained is spectroscopically pure (according to the ^1H and ^{13}C NMR spectra, see Note 17). It can be further purified by dissolution in methanol with 5% w/w activated charcoal and filtration of the resulting suspension through Celite. In spite of the poor crystallizing tendency of most amino acids, 2-methylproline can be recrystallized from methanol/ethyl acetate to yield colorless platelets.

17. The spectra are as follows: ^1H NMR (200 MHz, D_2O , $\text{HDO} = 4.80$) δ : 1.52 (s, 3 H), 1.75-2.40 (m, 4 H), 3.20-3.45 (m, 2 H); ^{13}C NMR (50 MHz, D_2O) δ : 23.99, 25.85, 38.27, 48.06, 73.21, 179.87.

18. For gas chromatography, derivatives of the two enantiomers of the amino acid (the isopropyl amido isopropyl amides) were obtained according to the procedure developed by König:⁵ In a 1-mL, sealed flask, 5 mg of the amino acid is treated with 0.3 mL of CH_2Cl_2 and 0.3 mL of isopropyl isocyanate at 100°C for 15 min. After the solution is cooled, both CH_2Cl_2 and excess isopropyl isocyanate are driven out by a strong stream of dry air. The residue is treated with 1 mL of diethyl ether and the resulting suspension is filtered through cotton wool. The solution can be used directly for determination of the ee by GC. This analysis was not checked by the checkers.

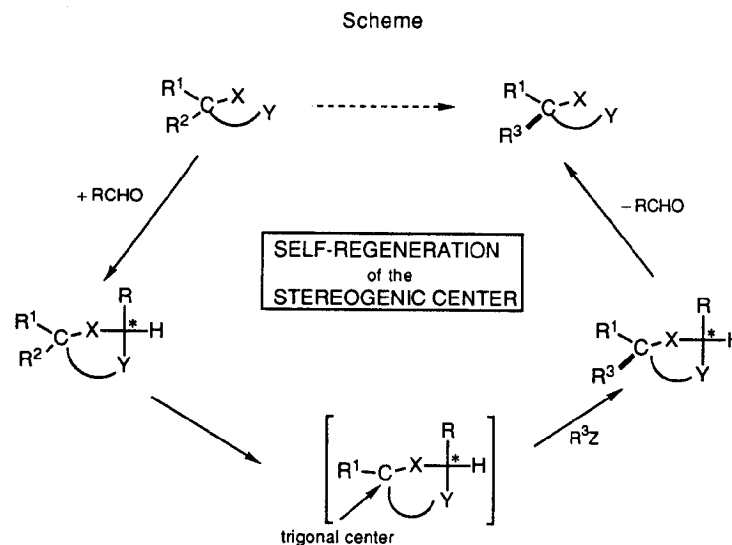
19. The solution, 10 μL , prepared as outlined in Note 18 was loaded on a Chirasil-Val fused-silica capillary column of Machery-Nagel (25 m, 0.4 mm) in a Carlo-Erba-Fraktovap 4160 HR GC. After 5 min at 160°C , the column temperature was increased by 2°C per min up to 200°C .

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

rac-2-Methylproline has been obtained previously by Ellington and Honigberg⁶ from 5-(3-hydroxypropyl)-5-methylhydantoin. For other preparations of enantiopure 2-methylproline see references 7 and 8. Methylation of proline with retention of configuration as described here is an example of a general principle that has been applied to chiral α - and β -HX-substituted carboxylic acids (X = NH, O, S).⁹⁻¹¹ It involves a three-step sequence: diastereoselective conversion of the enantiopure carboxylic acid to a cyclic acetal derivative, diastereoselective replacement of one of the substituents on the original asymmetric carbon atom, and cleavage of the acetal. Since no chiral auxiliary molecule is employed in the procedure, in which the one and only chirality center of the starting material is temporarily eliminated (i.e., converted to a trigonal center), the overall transformation has been called self-regeneration of a stereogenic center,¹² as shown in the accompanying scheme.

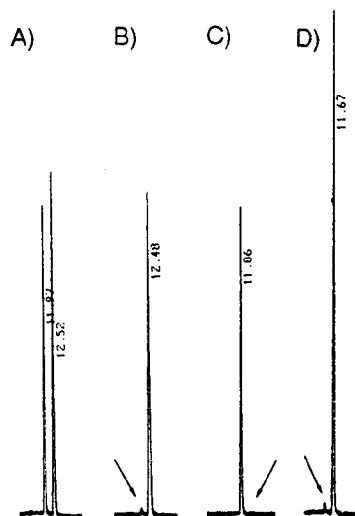


The intermediate trigonal center may be cationic, radical, anionic, or part of a double bond. By this methodology, the large supply of simple, mostly naturally occurring enantiopure compounds ("chiral pool"¹³) can be used in many ways.⁹⁻¹²

α -Methylproline is an especially interesting α -branched amino acid for the synthesis of peptides and proteins that show an unusual stability to proteases.¹⁴ Moreover incorporation of α -methylproline into a peptide to replace proline in a β -turn causes a significant increase in stability of this particular structural element.^{15,16}

Following exactly the same procedure, Parts A, B and C, but starting with (R)-proline gives (R)-2-methylproline, $[\alpha]_D^{RT} +73.1^\circ$ (MeOH, c 1.7) in an overall yield of 55%.

Figure 1



Gas chromatograms for the determination of the enantiomeric purity of the derivatives of 2-methylproline (Notes 18 and 19): A) (R)- and (S)-2-methylproline; B) (S)-2-methylproline; C) (R)-2-methylproline; D) 1% (R)- in (S)-2-methylproline.

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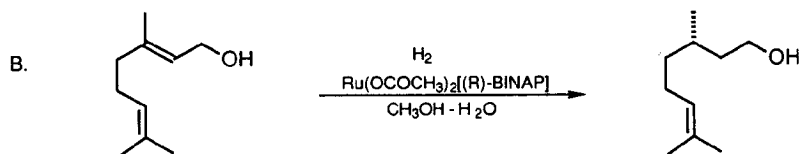
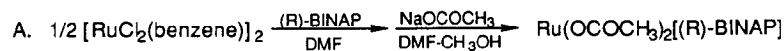
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S)-2-Methylproline: L-Proline, 2-methyl- (9); (42856-71-3)
 L-Proline: L-Proline (8,9); (147-85-3)
 (2R,5S)-2-tert-Butyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one:
 1H,3H-Pyrrolo[1,2-c]oxazol-1-one, 3-(1,1-dimethylethyl)tetrahydro-, (3R-cis)- (11);
 (81286-82-0)
 Pentane (8,9); (109-66-0)
 Pivalaldehyde (8); Propanal, 2,2-dimethyl- (9); (630-19-3)
 Trifluoroacetic acid: Acetic acid, trifluoro- (8,9); (76-05-1)

(2R,5S)-2-tert-Butyl-5-methyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one:
 1H,3H-Pyrrolo[1,2-c]oxazol-1-one, 3-(1,1-dimethylethyl)tetrahydro-7a-methyl-,
 (3R-cis)- (11); (86046-11-9)
 Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)
 Butyllithium: Lithium, butyl- (8,9); (109-72-8)
 Iodomethane: Methane, iodo- (8,9); (74-88-4)
 (R)-Proline: D-Proline (8,9); (344-25-2)
 (R)-2-Methylproline: D-Proline, 2-methyl- (10); (63399-77-9)

**ASYMMETRIC HYDROGENATION OF ALLYLIC ALCOHOLS USING
BINAP-RUTHENIUM COMPLEXES: (S)-(-)-CITRONELLOL
(6-Octen-1-ol, 3,7-dimethyl, (S)-)**



Submitted by Hidemasa Takaya,¹ Tetsuo Ohta,¹ Shin-ichi Inoue,²
Makoto Tokunaga,² Masato Kitamura,² and Ryoji Noyori.²
Checked by Andrew Madin and Larry E. Overman.

1. Procedure

Caution! BINAP-Ru complexes are rapidly oxidized in solution in the presence of air, and all procedures should be carried out under anaerobic conditions using degassed solvents.

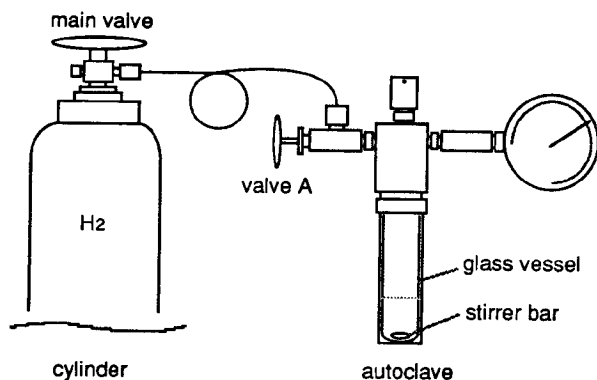
A. [(R)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium diacetate, $\text{Ru}(\text{OCOCH}_3)_2[(\text{R})\text{-BINAP}]$. A dry, 150-mL Schlenk tube (Note 1) connected to a supply of argon (Note 2) is equipped with a Teflon-coated magnetic stirring bar and a glass stopper. The vessel is charged with benzeneruthenium(II) chloride dimer, $[\text{RuCl}_2(\text{benzene})]_2$, (800 mg, 1.60 mmol) (Note 3) and (R)-BINAP (1.89 g, 3.04 mmol)

(Note 4), evacuated, and then filled with argon. N,N-Dimethylformamide (DMF) (30 mL) (Note 5) is introduced with a hypodermic syringe under the stream of argon. The reddish brown suspension is stirred at 100°C for 10 min (Note 6) and the resulting clear reddish brown solution (Note 7) is cooled. Another dry, 60-mL Schlenk tube is charged with sodium acetate (5.20 g, 63.4 mmol) and methanol (50 mL) (Note 8) and the solution is degassed by three freeze-thaw cycles. It is transferred into the DMF solution of BINAP-Ru(II) complex prepared above via cannula and the solution is stirred at 25°C for 5 min. To the solution are added water (50 mL) and toluene (25 mL) under argon and the resulting two layers are mixed by vigorous stirring. The upper organic layer is transferred into another 200-mL Schlenk tube (Note 9) using a cannula. The aqueous layer is vigorously mixed with toluene (25 mL) and the upper organic layer is again transferred into the Schlenk tube. This procedure is repeated once more. The combined organic layers are washed with four 10-mL portions of water (Note 10). Removal of the solvent at 1 mm and 40°C for 30 min with vigorous stirring (Note 11) and evacuation at 0.1 mm and 25°C for 12 hr gives 2.54-2.67 g of solid $\text{Ru}(\text{OCOCH}_3)_2[(\text{R})\text{-BINAP}]$ (99-104% crude yield based on BINAP) (Note 12). It is dissolved in toluene (20-25 mL) with heating. Hexane (80-100 mL) is added very carefully to the solution down the side of the flask to form two layers. The solution is left at 25°C for 12 hr and then at 4°C for 3 days to give solid material. Removal of the mother liquor is followed by washing with hexane (20 mL) and drying under reduced pressure to afford 1.8-2.2 g (71-85% yield) of pure $\text{Ru}(\text{OCOCH}_3)_2[(\text{R})\text{-BINAP}]$ as fine yellow needles or powdery crystals; mp 188-190°C dec (Note 13).

B. (S)-(-)-Citronellol. Geraniol (12.9 mL, 74 mmol) (Note 14) and 95% methanol (15 mL) (Note 15) are placed in a dry, 80-mL Schlenk tube and the mixture is degassed by five freeze-thaw cycles. Another dry, 80-mL Schlenk tube, equipped with a rubber septum and a magnetic stirring bar and filled with argon, is charged with $\text{Ru}(\text{OCOCH}_3)_2[(\text{R})\text{-BINAP}]$ (45 mg, 53 μmol) (Note 16). The system is evacuated and

refilled with argon three times. By use of a cannula, the solution of geraniol in methanol is introduced into the Schlenk tube containing the ruthenium complex under argon. The resulting light yellow solution (Note 17) is then transferred with a cannula into a 100-mL, stainless steel autoclave equipped with a glass vessel (Note 18) and a magnetic stirring bar by use of a slight positive pressure of argon. The autoclave is connected to a hydrogen source (Note 19) using the arrangement shown in Figure 1, and the air originally present in the gas-inlet tube is replaced by hydrogen (Note 20). Valve A is opened and hydrogen is introduced until pressure gauge B indicates 100 atm. The solution is stirred at 20°C for 8-16 hr (Note 21). During hydrogenation, the hydrogen pressure is kept above 90 atm by the occasional introduction of hydrogen from the cylinder (Note 22). When consumption of hydrogen ceases, the gas-inlet tube is disconnected. Excess hydrogen is carefully released by opening valve A and then the apparatus is disassembled. The yellowish brown contents (Note 23) are transferred to a 50-mL flask and the solvent is removed by a rotary evaporator. The residue (Note 24) is distilled under reduced pressure to give 10.7-11.2 g (93-97% yield) of (S)-(-)-citronellol in 98% ee (Notes 25 and 26); bp 58-62°C/0.01 mm.

Figure 1



2. Notes

1. Before use, all apparatus is dried overnight in a 120°C oven.
2. Argon (99.998%) is purified by passing through a BASF catalyst RC-11 column at 80°C and then through 4 Å molecular sieves.
3. $[\text{RuCl}_2(\text{benzene})]_2$, available from Aldrich Chemical Company, Inc., is used without purification.
4. BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] is commercially available or can be prepared according to a literature procedure.³ The diphosphine is slowly oxidized in air to give the corresponding mono- and diphosphine oxides that can be removed by column chromatography (silica gel, benzene) under an inert atmosphere.
5. Guaranteed grade DMF, available from NACAL TESQUE, INC., is distilled over 4 Å molecular sieves under argon before use and stored in a 100-mL Schlenk tube. It is degassed by three freeze-thaw cycles.
6. Reaction at a higher temperature for a longer period leads to formation of the ruthenium carbonyl complex $[\text{IR}(\text{KBr}) 1964 \text{ cm}^{-1}]$.
7. The solution may be a crude mixture of cationic BINAP-Ru(II) complexes such as $[\text{RuCl}(\text{BINAP})(\text{DMF})_3]\text{Cl}$ and $[\text{Ru}(\text{BINAP})(\text{DMF})_4]\text{Cl}_2$. Physical properties include conductivity, 27 Scm^2/mol (DMF); ^{31}P NMR (4:1 DMF- CDCl_3) δ : 60.6 (d, $J = 46$), 61.4 (d, $J = 46$), 61.8 (s). The (R)-BINAP-Ru(II) complex obtained by removal of the solvent can catalyze hydrogenation of geraniol (98.7% pure commercial geraniol containing 1.3% of nerol, distilled from 4 Å molecular sieves). However, in addition to (S)-citronellol in 95-96% ee, dihydrocitronellol, an overreduction product, is obtained in 3-7% yield (1.1 M substrate in 95% aqueous methanol, 1.7 mM catalyst, 100 atm of H_2 , 20°C, 8 hr).
8. Guaranteed grade methanol is distilled under argon.

9. The diameter is about 4 cm.
10. The extraction procedure must be carried out under an argon atmosphere.
11. Under reduced pressure, the solution sometimes foams. This can be avoided by heating the top part of the Schlenk tube with a hot air gun.
12. Crude BINAP-Ru complex with consistent spectral characteristics can be used for hydrogenation of geraniol (98.7% pure commercial geraniol containing 1.3% of nerol, distilled from 4 Å molecular sieves, 4.7 M substrate in 95% aqueous methanol, 2.8 mM Ru(OCOCH₃)₂[(R)-BINAP], 100 atm of H₂, 20°C, 8 hr), to give (S)-citronellol in 96% ee, 97% isolated yield.
13. The product has the following spectral properties: ¹H NMR (CDCl₃) δ: 1.80 (s, 2 OCOCH₃), 6.47-7.84 (m, aromatic protons); ³¹P NMR (CDCl₃) δ: 65.13 (s); ¹³C NMR (CDCl₃) δ: 23.50, 125.2-138.3, 188.1; IR (CH₂Cl₂) cm⁻¹: 1452, 1518. An analytical sample is prepared by drying at 110°C and 0.01 mm for 12 hr: Calcd for C₄₈H₃₈O₄P₂Ru: C, 68.5; H, 4.6. Found: C, 68.4; H, 4.5).
14. Pure geraniol is obtained by fractional distillation using a 1000 theoretical plate column. The checkers obtained geraniol, > 99.5% purity by GC analysis, from Fluka Chemical Company and used it directly.
15. The 95% methanol is prepared by mixing distilled, guaranteed methanol (95 mL) and water (5 mL). If absolute methanol or 90% aqueous methanol is used as solvent, somewhat longer reaction times are needed.
16. The complex can be stored under argon without noticeable loss of catalytic activity. It is weighed under an argon atmosphere.
17. The ruthenium complex is moderately soluble in methanol. Ultrasonic stirring is employed for complete solution.
18. A glass vessel is used for keeping the reaction mixture away from the stainless steel wall. The reaction system is evacuated and filled with argon three times before use.

19. The purity of hydrogen (Nippon Sanso Co.) used by the submitters is 99.99999%. The checkers used hydrogen of 99.99% purity.
20. The gas-inlet tube is attached to the autoclave and then the main valve of the cylinder is opened. After closing the main valve of the cylinder, the connector of the gas-inlet tube is loosened to release hydrogen pressure and tightened immediately. This procedure is repeated five times.
21. To maintain an internal temperature of 20°C the checkers placed the autoclave in a 18°C bath. Reactions terminated after 8 hr by the checkers showed the presence of unreacted geraniol (2-4%).
22. Enantioselectivity is very dependent on hydrogen pressure. Optical purities of citronellol products are 70% and 95% at 4 and 30 atm, respectively. Thus, hydrogen pressure greater than 90 atm is required for high optical yields.
23. In air, the color gradually changes to dark green.
24. Gas chromatographic analysis indicates that this consists of 97-99% of citronellol and 1-3% of dihydrocitronellol; column, SHIMADZU HiCap-CBP20, 25 m x 0.2-mm fused silica; column temperature, 140°C; injection temperature 160°C; helium pressure as carrier gas, 1.0 kg/cm²; t_R of geraniol, citronellol, and dihydrocitronellol are 16.2, 13.7, and 8.6 min, respectively.
25. The product has the following spectral properties; ¹H NMR (400 MHz, CDCl₃) δ: 0.89 (d, J = 6.6, CH₂CH(CH₃)CH₂), 1.18 (m, CH₂CH₂CH(CH₃)CH₂), 1.36 (m, CH₂CH₂CH(CH₃)CH₂), 1.57 (m, CH₂CH(CH₃)CH₂), 1.59 (s, (CH₃)₂C=CH), 1.67 (s, (CH₃)₂C=CH), 1.71 (s, CH₂CH₂OH), 1.97 (m, (CH₃)₂C=CHCH₂), 3.66 (m, CH₂CH₂OH), 5.08 (t, J = 6.96, (CH₃)₂C=CH), [α]_D²⁹ -4.5° to -4.7° (neat) [lit.⁴ [α]_D²⁰ -4.76° (neat)]. The submitters determined the enantiomeric excess by HPLC analysis of the diastereomeric amide prepared by condensation of citronellic acid (Note 27), obtained by the Jones oxidation of the alcohol, and (R)-1-(1-naphthyl)ethylamine (Note 28). HPLC analysis of this amide (column, TOYO SODA SILICA-60, 4.6 x 500

mm, a 3:7 ether-hexane mixture; flow rate 1 mL/min; detection 254 nm light) showed two peaks with t_R at 33.0 and 36.0 min in 1:99 ratio assignable to the R,R- and R,S-diastereomers, respectively.

26. With a commercially available 98.7:1.3 mixture of geraniol and nerol as substrate, (S)-citronellol in 96% ee is obtained. See also Note 7.

27. In a 100-mL, round-bottomed flask equipped with a magnetic stirring bar are placed β -citronellol (1.63 g, 10.4 mmol) and acetone (25 mL). To this is slowly added Jones reagent [$\text{Na}_2\text{Cr}_2\text{O}_7$ (0.73 M in H_2O)/ H_2SO_4 (concn = 1/4.2 v/v)] at 0-5°C until the orange color remains unchanged. To this mixture is added 2-propanol (5 mL) to decompose excess Jones reagent. After the orange color disappears, insoluble material is filtered off and the solvent is removed under reduced pressure. The residue is dissolved in ether (10 mL) and the solution is washed with brine (10 mL). The water layer is extracted with ether and the combined organic layers are extracted with 1 N aqueous sodium hydroxide (50 mL) at 0°C. The alkaline aqueous layer is acidified and extracted with three, 20-mL portions of ether at 0°C. The combined ether layers are dried over anhydrous magnesium sulfate and the solvent is evaporated. To the residue is added a small amount of benzene; the benzene is then removed under reduced pressure to give 977 mg (55% yield) of citronellic acid.

28. In a 50-mL, round-bottomed flask, equipped with a rubber septum and a magnetic stirring bar and filled with argon, are placed citronellic acid (112 mg, 0.658 mmol) and a solution of (R)-1-(1-naphthyl)ethylamine (140 mg, 0.818 mmol) (Note 29) in dry DMF (4 mL) (Note 5). To this mixture in an ice bath are added a solution of diethyl cyanophosphonate (224 mg, 1.37 mmol) (Note 30) in dry DMF (2 mL) and then dry triethylamine (0.1 mL). The mixture is stirred and the reaction is followed by TLC. When the carboxylic acid has been consumed, which takes approximately 2 hr at room temperature, the reaction mixture is dissolved in a mixture of benzene (5 mL) and ethyl acetate (5 mL). The mixture is washed successively with cold 5% hydrochloric acid,

ice-water, saturated sodium hydrogen carbonate solution, and brine, dried over anhydrous sodium sulfate, and finally concentrated under vacuum to give 207 mg (97% yield) of the amide.

29. (R)-(+)-1-(1-Naphthyl)ethylamine is purchased from Aldrich Chemical Company, Inc. The reagent is purified by recrystallization of its tartaric acid salt three times from 94% aqueous methanol followed by treatment with base and distillation of the free amine.

30. Commercial grade diethyl cyanophosphonate is distilled under argon before use.

Waste Disposal Information

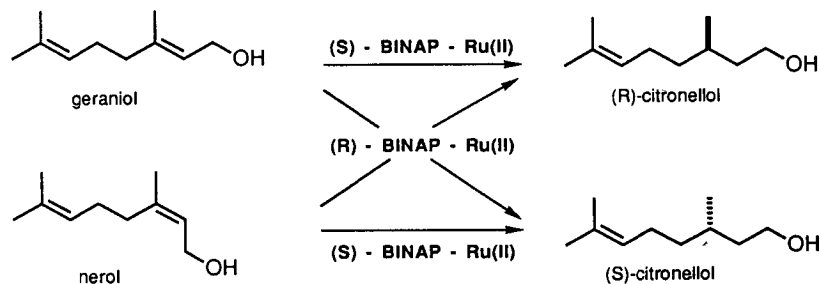
All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

The procedure for the synthesis of the title compound is a representative example of asymmetric hydrogenation in the presence of BINAP-Ru(II) diacetate.⁵ The method is based on the synthesis of BINAP-Ru(II) dicarboxylate complexes⁶ and enantioselective hydrogenation of geraniol.⁷ The present method provides the first practical means for asymmetric synthesis of (S)- and (R)-citronellol. (S)-(-)-Citronellol of optical purity up to 92% can be obtained in a limited quantity from rose oil. A microbiological reduction of geraniol was reported to give enantiomerically pure (R)-(+)-citronellol.⁸

Nerol can also be used as a substrate. The stereochemical outcome is shown in Scheme 1, which indicates that the BINAP-Ru species differentiates the C(2) enantiofaces. The C(6)-C(7) double bonds are left intact. Thus, both R and S enantiomers are accessible by either variation of allylic olefin geometry or choice of handedness of the catalysts.

Scheme 1



The complex formulated as $\text{Ru}(\text{OCOCH}_3)_2(\text{BINAP})$, that is prepared from $\text{Ru}(\text{OCOCH}_3)_2(\text{BINAP})$ and excess trifluoroacetic acid, shows high catalytic activity ($\text{S/C} = 5000$, 20°C , 100 atm, 96% ee). The cationic complex $[\text{Ru}(\text{BINAP})(\text{p-cymene})]^+$ ⁹ also acts as an efficient catalyst (96% ee). In the presence of the catalyst system derived from $\text{Ru}(\text{OCOCH}_3)_2(\text{BINAP})$ and 1 equiv of aqueous perchloric acid, hydrogenation proceeds very rapidly ($\text{S/C} = 2000$, completion after 15 min), but results in low enantioselectivity (94% ee). ToIBINAP^{10} [2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl] can also be used. Hydrogenation of geraniol using $\text{Ru}_2\text{Cl}_4[(\text{R})\text{-BINAP}]_2[\text{N}(\text{C}_2\text{H}_5)_3]^{11}$ as catalyst (6:1 ethanol-dichloromethane, H_2 , 40 atm, 24°C , 90 hr) gives (S)-citronellol in 47% yield and 93% ee (92% conversion) in addition to dihydrocitronellol (40% yield) (see also Note 7).

This procedure has been successfully applied to the asymmetric synthesis of (3R,7R)-3,7,11-trimethyldodecanol, a versatile intermediate for synthesis of α -tocopherol (vitamin E). Hydrogenation of homogeneraniol also proceeds smoothly to give 4,8-dimethylnon-7-enol in 92% ee in 96% yield. Hydrogenation of racemic allylic secondary alcohols in the presence of BINAP-Ru(II) diacetate brings about a high level of kinetic enantiomer selection.¹² This method provides a practical route to (R)-4-hydroxy-2-cyclopentenone, an important building block for the three-component prostaglandin synthesis.¹³ A useful intermediate for synthesis of 1β -methylcarbapenems can be prepared by the hydrogenation of a chiral allylic alcohol.¹⁴

BINAP-ruthenium dicarboxylate complexes are also efficient catalysts for asymmetric hydrogenation of enamides, α,β - and β,γ -unsaturated carboxylic acids, α -amino ketones, and α -acylaminoacrylic acids.⁵

The previous volume of Organic Syntheses provides a detailed procedure for the asymmetric hydrogenation of β -ketoesters using a BINAP-ruthenium complex.¹⁵

1. Department of Industrial Chemistry, Faculty of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-01, Japan.
2. Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464-01, Japan.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S)-Citronellol: 6-Octen-1-ol, 3,7-dimethyl-, (S)-(-)- or (-)- (8); 6-Octen-1-ol, 3,7-dimethyl-, (S)- (9); (7540-51-4)

[(R)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium diacetate:
Ruthenium, bis(acetato-O,O')[[1,1'-binaphthalene]-2,2'-diylbis(diphenylphosphine)]-

P,P']-, [OC-6-22-Δ-(R)]- (12); (104621-48-9)

Benzeneruthenium(II) chloride dimer: Ruthenium, bis(η⁶-benzene)di-μ-chlorodichlorodi- (9); (37366-09-9)

(R)-BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl: Phosphine, [1,1'-binaphthalene]-2,2'-diylbis(diphenyl-, (R)- (10); (76189-55-4)

N,N-Dimethylformamide: Formamide, N,N-dimethyl-, (8,9); (68-12-2)

Methanol (8,9); (67-56-1)

Geraniol: 2,6-Octadien-1-ol, 3,7-dimethyl- (E)- (8,9); (106-24-1)

Citronellic acid: 6-Octenoic acid, 3,7-dimethyl-, (R)-(+)- (8,9); (18951-85-4)

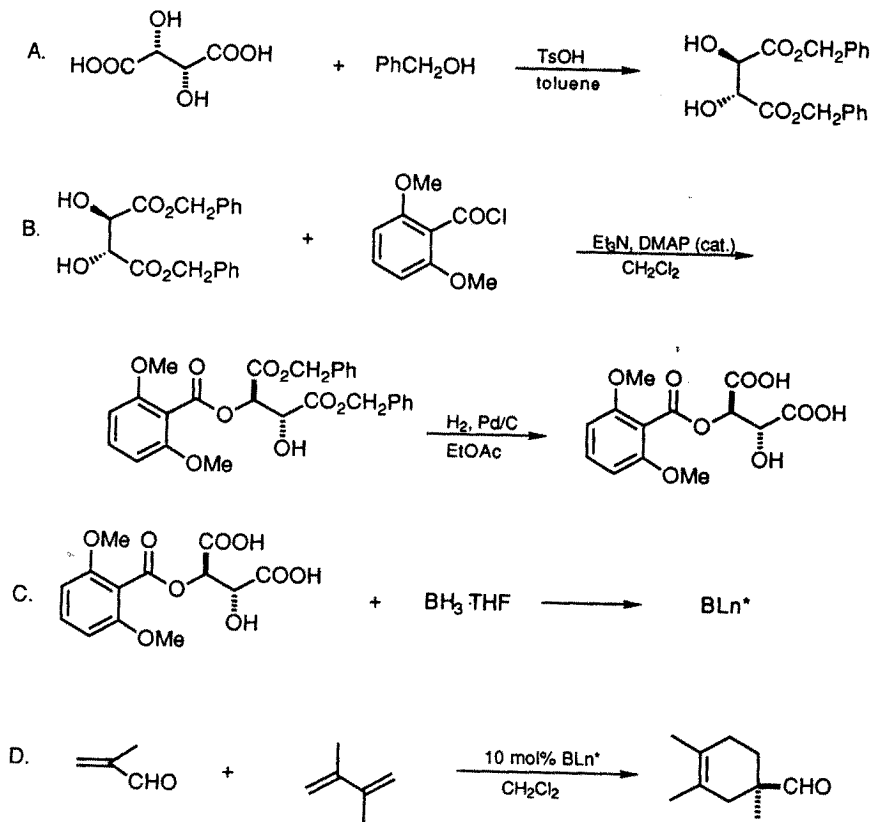
(R)-1-(1-Naphthyl)ethylamine: 1-Naphthalenemethylamine, α-methyl-, (R)-(+)- (8); 1-Naphthalenemethanamine, α-methyl-, (R)- (9); [3886-70-2]

β-Citronellol: 6-Octen-1-ol, 3,7-dimethyl- (8,9); (106-22-98)

2-Propanol (8,9); (67-63-0)

Diethyl cyanophosphonate: Phosphonic acid, cyano-, diethyl ester (9); (2942-58-7)

**CHIRAL (ACYLOXY)BORANE COMPLEX-CATALYZED ASYMMETRIC
DIELS-ALDER REACTION: (1R)-1,3,4-TRIMETHYL-
3-CYCLOHEXENE-1-CARBOXALDEHYDE
(3-Cyclohexene-1-carboxaldehyde, 1,3,4-trimethyl-, (-)-)**



Submitted by Kyoji Furuta, Qing-zhi Gao, and Hisashi Yamamoto.¹

Checked by Stephane Borrelly and Leo A. Paquette.

1. Procedure

A. (-)-Dibenzyl tartrate. A 300-mL, one-necked, round-bottomed flask is equipped with a magnetic stirrer, Dean-Stark trap, and a reflux condenser. The flask is charged with 3.0 g (20 mmol) of L-(+)-tartaric acid, 6.5 g (60 mmol) of benzyl alcohol, 47.5 mg (0.25 mmol) of p-toluenesulfonic acid monohydrate, and 40 mL of toluene (Note 1). The mixture is heated under reflux in an oil bath (about 130°C) for 13 hr. During this period the theoretical amount of water (0.62 mL) is collected. The mixture is allowed to cool to ambient temperature, diluted with ether, and poured into 50 mL of aqueous, saturated sodium bicarbonate. The organic phase is separated and the aqueous phase is extracted twice with 20 mL of ether. The combined organic phases are dried over sodium sulfate. The solvent is removed with a rotary evaporator, and the resulting crude product is triturated with hexane-ether (20:1, 210 mL) to give white crystals of (-)-dibenzyl tartrate. The precipitate is collected by filtration and washed with hexane-ether (20:1). The filtrate is further concentrated to give a second crop. The total yield is 6.2 g (94%), mp 49-50°C (Note 2).

B. Mono(2,6-dimethoxybenzoyl)tartric acid. In a 250-mL, three-necked, round-bottomed flask, equipped with a nitrogen inlet, a reflux condenser and a magnetic stirring bar are placed 6.1 g (18.5 mmol) of dibenzyl tartrate, 100 mL of dry dichloromethane, 4 mL (28.8 mmol) of triethylamine and 50 mg (0.4 mmol) of 4-(dimethylamino)pyridine. The stirred mixture is cooled to 0°C 3.65 g (18.2 mmol) of 2,6-dimethoxybenzoyl chloride (Note 3) is added portion-wise over 1 hr. The reaction mixture is then warmed to room temperature and refluxed for 12 to 18 hr (the reaction is easily monitored by TLC). The reaction mixture is then allowed to cool down to room temperature and poured in 100 mL of water. The aqueous phase is extracted with 2 x 75 mL of dichloromethane. The organic phases are combined, dried over sodium sulfate, filtered and concentrated to give a viscous oil. This is purified by

column chromatography on silica gel using a mixture of hexane, ether and dichloromethane (3:1:5) as eluent (Note 4) to afford 7.1-7.5 g (78-82%) of a clear oil identified as dibenzyl mono(2,6-dimethoxybenzoyl)tartrate (Note 5). A 200-mL, pressure bottle is flushed with dry argon and charged with 5.8 g (11.7 mmol) of the above tartrate, 100 mL of ethyl acetate, and 580 mg of 10% palladium on charcoal (Note 6). The argon is then replaced by hydrogen and the reaction mixture is shaken on a Parr apparatus at 20 psi and room temperature for several hours (Note 7). The mixture is filtered through a pad of Celite and the filtrate is concentrated with a rotary evaporator, and dried completely under vacuum (80°C, ≤ 1 mm, overnight) (Note 8) to afford 3.5 g (97%) of mono(2,6-dimethoxybenzoyl)tartric acid as colorless solid, mp 184-186°C (Note 9). This material is practically pure and is used in Parts C, D without purification.

C, D. (1R)-1,3,4-Trimethyl-3-cyclohexene-1-carboxaldehyde. A 100-mL, three-necked round-bottomed flask containing a magnetic stirring bar is equipped with a rubber septum and a three-way stopcock with an argon inlet. The air is displaced by repeated flushing with dry argon. The flask is charged with 1.57 g (5 mmol) of mono(2,6-dimethoxybenzoyl)tartric acid obtained in Part B and 50 mL of dry dichloromethane (Note 10), and cooled in an ice bath. Through the septum, with a syringe, is added dropwise 3.57 mL (5 mmol) of borane-THF solution (1.40 M) at 0°C over a period of 30 min (Note 11). The reaction mixture is stirred for 15 min at 0°C and then cooled to -78°C in a dry ice-methanol bath. To this solution is added 4.14 mL (50 mmol) of freshly distilled methacrolein (Note 12) via a syringe dropwise. After the addition is complete, 8.49 mL (75 mmol) of 2,3-dimethyl-1,3-butadiene (Note 13) is introduced to the solution at the same temperature and the mixture is stirred for 12 hr. The cold reaction mixture is poured into 150 mL of ice-cold saturated sodium bicarbonate and the product is extracted with three 200-mL portions of hexane (Note 14). The combined organic phases are washed with brine (2 x 200 mL) (Note 15),

dried over sodium sulfate, filtered, and concentrated at atmospheric pressure. The residue is distilled at reduced pressure to afford 6.53 g (86%) of (1R)-1,3,4-trimethyl-3-cyclohexene-1-carboxaldehyde as a colorless liquid, bp 92-93°C (23 mm) (Note 16).

2. Notes

1. L-(+)-Tartaric acid, benzyl alcohol, and p-toluenesulfonic acid monohydrate were purchased from Wako Pure Chemical Industries, Ltd. (Japan). Guaranteed-grade toluene was dried and stored over sodium metal.

2. The physical properties are as follows: ^1H NMR (CDCl_3 , 200 MHz) δ : 3.15 (d, 2 H, $J = 7.5$), 4.6 (d, 2 H, $J = 7.5$), 5.27 (s, 4 H), 7.35 (s, 10 H); $[\alpha]_{\text{D}}^{24} -10.2^\circ$ (CHCl_3 , c 1.03).

3. 2,6-Dimethoxybenzoyl chloride was purchased from the Aldrich Chemical Company, Inc. and was used without purification.

4. The purity of the ligand depends largely on the purity of the dibenzyl ester. Flash chromatography was carried out with silica gel purchased from Merck (Kieselgel 60, Art. 9385). For TLC analysis, Merck silica gel F-254 TLC plates were used, with 3:1:5 hexane-ether-dichloromethane as eluent. Mono(2,6-dimethoxybenzoyl)tartrate has an R_f of ca. 0.35 in this solvent system.

5. The physical properties are as follows: ^1H NMR (CDCl_3 , 200 MHz) δ : 3.24 (d, 1 H, $J = 9$), 3.7 (s, 6 H), 4.89 (dd, 1 H, $J = 2.5$ and 9), 5.08-5.34 (4 H), 5.99 (d, 1 H, $J = 2.5$), 6.53 (d, 2 H, $J = 8.5$), 7.25-7.4 (m, 11 H); $[\alpha]_{\text{D}}^{24} -60.1^\circ$ (CHCl_3 , c , 1.15).

6. Ethyl acetate was obtained from Wako Pure Chemical Industries and was used without purification. The 10% palladium on charcoal was purchased from Aldrich Chemical Company, Inc.

7. This requires 4-12 hr, depending on catalyst conditions. Progress of the reaction can be monitored by TLC.

8. Thorough drying is essential to obtain the % ee as described.
9. The physical properties are as follows: ^1H NMR (CDCl_3 , 200 MHz) δ : 3.63 (s, 6 H), 4.61 (d, 1 H, $J = 2$), 5.61 (d, 1 H, $J = 2$), 6.38 (d, 2 H, $J = 9$), 7.13 (t, 1 H, $J = 9$); $[\alpha]_{\text{D}}^{24} -73.0^\circ$ (EtOH, c 1.03).
10. Dichloromethane was purchased from Wako Pure Chemical Industries and was dried over Linde-type 4 Å molecular sieves.
11. Borane-THF complex was obtained from Toso-Akzo Chemical Company, Ltd. in Japan and should be titrated before use. Vigorous evolution of hydrogen is observed during addition of borane-THF solution to the reaction mixture.
12. Methacrolein from Tokyo Kasei Kogyo Company, Ltd. was dried with calcium sulfate and distilled through a 20-cm Vigreux column under argon prior to use.
13. 2,3-Dimethyl-1,3-butadiene was purchased from Tokyo Kasei Kogyo Company, Ltd. and was distilled before use.
14. The tartaric acid ligand can be recovered (1.52 g, 97%) from the aqueous phase by an acidification-extraction (4 N HCl-ethyl acetate) sequence. The material is essentially pure for future use.
15. Careful washing with brine is important to avoid foaming during distillation.
16. The physical properties are as follows: ^1H NMR (CDCl_3 , 200 MHz) δ : 0.99 (s, 3 H), 1.3-2.1 (m, 5 H), 1.56 (s, 3 H), 1.61 (s, 3 H), 2.23 (br d, 1 H, $J = 17$), 9.43 (s, 1 H); $[\alpha]_{\text{D}}^{23} -64.1^\circ$ (CHCl_3 , c 1.0). The optical purity of this adduct was 95% as determined by 200 MHz ^1H NMR spectroscopy and GC analysis (capillary column PEG, 0.25 mm x 25 m, purchased from Gaskuro Kogyo Company, Ltd. in Japan) after conversion to the corresponding chiral acetal as follows: A solution of the adduct, (2R,4R)-(-)-pentanediol (1.2 equiv, obtained from Wako Pure Chemical Industries), triethyl orthoformate (1.2 equiv), and *p*-toluenesulfonic acid monohydrate (as a 5 mM solution) in dry benzene is stirred at ambient temperature for 3 hr. The mixture is poured into saturated sodium bicarbonate and the product is extracted with ether. The

combined organic phases are dried over sodium sulfate and concentrated on a rotary evaporator. The residue is purified by flash column chromatography on silica gel using hexane-ethyl acetate (25:1) as eluent to give the acetal quantitatively; ^1H NMR (CDCl_3 , 200 MHz) δ : 0.83 (s, 3 H), 1.15 (d, 3 H, $J = 6$), 1.28 (d, 3 H, $J = 6.5$), 1.56 (s, 6 H), 1.2-2.06 (m, 8 H), 3.86 (m, 1 H), 4.27 (m, 1 H), 4.42 (s, 1 H; diastereomer at 4.45).














Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

The procedure described here provides a simple and general method for the construction of optically active 3-cyclohexene-1-carboxaldehydes.² The reaction has been applied successfully to a series of α,β -unsaturated aldehydes with dienes (Table). Several methods are described in the literature for asymmetric Diels-Alder reactions of chiral α,β -unsaturated esters or amides;³ little is reported, however, for the reaction of achiral, simple aldehydes.⁴ The present method is characterized as a true catalytic process (only 10 mol % of chiral catalyst is needed), with good chemical and high optical yields, simple operation, preparation of both enantiomers with equal ease, and the ready availability of the starting materials.

TABLE
CHIRAL ACYLOXYBORANE CATALYZED ASYMMETRIC DIELS-ALDER REACTION

Dienophile	Diene	Temp (°C)	Yield (%)	Isomers endo/exo	ee (%)
		-78	85	11/89	96
		-78	84 ^a	10/90	96
		-78	61		97
		-78 -40	38 65	97/3 ^b 98/2 ^b	93 91
		-20	40	93/7	82
		-78	90	88/12	84
		-78	46	>99/1	80
		-78	53		84
		-78	53	90/10	2
		-78	91	3/97	90

^a(2S,3S)-Tartaric acid derivative was used as a chiral ligand.

^bRatio of regioisomers.

1. Department of Applied Chemistry, School of Engineering, Nagoya University, Chikusa, Nagoya 464-01, Japan.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(1R)-1,3,4-Trimethyl-3-cyclohexene-1-carboxaldehyde: 3-Cyclohexene-1-carboxaldehyde, 1,3,4-trimethyl-, (-)- (12); (130881-20-8)
 (-)-Dibenzyl tartrate: Tartaric acid, dibenzyl ester, (+)- (9); Butanedioic acid, 2,3-dihydroxy-, [R-(R*,R*)]-, bis(phenylmethyl)ester (10); (622-00-4)
 L-(+)-Tartaric acid: Tartaric acid, L- (8); Butanedioic acid, 2,3-dihydroxy-, [R-(R*,R*)]- (9); (87-69-4)

Benzyl alcohol (8); Benzenemethanol (9); (100-51-6)

p-Toluenesulfonic acid monohydrate (8); Benzenesulfonic acid, 4-methyl-, monohydrate (9); (6192-52-5)

Mono(2,6-dimethoxybenzoyl)tartronic acid: Butanedioic acid, 2-[(2,6-dimethoxybenzoyl)oxy-3-hydroxy-, [R-(R*,R*)]- (12); (116212-44-3)

2,6-Dimethoxybenzoic acid: Benzoic acid, 2,6-dimethoxy- (8,9); (1466-76-8)

Trifluoroacetic anhydride: Acetic acid, trifluoro-, anhydride (8,9); (407-25-0)

Borane-Tetrahydrofuran: Furan, tetrahydro-, compd. with borane (1:1) (8,9); (14044-65-6)

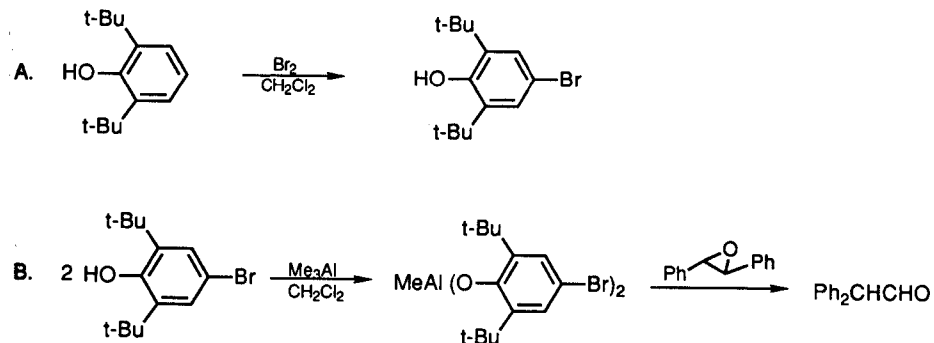
Methacrolein: 2-Propenal, 2-methyl- (9); (78-85-3)

2,3-Dimethyl-1,3-butadiene: 1,3-Butadiene, 2,3-dimethyl- (8,9); (513-81-5)

(2R,4R)-(-)-Pentanediol: 2,4-Pentanediol, [R-(R*,R*)]- (9); (42075-32-1)

Triethyl orthoformate: Orthoformic acid, triethyl ester (8); Ethane, 1,1',1''-[methylidynetris(oxy)]tris- (9); (122-51-0)

**REARRANGEMENT OF trans-STILBENE OXIDE TO
DIPHENYLACETALDEHYDE WITH CATALYTIC METHYLALUMINUM
BIS(4-BROMO-2,6-DI-tert-BUTYLPHENOXIDE)
(Oxirane, 2,3-diphenyl-, trans- to Benzeneacetaldehyde, α -phenyl-)**



Submitted by Takashi Ooi, Keiji Maruoka, and Hisashi Yamamoto.¹

Checked by Catherine Gasparski and Larry E. Overman.

1. Procedure

A. 4-Bromo-2,6-di-tert-butylphenol. A dry, 1-L, three-necked, round-bottomed flask is fitted with a gas inlet, rubber septum, pressure-equalizing dropping funnel, magnetic stirring bar, and a gas outlet tube that is connected to a gas trap containing 0.5 M sodium hydroxide (NaOH). The flask is charged with 103.2 g (500 mmol) of 2,6-di-tert-butylphenol (Note 1) and flushed with argon, after which 200 mL of dry dichloromethane (Note 2) is added. The dropping funnel is charged with 28.2 mL (550 mmol) of bromine and 20 mL of dry dichloromethane. The reaction vessel is immersed in an ice-water bath, stirring is initiated, and bromine in dichloromethane is added over

1 hr. The reaction mixture is stirred at 0°C for 10-20 min (Note 3). Then 60 mL of saturated aqueous sodium sulfite is added slowly at 0°C and stirring is continued at room temperature until the light orange color of bromine is discharged. The mixture is poured into a 1-L separatory funnel containing 400 mL of saturated aqueous sodium bicarbonate (Note 4). The heavier organic layer is separated and the aqueous layer is extracted with two 75-mL portions of dichloromethane. The combined extracts are dried over sodium sulfate and concentrated with a vacuum rotary evaporator. The residue is recrystallized twice from ethanol-water (first with 130 mL of ethanol and 18 mL of water, then with 110 mL of ethanol and 11 mL of water) to furnish 109 g (76% yield) of 4-bromo-2,6-di-*tert*-butylphenol (Note 5) as light yellow crystals, mp 83-85°C. Pure 4-bromo-2,6-di-*tert*-butylphenol is reported to melt at 81-82°C.²

B. Diphenylacetaldehyde. A dry, 1-L, three-necked, round-bottomed flask is equipped with a gas inlet, rubber septum, pressure-equalizing dropping funnel, and a magnetic stirring bar. The flask is charged with 3.42 g (12 mmol) of 4-bromo-2,6-di-*tert*-butylphenol and flushed with argon, after which 600 mL of freshly distilled dichloromethane is added. The mixture is stirred, degassed under vacuum, flushed with argon, and 3 mL (6 mmol) of a 2 M hexane solution of trimethylaluminum (Me_3Al , Note 6) is injected through the septum to the flask at room temperature. The resulting solution is stirred at this temperature for 1 hr to give methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) almost quantitatively (Note 7). The reaction vessel is cooled to a temperature of -20°C in a dry ice/*o*-xylene bath (Note 8). Then 11.8 g (60 mmol) of trans-stilbene oxide (Note 9) is dissolved in 25 mL of dry dichloromethane, transferred to the dropping funnel, and added over 15-20 min at -20°C. The mixture is stirred at -20°C for 4 hr. After addition of 1.01 g (24 mmol) of sodium fluoride, 324 μL (18 mmol) of water is injected dropwise at -20°C (Note 10). The entire mixture is vigorously stirred at -20°C for 5 min and at 0°C for 30 min. The contents of the flask are filtered with the aid of three 50-mL portions of dichloromethane (Notes 11-15). The combined

filtrates are concentrated to ca. 100 mL under reduced pressure with a rotary evaporator. Silica gel (35 g) is added and the remainder of the dichloromethane is removed using a rotary evaporator. The residue is layered on a column of silica gel (500 g, column diameter: 9.5 cm) (Note 12) and eluted (ether/dichloromethane/hexane, 1:2:20 to 1:1:10 as eluants) to give 10.3 g (87%) of diphenylacetaldehyde as a colorless oil (Notes 16 and 17).

2. Notes

1. 2,6-Di-*tert*-butylphenol was obtained from Nacalai Tesque Co. and used without any purification.
2. Solvent grade dichloromethane was dried and stored over Linde type 4A molecular sieves.
3. The reaction is conveniently followed by TLC (silica gel, 10:1:1 hexane- CH_2Cl_2 -ether).
4. The extractive workup is performed carefully to avoid vigorous evolution of carbon dioxide gas.
5. The product has the following spectral properties: ^1H NMR (200 MHz, CDCl_3) δ : 1.39 (s, 18 H, 2 *t*-Bu), 5.15 (s, 1 H, OH), 7.24 (s, 2 H, Ar-H).
6. Neat trimethylaluminum was obtained from Toso-Akzo Chemical Company Ltd. (Japan) and used as a 2 M hexane solution. The checkers used similar material obtained from Aldrich Chemical Company, Inc.
7. During this operation, nearly 2 equiv of methane gas are evolved per 1 equiv of trimethylaluminum.
8. *o*-Xylene is recommended as refrigerant in place of carbon tetrachloride.
9. trans-Stilbene oxide was obtained from Aldrich Chemical Company, Inc., and used without any purification.

10. To avoid excessive foaming on hydrolysis water should be added carefully by syringe.

11. The sodium fluoride-water workup offers an excellent method for large-scale preparations, and is generally applicable to product isolation in the reaction of organoaluminum compounds.³

12. The checkers report that GLC analysis (Note 13) at this point shows that the product is contaminated with ca. 4% of trans-stilbene oxide and <1% of the Tischenko product (Note 14).

13. Gas chromatography conditions are as follows: Supelco fused silica capillary SPB-1 column (30 m, 0.32-mm ID, 0.25 micrometers df), 100°C initial temperature, 280°C final temperature, 10°C/min. The following retention times were obtained: diphenylacetaldehyde (6.7 min), trans-stilbene oxide (7.4 min), Tischenko product (18.2 min).

14. The Tischenko product, $\text{Ph}_2\text{CHCO}_2\text{CH}_2\text{CHPh}_2$, has the following properties: mp, 95-98°C, ^1H NMR (300 MHz, CDCl_3) δ : 4.35 (t, 1 H, $J = 7.5$), 4.70 (d, 2 H, $J = 7.5$), 4.92 (s, 1 H), 7.11-7.40 (m, 20 H); ^{13}C NMR (75 MHz, CDCl_3) δ : 49.7, 57.2, 67.4, 126.8, 127.1, 128.2, 128.47, 128.53, 138.3, 140.8, 172.2; HRMS (CI, isobutane) Calcd for $\text{C}_{28}\text{H}_{24}\text{O}_2$: 393.1854 (MH); Found: 393.1829; IR (CCl_4) cm^{-1} : 3094-2906, 1737, 1600, 1494, 1450, 1144.

15. Merck Kieselgel 60 (Art. 9385) was used. The checkers found that loading the column in this way avoids precipitation of a by-product during column elution. The chromatography removes a few percent of remaining epoxide and 4-bromo-2,6-di-tert-butylphenol.

16. The product is >99% pure by capillary GLC analysis (Note 13) and has the following spectral characteristics: ^1H NMR (200 MHz, CDCl_3) δ : 4.92 (d, 1 H, $J = 2.6$, CH), 7.20-7.49 (m, 10 H, 2 Ph), 9.98 (d, 1 H, $J = 2.6$, CHO).

17. The rearrangement is considerably faster when the reaction solution is more concentrated. If 480 mL of dichloromethane is used, the rearrangement is complete within 20 min at -20°C. However, the checkers found that the crude product is contaminated with 3-10% of the Tischenko product (Note 14), which is difficult to remove by chromatography. This by-product can be removed by vacuum distillation (bp 136-144°C, 2 mm). Using this combined purification procedure, the checkers obtained 9.6 g (81%) of diphenylacetaldehyde of >99% purity by capillary GLC analysis (Note 13).

3. Discussion

This catalytic procedure illustrates a general method for preparing a wide range of carbonyl compounds by the selective rearrangement of epoxides under the influence of the exceptionally bulky, oxygenophilic methylaluminum bis(4-bromo-2,6-di-tert-butylphenoxide) (MABR) as catalyst.⁴ The advantages of catalytic versions include economy, ease of large-scale preparation and isolation, and the synthetic potential for in situ derivatization of the carbonyl products. Use of a sodium fluoride-water ($\text{NaF-H}_2\text{O}$) workup³ further simplifies the experimental operation. As revealed in Tables I and II, the amount of the catalyst varies from 5 to 20 mol% depending on the epoxy substrates. Yields when MABR is used stoichiometrically are also included for comparison. Certain epoxy substrates require stoichiometric MABR. Neither epoxides derived from monsubstituted olefins nor from certain internal dialkyl-substituted olefins can be rearranged by MABR, however, even using two equivalents.

The MABR-promoted rearrangement, when applied to optically active epoxy substrates, has been shown to proceed with rigorous transfer of the epoxide chirality. Accordingly, used in combination with the Sharpless asymmetric epoxidation of allylic alcohols,⁵ this rearrangement represents a new approach to the synthesis of various

optically active β -siloxy aldehydes, useful intermediates in natural product synthesis (Table II).^{4,6}

The stronger coordination of a carbonyl oxygen than an epoxide oxygen to an aluminum reagent requires the stoichiometric use of MABR at low temperature. The key element of the present modification is the use of a higher reaction temperature (though still at or below 0°C) than the previously reported conditions⁷ in order to induce dissociation of the aluminum reagent-carbonyl complex, thereby allowing regeneration of MABR as catalyst for further use in the catalytic cycle of the reaction. The facile dissociation of the organoaluminum-carbonyl complex as well as the smooth rearrangement of epoxides is apparently ascribable to the exceptional bulkiness of MABR compared to other ordinary Lewis acids.⁸ The less bulky methylaluminum bis(4-bromo-2,6-diisopropylphenoxide) was found to be totally ineffective for the rearrangement of the *tert*-butyldimethylsilyl ether of epoxy geraniol.

1. Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa, Nagoya 464-01, Japan.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

trans-Stilbene oxide: Oxirane, 2,3-diphenyl-, *trans*- (9); (1439-07-2)

Diphenylacetaldehyde: Acetaldehyde, diphenyl- (8); Benzeneacetaldehyde, α -phenyl- (9); (947-91-1)

Methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide): Aluminum, bis[4-bromo-2,6-bis(1,1-dimethylethyl)phenolato]methyl- (12); (118495-99-1)

4-Bromo-2,6-di-*tert*-butylphenol: Phenol, 4-bromo-2,6-di-*tert*-butyl- (8); Phenol, 4-bromo-2,6-bis(1,1-dimethylethyl)- (9); (1139-52-2)

2,6-Di-*tert*-butylphenol: Phenol, 2,6-di-*tert*-butyl- (8); Phenol, 2,6-bis(1,1-dimethylethyl)- (9); (128-39-2)

Trimethylaluminum: Aluminum, trimethyl- (9); (75-24-1)
(1139-52-2)

Table I. MABR-Catalyzed Rearrangement of Epoxides

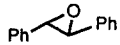
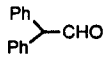

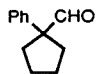
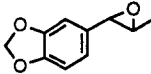
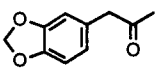
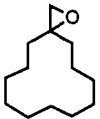
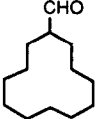
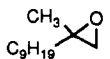
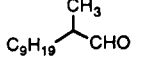

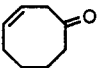
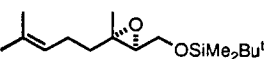
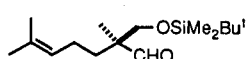
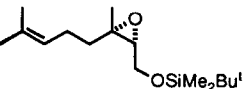
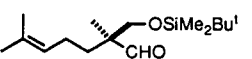
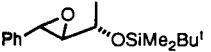
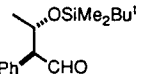
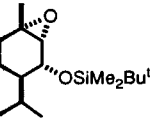
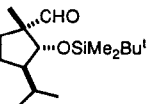
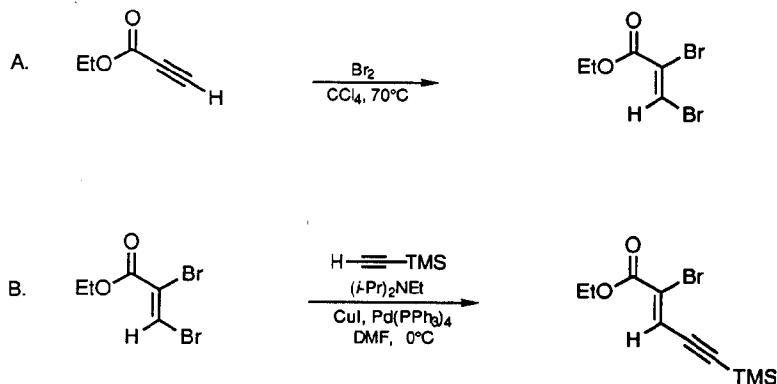
Epoxide	MABR (mol %)	Product	Yield (%)
	200 10		93 95
	200 10 5		98 96 91
	200 10 5		87 90 84
	200 20		94 58
	200 20		96 0
	200 20		73 0

Table II. MABR-Catalyzed Rearrangement of Chiral Epoxy Silyl Ethers

Epoxy Silyl Ether	MABR (mol %)	β -Siloxy Aldehyde	Yield (%)
	200 20 10		99 82 74
	200 .20 10		98 79 68
	200 20 10		87 74 71
	200 20		88 77

**SYNTHESIS OF FUNCTIONALIZED ENYNES BY
PALLADIUM/COPPER-CATALYZED COUPLING REACTIONS OF
ACETYLENES WITH (Z)-2,3-DIBROMOPROPENOIC ACID ETHYL
ESTER: (Z)-2-BROMO-5-(TRIMETHYLSILYL)-2-PENTEN-4-YNOIC
ACID ETHYL ESTER**

(2-Penten-4-ynoic acid, 2-bromo-5-(trimethylsilyl)-, ethyl ester, (Z)-)



Submitted by Andrew G. Myers and Peter S. Dragovich.¹

Checked by Rhonda A. Musselman and Robert K. Boeckman, Jr.

1. Procedure

A. *(Z)-2,3-Dibromo-2-propenoic acid ethyl ester.*² Ethyl propiolate (9.01 g, 91.8 mmol) and carbon tetrachloride (75 mL) are added in sequence to a 250-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar (Note 1). The flask is fitted with a 30-mL pressure equalizing addition funnel to which elemental bromine

(5.00 mL, 97.0 mmol) is added by transfer pipette (Note 2). The flask is partially immersed in an oil bath heated to 70°C. After 10 min for temperature equilibration, dropwise addition of bromine is initiated and completed within 10 min. Complete bromine transfer is achieved by rinsing the addition funnel with a 5-mL portion of carbon tetrachloride. The red-brown solution is heated at 70°C for 30 min, allowed to cool to ambient temperature, and carbon tetrachloride and excess bromine are removed by rotary evaporation. The pale yellow concentrate is applied to the top of a short column of flash-grade silica gel (150 g, 7-cm diam x 10 cm) loaded with 5% ethyl acetate-hexanes solution; the product dibromide elutes rapidly with this solvent system (< 1 L total solvent volume, 150-mL fractions, Note 3). Fractions containing the dibromide ($R_f = 0.66$, 5% ethyl acetate-hexanes) are combined and concentrated. The last traces of solvent are removed at 1 mm (0.5 hr) to afford (Z)-2,3-dibromo-2-propenoic acid ethyl ester (21.5–22.0 g, 91–93%) as a colorless liquid (Notes 4, 5).

B. *(Z)-2-Bromo-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester.* An oven-dried, 500-mL, modified Schlenk flask (Kjeldahl shape with 24/40 female top), equipped with a Teflon-coated magnetic stirring bar and rubber septum, is connected at the side-arm to a source of argon and vacuum. The flask is charged with (Z)-2,3-dibromo-2-propenoic acid ethyl ester prepared in part A (21.5 g, 83.4 mmol) and N,N-dimethylformamide (150 mL). With efficient stirring, it is alternately evacuated and flushed with argon at ambient temperature to deoxygenate the solution (Notes 6, 7). The flask is cooled in ice and (trimethylsilyl)acetylene (20.0 mL, 142 mmol) and N,N-diisopropylethylamine (24.7 mL, 142 mmol) are added in sequence (Note 8). The resulting pale yellow solution is deoxygenated as above. Cuprous iodide (3.18 g, 16.7 mmol) and tetrakis(triphenylphosphine)palladium (4.82 g, 4.17 mmol) are added, followed by a third deoxygenation cycle (Note 9). The brown reaction mixture is maintained at 0°C while the progress of reaction is monitored by thin layer chromatography (TLC), as follows: An aliquot (ca. 0.1 mL) of the reaction mixture is

withdrawn with an argon-flushed hypodermic syringe and is injected into a small test tube containing ethyl ether (0.25 mL) and water (0.5 mL). After the biphasic mixture is swirled briefly, the ether layer is allowed to separate and is analyzed by TLC using 20% ethyl ether-hexanes as eluent (R_f of the starting dibromide = 0.67, of the product = 0.76, visualization with ultraviolet light). When TLC analysis indicates consumption of the starting dibromide, typically 3-6 hr at 0°C, the reaction mixture is poured into a 1-L separatory funnel containing water (300 mL), saturated aqueous ammonium chloride solution (75 mL), and the tetrasodium salt of ethylenediaminetetraacetic acid (4.50 g, Note 10). The resulting brown suspension is extracted with four 150-mL portions of 50% ethyl acetate-hexanes. The organic layers are combined and washed with three 100-mL portions of water, then dried over sodium sulfate and concentrated. The brown oil thus obtained is filtered through a short column of flash-grade silica gel (150 g, 7-cm diam x 10 cm), using 20% toluene-hexanes as eluent (< 1.5 L total solvent volume, 150-mL fractions). Fractions containing product (R_f = 0.23, 20% toluene-hexanes) are combined and concentrated. The light brown concentrate is combined with silicone oil (7.0 g) in a 250-mL, 14/20 round-bottomed flask. An insulated 6" Vigreux column and a short-path distillation head are affixed for vacuum distillation. The system is evacuated (0.9 mm) and the pot is heated to 110°C whereupon bis(trimethylsilyl)butadiyne sublimes from the mixture. A heat gun is used to assist in the transfer of this component; the flow of condenser water is initiated only after this phase of the distillation. A liquid forerun is collected (ca. 0.5 mL, head temperature 94°C, pot temperature ~125°C) prior to collection of the product. (Z)-2-Bromo-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester is collected (bp 105-108°C, 0.9 mm, pot temperature < 125°C) as a pale yellow oil (10.95-12.85 g, 48-56%) and is shown by capillary GC to be 87-94% pure (contaminants include bis(trimethylsilyl)butadiyne, ≤ 2% and (E)-2-[(trimethylsilyl)ethynyl]-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester, 6-11%; Notes 11-13).

2. Notes

1. Ethyl propiolate was used as received from Aldrich Chemical Company, Inc. (pure by 400 MHz ^1H NMR analysis). Carbon tetrachloride was spectrophotometric grade and was used without purification.

2. Elemental bromine was used as received from EM Science.

3. Although the crude dibromide is essentially pure, the submitters found the subsequent coupling reaction to be more reproducible and to proceed in higher yield when this simple purification procedure is employed.

4. The purified compound displayed the following characteristics: ^1H NMR (400 MHz, CDCl_3) δ : 1.35 (t, 3 H, J = 7.1, CH_3), 4.31 (q, 2 H, J = 7.1, CH_2), 8.23 (s, 1 H, $\text{HC}=\text{C}$); ^{13}C NMR (100 MHz, CDCl_3) δ : 14.0, 63.0, 122.6, 126.4, 160.7; IR (thin film) cm^{-1} : 3072, 2983, 1732, 1569, 1253, 1213, 1037, 737; HRMS calcd for $\text{C}_5\text{H}_6\text{Br}_2\text{O}_2$: 255.8735, found: 255.8739. A trace impurity is visible in the ^1H NMR spectrum (δ 6.35, s). This impurity is tentatively identified as 2,2,3,3-tetrabromopropanoic acid ethyl ester and is estimated by integration to constitute less than 2 mol percent of the mixture.

5. The checkers found three distinct signals due to impurities at δ 7.74 (s), 7.14 (q), 6.34 (s) which totaled 4-7% by NMR integration.

6. N,N-Dimethylformamide was distilled from calcium sulfate under reduced pressure (40 mm) and was stored over 4 Å molecular sieves under argon.

7. Typically three to five evacuation/argon flush cycles are employed. This deoxygenation protocol is simpler and faster than a freeze-pump-thaw procedure.

8. (Trimethylsilyl)acetylene was used as received from Aldrich Chemical Company, Inc. N,N-Diisopropylethylamine was distilled from calcium hydride (atmospheric pressure) and stored over 4 Å molecular sieves under argon.

9. Cuprous iodide (EM Science) was purified by continuous extraction (12 hr) with tetrahydrofuran in a Soxhlet apparatus. The purified compound was stored in a brown bottle and was light grey in appearance. Tetrakis(triphenylphosphine)-palladium, $\text{Pd}(\text{PPh}_3)_4$, was prepared according to a published procedure³ and was stored in a dry box under a nitrogen atmosphere. It was a bright yellow solid. The purity of this reagent is crucial for the stoichiometry and reaction times reported to be observed. It must be handled with care to avoid exposure to air. Dark colored or yellow-green samples of $\text{Pd}(\text{PPh}_3)_4$ are not suitable.

10. For optimum results, it is important to monitor the reaction carefully. Extended reaction times lead to formation of bis-coupled product. Optimum results are obtained when the dibromide (Note 3) and the palladium catalyst (Note 9) are prepared as described.

11. Capillary gas chromatography is conducted with a cross-linked phenyl methyl silicone stationary phase (5%, 25 m x 0.2 mm x 0.5 μm film thickness, injector temp. 225°C, detector temp. 250°C, column temp. 40-200°C, 15°C/min after 1 min initial time). (Z)-2-Bromo-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester is observed to have a retention time of 14.0 min. GC data for bis(trimethylsilyl)butadiyne is as follows: retention time 10.0 min, response factor (GC area produced relative to an equimolar quantity of (Z)-2-bromo-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester) 1.29. For (E)-2-[(trimethylsilyl)ethynyl]-5-(trimethylsilyl)-2-penten-4-ynoic acid ethyl ester the retention time is 17.0 min, the response factor 1.19.

12. The purified product displays the following characteristics: ^1H NMR (400 MHz, CDCl_3) δ : 0.25 (s, 9 H, SiCH_3), 1.34 (t, 3 H, $J = 7.1$, CH_3), 4.30 (q, 2 H, $J = 7.1$, CH_2), 7.29 (s, 1 H, $\text{HC}=\text{C}$); ^{13}C NMR (100 MHz, CDCl_3) δ : -0.6, 14.0, 62.6, 100.4, 111.9, 123.7, 124.6, 161.7; IR (CH_2Cl_2 solution) cm^{-1} : 2964, 1723, 1584, 1252, 1082, 1044, 850; HRMS calcd for $\text{C}_{10}\text{H}_{15}\text{BrO}_2\text{Si}$: 274.0025, found: 274.0024. Additional purification of the distilled product (1.09 g) by silica gel chromatography (5 cm diam x

14-cm column, 100 g of silica gel, eluent, 20% toluene-hexanes) provided an analytical sample (1.02 g, 94% recovery) that was shown to be >99% pure by capillary GC analysis. Anal. Calcd for $\text{C}_{10}\text{H}_{15}\text{BrO}_2\text{Si}$: C, 43.64; H, 5.49. Found: C, 43.74; H, 5.26.

13. The fractions containing the product were combined and analyzed by capillary GC, which showed them to be 87-94% pure with the major impurity (~6-11%) being the bis-coupled product.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

The procedure outlined above describes the selective, retentive, β -coupling of (Z)-2,3-dibromopropenoic acid ethyl ester with (trimethylsilyl)acetylene employing the palladium-modified version of the Castro-Stephens reaction.^{4,5} The dibromide starting material is readily available by bromination of ethyl propiolate (Procedure A), as described by Trippett and Hall.² The coupling product has been shown to be a versatile precursor for the synthesis of variously substituted enynes and enediynes. For example, a second acetylene may be introduced into the α -position under modified coupling conditions. Alternatively, reduction of the ester with diisobutylaluminum hydride and protection of the resultant alcohol with tert-butyldiphenylsilyl chloride affords a vinyl bromide that can be metalated and trapped with various electrophiles. These procedures have been used on the gram and multigram scale.⁵

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl (Z)-2,3-dibromopropenoate: Acrylic acid, 2,3-dibromo-, ethyl ester, (Z)- (8);
2-Propenoic acid, 2,3-dibromo-, ethyl ester, (Z)- (9); (26631-66-3)
Ethyl (Z)-2-bromo-5-(trimethylsilyl)-2-penten-4-ynoate: 2-Penten-4-ynoic acid,
2-bromo-5-(trimethylsilyl)-, ethyl ester, (Z)- (12), (124044-21-9)
Ethyl propiolate: Propiolic acid, ethyl ester (8); 2-Propynoic acid, ethyl ester (9);
(623-47-2)
Carbon tetrachloride (8); Methane, tetrachloro- (9); (56-23-5)
Bromine (8,9); (7726-95-6)
N,N-Dimethylformamide: Formamide, N,N-dimethyl- (8,9); (68-12-2)
Trimethylsilylacetylene: Silane, ethynyltrimethyl- (8,9); (1066-54-2)
N,N-Diisopropylethylamine: Triethylamine, 1,1'-dimethyl- (8); 2-Propanamine,
N-ethyl-N-(1-methylethyl)- (9); (7087-68-5)
Cuprous iodide: Copper iodide (8,9); (7681-65-4)

Tetrakis(triphenylphosphine)palladium(0): Palladium, tetrakis(triphenylphosphine)-
(8); Palladium, tetrakis(triphenylphosphine)-, (T-4)- (9); (14221-01-3)
Ethylenediaminetetraacetic acid, tetrasodium salt; Glycine, N,N'-1,2-ethanediylbis[N-
(carboxymethyl)-, tetrasodium salt, trihydrate (9); (67401-50-7)
Silicone oil: Siloxanes and silicones, dimethyl (10); (63148-62-9)

STEREOSPECIFIC SYNTHESIS OF ETHYL

(Z)-3-BROMO-2-PROPENOATE

(2-Propenoic acid, 3-bromo-, ethyl ester, (Z)-)



Submitted by Shengming Ma and Xiyan Lu.¹

Checked by Qingzhi Gao and Hisashi Yamamoto.

1. Procedure

Ethyl (2Z)-3-bromopropenoate. To a three-necked, round-bottomed flask are added lithium bromide (10.0 g, 0.115 mol, Note 1), acetonitrile (100 mL, Note 2), acetic acid (7.0 g, 0.116 mol, Note 3), and ethyl 2-propynoate (9.0 g, 0.092 mol, Notes 4, 5) under nitrogen. The reaction is carried out with magnetic stirring under reflux and monitored by GLC (Note 6). The reaction is complete after 24 hr. The reaction is cooled, water (20 mL) is added to the flask, and the mixture is cautiously neutralized with solid potassium carbonate, added in portions (Note 3). The organic layer is separated, and the aqueous layer is extracted with ether (3 x 20 mL) (Note 3). The combined organic layers are dried with magnesium sulfate and filtered. After removal of the solvent, ethyl (2Z)-3-bromopropenoate is obtained by vacuum distillation (14.0 g, yield, 85%, Note 7).

2. Notes

1. Lithium bromide (reagent grade) was dried over phosphorus pentoxide (P_2O_5) with heating at 100°C under vacuum.
2. Acetonitrile was distilled from P_2O_5 before use.
3. Acetic acid, potassium carbonate and ether are reagent grade.
4. The optimum ratio of starting materials for this reaction is $\text{LiBr}:\text{CH}_3\text{CO}_2\text{H}:2\text{-propynoate} = 1.25:1.25:1$.
5. Ethyl 2-propynoate is available from Aldrich Chemical Company, Inc.
6. GLC was performed on a 2-m column (10% OV-1 supported on 102 silanized white support, 60-80 mesh) at 90°C.
7. Ethyl (2Z)-bromopropenoate boils at 92-93°C/40 mm. Isomerization was not detected during careful distillation (bath temperature: <115°C). The spectral data are as follows: IR (neat) cm^{-1} : 1730, 1605, 1200, 1185; MS m/e : 181 [$\text{M}^+(\text{Br})+1$]/179 [$\text{M}^+(\text{Br})+1$]; ^1H NMR (200 MHz, CDCl_3): δ : 1.31 (t, 3 H, $J = 7.0$), 4.24 (q, 2 H, $J = 6.2$), 6.61 (d, 1 H, $J = 8.4$), 6.99 (d, 1 H, $J = 8.4$). No E isomer was detected by ^1H NMR, GLC (Note 6), or TLC on silica gel (eluent: petroleum ether: $\text{CH}_3\text{CO}_2\text{Et} = 10:1$).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

3-Halopropenoic acids and their derivatives are valuable intermediates in organic synthesis because three functional groups are present: the C-X bond, the conjugated C=C bond, and the carbonyl group. These compounds can be used to react with nucleophiles,² and, as vinyl halides, to introduce a cis olefinic moiety into an organic molecule using organometallic methods, for the synthesis of (2Z)-en-4-ynoic and (2Z,4Z)- and (2Z,4E)-dienoic acid derivatives.³ Usually such compounds are prepared as a Z and E isomeric mixture. Only a few stereoselective synthetic methods have been reported, most of which are for E isomers. For example, the title compound was reported to be prepared as a Z and E isomeric mixture via the reaction of ethyl 2-propynoate with hydrogen bromide in acetic acid.⁴ The only possible route for its synthesis is by esterification of (2Z)-3-bromopropenoic acid⁵ according to the method for methyl (2Z)-3-chloropropenoate, but isomerization may occur during the prolonged heating of esterification.⁶ No one-step method for the synthesis of the pure Z isomer is available. The stereospecific method described here can also be applied to the synthesis of (2Z)-3-halopropenoic acids,^{7,8} (2Z)-3-halopropenoates,⁷⁻⁹ (2Z)-3-halopropenamides,⁸ and (2Z)-3-halopropenenitriles⁸ (X=I, Br, Cl). In the case of the iodide, sodium iodide and lithium iodide gave similar results, but it is necessary to carry out the reaction under N₂.⁹ With the bromide and chloride, lithium salts gave higher yields than sodium salts. The mechanism of this reaction is believed to involve nucleophilic addition of halide anion to the electron-deficient, carbon-carbon triple bond. The stability of a termolecular transition state or stereoelectronic stabilization of the anion intermediate formed in situ by the nucleophilic addition might be responsible for the high stereospecificity.⁸

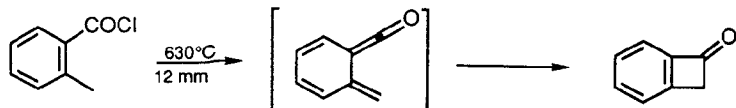
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl (2Z)-3-bromopropenoate: Acrylic acid, 3-bromo-, ethyl ester, (Z)- (8); 2-Propenoic acid, 3-bromo-, ethyl ester, (Z)- (9); (31930-34-4)
Ethyl 2-propynoate: Propiolic acid, ethyl ester (8); 2-Propynoic acid, ethyl ester (9); (623-47-2)

BENZOCYCLOBUTENONE BY FLASH VACUUM PYROLYSIS
(Bicyclo[4.2.0]octa-1,3,5-trien-7-one)



Submitted by Peter Schiess, Pratibha V. Barve, Franz E. Dussy, and
 Andreas Pfiffner.¹

Checked by Nobuyoshi Nomura and Hisashi Yamamoto.

1. Procedure

For flash vacuum pyrolysis experiments on a preparative scale the apparatus shown in Figure 1 is used.² It consists of a vertically-mounted assembly of fused silica and Pyrex tubing 3.2 cm in diameter. The high temperature section **A**, 45 cm in length, is made from fused silica. It carries inner 29/32 ground glass joints. The upper evaporation section **B**, 25 cm in length, is made of Pyrex. It is fitted with two outer 29/32 ground glass joints (Note 1). Both tubes are loosely filled with Raschig rings cut from thin-walled, fused silica tubing 1 cm in diameter. The evaporation zone is heated by glass fiber heating tape (180 x 1 cm) controlled by a variac transformer. Heat for the pyrolysis section is provided by an electric tube furnace (Note 2). The temperature is measured with a thermocouple fixed on the surface of the silica tube in the middle of the hot reaction zone. The substance to be pyrolyzed is added to the evaporator under reduced pressure and at a constant drop rate from a 250-mL, pressure-equalizing dropping funnel **C** (Note 3). A 250-mL, long-necked, round-bottomed flask **D** cooled to -78°C serves as a receiver. (*Caution! Flask D (Note 4) must be checked by visual*

inspection at regular intervals. If condensed product accumulates in the entrance neck, the cooling bath level must be lowered to prevent clogging. Flask D must always be cooled to the neck of the flask. Otherwise material might be transferred from the receiver into trap E, which might then become plugged). Flask **D** is connected by a wide glass tube (Note 4) to a cooling trap **E** kept at liquid nitrogen temperature (Note 5).

At a pyrolysis oven temperature of 630°C, an evaporator temperature of 200°C, and a pressure of 12 mm, 2-toluic acid chloride (240 g, 1.55 mol) (Note 6) is added in about 2.5 hr at a constant rate of 40-60 drops/min (Note 7). The pressure should be monitored in the addition funnel **C** during the pyrolysis. A sudden rise in pressure indicates that a restriction is building up between the pyrolysis reactor and the pump. In this case addition of reactant must be stopped. Ten minutes after the addition is complete the apparatus is flushed with nitrogen. The dark brown, oily condensate in the receiver is dissolved in 500 mL of acetone and diluted with 250 mL of cold water (Notes 8 and 9). The homogeneous solution is stirred at room temperature for 1 hr. It then is separated into two phases by the addition of 500 mL of 2 N sodium carbonate solution and 250 mL of ether. The aqueous layers are extracted twice with 250-mL portions of ether. The ether extracts are washed with 2 N sodium carbonate solution and with saturated sodium chloride solution. The combined ether layers are dried over sodium sulfate. Removal of the solvent and distillation of the residue yields 65 g of a yellow oil, bp 87-90°C/13 mm, with the following composition: Benzocyclobutenone (97%), benzyl chloride (3%) (Note 10). Fractionation at 12 mm through a 25-cm spinning band column (Note 11) gives 58 g of benzocyclobutenone (>99%) as a colorless oil, bp 84-86°C/12 mm (Notes 12 and 13). The product crystallizes at 0°C and then melts at 10-15°C (Note 14).

Most of the acetone is removed from the combined aqueous layers by distillation. Upon acidification with concentrated hydrochloric acid a thick precipitate

forms. Filtration and drying leads to 106 g of almost colorless 2-toluic acid, mp 103-107°C. This material is of sufficient purity for conversion into the acid chloride and for subsequent flash vacuum pyrolysis.

2. Notes

1. Teflon sleeves are used to assure the vacuum tight connection between the ground joints subjected to heat. The checkers used clear-seal joints in all of the glass connections.

2. Electric tube furnaces of appropriate dimensions are available from various manufacturers. A model RO 4/25 by Heraeus GmbH, Hanau, FRG is suitable. However, a very satisfactory furnace can be built by any well equipped laboratory workshop at little cost and effort. The material required consists of thin walled ceramic tubing, 3.5 cm i.d., nichrome resistance wire, heat resistant insulation, and ordinary hardware material. A technical drawing will be provided by the submitters upon request. The temperature of the furnace can be adjusted by an electronic temperature controller using a thermocouple sensor. A 1.5 kW-Variac transformer and any high temperature thermometer would do as well for the budget-minded chemist.

3. A dropping funnel with a needle valve, NORMAG type 8056, manufactured by NORMAG GmbH, D-6238 Hofheim, FRG, has been used by the submitters. The checkers used a standard pressure-equalizing dropping funnel with a Teflon stopcock.

4. Receiver **D** is a 250-mL, round-bottomed flask with two, 15-cm long necks with a diameter of 3.5 to 5 cm (entrance neck) and 2.5 cm (exit neck) (see Figure 1). If a receiver **D** with a narrower entrance neck than indicated is used the neck can become plugged by condensate. A wide-bore connection is used between receiver **D** and the cold trap **E** to prevent a pressure drop during pyrolysis, which might be caused by a restriction in the HCl-gas flow.

5. *Caution!* Hydrogen chloride (bp -84.9°C) is condensed in trap **E**. Exercise care in its disposal.

6. 2-Toluic acid chloride (bp 213-214°C) is prepared from 2-toluic acid (EGA Chemie, Steinheim, FRG) by treatment with thionyl chloride (SOCl_2). The checkers purchased the acid chloride from Tokyo Chemical Co.

7. The pyrolysis temperature and the rate of addition are chosen such that about 50% of the acid chloride is recovered as 2-toluic acid after hydrolysis. Under these conditions only a small amount of benzyl chloride and polymeric material is formed in addition to benzocyclobutenone. The percentage of reactant conversion depends not only on the pyrolysis temperature, but also on the pressure in the reactor and on the rate of reactant addition. It is advisable, therefore, to optimize the pyrolysis temperature in trial runs keeping the other variables constant.

In the runs carried out by the checkers, conversion of reactant was slightly lower than 50% as shown by the recovery of 2-toluic acid in 63-74% yield. In these runs benzocyclobutenone was obtained in 17-20% yield only. However, the yield calculated with respect to reactant consumed and not recovered as 2-toluic acid amounted to 56-64% and thus did not differ significantly from the value given in the procedure.

8. If separation into two phases occurs, acetone is added until a homogeneous solution results.

9. Hydrolysis of unreacted acid chloride is carried out without neutralization of the acid generated. In the presence of a base such as sodium carbonate or sodium bicarbonate the anhydride of 2-toluic acid would be formed, in addition to the sodium salt of the free acid. This anhydride is much less reactive toward hydrolysis than the acid chloride.

10. VPC analyses were performed using a PEG column of 25 m x 0.25 mm.

11. A 25-cm spinning band column of 12 theoretical plates, manufactured by NORMAG GmbH, D-6238 Hofheim, FRG, has been used by the submitters. The checkers found a 30-cm Vigreux distillation column just as suitable for the separation.

12. A forerun, 4.9 g of a yellow oil, bp 52-85°C/12 mm, consisting of a mixture of benzyl chloride and benzocyclobutenone, is discarded.

13. This corresponds to a yield of benzocyclobutenone, >99% homogeneous by VPC, of 32% with respect to the 2-toluic acid chloride subjected to pyrolysis, and of 63% with respect to the 2-toluic acid chloride consumed in the reaction.

14. The spectral properties are as follows: ^1H NMR (CDCl_3 , 300 MHz) δ : 4.00 (s, 2 H), 7.34-7.45 (m, 2 H), 7.50-7.57 (m, 2 H); IR (liquid film) cm^{-1} : 3060, 2920, 1780, 1760, 1585, 955, and 755.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Benzocyclobutenone was first prepared from 1-bromobenzocyclobutene by hydrolysis followed by chromium trioxide oxidation.^{3,4} More recent procedures involve hydrolysis of 1,1-dichloro- or 1,1-dimethoxybenzocyclobutene which in turn have been obtained through cycloaddition of the appropriate 1,1-disubstituted ethylenes to benzyne generated either from anthranilic acid through diazotization^{5,6} or from bromobenzene through sodium amide treatment.^{7,8} Benzocyclobutenone has

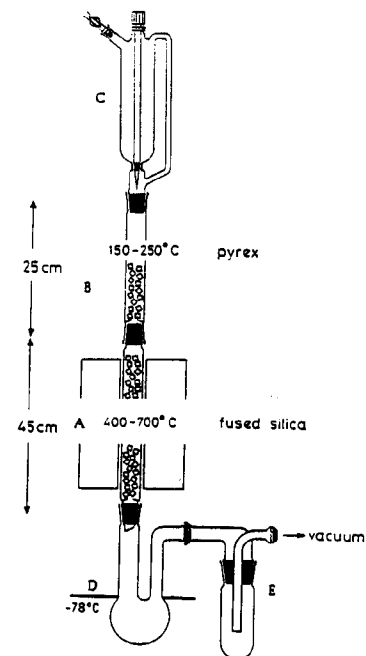
also been obtained through flash vacuum pyrolysis from homophthalic anhydride,⁹ from indane-1,2-dione,¹⁰ and from 2-trimethylsilylmethylbenzoyl chloride.¹¹

The present pyrolytic method is based on a communication by the authors¹² with some modifications of the pyrolysis apparatus for preparative scale.¹³ This method is applicable to the preparation of benzocyclobutenones carrying various substituents on the aromatic ring (see Table). Its merit lies in its simplicity for generating the strained bicyclic ring system from inexpensive precursors. Benzocyclobutenones in general are thermolabile, losing carbon monoxide at higher temperature.¹⁰ It therefore is advisable to keep thermolytic conversion below 100%. Unconverted starting material can be recovered after hydrolysis of the crude reaction mixture as carboxylic acid and reused for the conversion to acid chloride without further purification. Gas phase pyrolysis has been available as a preparative method in organic chemistry for a long time.¹⁴ Various procedures using this method have been described in previous volumes of *Organic Syntheses*.¹⁵ Several reviews describing applications of the pyrolytic method in preparative organic chemistry have appeared in recent years.¹⁶

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Figure 1



Appendix

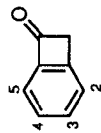
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Benzocyclobutenone: Bicyclo[4.2.0]octa-1,3,5-trien-7-one (8,9); (3469-06-5)

2-Toluic acid chloride: o-Toluoyl chloride (8); Benzoyl chloride, 2-methyl- (9); (933-88-0)

TABLE

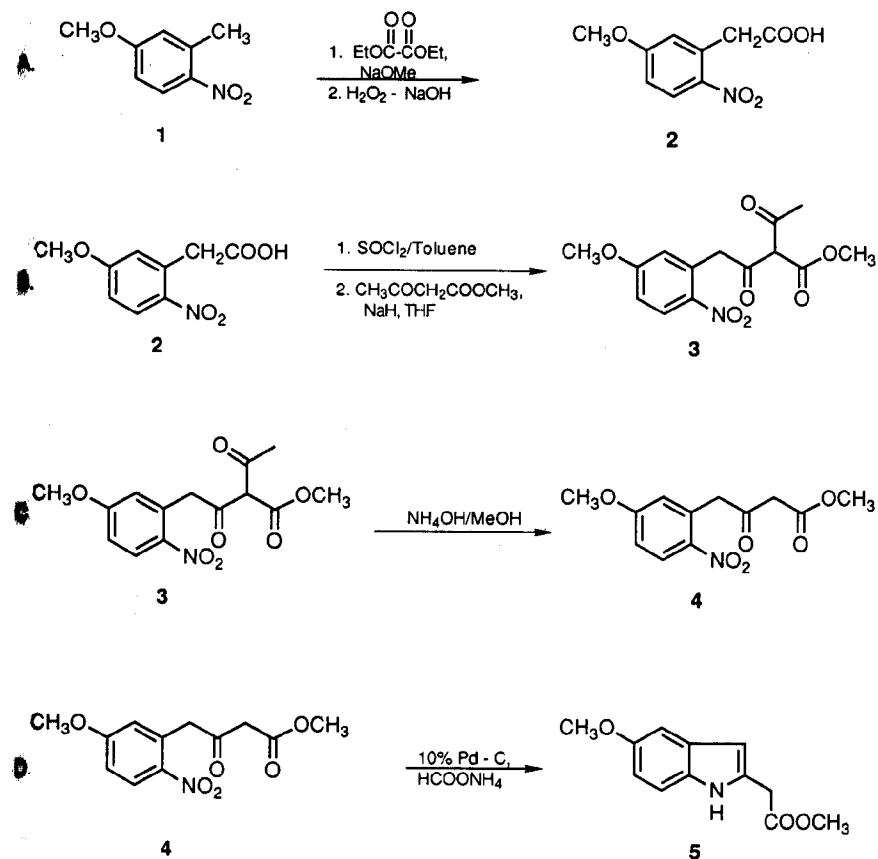
BENZOCYCLOBUTENONES PREPARED THROUGH FLASH VACUUM PYROLYSIS OF

2-METHYLBENZOIC ACID CHLORIDES^{13,15}

2	3	4	5	Reaction Conditions (°C/mm)	Acid Recovered, %	Yield, ^a %	mp (°C)
H	H	H	H	630/13	50	65	10-15
H	CH ₃	H	CH ₃	560/13	5	77	47-48
CH ₃	CH ₃	CH ₃	CH ₃	550/13	-	83	156-157
H	O-CH ₂ -O	H	H	570/13	12	81	122-124
H	OCH ₃	H	H	570/13	41	67	49-50
H	H	H	OCH ₃	590/0.1	51	63	32-33
OCH ₃	H	H	OCH ₃	590/0.1	20	63	106-107
H	OCH ₃	OCH ₃	H	530/13	57	37	142-143
H	H	CH=CH-CH=CH	H	550/13	11	82	96-97

AN EFFICIENT SYNTHESIS OF INDOLE-2-ACETIC ACID METHYL ESTERS

(1H-Indole-2-acetic acid, 5-methoxy-, methyl ester)

Submitted by Sandeep P. Modi,¹ R. Christopher Oglesby,² and Sydney Archer.¹

Checked by Katerina Matcheva and Ekkehard Winterfeldt.

1. Procedure

A. *5-Methoxy-2-nitrophenylacetic acid*, 2.^{3,4} A 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, 50-mL addition funnel, and a reflux condenser fitted with an inert gas (argon) inlet tube that is attached to a mineral oil bubbler. The system is flushed with argon, flame dried, cooled to room temperature, and maintained under a positive pressure of argon. The reaction flask is charged with 18.8 g (0.34 mol) of anhydrous powdered sodium methoxide (Note 1) in 60 mL of anhydrous diethyl ether (Note 2). The flask is cooled in an ice bath and 47.5 mL (0.35 mol) of diethyl oxalate (Note 1) is added over 5 min from the addition funnel. The ice bath is removed and the resulting mixture is stirred at room temperature for 15 min. At the end of this time a pale yellow, thick suspension results, to which 50 g (0.3 mol) of anhydrous powdered 3-methyl-4-nitroanisole, 1, (Note 1) is added, followed by 75 mL of anhydrous ether (Note 2). The orange-red mixture is heated to reflux for 4 hr. After the flask is cooled to room temperature approximately 1 L of water is added to dissolve the resulting thick orange precipitate (Note 3). The red solution is transferred to a 4-L beaker and kept cold using an ice-water mixture. Alternate portions of 30% hydrogen peroxide (Note 1) and 10 N sodium hydroxide (Note 4) are added to the cold red solution. Addition of hydrogen peroxide bleaches the solution and addition of sodium hydroxide restores the red color. This procedure is repeated 3 to 4 times until further addition of 10 N sodium hydroxide solution does not result in a color change (Note 5). The yellow brown solid is collected by filtration; it is impure starting material (wt 6-10 g) (Note 6). The filtrate is poured into a 4-L beaker, cooled to 0°C, and acidified with concentrated hydrochloric acid (Note 2) to precipitate 5-methoxy-2-nitrophenylacetic acid. The solid is collected on a Büchner funnel, washed with cold water until the filtrate is neutral, and then dried to give 45.3-48.5 g (70-75%) of an

almost colorless product, mp 172-176°C (Note 7). Two recrystallizations in methanol give colorless product, mp 175-176°C (Note 8).

B. *Methyl (5-methoxy-2-nitrophenylacetyl)acetoacetate*, 3 (Caution, see Note 13). A 2-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, inert gas inlet, and two stoppers is flame dried and cooled to room temperature under an atmosphere of argon. The flask is charged with 42.5 g (0.20 mol) of 2 in 480 mL of anhydrous toluene (Note 2). To the resulting suspension is added 15.3 mL (0.21 mol) of thionyl chloride (Note 9) followed by 2 mL of anhydrous N,N-dimethylformamide (DMF) (Note 2). As soon as the DMF is added the color of the mixture turns light red. The mixture is stirred at room temperature overnight (Note 10). A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, 250-mL pressure-equalizing funnel, and an inert gas inlet is flame dried and allowed to cool to room temperature under argon. The flask is charged with 10.1 g (0.49 mol) of 97% sodium hydride (Note 1) in 280 mL of dry tetrahydrofuran (THF) (Note 11) and then cooled to 0°C in an ice bath. A solution of 45.3 mL (0.42 mol) of methyl acetoacetate (Note 1) in 160 mL of dry THF (Note 11) is placed in the addition funnel and added dropwise to the reaction flask over a period of 45-50 min. After the addition is complete the light gray-colored solution is quickly transferred to a dried, 500-mL addition funnel (Note 12). The funnel is mounted on the flask containing the acid chloride solution. The solution of methyl acetoacetate anion is added to the crude acid chloride solution (Note 13) over 5 min and the resulting mixture is stirred overnight at room temperature. Water (350 mL) is added to the reaction mixture and the mixture is stirred for 15 min before being poured into a 2-L separatory funnel. The layers are separated and the aqueous layer is extracted with ether (2 x 150 mL). The combined organic layers are washed with brine and dried over sodium sulfate (Note 1). The filtered organic layer is concentrated under reduced pressure and the residue is dissolved in 100 mL of methanol. After cooling in the freezer overnight, the yellow crystals that separate are

collected and dried to give 34.8-37.3 g (56-60%) of **3** (Notes 14, 15), suitable for use in the next step.

C. *Methyl 4-(5-methoxy-2-nitrophenyl)-3-oxobutylate*, **4**. A 1-L, three-necked flask equipped with a magnetic stirring bar, an inert gas inlet, and a stopper is charged with 25.2 g (0.08 mol) of **3** in 200 mL of reagent grade methanol (Note 2) followed by 20 mL of ammonium hydroxide (Note 2). The beige suspension turns red as soon as ammonium hydroxide is added. After about 15 min a white solid precipitates (Note 16). The mixture is stirred at room temperature for 30 min, filtered and the solid is washed with 10-15 mL of cold methanol. The filtrate is concentrated under reduced pressure and the residue is collected on a filter. This procedure is repeated once more (Note 17). After three filtrations the combined solid weighs 16.3-17.4 g (75-80%), which is suitable for use in the next step. Recrystallization from methanol gives a colorless product (Note 18).

D. *Methyl 5-methoxyindole-2-acetate*, **5**. A flame dried, 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar and a condenser under argon is charged with 19.6 g (0.07 mol) of **4** followed by 450 mL of anhydrous methanol (Note 2). A slurry of 1.9 g of 10% palladium over activated carbon (Note 1) in 20 mL of anhydrous methanol is added to the flask (Note 19) followed by 53.5 g (0.8 mol) of ammonium formate (Notes 1, 20). The reaction mixture is stirred at room temperature for 1 hr (Note 21) and then filtered through a bed of Celite. The Celite is washed with 100 mL of anhydrous methanol and the solvents are removed under reduced pressure to give a beige solid. The residue is triturated with 350 mL of cold water and the insoluble material (Note 22) is filtered and then dried to give 13.5-14.3 g (84-89%) of **5** (Note 23).

2. Notes

1. Sodium methoxide, 3-methyl-4-nitroanisole, diethyl oxalate, 30% hydrogen peroxide, 97% sodium hydride, methyl acetoacetate, sodium sulfate, 10% palladium on activated carbon, ammonium formate, and 2-nitrophenylacetic acid were purchased from Aldrich Chemical Company, Inc., and were used without further purification.

2. Anhydrous solvents such as diethyl ether, N,N-dimethylformamide, toluene, and methanol were purchased from Mallinckrodt Inc. and were used without further drying. Concentrated hydrochloric acid and ammonium hydroxide were also purchased from Mallinckrodt Inc.

3. Water was added in portions of 300-400 mL each to the reaction flask. The mixture was stirred for 5-10 min and the red solution was decanted into a separate flask. This procedure was repeated until all the solid went into solution.

4. Sodium hydroxide was purchased from Fischer Scientific Company.

5. The total amounts of 30% hydrogen peroxide and 10 N sodium hydroxide used were 60-70 mL and 20-25 mL, respectively.

6. The melting point of the crude compound is 50-60°C; the NMR and IR correspond to starting material.

7. The physical properties are as follows: m.p. 175-176°C (lit value:³ 174-176°C); IR (KBr) cm^{-1} : 3140-2740, 2660, 1715, 1620, 1580, 1510, 1410, 1340, 1320, 1290, 1260, 1200, 1175, 1090, 1040, 955, 850, 830, 760, 710, 630; NMR (DMSO- d_6) δ : 3.86 (s, 3 H, OCH₃), 3.97 (s, 2 H, CH₂), 7.04-7.10 (m, 2 H, H₄, H₆), 8.13 (d, 1 H, J = 8.8, H₃); MS m/e 212 (M+1).

8. It is essential to have compound **2** as a colorless product; otherwise the yield in the next step is poor.

9. Thionyl chloride was purchased from Aldrich Chemical Company, Inc., and distilled prior to use.

10. If a clear solution did not result at the end of 16-18 hr, the mixture was warmed at 35-40°C for 1 hr or until a clear solution resulted; then it was cooled to room temperature.

11. Reagent grade tetrahydrofuran was purchased from Mallinckrodt Inc. and freshly distilled from sodium metal and benzophenone.

12. A 500-mL, pressure-equalizing funnel was oven-dried and then cooled under argon.

13. 5-Methoxy-2-nitrophenylacetyl chloride was never isolated from the reaction mixture. It is known^{5,6} that 2-nitrophenylacetyl chloride is a potentially explosive material, but it is not documented that the 5-methoxy derivative is also hazardous. 5-Methoxy-2-nitrophenylacetyl chloride was also prepared as described by Rosenmund and his co-workers,⁷ and was used in the crude form.

14. Depending on the purity of the starting material, the yield of **3** has been as high as 80%.

15. The analytical sample melted at 78-79°C after crystallization from methanol. The spectra are as follows: IR (KBr) cm^{-1} : 2960, 2850, 1710, 1620-1390, 1350-1250, 1190, 1090, 1035, 950, 910, 890, 840, 760, 730, 630; NMR (CDCl_3) δ : 2.40 (s, 3 H, COCH_3), 3.84 (s, 3 H, COOCH_3), 3.99 (s, 3 H, OCH_3), 4.50 (s, 2 H, CH_2), 6.77 (d, 1 H, $J = 2.6$, H_6), 6.90 (dd, 1 H, $J = 2.8, 9.0$, H_4), 8.19 (d, 1 H, $J = 9.0$, H_3); MS m/e 310 ($M+1$).

16. If there is no precipitate, a few crystals of starting material **3** are added to the reaction flask to initiate crystallization.

17. After a total of three filtrations, the filtrate contained 5-methoxy-2-nitrophenylacetamide and 4-(5-methoxy-2-nitrophenyl)-4-oxobutyramide as the by-products in varying amounts.

18. The physical properties are as follows: mp 85-87°C; IR (KBr) cm^{-1} : 3470, 3130, 2980, 2850, 1710, 1590, 1500, 1440, 1400, 1200, 1065, 1010, 865, 850, 760, 750, 700, 630, 620; NMR (CDCl_3) δ : 3.66 (s, 2 H, CH_2), 3.77 (s, 3 H, COOCH_3), 3.87 (s, 3 H, OCH_3), 4.20 (s, 2 H, ArCH_2), 6.73 (d, 1 H, $J = 2.8$, H_6), 6.89 (dd, 1 H, $J = 2.8, 9.2$, H_4), 8.19 (d, 1 H, $J = 9.2$, H_3); MS m/e 268 ($M+1$).

19. Excess ammonium formate was necessary for completion of the reaction.

20. The slurry was prepared by adding ice-cold methanol to 10% palladium on activated charcoal. The slurry was transferred to the reaction flask with a pipet.

21. The reaction was monitored by TLC, using silica gel plates and 2:1 ethyl acetate-hexane.

22. If an oil resulted, it was taken up in ethyl acetate (150 mL) and the two layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 50 mL); the organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure at 35-40°C to give 12.7-13.5 g (80-85%) of product **5** as an oil that solidifies on cooling in the freezer.

23. The physical properties are as follows: mp 96-98°C; IR (KBr) cm^{-1} : 3370, 3020, 2970, 2840, 1720, 1595, 1485, 1445, 1395, 1330, 1205, 1120, 1035, 1010, 980, 950, 845, 810, 770, 735, 695, 625-1; NMR (CDCl_3) δ : 3.74 (s, 3 H, COOCH_3), 3.82 (s, 2 H, CH_2), 3.83 (s, 3 H, CH_3), 6.27 (d, 1 H, $J = 1.0$, H_3), 6.81 (dd, 1 H, $J = 2.4, 8.8$, H_6), 7.01 (d, 1 H, $J = 2.4$, H_4), 7.23 (d, 1 H, $J = 8.8$, H_7), 8.53 (s, 1 H, NH); MS m/e 220 ($M+1$). The product must be stored in the freezer; on the bench top it turns red.

24. The physical properties for methyl (2-nitrophenylacetyl)acetoacetate are as follows: mp 82-83°C; IR (KBr) cm^{-1} : 2960, 1705, 1515, 1400, 1335, 1080, 860, 790, 720 cm^{-1} ; NMR (CDCl_3) δ : 2.41 (s, 3 H, COCH_3), 3.85 (s, 3 H, COOCH_3), 4.20 (s, 2 H, CH_2), 4.50 (s, 2 H, CH_2), 7.36-7.65 (m, 3 H), 8.16 (t, 1 H).

25. The physical properties for methyl 4-(2-nitrophenyl)-3-oxobutyrate are as follows: mp 50-51°C; IR (KBr) cm^{-1} : 2960, 1750, 1715, 1610, 1575, 1520, 1440,

1340, 1265, 1200, 1070, 1010, 795, 730, 705 cm^{-1} ; NMR (CDCl_3) δ : 3.66 (2 H, $\text{COCH}_2\text{COOMe}$), 3.76 (s, 3 H, COOCH_3), 4.25 (s, 2 H, Ar-CH_2), 7.30 (d, 1 H, $J = 7.2$), 7.50 (t, 1 H), 7.6 (t, 1 H), 8.10 (d, 1 H, $J = 6.8$).

26. The physical properties for methyl indole-2-acetate are as follows: mp 71-74°C; IR (KBr) cm^{-1} : 3430, 3405, 3320, 3220, 1740, 1720, 1660, 1620, 1565, 1525, 1430, 1340, 1300, 1280, 1190, 1170, 1030, 860, 820, 790, 780, 730, 700 cm^{-1} ; NMR (CDCl_3) δ : 3.61 (s, 3 H, COOCH_3), 3.71 (s, 2 H, CH_2), 7.42-7.58 (m, 4 H), 7.93 (m, 1 H), 7.97 (d, 1 H, $J = 1.8$).

3. Discussion

Compound 5 and its 5-H-analog can be prepared in one to two steps from the known intermediates 5-methoxyindole-2-acetonitrile and indole-2-acetic acid, respectively. 5-Methoxyindole-2-acetonitrile is obtained in very poor overall yield when the patented procedure is followed.⁸ Indole-2-acetic acid is prepared from indole-2-carboxylic acid^{9,10} in five steps or from indole^{11,12} in three steps. The first method involves six steps for the one carbon homologation and the overall yield is 23%. The second method involves protection and deprotection of the indole nitrogen. In addition the reaction conditions for the lithiation step require a very low (-78°C) temperature and for the Wolff-Kishner step a very high (180°C) temperature. The procedure described here illustrates a general synthetic method for the preparation in three steps of substituted indole-2-acetic acid methyl esters from o-nitrophenylacetic acid and its derivatives. The overall yields are 30-40% and the reactions can be carried out on a large scale. The purity of the intermediates and the products is greater than 90% as determined by NMR. One of the intermediates, o-nitrophenylacetyl chloride, is considered to be a potentially explosive material; therefore it is never isolated, but is used in its crude form. Although it is not known

whether 5-methoxy-2-nitrophenylacetyl chloride is an explosive material, it is also prepared and used in its crude form.

Compound 5 and its 5-H-analog are useful intermediates in preparing a number of 5-substituted 6H-pyrido[4,3-b]carbazoles.^{9,10,13} These pyridocarbazoles are potential antitumor agents.

The corresponding 5-H analogs of the title compound are prepared using the procedure described for compounds 3, 4, and 5 in 55-61%, 65-70%, and 80-86% yield, respectively.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Methyl indole-2-acetate: Indole-2-acetic acid, methyl ester (8); 1H-Indole-2-acetic acid, methyl ester (9); (21422-40-2).

Methyl 5-methoxyindole-2-acetate: Indole-2-acetic acid, 5-methoxy-, methyl ester (8); 1H-Indole-2-acetic acid, 5-methoxy-, methyl ester (9); (27798-66-9)

5-Methoxy-2-nitrophenylacetic acid: Acetic acid, (5-methoxy-2-nitrophenyl)- (8);

Benzeneacetic acid, 5-methoxy-2-nitro- (9); (20876-29-3)

Sodium methoxide; Methanol, sodium salt (8,9); (124-41-4)

Diethyl oxalate: Oxalic acid, diethyl ester (8); Ethanedioic acid, diethyl ester (9); (95-92-1)

3-Methyl-4-nitroanisole: Anisole, 3-methyl-4-nitro- (8); Benzene, 4-methoxy-2-methyl-1-nitro- (9); (5367-32-8)

Hydrogen peroxide (8,9); (7722-84-1)

Methyl (5-methoxy-2-nitrophenylacetyl)acetoacetate: Benzenebutanoic acid, α -acetyl-,

5-methoxy-2-nitro-, β -oxo-, methyl ester (12); (130916-40-4)

Toluene (8); Benzene, methyl- (9); (108-88-3)

Thionyl chloride (8,9); (7719-09-7)

N,N-Dimethylformamide: Formamide, N,N-dimethyl- (8,9); (68-12-2)

Sodium hydride (8,9); (7646-69-7)

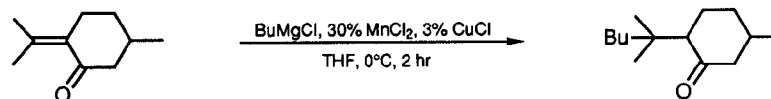
Methyl acetoacetate: Acetoacetic acid, methyl ester (8); Butanoic acid, 3-oxo-, methyl ester (9); (105-45-3)

Methyl 4-(5-methoxy-2-nitrophenyl)-3-oxo-butyrate: Benzenebutanoic acid, 5-methoxy-2-nitro-, β -oxo-, methyl ester (12); (130916-41-5)

Ammonium formate: Formic acid, ammonium salt (8,9); (540-69-2)

MANGANESE-COPPER-CATALYZED CONJUGATE ADDITION OF
ORGANOMAGNESIUM REAGENTS TO α,β -ETHYLENIC KETONES:

PREPARATION OF 2-(1,1-DIMETHYLPENTYL)-5-METHYL-
CYCLOHEXANONE FROM PULEGONE
(Cyclohexanone, 2-(1,1-dimethylpentyl)-5-methyl-)



Submitted by M. Alami, S. Marquais, and G. Cahiez.¹

Checked by Todd Gane and Stephen F. Martin.

1. Procedure

A 500-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, 100-mL, pressure-equalizing dropping funnel, and a Claisen head fitted with a low-temperature thermometer and a nitrogen inlet (Note 1). The flask is charged with 80 mL of anhydrous tetrahydrofuran (THF, Note 2), 1.9 g (15 mmol) of anhydrous manganese chloride (Note 3), 0.15 g (1.5 mmol) of cuprous chloride (Note 4), 1.28 g (30 mmol) of lithium chloride (Note 5), and 7.61 g (50 mmol) of (R)-(+)-pulegone (Note 6). The mixture is stirred at room temperature until dissolution of the salts is complete (1 to 2 hr) (Note 7), then a solution of butylmagnesium chloride (58 mmol) in THF (Note 8) is added dropwise at 0°C over a 25-30 min period. Stirring is continued for 1.5 hr at 0°C. The reaction mixture is hydrolyzed by dropwise addition of 2 M hydrochloric acid (HCl, 100 mL). After addition of 80 mL of petroleum ether (35-60°C) and decantation (Note 9), the aqueous layer is extracted three times with 100-mL portions of petroleum

ether (35-65°C). The combined organic layers are successively washed with 50 mL of 1 M HCl, 50 mL of a diluted ammonium chloride/ammonium hydroxide (NH₄Cl/NH₄OH) solution and 50 mL of a saturated sodium bicarbonate solution, then dried over magnesium sulfate. After filtration, the solvents are removed with a rotary evaporator (20 mm, room temperature). The product is obtained in crude form in almost quantitative yield as a 61.5:38.5 mixture of diastereoisomers, purity > 96% (Note 10). Distillation under reduced pressure affords 9.85 g of pure 2-(dimethylpentyl)-5-methylcyclohexanone (94%, Note 12), bp 101-105°C (3 mm).

2. Notes

1. The apparatus is flame-dried under a stream of dry nitrogen or argon. Later a slight positive nitrogen pressure is maintained with an oil bubbler throughout the reaction.

2. THF is freshly distilled from sodium benzophenone ketyl under a nitrogen atmosphere.

3. Manganese chloride, 98%, was purchased from Aldrich Chemical Company, Inc., or from Janssen Chimica. It must be finely pulverized then dried by heating at 180°-200°C (0.1 mm to 0.01 mm) for 6 hr (for example, in a vacuum oven) prior to use. The anhydrous salt is very hygroscopic and must be protected against moisture (a well-closed bottle is convenient). It can, however, be handled *very quickly* without any special precaution.

4. Pulverized cuprous chloride purchased from Aldrich Chemical Company, Inc., was used.

5. Anhydrous lithium chloride purchased from Aldrich Chemical Company, Inc., was used. It is finely pulverized then dried by heating at 200°C (0.1 mm to 0.01 mm) for 6 hr (vacuum oven) before use. The salt is hygroscopic and must be handled *very*

quickly. The reaction can be achieved by using only 1.2 equiv of lithium chloride (18 mmol) instead of 2 equiv.

6. (R)-(+)-Pulegone available from Fluka AG (puriss; 99%), was distilled before use.

7. Generally a green-brown solution is obtained; this color is primarily due to the presence of the copper salt. However, the rate of dissolution (formation of the ate-complex MnCl₄Li₂) is very dependent on both the grain size of the two salts (MnCl₂ and LiCl) and on their purity. When unpulverized Aldrich or Janssen material is used it is necessary to stir for at least 4 hr to obtain complete dissolution. On the other hand, with finely pulverized anhydrous manganese chloride obtained by drying an analytical grade manganese chloride tetrahydrate (e.g., manganese chloride tetrahydrate p.a., Janssen Chimica), it is possible to obtain complete dissolution after only 5 to 10 min. Moreover, formation of the ate-complex is exothermic.

8. THF solutions of butylmagnesium chloride purchased from Aldrich Chemical Company, Inc., or, preferably, freshly prepared from butyl chloride and magnesium under a nitrogen atmosphere (Note 11), were used. They were standardized immediately before use according to the titration procedure of Watson and Eastham² (see also Note 6, Gall, M.; House, H. O. *Org. Synth., Coll. Vol. VI* 1988, 121). During addition of the butylmagnesium chloride solution (about 1.5 M) a brownish color appears, indicating the formation of the intermediate organomanganese reagent. Magnesium-manganese exchange occurs instantaneously.

9. Metallic copper can be filtered off (on Celite) before decantation.

10. Purity was determined by capillary GC analysis, OV-1, 25 m x 0.33 mm i.d., 0.5 µm film thickness.

11. To prepare a THF solution of butylmagnesium chloride from butyl chloride, the procedure described by Olah and Arvanaghi (Olah, G. A.; Arvanaghi, M. *Org. Synth., Coll. Vol. VII* 1990, 451) for the preparation of 2-phenylethylmagnesium

chloride ($\text{PhCH}_2\text{CH}_2\text{MgCl}$) is convenient. However one should adjust the addition rate of the THF solution of butyl chloride to keep the temperature of the reaction mixture between 40°C to 45°C, then stir for 6 hr at this temperature.

12. Yields of 92 to 95% were obtained on several runs. The spectra are as follows: ^{13}C NMR (CDCl_3) δ (the values separated by a slash correspond to the diastereoisomers): 14.20, 19.45/22.40, 23.60, 24.60/24.95, 25.05/25.25, 26.05, 24.15/28.25, 31.50/34.05, 34.60/34.90, 32.35/36.45, 40.35/40.55, 50.50/52.55, 57.25/57.30, 212.25/213.20; IR (neat) cm^{-1} : 1710.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Manganese-copper-catalyzed conjugate addition of organomagnesium reagents to α,β -enones is a general synthetic method. Table I shows that the reaction can be successfully performed even with enones of low reactivity. 30% Manganese chloride is necessary to obtain good yields. In most cases, however, 0.1% cuprous chloride is sufficient.³

This manganese-copper-catalyzed conjugate addition reaction compares favorably with the classical copper-catalyzed reaction. The two reactions are easily and similarly carried out under mild conditions, but the first one gives higher yields. This difference, already observed in the case of β -monosubstituted α,β -ethylenic ketones, is especially noticeable with β,β -disubstituted or α,β,β -trisubstituted α,β -

ethylenic ketones which are known to be less reactive.⁴ Thus, in the case of the title compound, the manganese-copper catalyzed reaction is clearly superior (see Table II).

A comparison with various organocopper or cuprate reagents is also favorable since the procedure described here gives higher yields. In addition, the reaction is simpler and more economic, since it is performed at 0°C, using only 1 equiv of organometallic reagent, and no special additive such as HMPA, Bu_3P , $\text{BF}_3\text{-Et}_2\text{O}$ or Me_3SiCl is required. (See ref. 3 for a comparison with the case of the mesityl oxide.)

Manganese chloride is inexpensive and the work-up is easier with manganese than with copper. This is an advantage, especially for large-scale preparations.

The procedure described here is a variant of the copper-catalyzed conjugate-addition of organomanganese reagents to α,β -ethylenic ketones. Thus, alkyl, alkenyl, or arylmanganese chloride reagents react with a vast array of α,β -ethylenic ketones in THF³ and in the presence of copper chloride to give 1,4-addition products in high yields (see Table III).

The scope of the reaction has been successfully extended to α,β -ethylenic aldehydes,⁵ esters,⁶ and amides⁷ as well as to α,β -acetylenic ketones⁸ (see Table IV). With esters, the reaction must be performed in the presence of chlorotrimethylsilane (Me_3SiCl) to avoid the Claisen reaction by trapping the intermediate enolate. In most cases the organomanganese procedure is simple and more efficient than the organocopper procedure.

Good yields of 1,4-addition products have also been obtained with alkylidene malonate esters which generally react with organomanganese reagents in the absence of copper salts⁹ (see Table IV).

In conclusion, copper-manganese-catalyzed organomagnesium reagents and copper-catalyzed organomanganese reagents are a simple, efficient, and economic alternative to copper-catalyzed organomagnesium reagents and especially to

organocopper or cuprate reagents for conjugate addition reactions to α,β -unsaturated carbonyl compounds.

Organomanganese reagents have also been used to prepare numerous simple or functionalized ketones in high yields.¹⁰ They can be also used to carry out in high yields, at room temperature, various chemoselective 1,2-addition reactions, for example to keto aldehydes.¹¹

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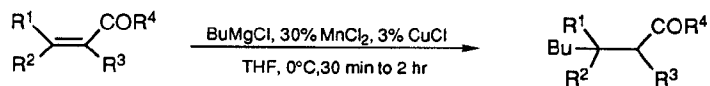
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-(1,1-Dimethylpentyl)-5-methylcyclohexanone: Cyclohexanone,
2-(1,1-dimethylpentyl)-5-methyl- (12); (109539-17-5)
Manganese chloride (8,9); (7773-01-5)
Cuprous chloride: Copper chloride (8,9); (7758-89-6)
Lithium chloride (8,9); (7447-41-8)
(R)-(+)-Pueigone: p-Menth-4(8)-en-3-one, (R)-(+)- (8); Cyclohexanone,
5-methyl-2-(1-methylethylidene)-, (R)- (9); (89-82-7)
Butylmagnesium chloride: Magnesium, butylchloro- (8,9); (693-04-9)

TABLE I

MANGANESE-COPPER-CATALYZED CONJUGATE ADDITION OF
ORGANOMAGNESIUM CHLORIDES TO α,β -ETHYLENIC KETONES IN THF AT 0°C



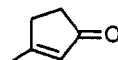
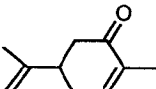
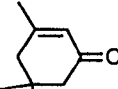
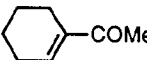
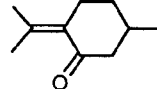
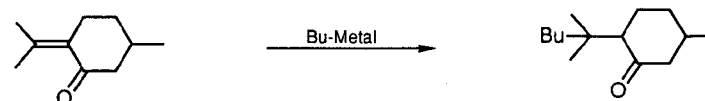
α -Enone	Isolated Yield %	α -Enone	Isolated Yield %
$\text{Me}_2\text{C}=\text{CHCOMe}$	94		81
	87		93
	87		94

TABLE II

CONJUGATE ADDITION OF Bu-METAL COMPOUNDS TO PULEGONE

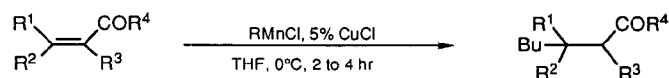


Bu-Metal	Reaction Conditions	Isolated Yield (%) ^a
BuMgCl	30% MnCl ₂ - 3% CuCl THF, 0°C, 2 hr	94
BuMnCl	3% CuCl; THF, 0°C, 1 hr	95
BuMgCl	5% CuCl; THF, 0°C	51 ^b
BuCu	Ether-Me ₂ S, -50°C to -10°C	43 ^c
BuCu	1.1 equiv Me ₃ SiCl; ether, -10°C	70 ^c
Bu(CN)CuLi	Ether, -50°C to -10°C	13
0.6 equiv Bu ₂ CuLi	Ether, -78°C to -30°C	33
1.2 equiv Bu ₂ CuLi	Ether, -50°C to -10°C	85 ^d
1.2 equiv Bu ₂ CuMgCl	THF; -50°C to -10°C	47 ^d
2 equiv Bu ₂ (CN)CuLi ₂	Ether, -78°C, 5 hr then 0°C	69 ^{d,e}

(a) All reactions have been performed on a 30-mmol scale. (b) Conjugate addition of copper-catalyzed butylmagnesium halide to pulegone gives a better yield in THF than in ether. (c) BuCu from CuBr-Me₂S. (d) Yield based on the starting enone. (e) There is some 1,2-addition.

TABLE III

COPPER-CATALYZED CONJUGATE ADDITION OF ORGANOMANGANESE
CHLORIDES, ^a RMnCl, to α,β -ETHYLENIC KETONES IN THF AT 0°C




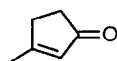
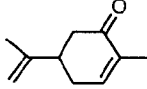
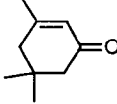
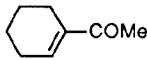
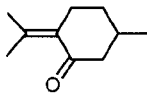
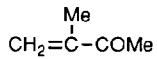
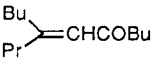
α -Enone	R	Isolated Yield %	α -Enone	R	Isolated Yield %
	Bu Ph Me ₂ C=CH	95 94 92		Bu	90
	Bu	98		Bu	95
	Bu	86 ^b		Bu	88 ^d
CH ₂ =CHCOMe	C ₇ H ₁₅	90 ^c	Me ₂ C=CHCOC ₇ H ₁₅	Me	82
	C ₇ H ₁₅	89	Me ₂ C=CHCOMe	Bu Ph PrCH=CH	94 89 91
PentCH=CHCOMe	Bu Me Me ₂ C=CH	90 85 81		Bu	90

Table III (contd.)

(a) Unless otherwise stated 1.05 equiv of RMnCl was used. Organomanganese reagents RMnCl were prepared from RLi or RMgX (X = Cl, Br, I). (b) 1.5 equiv of BuMnCl was used. With 1.05 equiv of BuMnCl the yield drops to 77%. (c) The reaction was performed in the presence of 1.2 equiv of Me₃SiCl to trap the intermediate enolate to prevent its addition to the starting methyl vinyl ketone (Michael addition or aldol condensation). A mixture THF/AcOEt 50:50 was used as solvent. (d) A mixture THF/AcOEt 50:50 was used as solvent (an 82% yield was obtained in THF alone).

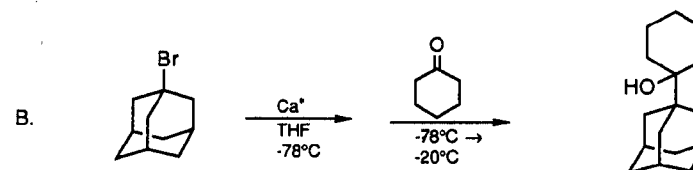
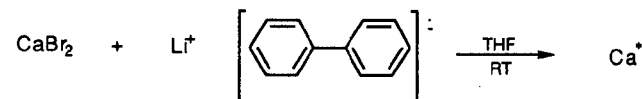
TABLE IV
COPPER-CATALYZED CONJUGATE ADDITION OF ORGANOMANGANESE
CHLORIDES, RMnCl, TO α,β -UNSATURATED CARBONYL SUBSTRATES IN THF

α,β -Unsaturated Carbonyl Substrates	RMnCl	Yield (%) of 1,4-Addition Product
$\text{Me}_2\text{C}=\text{CHCHO}$	$\text{C}_7\text{H}_{15}\text{MnCl}$	80 ^a
$\text{MeCH}=\text{CHCOOEt}$	$i\text{-PrMnCl}$	96 ^b
$\text{MeCH}=\text{CHCONEt}_2$	BuMnCl	87 ^b
$\text{C}_5\text{H}_{11}\text{C}\equiv\text{CCOBu}$	BuMnCl	79 ^c
$\text{Me}_2\text{C}=\text{C}(\text{COOEt})_2$	$\text{PrCH}=\text{CH}$	92 ^d
$\text{Me}_2\text{C}=\text{C}(\text{COOEt})_2$	Ph	87 ^e

(a) 3% CuCl, 1.2 equiv Me_3SiCl , -30°C . (b) 3% CuCl, 1.2 equiv Me_3SiCl , 0°C .

(c) 3% CuCl, -20°C . (d) 3% CuCl, 0°C to 20°C . (e) Without CuCl, 20°C .

HIGHLY REACTIVE CALCIUM FOR THE PREPARATION OF
ORGANOCALCIUM REAGENTS: PREPARATION OF 1-ADAMANTYL
CALCIUM HALIDES AND THEIR ADDITION TO KETONES:
1-(1-ADAMANTYL)CYCLOHEXANOL
(Cyclohexanol, 1-tricyclo[3.3.1.1^{3,7}]dec-1-yl)



Submitted by Reuben D. Rieke,¹ Tse-Chong Wu, and Loretta I. Rieke.

Checked by Katsutaka Yasue and Hisashi Yamamoto.

1. Procedure

A. *Active calcium.* Freshly cut lithium (41.7 mg, 6.01 mmol) and biphenyl (1.020 g, 6.61 mmol) in freshly distilled tetrahydrofuran (THF, 15 mL) (Note 1) are vigorously stirred at room temperature under argon (Note 2) until the lithium is completely

consumed (approx. 2 hr). The preformed lithium biphenylide is transferred via a cannula at room temperature to a well-dispersed suspension of calcium bromide (CaBr_2 , 1.213 g, 6.07 mmol) (Note 3) in freshly distilled THF (15 mL). The reaction mixture is stirred for 1 hr at room temperature prior to use (Note 4).

B. Grignard - type reaction to form 1-(1-adamantyl)cyclohexanol. Activated calcium prepared from preformed lithium biphenylide and excess CaBr_2 in THF is cooled to -78°C (Note 5). 1-Bromoadamantane (543 mg, 2.52 mmol) (Note 6) in THF (10 mL) is added via a cannula at -78°C and the mixture is stirred at -78°C for 20 min (Note 7). Excess cyclohexanone (520 mg, 5.30 mmol) is added via a disposable syringe at -78°C . The resulting mixture is gradually warmed to -20°C and stirred at -20°C for 30 min. The reaction mixture is then quenched with water at -20°C (20 mL) and warmed to room temperature. At this temperature it is filtered through a small pad of Celite which is washed with diethyl ether (Et_2O , 100 mL). The aqueous layer is extracted with Et_2O (3 x 50 mL). The combined organic phases are washed with water (15 mL) and dried over anhydrous magnesium sulfate (MgSO_4). Removal of the solvent and flash-column chromatography on silica gel (150 g, 230-400 mesh, eluted sequentially with hexane/ EtOAc [0% to 15%]) affords a white solid of reasonably pure 1-(1-adamantyl)cyclohexanol. 1-(1-Adamantyl)cyclohexanol is recrystallized from hexanes as follows: The white crystals are dissolved in a limited amount of dichloromethane (CH_2Cl_2), hexane (15 mL) is added, the solvent is evaporated to 8 mL, more hexane (15 mL) is added, the solvent is evaporated to about 15 mL, and the solution is gradually cooled and allowed to stand for 24 hr to afford 469-476 mg (80-82% yield) of product as colorless needles, mp $169-171^\circ\text{C}$ (Notes 8,9).

2. Notes

1. Lithium was weighed out and charged into reaction flasks under argon in a Vacuum Atmospheres Company dry box. (The checkers did not use a dry box: Lithium was freshly cut in air, rinsed in hexane, and charged into reaction flasks under argon.) Biphenyl was purchased from Aldrich Chemical Company, Inc. Tetrahydrofuran anhydrous, 99.9% purity, was purchased from Aldrich Chemical Company, Inc. It was freshly distilled over Na/K alloy under argon before use.

2. All glassware, syringes, needles, and cannulas were kept in a 120°C oven overnight prior to use. All manipulations were carried out on a dual manifold vacuum/argon system. The Linde prepurified grade argon was further purified by passing it through a 150°C catalyst column (BASF R3-11), a phosphorus pentoxide column, and a column of granular potassium hydroxide. (The checkers used argon as received.)

3. Anhydrous calcium(II) bromide was purchased from Cerac, Inc. Commercially available reagents were used as received unless specially noted.

4. Good stirring is important for the preparation of highly reactive calcium. A Schlenk tube is better than a flask for the reactor. Excess calcium salt was present during the oxidative addition reaction with 1-bromoadamantane.

5. Low-temperature reactions were performed using a Neslab endocal ULT-80 refrigerated circulating bath or a dry ice/acetone bath.

6. 1-Bromoadamantane, 99%, was purchased from Aldrich Chemical Company, Inc.

7. The reaction was checked by GC; all the starting material was consumed.

8. Melting points were determined on a Thomas Hoover melting point apparatus or an Electrothermal melting point apparatus and are corrected.

IR spectra were taken on an Analect RFX-30 FTIR spectrophotometer neat between NaCl or KBr plates or as KBr disks. ^1H NMR spectra were recorded on a Nicolet NT-360 (360 MHz) or on a Varian VXR-200 (200 MHz) spectrometer. All chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Fully decoupled ^{13}C NMR spectra and DEPT experiments were recorded on a Varian VXR-200 (50 MHz) spectrometer. The center peak of CDCl_3 (77.0 ppm) was used as the internal reference.

9. The physical properties are as follows: IR (KBr) cm^{-1} : 3465, 2931, 2902, 2844, 1448, 1344, 980, 955, 935; ^1H NMR (200 MHz, CDCl_3) δ : 0.95-2.05 (m, 26 H); ^{13}C NMR (50 MHz, CDCl_3) δ 21.9, 26.0, 28.7, 29.8, 35.8, 37.3, 39.1, 74.6; MS (EI) m/e (relative intensity) 234 (M^+ , 0.2), 135 (26.0), 98 (100.0); HRMS calcd for $\text{C}_{16}\text{H}_{26}\text{O}$ m/e 234.1984, found m/e 234.1982. Anal. Calcd: C, 81.99; H, 11.18. Found: C, 82.13; H, 11.41.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

The development of organocalcium chemistry has been slow compared with the extensive studies of organometallic reagents of other light metals,² due in part to the lack of a facile method of preparing organocalcium compounds. Direct oxidative addition to calcium has been limited by the reduced reactivity of calcium metal with organic substrates, presumably because of surface poisoning. The organocalcium

derivatives RCaX were formed most readily when $\text{X} = \text{I}$; the preparation of RCaX ($\text{X} = \text{Br}, \text{Cl}$) usually required activated calcium. Few examples have been reported and overall yields tend to be low.² Although simple primary and secondary alkyl iodides react with calcium in reasonable yields,³ tertiary alkyl iodide compounds are very difficult to prepare and most workers have reported only trace amounts.⁴ In contrast, the highly reactive calcium complexes reported here react readily with all these substrates to generate excellent yields of the corresponding organocalcium compounds.

Highly reactive calcium can be readily prepared by the reduction of calcium halides in tetrahydrofuran solution with preformed lithium biphenylide under an argon atmosphere at room temperature.⁵ This colored calcium species seems to be reasonably soluble in THF. However, the reactive calcium complex prepared from preformed lithium naphthalenide was insoluble in THF solution and precipitated out of solution to give a highly reactive black solid. The exact nature of this black calcium complex has not been determined. Acid hydrolysis of the black material releases naphthalene as well as THF. Accordingly, the most likely structure of the black material is a Ca-naphthalene-THF complex similar in nature to the soluble magnesium-anthracene complex recently reported.⁶

Highly reactive calcium was prepared by the lithium biphenylide reduction of calcium salts in THF. Both CaBr_2 and CaI_2 generate the reactive calcium species. The organocalcium compounds, prepared directly from this calcium complex and organic halides, were found to undergo Grignard-type reactions efficiently. Alkyl bromides and alkyl chlorides reacted rapidly with the calcium complex at temperatures as low as -78°C . 1-Chlorooctane gave 1-octylcyclohexanol in 83% yield.⁵ Similar results were noted for secondary halides. Bromocyclohexane reacted readily with the calcium species at -78°C and the resulting organocalcium reagent underwent carbonyl addition to give the alcohol in 75% yield. Significantly, the highly reactive

calcium complex reacted rapidly with tertiary bromides at -78°C. For example, the Grignard-type reaction of 1-bromoadamantane with the reactive calcium afforded 1-(1-adamantyl)cyclohexanol in 80% yield. The direct reaction of 1-bromoadamantane with metals is known to yield mainly reductive cleavage or dimerization.⁷ Accordingly, this method represents a significant new approach to the 1-metalloadamantane.

Reactions of aryl halides with the reactive calcium required slightly higher temperatures, up to -30°C for aryl bromides and up to -20°C for aryl chlorides.⁵ Surprisingly, the active calcium reacted readily with fluorobenzene at room temperature to form the corresponding organocalcium reagent in near quantitative yield.

Addition of copper(I) salts to the organocalcium reagents form novel organocalcium copper reagents that cross-couple with acid chlorides to yield ketones, and undergo conjugate addition to α,β -unsaturated ketones. The highly reactive calcium also reacts readily with 1,3-dienes to form bisorganocalcium complexes. Reaction of these calcium reagents with biselectrophiles generates a wide variety of complex cyclic hydrocarbons.⁵

1. Department of Chemistry, University of Nebraska, Lincoln, NE 68588-0304.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-(1-Adamantyl)cyclohexanol: Cyclohexanol, 1-tricyclo[3.3.1.1^{3,7}]dec-1-yl- (11); (84213-80-9)

Lithium (8,9); (7439-93-2)

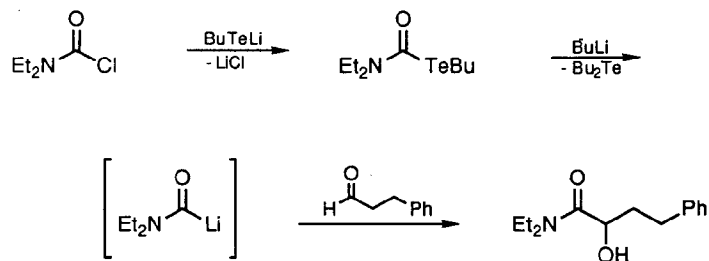
Biphenyl (8); 1,1'-Biphenyl (9); (92-52-4)

Calcium bromide (8,9); (7789-41-5)

1-Bromoadamantane: Adamantane, 1-bromo- (8); Tricyclo[3.3.1.1^{3,7}]decane, 1-bromo- (9); (768-90-1)

Cyclohexanone (8,9); (108-94-1)

SYNTHESIS OF AN α -HYDROXYAMIDE: N,N-DIETHYL-2-HYDROXY-4-PHENYLBUTANAMIDE. GENERATION OF N,N-DIETHYLCARBAMOYL LITHIUM VIA LITHIUM-TELLURIUM EXCHANGE AND ITS REACTION WITH 3-PHENYLPROPANAL (Benzenebutanamide, N,N-diethyl- α -hydroxy-)



Submitted by Nobuaki Kambe, Toru Inoue, and Noboru Sonoda.¹

Checked by Thomas G. Gant and Albert I. Meyers.

1. Procedure

Finely ground elemental tellurium (13.40 g, 105 mmol) (Note 1) and tetrahydrofuran (THF, 400 mL) (Note 2) are placed under nitrogen (N_2) in a flame-dried, 1-L, three-necked, round-bottomed flask equipped with a N_2 inlet, 100-mL pressure-equalizing dropping funnel, and a rubber septum. Into the mixture is added ca. 65.5 mL (1.6 N in hexane, ca. 105 mmol) of butyllithium (Note 3) dropwise with a syringe through the septum with stirring at room temperature until the mixture becomes a pale yellow homogeneous solution (Note 4). The solution is stirred for 10 min, then cooled to -78°C . Diethylcarbamoyl chloride (12.7 mL, 13.56 g, 100 mmol) (Note 5) is

injected through the septum with a syringe, and the solution is stirred at -78°C for 10 min. The cold bath is removed and the solution is allowed to warm to room temperature, then stirred for 1 hr. It is cooled again to -78°C , and 62.5 mL (1.6 N, 100 mmol) of butyllithium (Note 3) is injected over a 3-min period. After the solution is stirred at -78°C for 5 min, 13.42 g (100 mmol) of 3-phenylpropanal (Note 6) in 50 mL of THF is added from the dropping funnel over a 5-min period. The mixture is stirred for 10 min, warmed to room temperature, and stirred for 1 hr. The mixture is poured into 200 mL of a saturated ammonium chloride solution and extracted with diethyl ether (Et_2O) three times, 30 mL each. The combined organic layers are dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator at ca. 5 mm. The residual yellowish brown oil is chromatographed (silica gel, $\phi 50$ mm x 25 cm) (Note 7). The first, pale yellow fraction eluted with ca. 400 mL of hexane contains dibutyl telluride (23.62 g, 93% based on tellurium used) (Note 8). The next 500-mL fraction (eluted with hexane/ Et_2O , 10/1) contains by-products (Note 9). The desired product is eluted in the third fraction (ca. 500 mL of Et_2O) that is concentrated on a rotary evaporator and distilled to afford 19.35 g of N,N-diethyl-2-hydroxy-4-phenylbutanamide as a pale yellow viscous oil (bp 155 – 156°C at 0.6 mm, 82%) (Notes 10–12).

2. Notes

1. The submitters used tellurium pieces from Aldrich Chemical Company, Inc., that were ground with a mortar and pestle just before use. The checkers found that direct use of tellurium powder (~ 60 mesh, Aldrich Chemical Company, Inc.) gave similar results.

2. THF purchased from Wako Pure Chemical Industries, Ltd. (Japan) was used after distillation from Drynap. Drynap is a registered trademark of an alloy of sodium

(above 8 wt%) and lead (90 wt%) produced by Dojin Chemical Research Center, Ltd. (Japan). Although Drynap is not essential and any procedure can be used for drying THF provided that the THF is sufficiently dry for the usual reactions of organolithium compounds, the submitters often use this drying reagent when a large amount of solvent is needed since it is mild, much safer than sodium, and is easy to handle.

3. The submitters used butyllithium (1.6 M in hexane) from Nacalai Tesque Company, Ltd. (Japan). The checkers used butyllithium (1.6 M in hexane) from Aldrich Chemical Company, Inc.

4. The reaction is slightly exothermic. At this stage, lithium butanetelluroate (BuTeLi) is formed. (The checkers noted a deep red color as the BuLi was added.) BuTeLi should be prepared slightly in excess to the carbamoyl chloride. The subsequent step produces carbamoyllithium that may react with any excess carbamoyl chloride to give an undesired oxamide by-product.

5. The submitters used diethylcarbamoyl chloride from Aldrich Chemical Company, Inc., after fractional distillation. The checkers used the reagent without further purification with similar results.

6. The submitters used 3-phenylpropanal from Wako Pure Chemical Industries, Ltd., after distillation. The checkers used reagent obtained from Lancaster Synthesis without further purification with similar results.

7. The submitters used silica gel (mesh 100-200, BW-820 MH) from Fuji Davison Chemical, Ltd. (Japan). The checkers used radial chromatography (silica gel 60 PF 254 with gypsum, EM Science) with hexane/ethyl acetate (4/1) as eluent for small scale reactions. The checkers used flash chromatography (240 g of silica gel, grade 633, 47 x 61 microns, Davison Chemical) with hexane (1.5 L), hexane/ether (10/1, 1.5 L), and ether (1.5 L) as eluent for large scale reactions (100 mmol).

8. Elemental tellurium can be recovered from dibutyl telluride by the following procedure. Under nitrogen, naphthalene (4.0 g) and dry THF (100 mL) are placed in a

flame-dried, 200-mL, three-necked, round-bottomed flask equipped with a N₂ inlet, reflux condenser, and rubber septum. Sodium pieces (4.28 g, 186 mmol) are added to the solution slowly with stirring. After the solution turns deep blue, 4.50 g (18.6 mmol) of dibutyl telluride is added over a 3-min period with a syringe at room temperature. The rubber septum is replaced with a glass stopper and the mixture is refluxed for 2 days. The mixture is cooled to room temperature and ethanol is added very slowly until the sodium completely disappears. Air is bubbled into the solution with stirring for one day. The black solids that are obtained by filtration are washed well with Et₂O and dried (0.2 mm, 250°C, 4 hr) to give 2.22 g of elemental tellurium (93%, based on dibutyl telluride used). These conditions have not been optimized.

9. This fraction contains 3-phenylpropanal and 1-phenylheptan-3-ol that is formed by the addition of butyllithium to 3-phenylpropanal.

10. The physical properties are as follows: ¹H NMR (270 MHz, CDCl₃) δ: 1.09 (t, 3 H, J = 6.9), 1.10 (t, 3 H, J = 6.9), 1.72-1.94 (m, 2 H), 2.72-2.87 (m, 2 H), 2.98-3.13 (m, 2 H), 3.25 (dq, 1 H, J = 13.8, 6.9), 3.52 (dq, 1 H, J = 13.8, 6.9), 3.87 (d, 1 H, J = 7.8), 4.24 (ddd, 1 H, J = 7.8, 7.8, 2.9), 7.16-7.37 (m, 5 H); ¹³C NMR (68 MHz, CDCl₃) δ: 12.8, 14.0, 31.3, 37.4, 40.2, 40.8, 67.0, 120.0, 128.5, 128.6, 141.4, 173.6; IR (NaCl, neat) cm⁻¹: 3408, 1636. Anal. Calcd for C₁₄H₂₁NO₂: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.17; H, 9.08; N, 6.01.

11. Glassware is cleaned by soaking it overnight in a concd nitric acid bath.

12. When methyl benzoate was used as an electrophile instead of 3-phenylpropanal, N,N-diethylphenylglyoxylamide [Et₂NC(O)C(O)Ph] was obtained in a similar manner as a pale yellow viscous oil (bp 118-120°C at 0.2 mm, 13.40 g, 65 mmol, 65%), ¹H NMR (270 MHz, CDCl₃) δ: 1.15 (t, 3 H, J = 7.2), 1.29 (t, 3 H, J = 7.2), 3.24 (q, 2 H, J = 7.2), 3.56 (q, 2 H, J = 7.2), 7.50 (t, 2 H, J = 7.3), 7.63 (t, 1 H, J = 7.3), 7.94 (d, 2 H, J = 7.3); IR (NaCl, neat) cm⁻¹: 1681, 1636, 1448, 1232, 721.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Organic tellurium compounds react readily with organolithium reagents to give the thermodynamically more stable organolithium compounds via tellurium ate complexes. The lithium-tellurium exchange reaction proceeds quite rapidly at low temperatures, and can be used for the generation of a variety of organolithium compounds,²⁻⁵ including very reactive umpolung species, such as acyl-,³ aroyl-,³ and carbamoyllithiums.⁴ Among these, acyl- and aroyllithiums are kinetically very unstable, even at low temperatures, and dimerize quickly unless a suitable electrophile is present when generated. In contrast N,N-dialkylcarbamoyllithiums are potentially useful synthetically since they are stable in THF at -78°C and can be efficiently trapped with various electrophiles.⁴

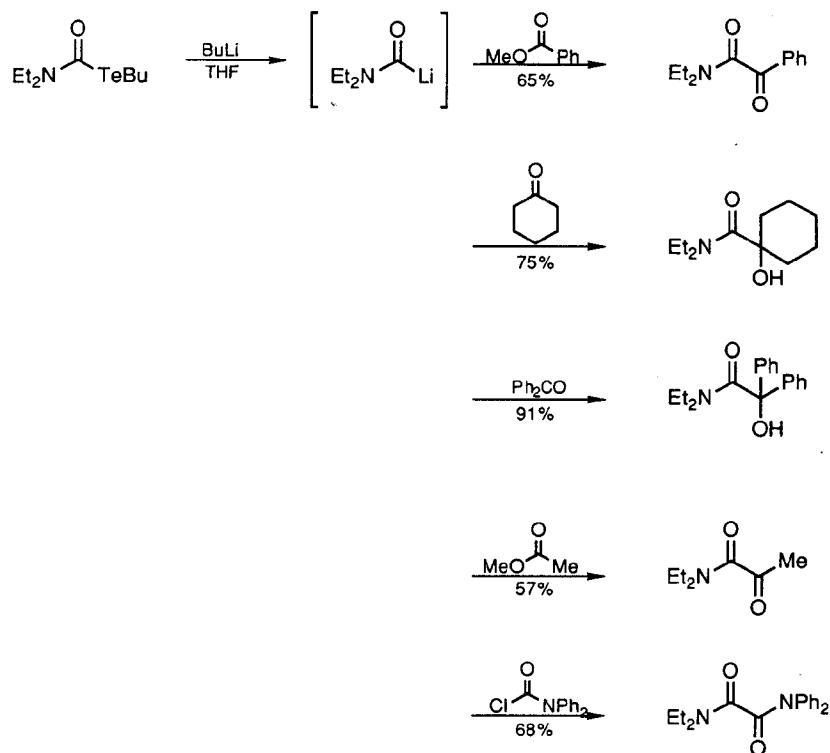
Carbamoyllithiums are attractive umpolung species that enable the straightforward introduction of carbamoyl moieties into organic molecules as nucleophiles. Although several methods have been reported for the generation of carbamoyllithiums, such as abstraction of the formyl hydrogen,⁶ insertion of carbon monoxide into lithium amides⁷ or lithium diaminocuprates,⁸ and transmetalation of a biscarbamoylmercury,⁹ these procedures have some disadvantages. Very few examples of hydrogen abstraction are reported, and satisfactory yields of the addition products are obtained only in the case of N,N-diisopropylcarbamoyllithium, or when the reaction is conducted in the presence of an electrophile. Reaction of carbon

monoxide (CO) with lithium amides often gave complex results arising from the incorporation of two CO molecules. Diaminocuprates do not react satisfactorily with CO under atmospheric pressure.

The lithium-tellurium exchange reaction illustrated here provides a useful alternative to known methods. The reaction can be used to produce various α -hydroxyamides by using aldehydes and ketones as the electrophiles. Trapping the generated carbamoyllithium compounds with esters affords α -ketoamides in good yields (Scheme 1). α -Ketoamides with an aliphatic substituent on the carbonyl carbon cannot be obtained by palladium-catalyzed double carbonylation.¹⁰ Successful trapping of N,N-diethylcarbamoyllithium with N,N-diphenylcarbamoyl chloride to give an unsymmetrical oxamide demonstrates a synthetic use of carbamoyllithiums as the umpolung species of carbamoyl halides. A limitation of this procedure may arise from elimination of CO from the carbamoyllithiums. This becomes appreciable when a carbamoyl halide with an aromatic substituent on the nitrogen is used as a starting material. A variety of N,N-dialkylcarbamoyllithiums, such as N,N-diethyl-, N,N-dimethyl-, and N,N-pentamethylenecarbamoyllithiums can, however, be generated efficiently by the lithium-tellurium exchange reactions and trapped with various electrophiles to give the corresponding adducts in good yields.²

The present procedure provides a convenient method for the generation of carbamoyllithiums from carbamoyl halides and is very useful synthetically for the introduction of carbamoyl groups into organic molecules.

Scheme 1



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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N,N-Diethyl-2-hydroxy-4-phenylbutanamide: Benzenebutanamide,

N,N-diethyl- α -hydroxy- (12); (134970-54-0)

3-Phenylpropanal: Hydrocinnamaldehyde (8); Benzenepropanal (9); (104-53-0)

Tellurium (8,9); (13494-80-9)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

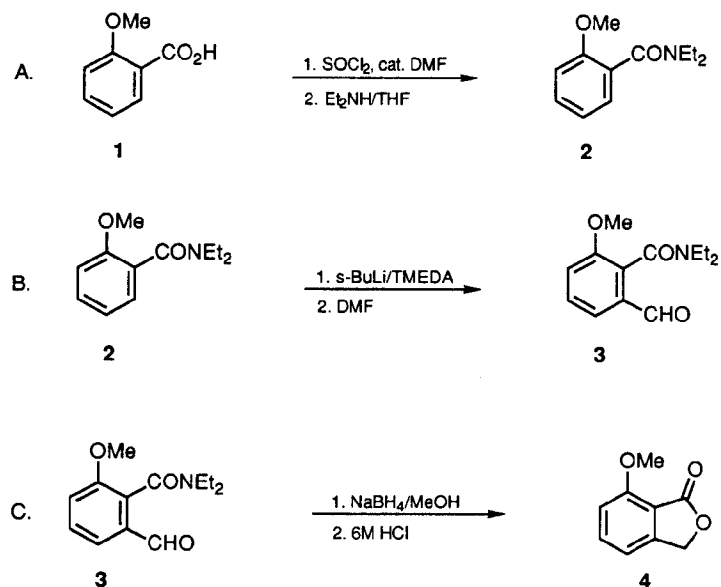
Diethylcarbamoyl chloride: Carbamic chloride, diethyl- (8,9); (88-10-8)

Dibutyl telluride: Butane, 1,1'-tellurobis- (9); (38788-38-4)

Naphthalene (8,9); (91-20-30)

7-METHOXYPHTHALIDE

(1(3H)-Isobenzofuranone, 7-methoxy-)



Submitted by X. Wang, S. O. de Silva, J. N. Reed, R. Billadeau, E. J. Griffen, A. Chan, and V. Snieckus.¹

Checked by Chris Limberakis and Stephen F. Martin.

1. Procedure

A. *N,N*-Diethyl-2-methoxybenzamide (2). An oven-dried, two-necked, 500-mL flask equipped with a septum cap, nitrogen bubbler, and magnetic stirrer is charged with 2-methoxybenzoic acid (20 g, 0.13 mol) (Note 1) under nitrogen. Thionyl chloride

(135 mL, 220 g, 1.85 mol) (Note 2) is added with stirring, resulting in slow effervescence. Dimethylformamide (DMF, 0.34 mL, 320 mg, 4.4 mmol) (Notes 3, 4) is added dropwise via syringe after which effervescence becomes much more vigorous (*Caution: Sulfur dioxide and hydrogen chloride are evolved*). The solution is stirred for 0.5 hr, at which time no further effervescence is visible. Half of the thionyl chloride is removed under reduced pressure on a rotary evaporator, toluene (100 mL) is added, and the mixture is evaporated to dryness. A further 100 mL of toluene is added and the process of evaporation is repeated twice more to ensure complete removal of all excess thionyl chloride (Note 5). The colorless oil is dissolved in dry tetrahydrofuran (THF, 150 mL) (Note 6), the resulting solution is cooled in an ice water bath, and treated slowly with diethylamine (50 mL, 35.3 g, 0.48 mol) (Note 7), with stirring to prevent the reaction from becoming too vigorous. A copious white precipitate forms.

When all the diethylamine has been added the mixture is stirred for a further 10 min and then concentrated under reduced pressure. The residue is dissolved in methylene chloride (200 mL), washed with water (2 x 200 mL) and saturated brine (2 x 50 mL), and concentrated under reduced pressure to give an orange oil. The oil is distilled at reduced pressure to give 23.5-24.5 g (86-90%) of N,N-diethyl-2-methoxybenzamide (118-120°C/0.1 mm) as a straw-colored liquid.

B. *N,N*-Diethyl-2-formyl-6-methoxybenzamide (3). An oven-dried, three-necked, 1-L flask equipped with a 100-mL pressure equalizing dropping funnel, nitrogen bubbler, internal low temperature thermometer pocket, and overhead stirrer is flamed under reduced pressure and allowed to cool under a stream of nitrogen. The flask is charged with 500 mL of THF (Note 6) and cooled to an internal temperature of -72°C. N,N,N',N'-Tetramethylethylenediamine (TMEDA) (Note 8) (23.5 mL, 0.156 mol) followed by 128.7 mL (0.157 mmol) of 1.22 M sec-butyllithium in cyclohexane (Note 9) are then added. The internal temperature rises a little as the reagents are added. The fluorescent yellow solution is allowed to recool to an internal temperature of -73°C.

N,N-Diethyl-2-methoxybenzamide (2) 24.9 g (0.121 mmol) is dissolved in 100 mL of THF and added dropwise via the dropping funnel, while the internal temperature is maintained below -68°C. The solution is stirred for 1 hr during which time the color changes from fluorescent yellow to yellow with a white precipitate. Dimethylformamide (DMF, 11.2 mL) is added via the dropping funnel, and the cooling bath is removed after 2 min. The solution is allowed to warm to room temperature over 16 hr after which time the solution is yellow. The reaction mixture is concentrated under reduced pressure to 150 mL, and the residue is cooled to 0°C and made acidic (pH 4-5) by the addition of 90 mL of 6 M aqueous hydrochloric acid. The solution is extracted with ethyl acetate (5 x 100 mL) (Note 10), the combined organic layers are washed with water (100 mL) and brine (2 x 200 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residual, yellow oil is dried overnight under reduced pressure to give 26.9 g of crude product ² (Note 11).

C. *7-Methoxyphthalide* (4). The crude product from Step B (26.9 g), in a 1-L, one-necked, round-bottomed flask with a magnetic stirring bar, is dissolved in 465 mL of absolute methanol (Note 12). To this solution, cooled to 0°C, is added 7.4 g (0.20 mol) of powdered sodium borohydride, in small portions (Note 13), and the mixture is stirred at room temperature for 18 hr. The reaction mixture is cooled in an ice water bath and taken to pH 4-5 with about 35 mL of 6 M aqueous hydrochloric acid. A further 48 mL (0.288 mol) of 6 M hydrochloric acid is added, the flask is fitted with a reflux condenser and the reaction mixture is heated under reflux for 12 hr. The reaction mixture is then allowed to cool to room temperature and most of the methanol is evaporated under aspirator pressure. The residue is dissolved in 400 mL of methylene chloride, the phases are separated, and the organic fraction is washed with saturated ammonium chloride (3 x 200 mL) and water (1 x 100 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The pale yellow solid is recrystallized from ethyl acetate-hexane (1:1) (Note 10) to give 15.4 g

(81% overall from 2) of 7-methoxyphthalide, mp 106-108°C, lit³ mp 107-109°C (Note 14).

2. Notes

1. 2-Methoxybenzoic acid, purchased from Lancaster Synthesis Ltd., was used as received.

2. Thionyl chloride, purchased from J.T.Baker Ltd., was used as received.

3. Dimethylformamide was distilled from calcium hydride and stored over 4 Å molecular sieves under nitrogen.

4. The use of DMF to accelerate the formation of acid chlorides from carboxylic acids has been reviewed previously,⁴ and is believed to occur via an imidoyl chloride intermediate.⁵

5. The removal of excess thionyl chloride by formation of an azeotrope with benzene was used in a previous *Organic Syntheses* procedure,⁶ however, toluene is much less toxic than benzene and is therefore recommended.

6. Tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl at atmospheric pressure under nitrogen.

7. The use of acid chlorides in the preparation of amides has been reviewed.⁷ The diethylamine was distilled from calcium hydride prior to use.

8. N,N,N',N'-Tetramethylethylenediamine was distilled from calcium hydride and stored under nitrogen.

9. sec-Butyllithium purchased from Aldrich Chemical Company, Inc., was standardized by titration using 2,5-dimethoxybenzyl alcohol as indicator.⁸

10. Reagent grade ethyl acetate, methylene chloride, and hexane purchased from British Drug House, Inc., were distilled before use.

11. N,N-Diethyl-2-methoxy-3-formylbenzamide may be purified by silica gel (mesh 230-400) column chromatography using ethyl acetate-hexane (1:1) eluent. The compound shows the following physical and spectral data: bp 134-136°C (0.05 mm); IR (CHCl₃) ν (max) cm⁻¹: 1705, 1620; ¹H NMR (CDCl₃) δ : 1.01 (t, 3 H, J = 7.2), 1.29 (t, 3 H, J = 7.2), 3.11 (q, 2 H, J = 7.2), 3.49-3.61 (m, 1 H), 3.67-3.82 (m, 1 H), 3.86 (s, 3 H), 7.16 (dd, 1 H, J = 1.3, 7.8), 7.43-7.55 (m, 2 H), 9.99 (s, 1 H); mass spectrum, m/z (rel intensity) 235 (M⁺, 5), 206 (100); Anal. Calcd for C₁₃H₁₇NO₃: C, 66.36; H, 7.28; N, 5.95. Found: C, 67.44; H, 7.69; N, 5.75.

12. Absolute methanol, purchased from British Drug House, Inc., was used as received.

13. Sodium borohydride, purchased from Aldrich Chemical Company, Inc., was used as received.

14. 7-Methoxyphthalide shows the following spectral data: IR (CHCl₃) ν (max) cm⁻¹: 1755; ¹H NMR (CDCl₃) δ : 4.01 (s, 3 H), 5.23 (s, 2 H), 6.95 (d, 1 H, J = 8.2), 7.01 (d, 1 H, J = 8.2), 7.65 (t, 1 H, J = 8.2).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

7-Methoxyphthalide has also been prepared by nonregioselective bromination of substituted benzenes,⁹ by L-Selectride reduction^{10,11} of 3-methoxyphthalic anhydride,^{12,13} by metalation of 3-methoxybenzyl alcohol^{14,15} and its chromium

tricarbonyl complex,^{15,16} by metalation of N,N-dimethyl-3-methoxybenzylamine,^{17,18} and by Diels-Alder reaction of methoxycyclohexadiene with propargylic esters.¹⁹ The isomeric 4-methoxyphthalide, that is also available by the present method² has been prepared by methods that, in part, overlap those used for the synthesis of 7-methoxyphthalide: by bromination of o-toluic acids and o-xylenes,^{9,19,20} by metal hydride reduction²¹ of 3-methoxyphthalic anhydride, and by metalation of 3-methoxyphenyloxazoline.²² Some of these methods^{19,23,24} as well as others, have been used for the preparation of a variety of other methoxy-substituted phthalides.

The directed ortho metalation reaction has been widely applied for the preparation of phthalides.²⁵⁻²⁷ Since it lends itself well to the regiospecific construction of contiguously substituted aromatic compounds, the approach via metalation of N,N-diethylbenzamides has been particularly extensively adapted.^{28,29} The present procedure uses a readily available and inexpensive starting benzoic acid, proceeds in reproducible, high yields, does not require chromatographic separation, and furnishes usually crystalline phthalide products in high purity. A comparison of yields shows that 7-methoxyphthalide has been obtained by metalation of 3-methoxybenzyl alcohol (78%),¹⁴ Diels-Alder reaction of methoxycyclohexadiene with a propargylic ester (55%),¹⁹ and reduction of 3-methoxyphthalic anhydride (quantitative).¹⁰ The latter two methods are lengthy and require a several stage synthesis of precursors. The metalation method complements the present procedure, but has not been optimized. Based on the reported preparation of 4-methoxyphthalide,²² the synthesis of 7-methoxyphthalide via metalation of 2-methoxyphenyloxazoline would undoubtedly be successfully achieved, but would require the more expensive oxazoline.

Phthalides constitute a relatively minor class of natural products.^{25,30} However, their value as synthetic intermediates is shown by an extensive list of applications. The use of phthalides derived from metalation of N,N-diethylbenzamides in the

synthesis of anthraquinones, anthracyclones, isocoumarins, fluorenones, phenanthrenes, several classes of alkaloids, and polycyclic aromatic hydrocarbons has been summarized.²⁷ Phthalides derived by other methods have served as intermediates in the construction of anthraquinones,^{15,20,31-33} benzophenones,³⁴ cervicarcin,³⁵ dibenzofurans,^{36,37} lignans,²² naphthalenes and naphthoquinones,^{15,24,38-41} and polyketides.^{14,42,43}

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

7-Methoxyphthalide, Phthalide, 7-methoxy- (8); 1(3H)-Isobenzofuranone, 7-methoxy- (9); (28281-58-5)

N,N-Diethyl-2-methoxybenzamide: Benzamide, N,N-diethyl-2-methoxy- (9): (51674-10-3)

2-Methoxybenzoic acid: o-Anisic acid (8); Benzoic acid, 2-methoxy- (9); (579-75-9)

Thionyl chloride (8,9); (7719-09-7)

N,N-Dimethylformamide: Formamide, N,N-dimethyl- (8,9); (68-12-2)

Toluene (8); Benzene, methyl- (9); (108-88-3)

Tetrahydrofuran (8,9); (109-99-9)

Diethylamine (8); Ethanamine, N-ethyl- (9); (109-89-7)

N,N-Diethyl-2-formyl-6-methoxybenzamide: Benzamide,

N,N-diethyl-2-formyl-6-methoxy- (10); (70946-17-7)

N,N,N',N'-Tetramethylethylenediamine: Ethylenediamine, N,N,N',N'-tetramethyl- (8);

1,2-Ethanediamine, N,N,N',N'-tetramethyl- (9); (110-18-9)

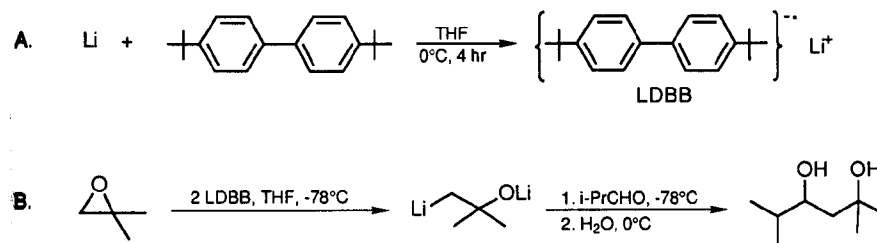
sec-Butyllithium: Lithium, sec-butyl- (8); Lithium, (1-methylpropyl)- (9); (598-30-1)

Sodium borohydride: Borate (1-), tetrahydro-, sodium (8,9); (16940-66-2)

1,3-DIOLS FROM LITHIUM β -LITHIOALKOXIDES GENERATED BY THE REDUCTIVE LITHIATION OF EPOXIDES:

2,5-DIMETHYL-2,4-HEXANEDIOL

(2,4-Hexanediol, 2,5-dimethyl-)



Submitted by Boguslaw Mudryk and Theodore Cohen.¹

Checked by Hiroaki Hibino and Hisashi Yamamoto.

1. Procedure

A. *Lithium 4,4'-di-tert-butylbiphenylide (LDBB).*² An oven-dried, three-necked round-bottomed, 1-L flask, equipped with a Teflon-coated magnetic stirring bar (Note 1), small, pressure-equalizing funnel, low temperature thermometer, and a gas inlet, is flushed with dry argon. The apparatus is charged with 600 mL (Note 2) of dry tetrahydrofuran (THF) (Note 3) and 56 g (0.21 mol) of 4,4'-di-tert-butylbiphenyl (DBB) (Note 4). Lithium pieces (1.5 g, 0.22 M) (Note 5) are then introduced under argon into the well-stirred DBB solution in THF at room temperature. As soon as the dark blue-greenish color of the LDBB solution appears, the flask is immersed in an ice-cold bath (Note 6) and the solution is vigorously stirred for 4 hr at 0°C. The LDBB solution so prepared is ready for further use.

B. 2,5-Dimethyl-2,4-hexanediol. Isobutylene oxide (7.2 g, 0.10 mol) (Note 7) is added dropwise from the pressure-equalizing funnel to the LDBB solution in THF at -78°C at such a rate (the addition lasts for 8-12 min) that the temperature inside the flask does not exceed -78°C. After all the epoxide has been added (8-11 min), the solution becomes deep red. After 5 more minutes of stirring, isobutyraldehyde (7.2 g, 0.10 mol) (Note 8) is added dropwise within 5 min. The mixture is stirred for 1 hr at -78°C; it is allowed to reach 0°C by removing the cold bath, and finally is quenched with water (100 mL). After the mixture is extracted with ether (1 x 300 mL, 2 x 100 mL), the combined organic layers are dried with anhydrous magnesium sulfate (MgSO₄) and the solvents are evaporated under reduced pressure. The addition of cold methanol (250 mL) results in precipitation of most of the DBB as a white solid. The latter is crushed in methanol to a fine powder with a spatula and the methanolic suspension is placed in a freezer for 1 hr. The solid is filtered, washed with 50-250 mL of ice-cold methanol and air-dried; the yield is 49.1 g (88% recovery). The methanol is evaporated under reduced pressure and the product is isolated by flash chromatography (25% ethyl acetate in hexane as the eluent); yield 11.3-12.3 g (77-88%). An additional vacuum distillation at 104-105°C/13 mm provides >99% pure product, yield 9.2 g (62-66%) (Notes 9,10).

2. Notes

1. A large size, football-shaped stirring bar is required to provide effective stirring.
2. At least this amount of THF is needed to ensure that the final LDBB concentration is below 0.4 M. More concentrated solutions solidify at -78°C.

3. Tetrahydrofuran was purchased from Wako Pure Chemical Industries, Ltd., Osaka, Japan (also available from Fisher Scientific Co.) and distilled from potassium benzophenone ketyl before use.

4. 4,4'-Di-tert-butylbiphenyl (97%) was used as purchased from Aldrich Chemical Company, Inc.

5. The submitters used lithium (99.9%, Alfa Products) as a ribbon (0.28 mm thick, 25 mm wide). [The checkers used lithium (99.9%, Aldrich Chemical Company, Inc.) as a wire (3.2 mm diam. in mineral oil).] Its surface was cleaned by scraping off the lithium oxide and nitride with an X-Acto knife under mineral oil. The ribbon was then cut into 20-30 mg pieces that were rinsed with pentane before use.

6. A 2.5-L Dewar flask (I.D. = 170 mm) was employed for the 0°C and -78°C cooling baths.

7. Isobutylene oxide was used as purchased from Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan (also available from TCI America).

8. Isobutyraldehyde purchased from Wako Pure Chemical Industries, Ltd., Osaka, Japan (also available from Aldrich Chemical Company, Inc.) was purified by distillation immediately before use.

9. The diol was characterized by ¹H NMR and ¹³C NMR; ¹H NMR (200 MHz, CDCl₃) δ: 0.92 (d, J = 6.8) and 0.93 (d, J = 6.8) (6 H), 1.28 (s) and 1.31 (s) (6 H), 1.49 (dd, 1 H, J = 2.5 and 14.5), 1.57-1.69 (m, 2 H), 3.00 (s, 2 H), 3.77 (ddd, 1 H, J = 2.5, 5.4 and 10.3); ¹³C NMR (50 MHz, CDCl₃) δ: 17.4, 17.6, 27.0, 31.5, 33.7, 43.2, 71.0, 73.8.

10. The submitters have employed the procedure described above for some other epoxides. The yields of diols resulting from trapping the intermediate β-lithioalkoxides with aldehydes were generally lower than in the small-scale experiments.³ This may be caused in part by the longer period of addition of the epoxide that is required to maintain a low temperature, thus allowing more time for destruction of the dianion that is being generated. In cases where the alkoxide group

is not tertiary, the product yield is lowered by transfer of the carbinol hydride ion to the aldehyde to produce a new alkoxide and an enolate ion. Thus, propylene oxide, after reductive cleavage with LDBB and trapping with isobutyraldehyde or *p*-anisaldehyde, provided 5-methyl-2,4-hexanediol in 40-50% yield or 1-*p*-anisyl-1,3-butanediol in 44% yield, respectively (in both cases about equal mixtures of diastereoisomers were obtained). The cyclohexene oxide-derived dianion, when trapped with isobutyraldehyde, gave 2-(1-hydroxy-2-methylpropyl)cyclohexanol in 71% yield as a mixture of only partially separable isomers in the ratio 15:11:39:35.

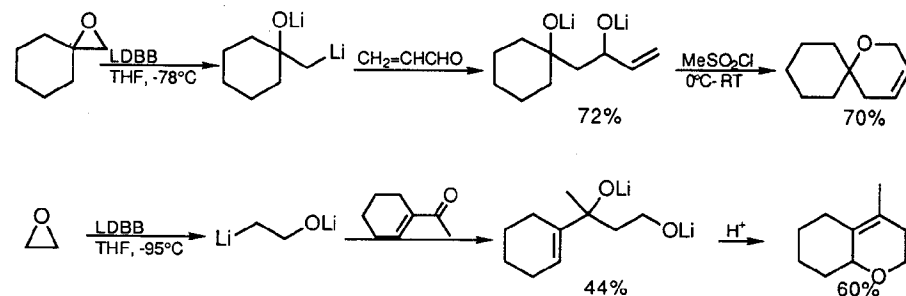
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories;" National Academy Press; Washington DC, 1983.

3. Discussion

The present example represents a larger-scale version of a recently described synthesis of 1,3-diols from aldehydes and lithium β -lithioalkoxides.^{3,4} These useful dianions can be conveniently generated from epoxides at -78°C in THF by the reductive cleavage of the carbon-oxygen bond using the powerful reducing agent LDBB. Previously reported reductions of epoxides with alkali metals were carried out in protic media and therefore the intermediate dianions were immediately destroyed by protonation by the solvent.⁵ The reductive opening of 2,2-dialkyl epoxides is highly regioselective and always leads to the less-substituted organolithium and the more-substituted alcoholate.^{3,6} The procedure can also be useful for monosubstituted epoxides, provided that they are employed in excess toward the aldehyde. They are

cleaved mainly to produce the primary organolithiums, but they do undergo a minor degree of ring cleavage yielding the secondary organolithiums, which are known to expel lithium oxide rapidly⁷ to form easily removable olefins. Lithium β -lithioalkoxides can be trapped at -78°C with a variety of aldehydes and ketones yielding 1,3-diols with different substitution patterns.³ When conjugated enones are employed as electrophiles, unsaturated cyclic ethers can be produced in one pot by activating the allylic hydroxyl group toward displacement by the other hydroxyl group with allylic inversion:³



Although lithium β -lithioalkoxides can also be generated from β -halo alcohols by deprotonation and subsequent reductive lithiation of the carbon-halogen bond^{7a,8} or from β -halo ketones by organolithium addition to the carbonyl group followed by reductive lithiation,⁸ the current method is more direct as well as more convenient, since epoxides are readily available either commercially or by a variety of procedures.

Despite the lack of diastereoselectivity and the moderate yields, the present procedure complements other syntheses of 1,3-diols such as hydride reductions of β -diketones,⁹ β -hydroxy ketones¹⁰ and β -keto esters,¹¹ or the opening of 2,3-epoxy alcohols¹² and 3,4-epoxy alcohols¹³ with Lipshutz cuprates.

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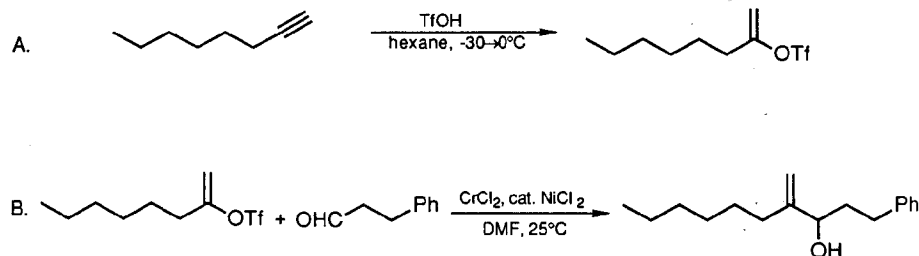
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2,5-Dimethyl-2,4-hexanediol: 2,4-Hexanediol, 2,5-dimethyl- (9); (3899-89-6)
 Lithium 4,4'-di-tert-butylbiphenylide: 1,1'-Biphenyl, 4,4'-bis(1,1-dimethylethyl)-, radical ion (1-), lithium (9); (61217-61-6)
 4,4'-Di-tert-butylbiphenyl: Biphenyl, 4,4'-di-tert-butyl- (8); 1,1'-Biphenyl, 4,4'-bis(1,1-dimethylethyl)- (9); (1625-91-8)
 Lithium (8,9); (7439-93-2)
 Isobutylene oxide: Propane, 1,2-epoxy-2-methyl- (8); Oxirane, 2,2-dimethyl- (9); (588-30-5)
 Isobutyraldehyde (8); Propanal, 2-methyl- (9); (78-84-2)

**PREPARATION AND REACTIONS OF ALKENYLCHROMIUM REAGENTS:
2-HEXYL-5-PHENYL-1-PENTEN-3-OL**



Submitted by Kazuhiko Takai, Koichi Sakogawa, Yasutaka Kataoka, Koichiro Oshima, and Kiitiro Utimoto.¹

Checked by Tadahiro Takemoto and Larry E. Overman.

1. Procedure

A. 1-Hexylethenyl triflate (Note 1). A dry, 300-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, nitrogen inlet, rubber septum, and a 100-mL, graduated, pressure-equalizing addition funnel that is sealed with a rubber septum. The flask is charged with 1-octyne (11 g, 0.10 mol, Note 2) and dry hexane (100 mL, Note 3). The contents of the flask are cooled to -30°C (dry ice-methanol). The addition funnel is charged with neat trifluoromethanesulfonic acid (TfOH, 4.9 mL, 55 mmol, Note 4) which is then added dropwise at -30°C to the stirring solution over a period of 30 min. The addition funnel is rinsed with dry hexane (10 mL). The dark brown solution is warmed to 0°C and stirred at 0°C for 10 min. Saturated sodium bicarbonate (NaHCO_3) solution (20 mL) is introduced at 0°C to the

reaction mixture. The organic layer is separated, washed with additional NaHCO_3 solution (2 x 50 mL), and then dried over potassium carbonate. The solvent is removed with a rotary evaporator. The crude product is distilled using a short-path still to give 9.6-10.4 g (67-73%) of 1-hexylethenyl triflate (Note 5), bp $97-98^{\circ}\text{C}$ at 19 mm.

B. 2-Hexyl-5-phenyl-1-penten-3-ol. A dry, 500-mL, four-necked, round-bottomed flask is equipped with a mechanical stirring bar, nitrogen inlet, rubber septum, and a 100-mL, graduated, pressure-equalizing addition funnel that is sealed with a rubber septum. In the flask are placed anhydrous chromium(II) chloride (CrCl_2) (10 g, 80 mmol, Note 6) and anhydrous nickel(II) chloride (NiCl_2) (52 mg, 0.40 mmol, Note 7) under an argon atmosphere. The flask is cooled to 0°C and dry, oxygen-free *N,N*-dimethylformamide (DMF, 250 mL, Note 8) is added to the flask with stirring. The salts are dissolved in a slightly exothermic process. The mixture is stirred at 0°C for 10 min. To the CrCl_2 - NiCl_2 reagent at 25°C is added a solution of 3-phenylpropanal (2.7 g, 20 mmol, Note 9) in DMF (20 mL) by syringe. A solution of 1-hexylethenyl triflate (10 g, 40 mmol, Note 5) in DMF (60 mL) is added at 25°C through the addition funnel over a period of 5 min. The entire mixture is stirred at 25°C for 30 min. The reaction mixture is diluted with ether (200 mL), poured into ice-cooled water (400 mL), and extracted with ether (3 x 200 mL) repeatedly. The combined extracts are washed with aqueous sodium chloride solution (150 mL), dried over anhydrous sodium sulfate, and concentrated with a rotary evaporator (25°C , water bath). The crude product is distilled using a short-path still to give 4.0-4.6 g (82-94%) of 2-hexyl-5-phenyl-1-penten-3-ol, bp $109-111^{\circ}\text{C}$ at 0.11 mm (Notes 10 and 11).

2. Notes

1. This procedure was reported by P. J. Stang and R. H. Summerville.²
2. 1-Octyne was distilled, bp $125-126^{\circ}\text{C}$.

3. Hexane was freshly distilled from sodium or calcium hydride.
4. Trifluoromethanesulfonic acid was distilled, bp 72-73°C at 20 mm.
5. The distilled triflate contained 3-9% of isomers, that were confirmed by capillary GLPC (Silicone OV-17, 50 m, 105°C, 1-hexylethenyl triflate: t_R = 11.1 min; isomers: t_R = 11.4 and 12.4 min) and ^1H NMR analysis. Because the isomers did not interfere with the second reaction, the triflate was employed without further purification. Spectral data of the distilled triflate was as follows: IR (neat) cm^{-1} : 2954, 2930, 2858, 1671, 1419, 1250, 1213, 1141, 943, 899, 703, 610; ^1H NMR (CDCl_3) δ : 0.89 (t, 3 H, J = 6.9), 1.2-1.4 (m, 6 H), 1.5-1.6 (m, 2 H), 2.34 (t, 2 H, J = 7.5), 4.93 (dt, 1 H, J = 3.5, 1.0), 5.08 (d, 1 H, J = 3.5), ^1H NMR peaks of the impurities appeared at δ 2.05-2.20 and 5.18-5.55; ^{13}C NMR (CDCl_3) δ : 13.9, 22.4, 25.9, 28.3, 31.3, 33.8, 103.9, 118.5 (q, J = 320, CF_3), 157.1.
6. Chromium(II) chloride (95% purity) was purchased from Aldrich Chemical Company, Inc., and used without further purification. The salt is easily oxidized and should be handled under an inert atmosphere.
7. Anhydrous nickel(II) chloride was purchased from Nacalai Tesque Co. and used without further purification. The salt is hygroscopic and should be handled under an inert atmosphere.
8. N,N-Dimethylformamide was refluxed in the presence of calcium sulfate under reduced pressure and distilled with nitrogen bubbling from a capillary, bp 76°C at 39 mm.
9. 3-Phenylpropanal was freshly distilled, bp 97-98°C at 12 mm.
10. The pot residue can be bulb-to-bulb distilled to give an additional 0.5-1 g of product to bring the combined yields to 94-95%. 2-Hexyl-5-phenyl-1-penten-3-ol has the following properties: R_f = 0.29 (ethyl acetate/hexane = 1/10); IR (neat) cm^{-1} : 3340, 3024, 2924, 2854, 1647, 1600, 1497, 1456, 1017, 900, 741, 697; ^1H NMR (CDCl_3) δ : 0.88 (t, 3 H, J = 6.8), 1.2-1.4 (m, 8 H), 1.7-2.2 (m, 5 H), 2.62 (ddd, 1 H, J = 6.6, 9.6,

13.9), 2.74 (ddd, 1 H, J = 6.1, 9.6, 13.9), 4.10 (dd, 1 H, J = 5.1, 7.5), 4.87 (d, 1 H, J = 1.5), 5.04 (s 1 H), 7.1-7.4 (m, 5 H). ^{13}C NMR (CDCl_3) δ : 14.1, 22.6, 27.9, 29.2, 31.4, 31.7, 31.9, 37.0, 74.7, 109.3, 125.7, 128.3, 128.4, 142.0, 152.0.

11. The following ratio of reactants, aldehyde/alkenyl triflate/ $\text{CrCl}_2/\text{NiCl}_2$ = 1/2/4/0.02 gave the best results. When the ratio of reagents was reduced to aldehyde/alkenyl triflate/ $\text{CrCl}_2/\text{NiCl}_2$ = 1/1/2/0.01, the reaction proceeded slowly. When the reaction was carried out at 25°C for 2 hr, 65% of the 2-hexyl-5-phenyl-1-penten-3-ol was isolated and 14% (GLPC analysis) of the 3-phenylpropanal remained.

Waste Disposal Information

Compounds of chromium and nickel are toxic. The aqueous layers from Step B and any other waste materials should be disposed of properly (see Preface).

3. Discussion

In the synthesis of a complex molecule, it is sometimes necessary to prepare an organometallic reagent under mild conditions. Because of the strong basicity and nucleophilicity of alkenyllithium and alkenylmagnesium compounds, only a few electrophilic functional groups are stable under the reaction conditions.³ In contrast, the alkenylchromium reagents described here react with aldehydes to give adducts in good to excellent yields in the presence of ketones, esters, amides, acetals, ethers, silyl ethers, and nitriles.⁴⁻⁶ The method is especially effective for highly oxygenated molecules.⁵ Intramolecular cyclization of iodo aldehydes leading to 13-membered lactones has also been reported.⁷

Addition of a catalytic amount of NiCl_2 to CrCl_2 is essential for the formation of alkenylchromium reagents.⁴⁻⁶ However, a substantial amount of 1,3-diene, the coupling product of the alkenyl iodide, is produced if a higher content of NiCl_2 is employed.^{8,9}

Reduction of alkenyl iodides and bromides to alkenylchromium reagents with CrCl_2 proceeds smoothly under the same conditions.⁴⁻⁶ Several examples of the Grignard-type addition of alkenyl halides and triflates to aldehydes with the combination of CrCl_2 and NiCl_2 are shown in the Table. Iodoalkenes are more reactive than bromoalkenes (compare run 1 and 2). In the case of an α,β -unsaturated aldehyde, the 1,2-addition product is the main product (run 4). The alkenylchromium reagent adds to an aldehyde group selectively (runs 5-7), as do allyl¹⁰ and alkynylchromium reagents.¹¹ Steric interaction of substituents at a position cis to halogen causes cis-trans isomerization in some cases.⁹ For example, while the reaction of (E)- and (Z)-2-bromostyrene and benzaldehyde proceeded stereospecifically (runs 8 and 9), both (E)- and (Z)-2-iodo-1-phenyl-1-propene reacted with benzaldehyde to give (E)-1,3-diphenyl-2-methyl-2-propen-1-ol as the sole product (runs 10 and 11). The regiochemistry of double bonds is maintained during the coupling reaction. The CrCl_2 - NiCl_2 system is also effective for the addition of iodobenzene to an aldehyde (run 12).⁶

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TABLE
GRIGNARD-TYPE COUPLING REACTIONS BETWEEN ALKENYL HALIDES (OR TRIFLATES)
AND ALDEHYDES, MEDIATED BY THE CrCl_2 - NiCl_2 SYSTEM^a

$\text{R}^1\text{C}(\text{CH}_3)=\text{CHX} + \text{R}^2\text{CHO} \xrightarrow[\text{DMF, 25}^\circ\text{C}]{\text{CrCl}_2, \text{cat. NiCl}_2} \text{R}^1\text{C}(\text{CH}_3)=\text{CHCH}(\text{R}^2)\text{OH}$					
Run	Alkenyl Halide (or Triflate)	Aldehyde	Time hr	Product	Yield ^b %
1		$n\text{-C}_8\text{H}_{17}\text{CHO}$	0.25		100
2		$n\text{-C}_8\text{H}_{17}\text{CHO}$	3		62
3	$\text{BuC}(\text{CH}_3)=\text{CHOTf}$	$n\text{-C}_8\text{H}_{17}\text{CHO}$	3		81
4		$(E)\text{-PrCH=CHCHO}$	4		64
5			1		87
6			2		78
7		PhCOMe	6	(recovery of PhCOMe , 87%) ^c	
8		PhCHO	1		82
9		PhCHO	1		78
10		PhCHO	3		91 ^d
11		PhCHO	3		90 ^d
12	PhI	$n\text{-C}_8\text{H}_{17}\text{CHO}$	3		83

Table (contd.)

^aA mixture of an alkenyl halide (or alkenyl triflate, 2.0 mmol) and an aldehyde (1.0 mmol) was treated at 25°C with CrCl_2 (4.0 mmol) and NiCl_2 (0.02 mmol) in DMF.

^bProducts are isolated by column chromatography on silica gel. ^cThe reaction mixture was heated at 60°C. ^dThe absence of (Z)-isomer was confirmed by GLPC (Silicone SE-30) and NMR analysis.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Hexylethenyl triflates: Methanesulfonic acid, trifluoro-, 1-methyleneheptyl ester (11);
(98747-02-5)

1-Octyne (8,9); (629-05-0)

Hexane (8,9); (110-54-3)

Trifluoromethanesulfonic acid: Methanesulfonic acid, trifluoro- (8,9); (1493-13-6)

Chromium(II) chloride, anhydrous: Chromium chloride (8,9); (10049-05-5)

Nickel(II) chloride, anhydrous: Nickel chloride (8,9); (7718-54-9)

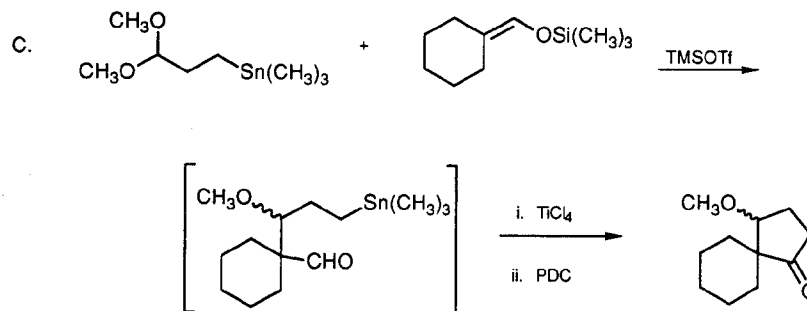
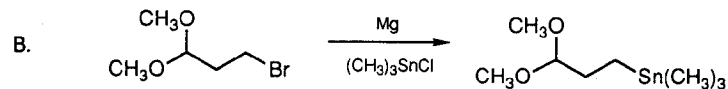
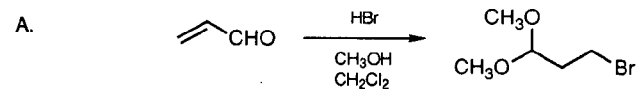
N,N-Dimethylformamide: Formamide, N,N-dimethyl- (8,9); (68-12-2)

3-Phenylpropionaldehyde: Hydrocinnamaldehyde (8); Benzenepropanal (9);
(104-53-0)

SPIROANNELETION OF ENOL SILANES:

2-OXO-5-METHOXYSPIRO[5.4]DECANE

(Spiro[4.5]decan-1-one, 4-methoxy-)



Submitted by Thomas V. Lee^{1a} and John R. Porter.^{1b}

Checked by Joseph L. Kent and Robert K. Boeckman, Jr.

1. Procedure

CAUTION! Many organotin compounds are known to be highly toxic² (Note 1), and hydrogen bromide (HBr), titanium tetrachloride (TiCl₄), and trimethylsilyl trifluoromethanesulfonate (TMSOTf) are corrosive. Steps A-C should be performed in an efficient fume hood while wearing gloves and adequate eye protection.

A. *1-Bromo-3,3-dimethoxypropane* (Note 2). Into a flame-dried, tared, 1-L, round-bottomed flask containing 500 mL of methylene chloride (CH₂Cl₂) (Note 3) at 0°C is bubbled anhydrous hydrogen bromide for approximately 15 min (33.0 g, 0.408 mol of HBr absorbed) (Notes 4,5). Acrolein (22.9 g, 27.2 mL, 0.408 mol) is added rapidly (30 sec) via syringe to the stirred solution (Note 6). After 2 min, a solution of 86.6 g (89.3 mL, 0.816 mol) of trimethyl orthoformate (Note 7) in methanol (100 mL) is introduced into the reaction mixture via cannula over 5 min. The reaction mixture is stirred for 10 min at 0°C, and solid anhydrous calcium carbonate (12.0 g, 0.120 mol) is then added in one portion. The reaction mixture is stirred for an additional 1 hr, the solution is filtered, and the filtrate concentrated under reduced pressure to ca. 50 mL. The residue is distilled through a 25-cm Vigreux column under reduced pressure to give, after a forerun of variable amount (~10 mL) (Note 8), 38.8 g (52%) of 1-bromo-3,3-dimethoxypropane as a colorless liquid, bp 67-69°C at 24 mm (Note 9).

B. *1-Trimethylstannyl-3,3-dimethoxypropane*. An oven-dried, 500-mL, three-necked, round-bottomed flask fitted with a reflux condenser, nitrogen inlet tube, pressure-equalizing addition funnel, and rubber septum is charged with magnesium turnings (1.34 g, 55.2 mmol). The apparatus is carefully flame-dried under a flow of nitrogen and allowed to cool to room temperature. Tetrahydrofuran (5 mL) (Note 10) is added to the flask and a solution of 1-bromo-3,3-dimethoxypropane (10.10 g, 55.2 mmol) in tetrahydrofuran (10 mL) is added to the dropping funnel. A small portion (0.5 mL) of the solution of 1-bromo-3,3-dimethoxypropane is added to the flask along

with 3 drops of 1,2-dibromoethane, with warming (Note 11), until reaction commences. Stirring is begun and the remainder of the bromide solution is added dropwise to the reaction mixture. After ca. 5 min the reaction becomes vigorous and a further 35 mL of tetrahydrofuran is added via a syringe. The reaction is allowed to stir at room temperature for 1 hr after addition is complete, by which time all the magnesium has been consumed. A solution of chlorotrimethylstannane (11.0 g, 55.2 mmol) (Note 12) in tetrahydrofuran (50 mL) is then added rapidly to the reaction mixture which is allowed to stir for 18 hr at room temperature before being poured into water (100 mL). The aqueous phase is washed with diethyl ether (3 x 100 mL), the combined organic phases are dried over anhydrous magnesium sulfate, and the solvent is removed under reduced pressure to afford a yellow liquid (14.18 g).

The crude product is dissolved in petroleum ether (10 mL) (Note 13) and poured onto a column (45-mm diameter) filled with 350 g of silica gel (Merck 230-400 mesh) for flash chromatography. Elution under pressure (Note 14), initially with 2% diethyl ether in petroleum ether (Note 15) and then with increasing amounts of diethyl ether (up to 10%) in petroleum ether, gives, after removal of the solvent under reduced pressure, 1-trimethylstannyl-3,3-dimethoxypropane as a colorless liquid (11.9 g; 81%).

C. *2-Oxo-5-methoxyspiro[5.4]decane*. An oven-dried, 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, nitrogen inlet tube, pressure-equalizing dropping funnel, and a rubber septum, and allowed to cool under a flow of dry nitrogen. The flask is charged with 1-trimethylstannyl-3,3-dimethoxypropane (8.69 g, 32.6 mmol), [(1-trimethylsilyloxy)methylene]cyclohexane (6.0 g, 32.6 mmol) (Note 16) and dichloromethane (100 mL) (Note 17). The mixture is stirred and cooled to -78°C using an acetone-dry ice bath, and trimethylsilyl trifluoromethanesulfonate (1.47 g; 6.6 mmol) (Note 18) is added dropwise. After 1.5 hr all starting materials have been consumed (Note 19), and a solution of titanium tetrachloride (7.40 g, 39.0 mmol) (Note 20) in dichloromethane (10 mL) is added dropwise at -78°C with stirring. On

completion of the reaction, which requires 2 hr (Note 19), dichloromethane (250 mL) is added slowly so that the temperature does not rise above -70°C . Pyridinium dichromate (PDC) (20.32 g, 54.0 mmol) (Note 21) is added in 2-g portions. Stirring is then continued overnight while the reaction is allowed to warm to room temperature. Sodium-dried diethyl ether (300 mL) is added and the reaction mixture filtered through a short column of Celite. The solid residues are washed thoroughly with diethyl ether (5 x 50 mL), and the combined filtrates are concentrated under reduced pressure (Note 22), redissolved in diethyl ether, washed with 10% aqueous HCl (1 x 100 mL), brine (1 x 100 mL), saturated aqueous sodium hydrogen carbonate solution (1 x 100 mL), dried over anhydrous magnesium sulfate, and the solvent is removed under reduced pressure to afford a yellow liquid (8.20 g).

The crude product is dissolved in diethyl ether / petroleum ether (1:5) (5 mL) and poured onto a column (45-mm diameter) filled with 200 g of silica gel (Merck 230-400 mesh for flash chromatography). Elution (Note 23) under pressure (Note 14) with diethyl ether / petroleum ether (1:5) gives 2-oxo-5-methoxyspiro[5.4]decane as a colorless liquid (4.43 g; 75%) (Note 24).

2. Notes

1. *Because of the highly toxic nature of many tin compounds all tin residues from these reactions, including those extracted by aqueous washing, were collected together by the submitters and dispatched to a licensed chemical waste disposal unit for burning in a chemical incinerator, equipped with an afterburner and scrubbers.*

2. This procedure is essentially that of Battersby and co-workers.³

3. Reagent grade methylene chloride was distilled from calcium hydride (CaH_2) prior to use.

4. A steady stream of HBr was introduced via a Pasteur pipette with the tip extending into the solution.

5. The solution is almost saturated after 15 min as judged by evolution of HBr.

6. Acrolein was obtained from the Aldrich Chemical Company, Inc., and distilled before use.

7. Trimethyl orthoformate was obtained from the Aldrich Chemical Company, Inc., and used as received.

8. The forerun consists primarily of methanol and trimethyl orthoformate.

9. The checkers found that commercially available 3-bromo-1,1-dimethoxypropane (Aldrich Chemical Company, Inc.) was unsatisfactory, even after purification, for preparation of the stannane in part B, resulting in greatly diminished yields.

10. Tetrahydrofuran was distilled under nitrogen from sodium/benzophenone ketyl radical immediately prior to use.

11. Warming was achieved by use of a water bath at 40°C .

12. Chlorotrimethylstannane was obtained from the Aldrich Chemical Company, Inc. and was used without further purification.

13. Petroleum ether boiling at $40-60^{\circ}\text{C}$ was distilled immediately prior to use.

14. The submitters used a compressed air line at a pressure that maintained a flow rate of 5 mL min^{-1} .

15. Preliminary elution allows removal of hexamethyldistannoxane, formed as a by-product in the reaction, which slowly precipitates from the elution solvent as a white solid. A total of 1200 mL of solvent was collected in 30-mL fractions.

16. 1[(Trimethylsilyloxy)methylene]cyclohexane was prepared from the corresponding carboxaldehyde according to the method of House.^{4a,b} Cyclohexane carboxaldehyde was obtained from the Aldrich Chemical Company, Inc., and purified by distillation at atmospheric pressure (bp $160-164^{\circ}\text{C}$).

17. Dichloromethane was distilled from CaH_2 immediately prior to use.

18. Trimethylsilyl trifluoromethanesulfonate was obtained from the Aldrich Chemical Company, Inc., and was purified by distillation under nitrogen (bp $142^\circ\text{C}/760\text{ mm}$), immediately prior to use.

19. The progress of the reaction is conveniently monitored by TLC on Kieselgel 60 F₂₅₄ eluting, for the first bond-forming reaction, with diethyl ether:petroleum ether (1:9). The intermediate aldehyde had an R_f of 0.5, and the starting acetal an R_f = 0.45. The second bond-forming reaction was monitored by elution with diethyl ether:petroleum ether (2:3), and the R_f of the product was 0.4.

20. Titanium tetrachloride was obtained from the Aldrich Chemical Company, Inc., and was purified by distillation under nitrogen (bp $136^\circ\text{C}/700\text{ mm}$) immediately prior to use.

21. Pyridinium dichromate was prepared by the method of Corey.⁵ The checkers employed PDC, obtained from the Aldrich Chemical Company, Inc., that was used as received.

22. This evaporation removes dichloromethane used in the original reaction, and assists isolation of the product.

23. A total of 600 mL of solvent was collected in 30-mL fractions.

24. The purity of the product was found to be 97% by high-field NMR (270 MHz). Physical properties are as follows: Anal. Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_2$: C, 72.49; H, 9.95%. Found: C, 72.60; H, 9.94%. ν_{max} 1720 ($\text{C}=\text{O}$), 1100 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.2-1.8 (10 H, m, CH_2), 1.81-2.40 (4 H, m, CH_2), 3.38 (3 H, s, OCH_3), 3.78 (1 H, m, CH-OCH_3); ^{13}C NMR (CDCl_3) δ : 22.13, 22.40, 22.77, 25.64, 25.94, 31.25, 34.12 (all t, CH_2), 54.11 (s, quat C), 56.92 (q, OCH_3), 83.87 (d, C- OCH_3), 221.30; m/z 182 (M^+).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983. See Note 1.

3. Discussion

The synthesis of spirocyclic compounds and quaternary carbon centers in general has been an area of intense synthetic activity,⁶ because of the widespread occurrence of such products in nature, and because of the challenge they present to synthetic methodology. The reaction described here is a very simple method for constructing such systems in a single step, a two-bond forming, annelation process, using readily available starting materials. This new process involves the chemoselective⁷ *intermolecular* reaction of the acetal function of a bifunctional alkyl stannane or allyl silane with an enol silane, followed by *intramolecular* ring closure to give an annelated product. By using a range of bifunctional reagents of this type, a highly efficient single-step construction of fused five-,^{8,9} six-,¹⁰ seven-,¹⁰ eight-,¹¹ and nine-membered rings,¹¹ and of five-, six-, and seven-membered spirocyclic ring systems has been developed.^{12,13}

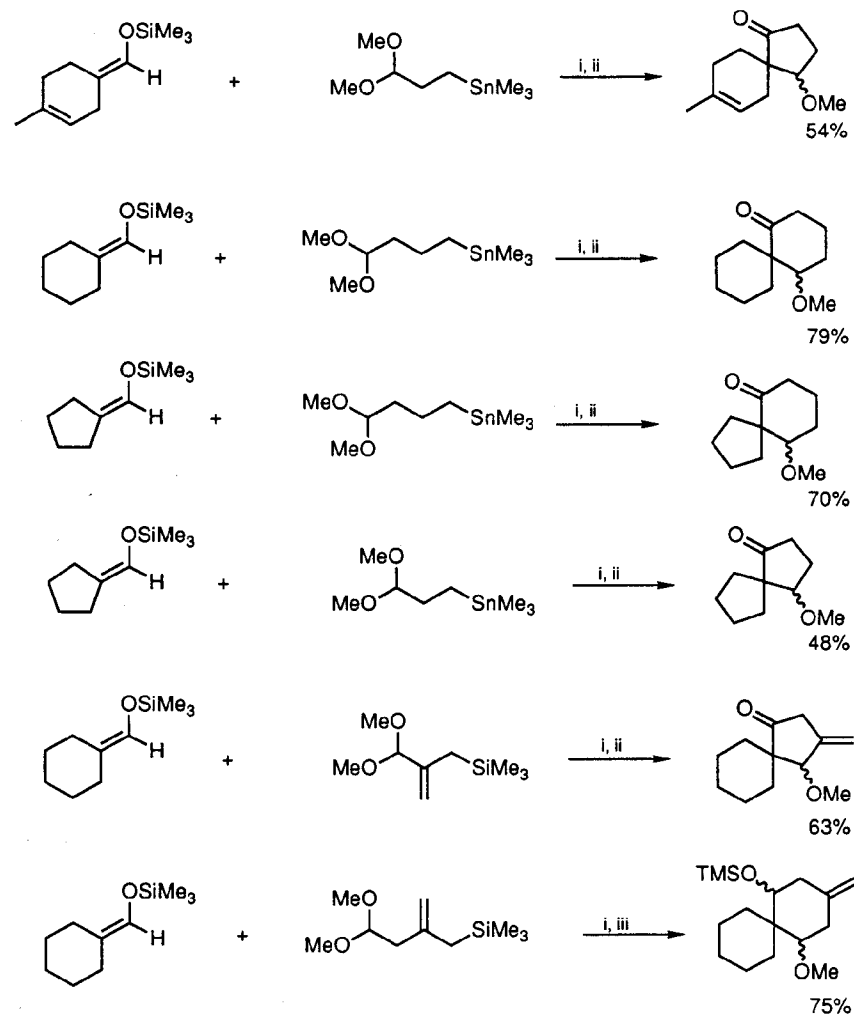
The new spiroannelation method gives, by use of both the tin and silicon chemistry, ready access to [4.4], [4.5], [5.5], [4.6], and [5.6] spirocyclic systems as well as five-, six-, and seven-membered rings possessing a quaternary center. An *in situ* oxidation, or protection of an initially formed crude secondary alcohol increases the ease of isolation of the product and leads to improved overall yields. Furthermore, for symmetrical substrates, this chemodifferentiates two oxygen functionalities at

equivalent carbon atoms. This makes the reaction potentially stereoconvergent at the newly formed quaternary center (see Table).

Probably the best alternative to the present procedure, in terms of generality, is the use of a cycloaddition strategy that can give access to a wide range of different sized spirocyclic molecules.¹⁴

1. (a) This work was carried out at the School of Chemistry, The University. Bristol, BS8 1TS, England, (*Thomas V. Lee is deceased); (b) Present address: Celltech Research Ltd., 216 Bath Road, Slough, SL1 4EN, UK.
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TABLE



i. TMSOTf - TiCl₄; ii. PDC; iii. TMSOTMS/DMAP

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-Oxo-5-methoxyspiro[5.4]decane: Spiro[4.5]decan-1-one, 4-methoxy- (12);
(108264-15-9)

Hydrogen bromide: Hydrobromic acid (8,9); (10035-10-6)

Titanium tetrachloride: Titanium chloride (8,9); (7550-45-0)

Trimethylsilyl trifluoromethanesulfonate: Methanesulfonic acid, trifluoro-, trimethylsilyl ester (8,9); (27607-77-8)

1-Bromo-3,3-dimethoxypropane: Propane, 3-bromo-1,1-dimethoxy- (9); (36255-44-4)

Acrolein (8); 2-Propenal (9); (107-02-8)

Trimethyl orthoformate: Orthoformic acid, trimethyl ester (8); Methane, trimethoxy- (9);
(149-73-5)

1-Trimethylstannyl-3,3-dimethoxypropane: Stannane, (3,3-dimethoxypropyl)trimethyl-
(12); (102402-80-2)

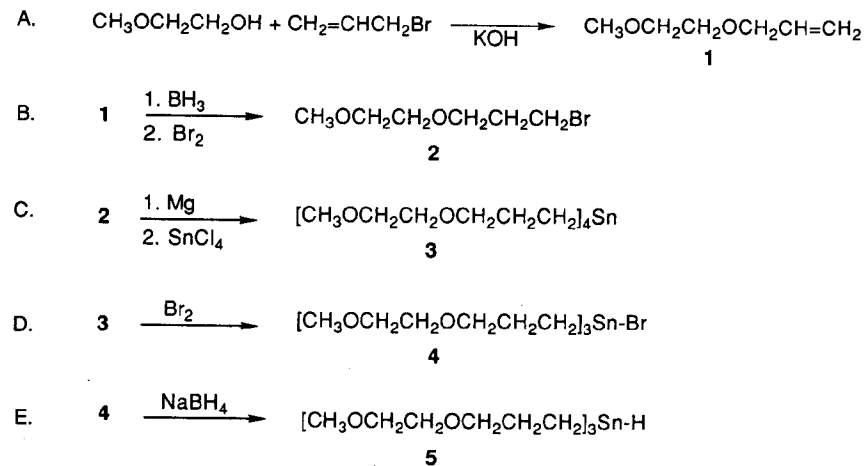
1,2-Dibromoethane: Ethane, 1,2-dibromo- (8,9); (106-93-4)

Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

[(1-Trimethylsilyloxy)methylene]cyclohexane: Silane, (cyclohexylidene-methoxy)trimethyl- (9); (53282-55-6)

Pyridinium dichromate: Dichromic acid, compd. with pyridine (1:2) (8); Chromic acid
(H₂Cr₂O₇), compd. with pyridine (1:2); (20039-37-6)

A WATER-SOLUBLE TIN HYDRIDE: TRIS[3-(2-METHOXYETHOXY)PROPYL]STANNANE (2,5,13,16-Tetraoxa-9-stannaheptadecane, 9-[3-(2-methoxyethoxy)propyl]-)



Submitted by James Light and Ronald Breslow.¹

Checked and substantially modified by Scott R. Breining and Robert K. Boeckman, Jr.

1. Procedure

A. *3-(2-Methoxyethoxy)propene* (1). A three-necked, 1000-mL flask equipped with a thermometer, mechanical stirrer, and dropping funnel is charged with 51 g (0.9 mol) of potassium hydroxide (KOH, Note 1) and 65 mL (62.3 g, 0.82 mol) of dry 2-methoxyethanol (Note 2). The resulting mixture is cooled in an ice bath, efficient stirring is begun, and 72 mL (100 g, 0.82 mol) of allyl bromide (Note 2) is added

dropwise, keeping the internal temperature below 10°C (Note 3). After the solution is stirred overnight, the sticky white solid is collected by suction filtration and the collected solids are washed with 300 mL of hexanes. The combined yellow filtrate and washings are dried thoroughly over sodium sulfate (Na_2SO_4), and the whole mixture is distilled from calcium hydride (CaH_2) through a 6-in. Vigreux column (Note 4). The product (67-69 g, 70-73%) is collected from 115-129°C with the bulk of the material distilling at bp 117-127°C, and is 94% pure (as judged by gas chromatography, Notes 5-7).

B. 1-Bromo-3-(2-methoxyethoxy)propane (2). A flame-dried, three-necked, 1000-mL flask that is equipped for magnetic stirring, and has a dry addition funnel and a thermometer, is placed under an inert atmosphere and charged with 209 mL (250 g, 0.209 mol) of a 1.0 M solution of borane-tetrahydrofuran complex (Note 2). The resulting solution is cooled to -10°C using a dry ice/ethylene glycol bath and 3-(2-methoxyethoxy)propene (1, 60 g, 0.52 mol) is added dropwise over ~1 hr keeping the internal temperature of the reaction mixture at or below 0°C. Methanol (1.5 mL) is added to destroy any excess borane, and the reaction mixture is stirred an additional 1 hr below 10°C.

After the reaction mixture is recooled to -15°C (internal temperature), 35 mL (107.8 g, 0.67 mol) of bromine (Br_2) is added dropwise over 1 hr, keeping the reaction temperature between -10° and 0°C. The mixture is stirred a further 1.5 hr at 0°C then recooled to -15°C. While cooling is maintained, 210 mL of a 4 M solution of sodium methoxide (0.84 mol) in methanol (freshly prepared from sodium metal) is added dropwise over 1.5 hr, keeping the reaction temperature between -15° and 0°C. The resulting orange brown solution and white precipitate are slowly warmed to room temperature and stirred overnight (16 hr).

Hexane (100 mL) is added to the reaction mixture causing more white precipitate to form. The mixture is filtered by suction, and the collected solids are washed with two 50-mL portions of hexane. The combined filtrate and washings are partitioned with 200 mL of a mixture (1:3 v/v) of saturated potassium carbonate solution and water (Note 8). The aqueous phase is extracted with three 200-mL portions of hexane. The combined organic phases are partitioned with 100 mL of saturated sodium chloride, dried thoroughly over anhydrous sodium sulfate and concentrated under reduced pressure to afford 65-75 g of crude product. A small amount of additional crude material can be isolated by continuously extracting the combined aqueous layers with hexane for 3 hr.

Distillation of the crude product through a 6-in. Vigreux column at 0.6 mm into a dry ice/acetone-cooled receiver affords 55-70 g of material bp >40°C/0.6 mm that is ~83% pure (as judged by gas chromatography, Note 6). To obtain material of greater purity (94%) suitable for further transformation, a second distillation through a 6-in. Vigreux column packed with glass beads is required to afford 53-57 g (52-56%) of the bromide as a colorless liquid, bp 55-65°C/0.6 mm (Note 9).

C. Tetra[3-(2-methoxyethoxy)propyl]stannane (3). A 500-mL, three-necked flask is fitted with a thermometer and a dried addition funnel, charged with 9.1 g (0.375 mol) of magnesium metal turnings (Note 2) and heated with a flame or heat gun while purging with argon. After the flask is cooled, 50 mL of dry tetrahydrofuran (THF) and a crystal of iodine are added, and the addition funnel is charged with 40 mL (52 g, 0.264 mol) of 1-bromo-3-(2-methoxyethoxy)propane (2, Note 10). Approximately 2 mL of the bromide is added to the reaction mixture, and the internal temperature of the mixture is monitored. When the temperature rises slightly (~3°C) and the iodine color is discharged indicating that formation of the Grignard reagent has begun, the reaction mixture is immediately cooled to -15°C in a dry ice/ethylene glycol bath, 100 mL of dry THF (Note 10) is added to the addition funnel, and 150 mL of dry THF (Note 10) is

directly added to the reaction mixture. The bromide solution is added dropwise over 2 hr while keeping the reaction temperature between -15° and 5°C (Note 11).

The concentration of the Grignard reagent solution is determined by titration. An oven-dried, 10-mL flask with septum is charged with 1 mg of phenanthroline and 3.0 mL of the reaction mixture. 2-Methylpropanol is added until the red-purple color is dissipated and a yellow endpoint is reached. The yield of Grignard reagent is 0.184 mol (70%).

A dry, 1000-mL flask is placed under a nitrogen atmosphere, charged with 4.9 mL (0.042 mol) of tin(IV) chloride (SnCl_4 , Note 1), and cooled to -78°C in a dry ice/acetone bath with swirling. After the SnCl_4 solidifies on the walls of the flask, the flask is equipped for magnetic stirring. The previously prepared Grignard solution is added to the SnCl_4 as a slow stream via cannula and the reaction mixture is allowed to warm to room temperature with stirring overnight (20 hr). After the solution is stirred at room temperature for ~20 hr, the addition funnel is replaced by a reflux condenser, and the reaction mixture is heated at reflux for 4 hr by means of a heating mantle (Note 12). After the solution is cooled, the solvent is removed under reduced pressure, 300 mL of water is added, and the resulting mixture (a heavy precipitate results) is continuously extracted with 750 mL of hexane for 12-24 hr. The hexane solution is dried over magnesium sulfate (MgSO_4), and the volatile material is removed under reduced pressure, to afford 23.6-24 g (96-97% based on SnCl_4) of the tetraalkylstannane that is not homogeneous as judged by NMR integration. Pure stannane suitable for further transformation is obtained by removal of a low boiling impurity (bp 90-100°C/0.6 mm) under high vacuum to afford 21-23 g of purified stannane. Stannane (bp 210-215°C at 0.005 mm) of even higher purity can be obtained by short-path distillation with some loss due to decomposition (Note 13).

D. Bromotris[3-(2-methoxyethoxy)propyl]stannane (4). A dry, 50-mL, round-bottomed flask is placed under a nitrogen atmosphere and charged with 8.25 g (14.0

mmol) of tetra[3-(2-methoxyethoxy)propyl]stannane (3), and 40 mL of dry carbon tetrachloride (CCl_4) (Note 1). After the mixture is cooled to ~0°C in an ice-water bath, 14 mL of a 1 M solution of bromine (0.014 mol) in CCl_4 is added dropwise (Note 14). The mixture is allowed to warm slowly to room temperature and stand overnight. The solvent is removed under reduced pressure, and the residual brown liquid is purified by Kugelrohr distillation at 0.1 mm. A low boiling fraction (bp <70°C) that contains alkyl bromide is discarded, and the residual material is distilled to afford 6.9-7.4 g (90-96%) of the bromotrialkylstannane (bp 100-110°C) as a pale tan viscous oil that is homogeneous as judged by NMR spectroscopy and of sufficient purity for further transformation (Notes 15-17).

E. Tris[3-(2-methoxyethoxy)propyl]stannane (5). A 100-mL, round-bottomed flask equipped for magnetic stirring is placed under an inert atmosphere and charged with 5.0 g (4.5 mmol) of freshly distilled bromotris[3-(2-methoxyethoxy)propyl]stannane (4) and 40 mL of dry 1,2-dimethoxyethane (Note 10). To the stirred solution is added 2.0 g (54 mmol) of sodium borohydride (NaBH_4) (Note 2) at room temperature in portions at such a rate as is required to control foaming. The resulting white suspension is stirred at room temperature for 2.5 hr (the reaction appears complete nearly instantaneously) and then concentrated under reduced pressure. The residue is taken up in 50 mL of ether, suction filtered through a bed of Celite, and concentrated under reduced pressure to afford 3.47-3.64 g (82-86%) of the trialkyltin hydride as a clear colorless oil that is homogeneous by NMR. The trialkyltin hydride is pure enough for most purposes, but further purification is possible by short-path distillation to afford pure trialkyltin hydride bp 100-120°C (pot temperature) at 0.005-0.01 mm (Note 18).

2. Notes

1. Potassium hydroxide was A.C.S. reagent grade obtained from J. T. Baker Chemical Company and used as received.

2. 2-Methoxyethanol was research grade obtained from Aldrich Chemical Company, Inc., and used as received.

3. The reaction is exothermic, and temperature control is required for control of the reaction. Good agitation is essential to avoid occlusion of unreacted starting materials in the sticky precipitate.

4. Substantial amounts (grams) of CaH_2 may be required (care should be taken on addition because of foaming) if predrying with Na_2SO_4 is incomplete.

5. The boiling range is broad because of codistillation of the product with small amounts of allyl bromide and 2-methoxyethanol.

6. Analysis was performed on a 25-m fused silica capillary column with DX-3 (polymethylsiloxane) stationary phase and a temperature program from 50°C-150°C.

7. The spectra are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 3.39 (s, 3 H), 3.59-3.61 (m, 4 H), 4.03 (dt, 2 H, $J = 5.7, 1.6$), 5.18 (dq, 1 H, $J = 10.3, 1.6$), 5.28 (dq, 1 H, $J = 17.2, 1.6$), 5.92 (ddt, 1 H, $J_1 = 17.2, J_2 = 10.3, J_3 = 5.7$); ^{13}C NMR (75.43 MHz, CDCl_3) δ : 58.64, 69.03, 71.70, 71.95, 116.62, 134.55.

8. Three phases may result. If three phases are present, add the minimum amount of additional water that affords two phases. Addition of large amounts of water should be avoided because of the significant water solubility of the product.

9. The spectra are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 2.18 (quintet, 2 H), 3.42 (s, 3 H), 3.54-3.68 (m, 8 H); ^{13}C NMR (75.4 MHz, CDCl_3) δ : 30.57, 32.71, 58.99, 68.61, 70.23, 71.81. The checkers noted a larger variability in yield (38-56%).

10. Tetrahydrofuran and 1,2-dimethoxyethane were dried and deoxygenated by distillation from sodium benzophenone ketyl under argon.

11. Inadequate temperature control leads to the formation of by-products resulting from elimination.

12. Magnetic stirring is difficult because of the formation of a sticky precipitate. A very vigorous reaction ensues upon heating the mixture to reflux if inadequate agitation occurs during addition of the Grignard reagent or if the SnCl_4 is allowed to solidify in a pool in the bottom of the flask.

13. The spectra are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 0.77 (m, 8 H, apparent t within a doublet), 1.78 (m, 8 H), 3.39 (s, 12 H), 3.39 (t, 8 H), 3.55 (AA'BB' m, 16 H); in D_2O , d_4 -TSP ref. δ : 0.89 (m, 8 H), 1.84 (m, 8 H), 3.64 (m, 16 H), 3.53 (t, 8 H), 3.40 (s, 12 H); ^{13}C NMR (75.4 MHz, CDCl_3) δ : 4.44, 26.69, 59.00, 69.95, 71.90, 74.82 (apparent ^{13}C - ^{119}Sn $1J = 322, 2J = 19, 3J = 66$); ^{119}Sn NMR 111.86 MHz (200 mg/mL) CDCl_3 , Me_4Sn ref. δ : -3.8 ppm (inverse gated decoupled).

14. Discharge of the yellow color is instantaneous until >13 mL of the bromine solution is added. A persistent yellow color was not observed until 1 equiv of bromine had been added.

15. No unreacted tetraalkylstannane is observed when a full equivalent of bromine is employed.

16. The bromotrialkylstannane is stable to storage under argon in the freezer, and can be converted to the tin hydride as needed.

17. The spectra are as follows: ^1H NMR (300 MHz, C_6D_6) δ : 1.38 (br t, 6 H), 1.95 (br quintet, 6 H), 3.14 (s, 9 H), 3.25 (m, 12 H), 3.35 (m, 6 H); ^{13}C NMR (75.4 MHz, CDCl_3) δ : 15.06 ppm (apparent ^{13}C - ^{119}Sn $1J = 413, 3J = 64$), 26.04, 58.90, 70.06, 71.71, 73.44; ^{119}Sn NMR 111.86 MHz (200 mg/mL), Me_4Sn ref. δ : +60.0 ppm (inverse gated decoupled). CI MS with NH_3 gave peaks at m/e 471 (base peak) and m/e 433 with the isotopic distribution expected for Sn and Br.

18. The spectra are as follows: ^1H NMR (300 MHz, C_6D_6) δ : 0.94 (td, 6 H, $J = 8, J_{\text{HSnCH}} = 1.8$), 1.85 (quintet, 6 H, $J_{\text{avg}} = 7$), 3.15 (s, 9 H), 3.36 (t, 6 H, $J = 6.4$), 3.40-

3.52 (m, AA'BB', 12 H), 5.17 (br septet, 1 H, J<2); ^{13}C NMR (75.4 MHz, C_6D_6) δ : 4.87, 27.54, 58.28, 70.00, 71.97, 74.03, (apparent ^{13}C - ^{119}Sn $1J = 354$, $2J = 22$, $3J = 52$, apparent ^{13}C - ^{117}Sn $1J = 336$, $2J = 22$, $3J = 52$); ^{119}Sn NMR 111.86 MHz (200 mg/mL), C_6D_6 , Me_4Sn standard δ -82.4 ppm (δ of septets, $^1J_{\text{Sn-H}} = 1612$, $^2J_{\text{Sn-H}} = 55$); IR (film on NaCl) cm^{-1} : 3500 weak, 2970-2930 strongest absorption, $\nu_{\text{Sn-H}}$ 1810, 1452, 1358, 1300, 1285, 1245, 1200, 1140-1100 broad, 1040, 985, 925, 885, 850, 715, 685.

Anal: Calcd for $\text{C}_{18}\text{H}_{40}\text{SnO}_6$, MW 471.19: C, 45.88; H, 8.56; Sn, 25.19.

Found: C, 45.74, 45.76; H, 8.71, 8.36; Sn, 25.08, 25.17.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Tributyltin hydride is a common reagent, used extensively in free radical chemistry.² However, it is soluble only in typical organic solvents. The tin hydride reagent prepared here³ can be used in free radical chemistry in many solvents. It is soluble in organic media, but also has sufficient water solubility (30 mM at room temperature, more on warming) to be useful in aqueous reactions. This reagent is not only of interest for use with water-soluble biomolecules but there is also increasing interest in the special effects of water as solvent on organic reactions.^{4,5,6} In addition, the reaction product of this reagent is the corresponding tin oxide species that can be easily recovered and recycled, and that is sometimes more easily removed from

organic products than is the corresponding product from tributyltin hydride. Most notably, this reagent is non-volatile and odorless.

This procedure illustrates the bromopropylation of an alcohol by allylation and then hydroboration/bromination,⁷ a clean, selective procedure compared with other approaches via 3-substituted propyl bromide derivatives. Conversion to the tetraalkyl tin, then brominative cleavage, is the standard sequence for preparation of trialkyl tin derivatives.⁸ The standard lithium aluminum hydride (LiAlH_4) reduction of the tin bromide was not usable here because of contamination of the product by LiAlH_4 by-products that were not easily separated, and the polymethylhydrosiloxane reduction method⁹ was not successful. However, use of NaBH_4 in 1,2-dimethoxyethane was effective and convenient.¹⁰

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Tris[3-(2-methoxyethoxy)propyl]stannane: 2,5,13,16-Tetraoxa-9-stannaheptadecane, 9-[3-(2-methoxyethoxy)propyl]- (12); (130691-03-1)

3-(2-Methoxyethoxy)propene: 1-Propene, 3-(2-methoxyethoxy)- (9); (18854-48-3)

2-Methoxyethanol: Ethanol, 2-methoxy- (8, 9); (109-86-4)

Allyl bromide: 1-Propene, 3-bromo- (8,9); (106-95-4)

1-Bromo-3-(2-methoxyethoxy)propane: Propane, 1-bromo-3-(2-methoxyethoxy)- (9); (59551-75-6)

Borane-tetrahydrofuran complex: Furan, tetrahydro, compd. with borane (1:1) (8,9); (14044-65-6)

Bromine (8,9); (7726-95-6)

Sodium methoxide: Methanol, sodium salt (8,9); (124-41-4)

Tetra [3-(2-methoxyethoxy)propyl]stannane: 2,5,13,16-Tetraoxa-9-stannaheptadecane, 9,9-bis[3-(2-methoxyethoxy)propyl]- (12); (130691-01-9)

Magnesium (8,9); (7439-95-4)

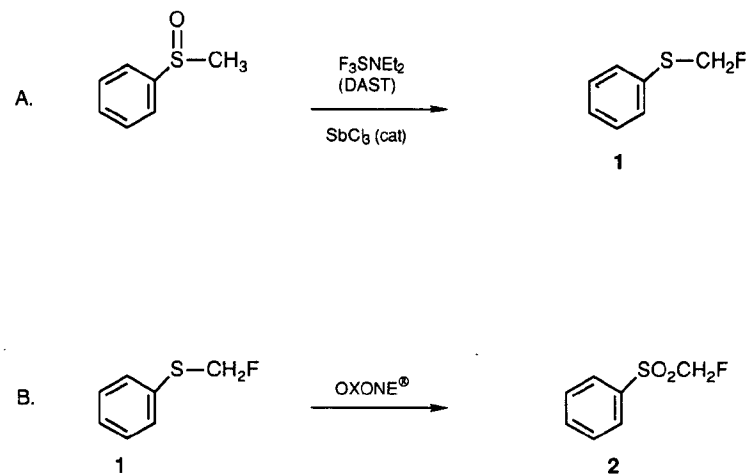
Tin(IV) chloride: Tin chloride (8); Stannane, tetrachloro- (9); (7646-78-8)

Bromotris[3-(2-methoxyethoxy)propyl]stannane: 2,5,13,16-Tetraoxa-9-stannaheptadecane, 9-bromo-9-[3-(2-methoxyethoxy)propyl]- (12); (130691-02-0)

Dimethoxyethane: Ethane, 1,2-dimethoxy- (8,9); (110-71-4)

Sodium borohydride: Borate (1-), tetrahydro-, sodium (8,9); (16940-66-2)

REACTION OF SULFOXIDES WITH DIETHYLAMINOSULFUR TRIFLUORIDE: PREPARATION OF FLUOROMETHYL PHENYL SULFONE, A REAGENT FOR THE SYNTHESIS OF FLUOROALKENES (Benzene, [(fluoromethyl)sulfonyl]-)



Submitted by James R. McCarthy, Donald P. Matthews, and John P. Paolini.¹

Checked by Carmen M. Simone and Albert I. Meyers.

1. Procedure

Caution! All reactions should be conducted in an efficient fume hood.

A. *Fluoromethyl phenyl sulfide* (1). To a 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, air condenser and thermometer are added methyl phenyl sulfoxide (25.2 g, 0.18 mol) (Note 1) and chloroform (150 mL) (Note 2).

The flask is placed in a cooling bath containing 3 L of water kept at 20°C (Note 3). Diethylaminosulfur trifluoride (DAST) (38.5 g, 31.6 mL, 0.24 mol) (Note 4) is added to the flask, followed by antimony trichloride (0.50 g, 0.0022 mol) (Note 5), and an additional 50 mL of chloroform. The light yellow reaction mixture is stirred under an argon atmosphere. After 2 to 8 hr, an exothermic reaction is observed and the solution turns dark orange (Note 6). The reaction mixture is poured slowly with stirring into 600 mL of ice-cold, saturated, aqueous sodium bicarbonate containing 10 g (0.25 mol) of sodium hydroxide (Caution: gas evolution). After 10 min, the chloroform layer is separated and the remaining aqueous layer is extracted with additional chloroform (3 x 100 mL). The combined organic layers are washed with saturated aqueous sodium bicarbonate (250 mL), saturated aqueous sodium chloride, and dried over potassium carbonate. The chloroform is removed with a rotary evaporator at 30-40°C and the crude fluoromethyl phenyl sulfide 1 (ca. 29 g), obtained as a yellow orange oil, is used immediately in the next step (Notes 7 and 8).

B. Fluoromethyl phenyl sulfone (2). To a 3-L, three-necked, round-bottomed flask, equipped with an overhead stirrer, thermometer, and 1-L addition funnel with sidearm are added Oxone (221.0 g, 0.36 mol) (Note 9) and water (700 mL). The mixture is cooled to 5°C and a solution of the crude fluoromethyl phenyl sulfide (1) in methanol (700 mL) is placed in the addition funnel and added in a slow stream to the stirring slurry. After addition of the sulfide, the reaction mixture is stirred at room temperature for 4 hr, (Note 10) and the methanol is removed on a rotary evaporator at 40°C. The remaining solution is extracted with methylene chloride (2 x 500 mL). The combined organic layers are dried over magnesium sulfate, concentrated to ca. 150 mL, filtered through a plug of silica gel (230-400 mesh, 300 mL, 10 x 6.5 cm), and washed with an additional 500 mL of methylene chloride (Note 11). The colorless filtrate is concentrated and the resulting oil or solid is dried under vacuum (0.1 mm) at room temperature to provide 29 g of crude fluoromethyl phenyl sulfone (2) as a solid

white mass. The solid is recrystallized from 250 mL of hot hexane (forms two layers) by cooling the two phase solution to room temperature with vigorous stirring and adding a seed crystal. The resulting white crystals of fluoromethyl phenyl sulfone (2) (25.0-28.5 g, 80-90%) are collected by filtration, mp 53-55°C (Notes 12 and 13).

2. Notes

1. Methyl phenyl sulfoxide was purchased from Aldrich Chemical Company, Inc., and used as received.

2. Chloroform is a suspected carcinogen. Follow manufacturer's recommended procedures for handling, storage, and disposal.

3. Both a sizable head space and a large heat sink are essential for this reaction since a vigorous, but latent, exothermic reaction occurs (see Note 5). This reaction was run twelve times without incident on a 25-125-g scale following these precautions.

4. Diethylaminosulfur trifluoride (DAST) should be handled using appropriate safety equipment (rubber gloves and goggles). DAST was purchased from Carbolabs, Inc., and used as received.

5. Antimony trichloride was purchased from Aldrich Chemical Company, Inc. and used as received. Excess antimony trichloride can cause a vigorous reaction.

6. Progress of the reaction can be followed by gas chromatography, TLC (ethyl acetate/hexane 1:5) or ¹H NMR. (Probe reactions can be carried out in CDCl₃ in an NMR tube).

7. Alternatively, the chloroform solution can be treated with 2 equiv of 3-chloroperbenzoic acid (MCPBA) to provide fluoromethyl phenyl sulfone (see reference 2).

8. The crude sulfide is readily purified by Kugelrohr distillation (bp 80-90°C, 0.8 mm), but the colorless liquid polymerizes to a white solid on standing overnight. A solution of the sulfide in chloroform was stored at -10°C for 2 days on one occasion with no decomposition. ¹H NMR (300 MHz, CDCl₃) δ: 5.72 (d, 2 H, J = 52.9), 7.29-7.52 (m, 5).

9. Oxone (potassium peroxymonosulfate, 2 KHSO₅·KHSO₄·K₂SO₄) was purchased from Aldrich Chemical Company, Inc.

10. Progress of the oxidation can be followed by TLC (ethyl acetate/hexane 1:5). The checkers found that the product crystallized from water when the methanol was removed.

11. Alternatively, the organic layer is concentrated to an oil and 2 is purified by Kugelrohr distillation, bp 120-125°C (1 mm).

12. The two step reaction was run on a 125-g scale with an overall yield of 88%.

13. The physical properties are as follows: ¹H NMR (300 MHz, CDCl₃) δ: 5.15 (d, 2 H, J = 47.1), 7.60-8.00 (m, 5 H); ¹⁹F NMR (282 MHz, CDCl₃) δ: -211.2 (t, J = 47.4); MS (EI) m/z 175 (M⁺); Anal. Calcd for C₇H₇FO₂S: C, 48.26; H, 4.05. Found: C, 48.35, H, 3.94.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

The first step of the present procedure is an example of the fluoro Pummerer or DAST Pummerer reaction³ and describes a convenient method for the synthesis of α-fluoro sulfides. α-Fluoro sulfides can subsequently be oxidized to the corresponding sulfoxide or sulfone. For aromatic sulfoxides, use of the 4-anisyl group can dramatically improve the yield and facility of the reaction. The submitters originally found that zinc iodide catalyzes the reaction.³ Recently, Robins and co-workers^{4,5} have reported that antimony trichloride is a superior catalyst for this transformation, eliminating the need for a 4-methoxy group for the conversion of aryl sulfoxides to α-fluoro sulfides. The submitters have subsequently utilized this catalyst in place of zinc iodide.^{2,6}

In most cases, the fluoro Pummerer reaction can be carried out with 1.33 to 2.0 equiv of DAST and a "catalytic" amount of antimony trichloride in either refluxing methylene chloride or chloroform at room temperature or 50°C. In the synthesis of fluoromethyl phenyl sulfide, however, the induction period makes room temperature conditions the preferred method for large scale synthesis.

Electron-withdrawing groups decrease the rate of the fluoro Pummerer reaction, which, in certain cases,⁷ allows a DAST-mediated deoxygenation to compete with the introduction of fluorine alpha to sulfur. The reaction is compatible with a number of functional groups and can readily be carried out with nucleosides. Robins and co-workers⁴ reported the synthesis of a 5'-fluoro-5'-S-phenyladenosine analog using antimony trichloride as catalyst at room temperature. It should be noted that α-fluoro sulfoxides provide a convenient entry to terminal fluoroalkenes.^{3,8,9,10}

In most cases, introduction of fluorine adjacent to sulfur can be monitored by proton NMR for small-scale probe reactions run in CDCl₃. The CHF peaks in the

proton NMR are generally found between δ 5 and 6 ppm (with proton-fluorine coupling constants around 55) and fall below the range for protons on DAST.

For the synthesis of the title compound, Oxone or 3-chloroperbenzoic acid² can be used to oxidize the sulfide to the sulfone. The title compound is a key reagent for the preparation of fluoroalkenes from aromatic¹¹ and aliphatic² aldehydes. Recently, a stereospecific method to (E)- and (Z)-fluoroalkenes was reported using this reagent.^{12,13,14}

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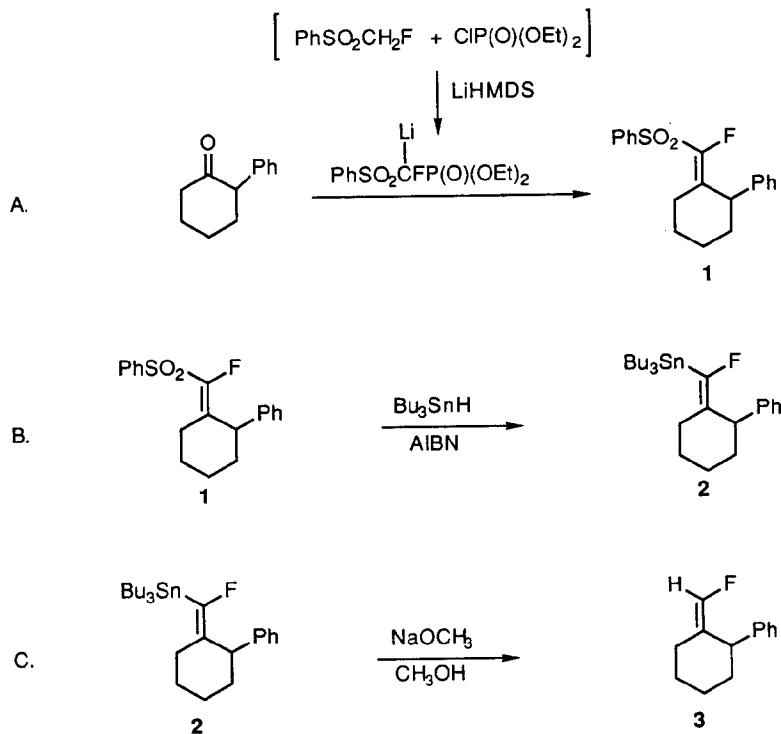
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Fluoromethyl phenyl sulfone: Sulfone, fluoromethyl phenyl (8);
Benzene, [(fluoromethyl)sulfonyl]- (9); (20808-12-2)
Diethylaminosulfur trifluoride: Sulfur, (diethylamino)trifluoro- (9); (38078-09-0)
Fluoromethyl phenyl sulfide: Benzene, [(fluoromethyl)thio]- (9); (60839-94-3)
Methyl phenyl sulfoxide (8); Benzene, (methylsulfinyl)- (9); (1193-82-4)
Chloroform (8); Methane, trichloro- (9); (67-66-3)
Oxone: Peroxymonosulfuric acid, monopotassium salt, mixt. with dipotassium sulfate and potassium hydrogen sulfate (9); (37222-66-5)

**STEREoselective SYNTHESIS OF 2,2-DISUBSTITUTED 1-FLUORO-
ALKENES: (E)-[1-FLUORO(2-PHENYLCYCLOHEXYLIDENE)-
METHYL]SULFONYLBENZENE AND
(Z)-[2-(FLUOROMETHYLENE)CYCLOHEXYL]BENZENE**



1. Procedure

Caution! All reactions should be conducted in an efficient fume hood.

A. (E)-[1-Fluoro(2-phenylcyclohexylidene)methyl]sulfonylbenzene (**1**). To an oven-dried, 1-L, three-necked, round-bottomed flask, equipped with a nitrogen inlet with gas bubbler, thermometer, magnetic stirring bar, and a 500-mL addition funnel with side arm and septum, are added 25.0 g (0.14 mol) of fluoromethyl phenyl sulfone (Note 1), diethyl chlorophosphate (24.8 g, 0.14 mol) (Note 2), and anhydrous tetrahydrofuran (THF) (300 mL). The solution is kept under a nitrogen atmosphere and cooled to -70°C with a dry ice-acetone bath. A solution of 1 M lithium bis(trimethylsilyl)amide (LiHMDS) in THF (310 mL, 0.31 mol) (Note 3) is transferred via cannula to the dropping funnel and added over 15 min. After the reaction mixture is stirred for 1 hr at $\leq -70^{\circ}\text{C}$ (Note 4), the addition funnel is replaced with a septum. 2-Phenylcyclohexanone (17.4 g, 0.10 mol) (Note 5) is dissolved in THF (65 mL) and added via a syringe. The reaction mixture is allowed to warm to ambient temperature. Stirring is continued for 2 hr at room temperature and, during this time, a white precipitate forms in solution. The reaction mixture is poured into an ice-cold mixture of ethyl acetate (250 mL), saturated aqueous ammonium chloride (250 mL), and concd hydrochloric acid (30 mL). The organic layer is collected and the aqueous layer is extracted with ethyl acetate (250 mL). The combined organic layers are washed with saturated aqueous sodium chloride (100 mL) and dried (magnesium sulfate). The solvent is removed under reduced pressure and the resulting orange-brown oil is purified by flash chromatography² (1.25 L of 230-400 mesh silica gel) using ether/hexane (1:10) to provide 23 g of colorless oil (Note 6). The oil is dissolved in hot ethanol (200 mL) and the solution is cooled in the freezer. The shiny white crystals that form are collected by filtration and dried under reduced pressure to afford 19.5-23.1 g (59-70%) of **1**, mp $75-78^{\circ}\text{C}$ (Note 7).

Submitted by James R. McCarthy, Donald P. Matthews, and John P. Paolini.¹

Checked by Carmen M. Simone and Albert I. Meyers.

B. (E)-Tributyl[fluoro(2-phenylcyclohexylidene)methyl]stannane (**2**). To a 1-L, round-bottomed flask with reflux condenser, magnetic stirring bar, and nitrogen inlet with gas bubbler are added fluorovinyl sulfone **1** (22.0 g, 0.067 mol), tributyltin hydride (42.0 g, 38.9 mL, 0.14 mol), azobisisobutyronitrile (AIBN) (500 mg) (Note 8) and benzene (700 mL) (Note 9). The solution is refluxed for 3 hr under a nitrogen atmosphere (Note 10), cooled to room temperature, and 125 mL of silica gel (230-400 mesh) is added. The mixture is concentrated on a rotary evaporator to a white powder (Note 11) and applied to the top of a flash silica gel column² (1.3 L) packed with hexane. The column is eluted with hexane and fractions containing **2** (Note 12) are combined and concentrated on a rotary evaporator to give 23.4-27.5 g (74-87% yield) of **2** as a colorless oil (Note 13).

C. (Z)-[2-(Fluoromethylene)cyclohexyl]benzene (**3**). To a solution of (fluorovinyl)stannane **2** (26.0 g, 0.054 mol) in dry THF (150 mL) is added 65 mL of 1 M sodium methoxide in methanol (prepared by the addition of 1.50 g (0.065 g-atom) of sodium to 65 mL of methanol). The solution is refluxed for 18 hr under nitrogen (Note 14), cooled to ambient temperature and concentrated on a rotary evaporator. The residue is partitioned between water (200 mL) and hexane (200 mL). The aqueous layer is separated and extracted with hexane (100 mL). The combined organic layers are dried (magnesium sulfate) and concentrated on a rotary evaporator to give a colorless oil (30 g). Kugelrohr distillation gives 10.0-10.2 g (97-100%) of fluoro olefin **3** (bp 85-90°C, 0.4 mm) as a colorless oil (Note 15).

2. Notes

1. See McCarthy, J. R.; Matthews, D. P.; Paolini, J. P. *Org. Synth.* **1993**, *72*, 209.
2. Diethyl chlorophosphate was purchased from Aldrich Chemical Company, Inc., and distilled before use; bp 60°C (2 mm). This reagent is a highly toxic acetylcholinesterase inhibitor and should be handled with care.
3. 1 M Lithium bis(trimethylsilyl)amide in THF was purchased from Aldrich Chemical Company, Inc.
4. Formation of the carbanion of diethyl 1-fluoro-1-(phenylsulfonyl)-methanephosphonate is followed by gas chromatography, by quenching a small aliquot of the reaction in ether/saturated aqueous ammonium chloride. The carbanion forms in ca. 85% to 95% yield after 1 hr.
5. 2-Phenylcyclohexanone was purchased from Aldrich Chemical Company, Inc., and used without further purification.
6. Alternatively, the orange-brown oil can be crystallized twice from ethanol (200 mL, 150 mL) (seed crystal) to provide 16.6 g (50%) of off-white crystals of **1**, mp 75-78°C. The checkers observed mp 68-70°C for this material.
7. Spectral and elemental analysis data for **1** are the following: ¹H NMR (300 MHz, CDCl₃) δ: 1.3-2.1 (m, 6 H), 2.46 (d, 1 H, J = 14.3), 3.61 (dd, 1 H, J = 3.5, 14.2), 4.22 (s, 1 H), 7.0-8.1 (m, 10 H); ¹³C NMR (75 MHz, CDCl₃) δ: 20.76, 23.34, 27.17 (d, ³J_{F,CH2} = 2.2), 29.42, 38.45 (d, ³J_{F,CH} = 7.5), 126.35, 127.11, 127.96, 128.65, 129.34, 134.07, 134.96 (d, ²J_{F,C} = 6.7), 139.46, 139.67, 147.80 (d, ¹J_{F,C} = 280.1); ¹⁹F NMR (282 MHz, CDCl₃) δ: -123.4 (s); MS (CI/CH₄) m/z 331 (MH⁺). Anal. Calcd for C₁₉H₁₉FO₂S: C, 69.06; H, 5.80. Found: C, 68.88; H, 5.86. The structure for **1** was confirmed by X-ray crystallography.³

8. Azobisisobutyronitrile (AIBN) was purchased from Aldrich Chemical Company, Inc. and used as received.

9. *Benzene is a known carcinogen.* Follow manufacturer's recommended procedures for handling, storage, and disposal. Cyclohexane was found to be a suitable alternate solvent for other examples of this reaction.

10. Progress of the reaction is followed by either gas chromatography or thin layer chromatography (silica gel, hexane) since the time required for completion of the reaction can vary up to 16 hr. An additional 500 mg of AIBN is added to the reaction mixture after 3 hr if starting material is still present.

11. An adapter tube containing a fritted disc prevents loss of silica gel into the condenser of the rotary evaporator. These tubes are available from Aldrich Chemical Company, Inc. Alternatively, the checkers found that the silica gel can be added to the crude mixture after removal of benzene.

12. Fractions containing **2** of ca. ≥90% purity by gas chromatography (flame ionization detector) were combined.

13. In some runs, material (≤5%) with the retention time of tributyltin hydride is present in product **2**. This impurity does not interfere in the last step of the reaction sequence. Spectral and elemental analysis data for **2** are the following: ¹H NMR (300 MHz, CDCl₃) δ: 0.91 (t, 9 H, J = 7.0), 1.0-1.1 (m, 6 H), 1.2-2.0 (m, 19 H), 2.41 (d, 1 H, J = 13.9), 4.4 (m, 1 H), 7.2 (m, 1 H), 7.3-7.4 (m, 4 H); ¹³C NMR (75 MHz, CDCl₃) δ: 10.44, 13.74, 21.68, 26.75 (d, ³J_{F,CH₂} = 11.8), 27.23, 28.37 (d, ⁴J_{F,CH₂} = 2.7), 29.06, 29.52, 36.31 (d, ³J_{F,CH} = 15.0), 125.42, 127.60, 128.21, 135.37, 142.02 (d, ²J_{F,C} = 5.2), 163.34 (d, ¹J_{F,C} = 306.2); ¹⁹F NMR (282 MHz, CDCl₃) δ: -110.52 (84%, m) (16%, dm, J = 282); MS (CI/CH₄) m/z 461 (MH⁺ -HR). Anal. Calcd for C₂₅H₄₁FSn: C, 62.65; H, 8.62. Found: C, 62.43; H, 8.61. Proton-fluorine NOE difference spectroscopy (CDCl₃) showed an enhancement in the fluorine signal (δ -110.5) when the benzylic proton (δ 4.4) was irradiated and showed no enhancement when the allylic protons (δ

2.41, equatorial proton and δ 1.77, axial proton) were irradiated. See reference 7 for a discussion of this technique.

14. Progress of the reaction is followed by either gas chromatography or thin layer chromatography (silica gel, hexane).

15. Spectral and elemental analysis data for **3** are as follows: ¹H NMR (300 MHz, CDCl₃) δ: 1.2-2.0 (m, 7 H), 2.37 (d, 1 H, J = 13.2), 4.2 (m, 1 H), 6.6 (dm, 1 H, J = 87.1), 7.2 (m, 1 H), 7.25-7.35 (m, 4 H); ¹³C NMR (75 MHz, CDCl₃) δ: 21.72, 25.06 (d, ³J_{F,CH₂} = 6.9), 27.71 (d, ⁴J_{F,CH₂} = 2.8), 29.74, 36.13 (d, ³J_{F,CH} = 5.2), 123.18 (d, ²J_{F,C} = 3.8), 125.73, 127.54, 128.31, 141.55, 142.19 (d, ¹J_{F,C} = 252.6); ¹⁹F NMR (282 MHz, CDCl₃) δ: -139.64 (dd, J = 3.4, 86.8); MS (CI/CH₄) m/z 191 (MH⁺). Anal. Calcd for C₁₃H₁₅F: C, 82.07; H, 7.95. Found: C, 82.13; H, 8.15.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

The procedure described here provides a stereospecific synthesis of (E)- and (Z)-fluoroalkenes from the corresponding (E)- and (Z)-fluorovinyl sulfones. Fluorovinyl sulfones obtained from ketones are, in most cases, readily separable into (E) and (Z) isomers either by crystallization or by chromatography.⁴ In the example described, only the (E)-fluorovinyl sulfone **1** is formed (which is converted into the (Z)-fluoroalkene **3** with complete retention of configuration). The reaction sequence has been used for the stereospecific synthesis of fluoroalkene nucleosides⁵ as well as for

1-deutero-1-fluoroalkenes. In the case of fluoroalkenes obtained from aldehydes, conversion of the intermediate monosubstituted fluorovinyl sulfones to (fluorovinyl)stannanes does not proceed with retention of configuration.⁶ However, subsequent cleavage of the vinyltributyltin group with either sodium methoxide, cesium fluoride or methanolic ammonia does proceed with retention of configuration. Since (E)- and (Z)-vinylstannanes are usually separable, this method also provides a route to stereochemically-pure, terminal, mono-substituted fluoroalkenes.⁷ A significant property of the intermediate (fluorovinyl)stannanes is their ability to act as fluorovinyl carbanion equivalents. Thus, treatment of (fluorovinyl)stannanes with acid chlorides in the presence of a palladium(0) catalyst provides α -fluoro α,β -unsaturated ketones with complete retention of configuration.⁷ Iodine reacts with (fluorovinyl)stannanes to give 1-iodo-1-fluoroalkenes with complete retention of configuration.^{6,7}

It should be noted that addition of the tributyltin radical to 1-fluoro-1-(phenylsulfonyl)ethene provides phenyl vinyl sulfone as the only isolated product. However, 2-trimethylsilyl-1-fluoro-1-(phenylsulfonyl)ethene reacts with tributyltin hydride in the presence of AIBN to provide (E)-2-trimethylsilyl-1-fluoro-1-tributylvinylstannane. The vinylstannane is an equivalent for the synthon " $H_2C=CF-$ " providing a convenient route to 2-fluoro-1-alkenes.⁸ The trimethylsilyl group can be removed with potassium fluoride in dimethyl sulfoxide-water or oxalic acid-methanol at the end of the reaction sequence.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(E)-[[Fluoro(2-phenylcyclohexylidene)methyl]sulfonyl]benzene: Benzene, [[fluoro(2-phenylcyclohexylidene)methyl]sulfonyl]-, (E)-(±)- (12); (135790-01-1)
 Fluoromethyl phenyl sulfone: Sulfone, fluoromethyl phenyl (8); Benzene, [(fluoromethyl)sulfonyl]- (9); (20808-12-2)
 Diethyl chlorophosphate: Phosphorochloridic acid, diethyl ester (8,9) (814-49-3)
 Lithium bis(trimethylsilyl)amide (LiHMDS): Disilazane, 1,1,1,3,3,3-hexamethyl-, lithium salt (8); Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, lithium salt (9); (4039-32-1)

2-Phenylcyclohexanone: Cyclohexanone, 2-phenyl- (8,9); (1444-65-1)

(E)-Tributyl[fluoro(2-phenylcyclohexylidene)methyl]stannane: Stannane, tributyl[fluoro(2-phenylcyclohexylidene)methyl]-, (E)-(±)- (12); (135789-96-7)

Tributyltin hydride: Stannane, tributyl- (8,9); (688-73-3)

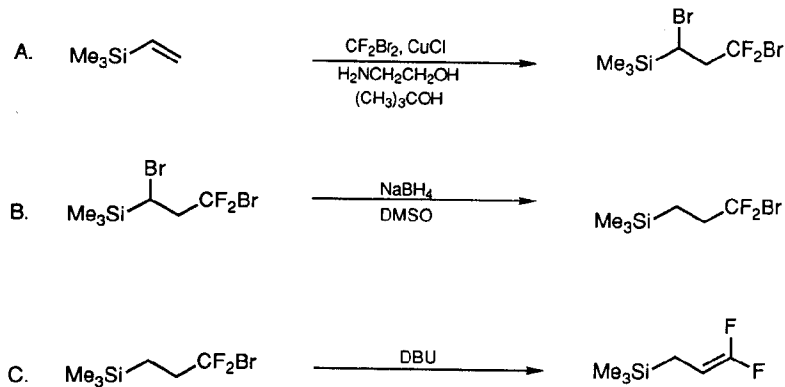
Azobisisobutyronitrile: Propionitrile, 2,2'-azobis[2-methyl- (8); Propanenitrile, 2,2'-azobis[2-methyl- (9); (78-67-1)

(Z)-[2-(Fluoromethylene)cyclohexyl]benzene: Benzene,

[2-(fluoromethylene)cyclohexyl]-, (Z)-(±)- (12); (135790-02-2)

(3,3-DIFLUOROALLYL)TRIMETHYLSILANE

(Silane, (3,3-difluoro-2-propenyl)trimethyl-)



Submitted by Javier Gonzalez, Matthew J. Foti, and Seth Elsheimer.¹

Checked by Louis Portland, Tai-Nang Huang, and David L. Coffen.

1. Procedure

A. *(1,3-Dibromo-3,3-difluoropropyl)trimethylsilane* (Note 1). A 250-mL pressure tube (Note 2) equipped with a magnetic stirring bar is charged with vinyltrimethylsilane (20 g, 30.8 mL, 0.20 mol), ethanolamine (6.11 g, 6.04 mL, 0.10 mol), dibromodifluoromethane (83.9 g, 36.5 mL, 0.4 mol), copper(I) chloride (0.18 g, 1.8 mmol), and tert-butyl alcohol (15 mL) (Notes 3 and 4). The tube is sealed and stirred for 20 hr in an oil bath at 90°C (Note 5). The reaction mixture is combined with that from another run at the same scale and diluted with 40 mL of hexane (the mixture separates into a cloudy supernatant and a brown resin). The hexane layer is

separated and the resinous precipitate extracted with two, 20-mL portions of hexane. The combined solutions are filtered through a bed of silica gel on a 60-mL fritted glass funnel and the resulting clear filtrate is concentrated by rotary evaporation using a water aspirator. The crude material is fractionally distilled to afford 71.9-78.3 g (58-61%) of the dibromide as a colorless oil, bp 78-79°C (12 mm) [lit.² bp 95°C (25 mm)] (Note 6).

B. (3-Bromo-3,3-difluoropropyl)trimethylsilane. A 1-L, four-necked flask is equipped with a mechanical stirrer, thermometer, Claisen adapter, septum inlet, reflux condenser (the top of which is connected to a calcium chloride drying tube), and a solid addition funnel. The flask is charged with (1,3-dibromo-3,3-difluoropropyl)trimethylsilane (78.3 g, 0.25 mol), and anhydrous dimethyl sulfoxide (200 mL), and the solid addition funnel is charged with sodium borohydride (11.5 g, 0.30 mol) (Notes 7 and 8). The stirred solution is warmed to 80°C, and sodium borohydride is added at a rate sufficient to maintain a reaction temperature of 80-90°C (Note 9). Toward the end of the addition, an additional portion of dimethyl sulfoxide (200 mL) is added via syringe to lower the viscosity of the reaction mixture. After the addition is complete, the mixture is cooled in an ice-water bath, diluted with 100 mL of pentane, and *cautiously* quenched with 12 M hydrochloric acid until no further gas evolution occurs. The mixture is transferred to a separatory funnel and washed with three, 100-mL portions of 5% brine. The pentane extract is dried over calcium chloride and the solvent removed through a 15-cm Vigreux column. Further fractionation yields 41.5 g (72%) of 3-bromo-3,3-difluoropropyltrimethylsilane, bp 139-141°C (Note 10).

C. (3,3-Difluoroallyl)trimethylsilane. A 100-mL, three-necked, round-bottomed flask is equipped with a magnetic stirrer, short-path distillation head, and an electric heating mantle. The flask is charged with 30.99 g (0.13 mol) of (3-bromo-3,3-difluoropropyl)trimethylsilane and 29.1 g (0.19 mol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Note 11). Stirring and gradual heating are begun and the reaction mixture

becomes thick with precipitate (Note 12). The product distilling from the mixture is collected from 80-100°C giving 11.88 g of colorless liquid.

Additional product is obtained by extractive workup of the residue. The cooled residue is acidified by adding 50 mL of 3 N hydrochloric acid and the resulting solution is extracted with 50 mL of pentane. The pentane layer is washed with 2 x 50 mL of water, dried over sodium sulfate, filtered and concentrated at 35°C under ca. 30 mm vacuum. The remaining liquid is distilled using a short-path distillation head to afford an additional 1.77 g of product (bp 86-95°C). The combined product, weighing 13.65 g (70% yield), has a purity of 85-90% based on NMR and capillary GC analysis (Note 13).

2. Notes

1. This procedure is based on a report by Burton and Kehoe.³
2. An Ace Model # 8648-83 tube with a FETFE O-ring was used.
3. Vinyltrimethylsilane, ethanolamine, copper(I) chloride (98+% ACS reagent grade), and dibromodifluoromethane were obtained from Aldrich Chemical Company, Inc. tert-Butyl alcohol was obtained from Fisher Scientific Company.
4. Dibromodifluoromethane (bp 22°C) was chilled and handled as a liquid.
5. The bottom third of the tube was immersed. The reaction mixture changed color from blue-green to brown during this period.
6. This material is 95-98% pure by GLC analysis (20% DC 200 on 80-100 mesh Chromosorb P, 4' X 0.25" column, 200°C). The presence of a lower-boiling impurity, 3-bromo-3,3-difluoro-1-propenyltrimethylsilane, does not affect the yield of the subsequent steps.
7. Dimethyl sulfoxide (99+% anhydrous grade) and sodium borohydride were purchased from Aldrich Chemical Company, Inc.

8. Other polar aprotic solvents (HMPA, DMPU) were used successfully in place of DMSO in small-scale runs.

9. Shortly after starting the addition, the exothermic reaction causes an increase in temperature, and external heating is discontinued. Care should be taken not to add the sodium borohydride too rapidly, as temperatures above 92°C have resulted in the formation of an over-reduced product, 3,3-difluoropropyltrimethylsilane. It is advisable to have an ice bath available in case the reaction requires external cooling.

10. This compound has the following spectral properties: ^1H NMR (200 MHz, CDCl_3) δ : 0.02 (s, 9 H, Me_3Si), 0.72-0.83 (m, 2 H, H-1), 2.14-2.38 (m, 2 H, H-2); ^{13}C NMR δ : -1.94 (Me_3Si), 10.8 (C-1), 40.0 (t, C-2, $J = 22.6$), 125.4 (t, $J = 307$, CF_2Br).

11. The 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was purchased from Aldrich Chemical Company, Inc.

12. On a smaller scale the reaction was run in a round-bottomed flask and the product isolated at this stage by direct distillation of the reaction mixture through a short-path distillation head.

13. This product has the following spectroscopic properties: ^1H NMR (200 MHz, CDCl_3) δ : 0.00 (s, 9 H, Me_3Si), 1.2 (dt, $^3J_{\text{HH}} = 8.9$, $^4J_{\text{FH}} = 1.5$, 2 H, CH_2), 4.1 (dtd, $^3J_{\text{FH}}$ (trans) = 25.2, $^3J_{\text{HH}} = 8.9$, $^3J_{\text{FH}}$ (cis) = 2.7, 1 H, =CH); ^{13}C NMR δ : -2.25 (Me_3Si), 10.8 (unresolved m, CH_2), 74.6 (t, $^2J_{\text{FC}} = 23.0$, =CH), 156.3 (dd, $^1J_{\text{FC}} = 284$, CF_2); IR (film) cm^{-1} : 1740 s ($\text{C}=\text{CF}_2$). The ^1H NMR and IR data are consistent with those previously reported.⁴

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Radical addition of dibromodifluoromethane to alkenes followed by sodium borohydride reduction is a convenient two-step method for the introduction of the difluoromethyl group.⁵ Either one or both carbon-bromine bonds in the intermediate dibromides may be reduced, depending on the reaction conditions. In the case of *acyclic* dibromodifluoromethane-alkene adducts, the reduction occurs *regioselectively* to yield the relatively inaccessible bromodifluoromethyl-substituted alkanes. The latter are potential building blocks for other fluorinated compounds. For example, they may be dehydrohalogenated to 1,1-difluoroalkenes; an example of this methodology is illustrated in this synthesis of (3,3-difluoroallyl)trimethylsilane.

(3,3-Difluoroallyl)trimethylsilane was first prepared in low yield from the high-temperature reaction of vinyltrimethylsilane with chlorodifluoromethane.⁶ An improved synthesis involving the insertion of difluorocarbene into the requisite β -silyl ylide has been reported.⁴ Although the yield is excellent, the reaction consumes a mole of the valuable Wittig reagent (it forms the phosphonium salt which must be recycled) in generating difluorocarbene from chlorodifluoromethane. Other (3,3-difluoroallyl)silanes have been synthesized via the $\text{S}_{\text{N}}2'$ reactions of silyl anions with 3,3,3-trifluoropropenes.⁷

(3,3-Difluoroallyl)silanes are of interest as carbon-carbon bond forming building blocks in organofluorine chemistry.^{4,7,8}

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Dimethyl sulfoxide: Methyl sulfoxide (8); Methane, sulfinylbis- (9); (67-68-5)
 Sodium borohydride: Borate(1-), tetrahydro-, sodium (8,9); (16940-66-2)
 1,8-Diazabicyclo[5.4.0]undec-7-ene: Pyrimido[1,2-a]azepine,
 2,3,4,6,7,8,9,10-octahydro- (8,9); (6674-22-2)

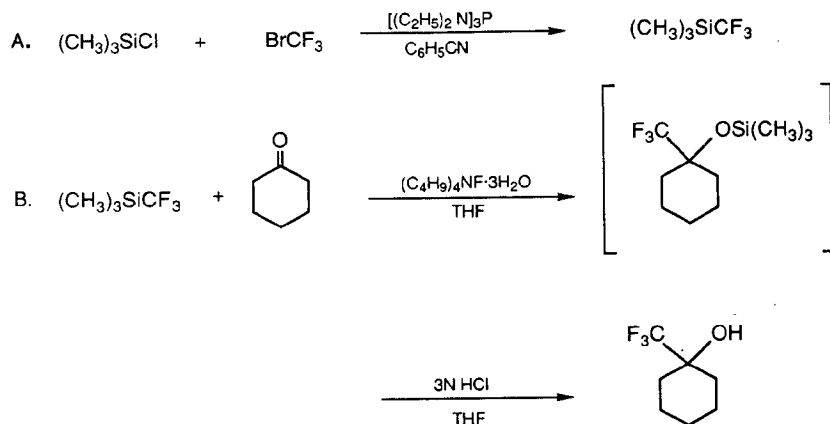
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(3,3-Difluoroallyl)trimethylsilane: Silane, (3,3-difluoro-2-propenyl)trimethyl-
 (9); (40207-81-6)
 (1,3-Dibromo-3,3-difluoropropyl)trimethylsilane: Silane, (1,3-dibromo-3,3-
 difluoropropyl)trimethyl- (9); (671-80-7)
 Vinyltrimethylsilane: Silane, trimethylvinyl- (8); Silane, ethenyltrimethyl-
 (9); (754-05-2)
 Ethanolamine: Ethanol, 2-amino- (8,9); (141-43-5)
 Dibromodifluoromethane: Methane, dibromodifluoro- (8,9); (75-61-6)
 Copper(I) chloride: Copper chloride (8,9); (7758-89-6)
 tert-Butyl alcohol (8); 2-Propanol, 2-methyl- (9); (75-65-0)
 (3-Bromo-3,3-difluoropropyl)trimethylsilane: Silane, (3-bromo-3,3-difluoropropyl)-
 trimethyl- (12); (134134-62-6)

1-TRIFLUOROMETHYL-1-CYCLOHEXANOL

(Cyclohexanol, 1-(trifluoromethyl)-)



Submitted by Pichika Ramaiah, Ramesh Krishnamurti, and G. K. Surya Prakash.¹

Checked by Zhen-Yu Yang and Bruce E. Smart.

1. Procedure

Caution! All operations should be performed in a well ventilated hood. Hexaethylphosphorous triamide is potentially toxic and should be handled with protective gear.

A. (Trifluoromethyl)trimethylsilane. A 2-L, three-necked flask is fitted with an efficient, over-head, sealed mechanical stirrer, a cold-finger condenser (30-cm in length and 8-cm in diameter) and a rubber septum (Note 1). The top outlet of the condenser is attached to an oil bubbler. The flask is flushed with dry nitrogen and charged with 118.8 g (1.09 mol) of chlorotrimethylsilane (Note 2) in 100 mL of

anhydrous benzonitrile (Note 3). The septum is replaced quickly under dry nitrogen with a 500-mL Ace dry ice gas condenser trap (15-cm in length and 8-cm in diameter) (Note 4). The outlet of the trap is protected from moisture by a tube packed with potassium hydroxide and the inlet is connected by tygon tubing to a cylinder of bromotrifluoromethane (Note 5). The 2-L flask is immersed in a dry ice-acetone bath maintained at -30°C (Note 6) and the condensers are filled with dry ice-acetone mixture (-78°C). The cylinder is opened and 250 mL ($d = 1.94 \text{ g/mL}$,² 485 g, 3.25 mol) of bromotrifluoromethane is condensed into the 500-mL Ace reservoir (Note 7). Stirring is started, and the condensed liquid bromotrifluoromethane is gradually added to the vessel at -30°C by slowly warming the reservoir to -45°C to -50°C . The resulting white slurry is further cooled to -60°C (Notes 6 and 8). The Ace dry ice gas condenser trap is disconnected under dry nitrogen and replaced with a 600-mL pressure-equalizing dropping funnel containing a solution of 325.0 g (1.31 mol) of hexaethylphosphorous triamide (Note 9) in 250 mL of dry benzonitrile. This solution is added with stirring at -60°C to the white slurry mixture over a period of 2.5 hr. After the addition is complete, the reaction mixture is stirred for an additional hour at -60°C (Note 10), and then allowed to warm gradually to room temperature (25°C) over a period of 14 hr, during which time it turns clear yellow (Note 11). The condenser and dropping funnel are removed and replaced by a glass stopper and joint adapter with its glass tube connected to two, 250-mL, dry ice-acetone-cooled traps; then aspirator vacuum (ca. 20 mm) is applied. The reaction flask is gently warmed to 50°C during which time (3 hr) all the volatile material collects in the cooled traps (Note 12). The cooling baths are removed and the material in the traps is brought to 0°C . The colorless liquid is transferred quickly to a 250-mL separatory funnel, washed rapidly with ice cold water ($3 \times 100 \text{ mL}$), and the top organic product layer is separated (Note 13). The product is dried over 5 g of anhydrous magnesium sulfate, and the dry liquid is decanted into a 250-mL flask. The product is fractionally distilled through a 15-cm

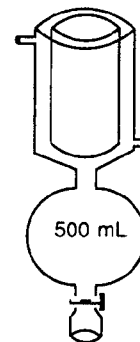
column packed with glass helices. Three fractions are collected. The first minor fraction (bp 45-54°C) and the second major fraction (bp 54-55°C) contain the main quantity of (trifluoromethyl)trimethylsilane. The third minor fraction (bp 55-65°C) consists mainly of hexamethyldisiloxane with a small quantity of product (trifluoromethyl)trimethylsilane (Note 14). The first and second fractions are combined to yield 116.9 g (75%) of clear liquid product (Notes 15 and 16), bp 54-55°C (Note 17).

B. 1-Trifluoromethyl-1-cyclohexanol. A 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and a reflux condenser is attached to a nitrogen source to maintain a positive pressure and the other neck is closed with a glass stopper. Tetrahydrofuran (70 mL) (Note 18) and 19.2 g (0.13 mol) of (trifluoromethyl)trimethylsilane are introduced into the flask through the septum using dry syringes (Note 19). The flask is immersed in an ice-water bath (0°C), and a solution of 10.2 g (0.104 mol) of cyclohexanone (Note 20) in 50 mL of tetrahydrofuran is added to the stirred solution of (trifluoromethyl)trimethylsilane using a syringe. Tetrabutylammonium fluoride trihydrate (33 mg) catalyst (Note 21, 22) is transferred into the reaction vessel. As the exothermic reaction proceeds, a yellowish brown color develops with the initial evolution of fluorotrimethylsilane (Note 23). The reaction mixture is stirred at 0°C for 30 min and then the cooling bath is removed. The reaction mixture is brought to room temperature and stirred for an additional hour. The reaction mixture is periodically analyzed by GC-MS and the reaction is complete within 1 hr at 25°C (Note 24). To the reaction mixture that contains crude 1-trifluoromethyl-1-O-(trimethylsilyl)cyclohexane are added 25 mL of tetrahydrofuran and 40 mL of 3 N hydrochloric acid. The mixture is stirred at room temperature for 8 hr and then transferred to a 500-mL separatory funnel containing 50 mL of water. The product is extracted with 50 mL of ether. The organic layer is separated and the aqueous layer is reextracted with 30 mL of ether. The combined organic layers are washed with 50 mL

of water, dried over 10 g of anhydrous magnesium sulfate, and filtered. The residue is repeatedly washed with dry ether (3 x 20 mL). The solvent is removed on a rotary evaporator and the residue is dried to give a semi solid that is purified by sublimation under vacuum (Note 25) to furnish 13.9-14.3 g (79-82%) of 1-trifluoromethyl-1-cyclohexanol as a white waxy solid, mp 60.8°C (Note 26).

2. Notes

1. All glass apparatus is dried in an oven at 100°C and assembled while still hot under dry nitrogen flow. All ground glass joints are tightly sealed with a Teflon tape and then wrapped with parafilm.
2. Chlorotrimethylsilane (98%) was obtained from the Aldrich Chemical Company, Inc. and was distilled over calcium hydride under a static atmosphere of dry nitrogen just prior to use.
3. Anhydrous benzonitrile (99+%) was purchased from the Aldrich Chemical Company, Inc. and used without further purification.
4. The trap was built in house. A 1000-mL Ace trap is available from the Aldrich Chemical Company, Inc.



Ace dry ice gas condenser trap

5. Bromotrifluoromethane, bp -57°C , was supplied by E.I. du Pont de Nemours & Co., Inc.

6. A temperature of -30°C to -60°C was maintained by adding dry ice to excess acetone.

7. The rate of bromotrifluoromethane transfer was monitored by a Nujol bubbler. A mark is made on the Ace reservoir trap to indicate the 250-mL volume.

8. If the temperature falls below -60°C , the reaction mixture solidifies but returns to a liquid upon warming. The inverse addition, i.e., addition of chlorotrimethylsilane to bromotrifluoromethane, causes formation of a solid block that impedes stirring.

9. Hexaethylphosphorous triamide (97%) was obtained from the Aldrich Chemical Company, Inc., and used as received. It can be prepared from diethylamine and phosphorus trichloride following the literature procedure.³

10. An exothermic reaction usually begins after all the hexaethylphosphorous triamide is introduced, and some of the bromotrifluoromethane escapes through the bubbler.

11. To recover excess unreacted bromotrifluoromethane, a dry ice-acetone cooled trap is connected to the condenser outlet before the reaction mixture is warmed to room temperature.

12. The proton NMR of the distillate shows the two methyl group absorptions of (trifluoromethyl)trimethylsilane and chlorotrimethylsilane in a ratio of about 85:15. The material solidifies in a dry ice-acetone cooled trap.

13. The distillate is shaken well with water to convert chlorotrimethylsilane to hexamethyldisiloxane.

14. The product from the third fraction could not be isolated pure by redistillation.

15. The yield is based on chlorotrimethylsilane. A comparable yield of 77% was obtained when the reaction was repeated on one-third the scale. GC and NMR analyses show the product to be 98-99% pure.

16. (Trifluoromethyl)trimethylsilane has the following spectroscopic properties: ^1H NMR (200 MHz, CDCl_3) δ : 0.25 (s, 9 H, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (50.0 MHz, CDCl_3) δ : 131.7 (q, $1J(^{13}\text{C}-^{19}\text{F}) = 321.9$), -5.2 ($\text{CH}_3\text{-Si}$); ^{19}F NMR (188.0 MHz, CDCl_3 , CFCI_3 external) δ : -66.1; ^{29}Si NMR (39.7 MHz, CDCl_3) δ : +4.7 (q, $2J(^{29}\text{Si}-^{19}\text{F}) = 37.9$). MS (m/z) 123 ($\text{M}^+ - 19$).

17. The boiling point for (trifluoromethyl)trimethylsilane is reported as 45°C .⁴ The submitters report a boiling point of 55.5°C .

18. Reagent grade tetrahydrofuran was purchased from the Fisher Scientific Company and freshly distilled from sodium benzophenone ketyl under dry nitrogen atmosphere.

19. Prior to use, the hypodermic syringes and needles were dried for several hours in an oven at 100°C and allowed to cool to ambient temperature in a desiccator.

20. Cyclohexanone (99%) was purchased from the Aldrich Chemical Company, Inc., and used as such.

21. Tetrabutylammonium fluoride (TBAF) trihydrate (99%) was purchased from the Aldrich Chemical Company, Inc.

22. TBAF trihydrate acts as an initiator and the water of hydration in TBAF does not pose any problem.

23. Bubbles of fluorotrimethylsilane are seen escaping during the initial stages of the reaction.

24. Progress of the reaction can be monitored by GC-MS using a Finnigan Model Inco-50 GC-MS spectrometer: Column: DB-5; temperature program: 50°C (4.5 min), $30^{\circ}\text{C}/\text{min}$, 250°C (30 min). Retention time: Cyclohexanone, 7.44 min. and 1-trifluoromethyl-O-(trimethylsilyl)cyclohexane, 11.20 min.

25. The product was sublimed at 2 mm at a bath temperature of 100°C. The receiver is cooled to 0°C, using an ice-bath.

26. The submitters report a melting point of 61.6°C. The product is pure (GC-MS) and has the following spectroscopic and analytical data : IR (KBr) cm^{-1} : 3364(s), 1255(s), 1146(s); ^1H NMR (200 MHz, CDCl_3) δ : 1.00-1.90 (m, 10 H), 1.93 (br, 1 H, OH); ^{13}C NMR (50.0 MHz, CDCl_3) δ : 20.2, 25.0, 29.8, 72.6 (q, $^2\text{JC-F} = 28.2$), 126.4 (q, $^1\text{JC-F} = 284.5\text{Hz}$, CF_3); ^{19}F NMR (188 MHz, CDCl_3 , CFCl_3 , external) δ : -85.0; MS (m/z): 149 ($\text{M}^+ - 19$, 0.57), 125 (1.25), 112 (1.23), 99 (100), 92 (1.50), 81 (66.79), 69 (10.49), 55 (26.01), 41 (37.26). Anal. Calcd for $\text{C}_7\text{H}_{11}\text{F}_3\text{O}$: C, 50.00; H, 6.59. Found: C, 49.69; H, 6.51.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

(Trifluoromethyl)trimethylsilane has been prepared by a modification⁵ of the procedure originally published by Ruppert.⁴ The optimized yield is 75%. Other less convenient methods are also available for its preparation.⁶ (Trifluoromethyl)trimethylsilane acts as an in situ trifluoromethide equivalent under nucleophilic initiation and reacts with a variety of electrophilic functional groups. Carbonyl compounds such as aldehydes, ketones and lactones react rather readily^{5,7} with (trifluoromethyl)trimethylsilane under fluoride initiation. The reagent also reacts with oxalic esters,⁸ sulfonyl fluorides,⁹ α -keto esters,¹⁰ fluorinated ketones,¹¹ and

sulfoxides.¹² Homologous trifluoromethyltrialkylsilanes have also been used as nucleophilic trifluoromethylating agents.¹³ In the presence of copper(I) iodide (CuI), homologous (trifluoromethyl)triethylsilane reacts with aromatic, allylic and benzylic halides to provide the corresponding trifluoromethyl derivatives.¹⁴

1. Donald P. and Katherine B. Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, CA 90089-1661.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Trifluoromethyl-1-cyclohexanol: Cyclohexanol, 1-(trifluoromethyl)- (10);
(80768-55-4)

Hexaethylphosphorous triamide (= HEPT): Diethylamine, N,N',N"-phosphinidynetris-
(8); Phosphorous triamide, hexaethyl- (8,9); (2283-11-6)

(Trifluoromethyl)trimethylsilane: Silane, trimethyl(trifluoromethyl)- (11); (81290-20-2)

Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

Benzonitrile (8,9); (100-47-0)

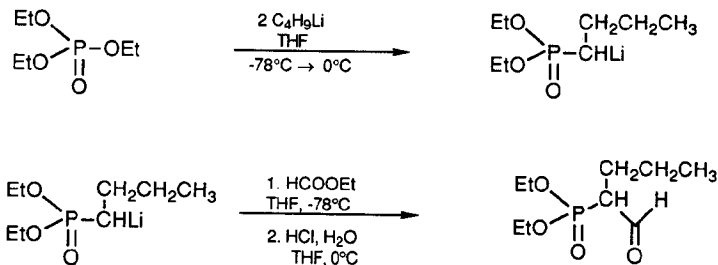
Bromotrifluoromethane: Methane, bromotrifluoro- (8,9); (75-63-8)

Cyclohexanone: (8,9); (108-94-1)

Tetrabutylammonium fluoride hydrate: Ammonium, tetrabutyl-, fluoride, hydrate (8,9);
(22206-57-1)

Fluorotrimethylsilane: Silane, fluorotrimethyl- (8,9); (420-56-4)

DIETHYL 1-PROPYL-2-OXOETHYLPHOSPHONATE (Phosphonic acid (1-formylbutyl)-, diethyl ester)



Submitted by Philippe Savignac and Carl Patois.¹

Checked by David R. Jones and Amos B. Smith, III.

1. Procedure

A four-necked, 500-mL, round-bottomed flask is fitted with an efficient mechanical stirrer, thermometer, reflux-condenser with a bubbler, and a 200-mL pressure-equalizing dropping funnel with a nitrogen inlet. The flask is flame-dried, flushed with nitrogen (the checkers used argon throughout), and charged with 100 mL of tetrahydrofuran (THF) (Note 1). The dropping funnel is charged with 140 mL of a 1.5 M solution of butyllithium in hexane (0.210 mol) (Note 2). The flask is cooled to -20°C with a dry ice/acetone bath (Note 3), stirring is started, and butyllithium is added to tetrahydrofuran over a few minutes. The resulting yellow solution is cooled to -78°C. The cooling bath is then kept just below the bottom of the flask while a solution of triethyl phosphate (18.2 g, 0.1 mol) (Note 4) in tetrahydrofuran (50 mL) is added dropwise from the dropping funnel over 15 min at such a rate that the temperature of

the reaction mixture slowly rises to 0°C (Note 5). The resulting solution is stirred for an additional 15 min at 0°C. By this time, the yellow color has practically disappeared and the solution is clear. The reaction mixture is cooled to -78°C and a solution of ethyl formate (7.9 g, 0.107 mol) (Note 6) in tetrahydrofuran (20 mL) is added dropwise at this temperature. The reaction mixture is stirred for 30 min, then allowed to warm up slowly to 0°C, and quenched by the dropwise addition of 80 mL of 3 M hydrochloric acid. The organic layer is separated, and the aqueous phase is extracted with three 50-mL portions of dichloromethane. The extracts are combined with the original organic layer, and dried over anhydrous magnesium sulfate. The magnesium sulfate is removed by filtration, and the solvents are evaporated on a rotary evaporator. The yellow, crude liquid is distilled through a short column (Note 7) to give 21.0 g (94%) of diethyl 1-propyl-2-oxoethylphosphonate (Note 8) as a pale yellow oil (Note 9), bp 110-115°C/0.05 mm (Note 10).

2. Notes

1. Tetrahydrofuran available from S.D.S. Company was purified by distillation from sodium and benzophenone.

2. The submitters used butyllithium in hexane available from Janssen Chimica and standardized before use by titration against a solution of benzylic alcohol in toluene and cuproine (2,2'-biquinoline). The checkers used butyllithium (1.6 M in hexane) available from Aldrich Chemical Company, Inc., which was standardized before use by titration with diphenylacetic acid in THF.

3. An alternative cooler was used by the submitters, consisting of a Dewar partially filled with liquid nitrogen.

4. The submitters used triethyl phosphate, 99%, available from Janssen Chimica without further purification. The checkers used triethyl phosphate (99+ %) available from Aldrich Chemical Company, Inc., without further purification.

5. The reaction mixture must be only slightly cooled by placing it just above the cooling bath, so that the reaction proceeds smoothly.

6. The submitters used ethyl formate, 97%, available from Janssen Chimica, without further purification. Dimethylformamide (DMF) can be used instead of ethyl formate with the same operating conditions. The checkers used ethyl formate (99%), available from Aldrich Chemical Company, Inc., without further purification.

7. The submitters used an 8-cm fractionating column equipped with a condenser for distillation.

8. The product displays the following spectroscopic data: $m/e = 222$; ^{31}P NMR (CDCl_3) δ : +19.4 (CHO form), +24.2 (=CHOH form); ^1H NMR (CDCl_3) δ : 0.88 (t, 3 H), 1.30 (t, 6 H), 1.1-2.3 (m, 4 H), 2.9 (m, 1 H), 4.1 (dq, 4 H), 9.6 (d, 1 H). In the presence of the enol form, the ^1H spectrum is more complex and exhibits the signal of the aldol proton at 7.3 ppm. ^{13}C NMR (CDCl_3) δ : 13.7 ($\text{CH}_3\text{-CH}_2$), 15.8 ($\text{CH}_3\text{-CH}_2\text{-O}$), 21.3 (CH_2), 25.5 (CH_2), 52.6 (d, J_{PC} 126.0, P-CH , CHO form), 61.0 and 62.6 (O-CH_2), 99.2 (d, J_{PC} 195.7, P-C= , CHOH form), 156.6 (d, J_{PC} 29.0, P-C= , CHOH form), 196.0 (C=O). When several grains of solid potassium carbonate were added to the NMR sample, the ^1H and ^{13}C NMR spectra were consistent with the spectral data provided by the submitters for the keto form of the title compound.

9. The distilled product was found to be slightly yellow. It should be stored at 0°C; under these conditions, the purified product is stable for at least several months.

10. The large temperature range is due to the distillation of a mixture of the keto-enol tautomers.

3. Discussion

This procedure, based on the alkylation-metalation of a trialkyl phosphate by alkyllithiums,² illustrates a general route to diethyl 1-formylalkylphosphonates. The method is general and characterized by good yields, mild conditions, and easy preparation of phosphonic aldehydes in pure form starting from readily available materials. It has been shown to be applicable to a wide variety of organolithium reagents, linear (MeLi, EtLi, PrLi) or branched (i-BuLi, isopentyllithium). It is superior to the multistep synthesis previously described which includes an Arbuzov reaction with a protected aldehyde, acidic hydrolysis, enaminophosphonate alkylation, and acidic hydrolysis.³ Diethyl 1-formylalkylphosphonates are useful intermediates in the Wittig-Horner synthesis of α,β -unsaturated aldehydes and in the synthesis of aminoalkylphosphonates by reductive amination.⁴

1. Laboratoire de Chimie du Phosphore et des Métaux de Transition, DCPH, Ecole Polytechnique, 91128 Palaiseau Cedex, France.
2. Teulade, M. P.; Savignac, P. *Tetrahedron Lett.* **1987**, *28*, 405; Teulade, M. P.; Savignac, P. *Janssen Chim. Acta* **1988**, *6*(2), 3; *Chem. Abstr.* **1989**, *110*, 95397m.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Diethyl 1-propyl-2-oxoethylphosphonate: Phosphonic acid, (1-formylbutyl)-, diethyl ester (12); (112292-30-5)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

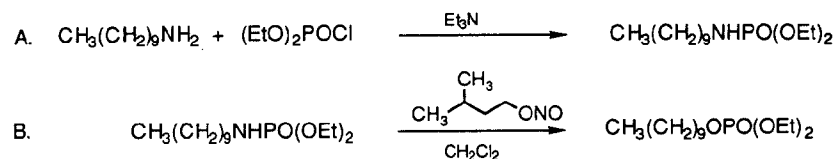
Triethyl phosphate: Phosphoric acid, triethyl ester (8,9); (78-40-0)

Ethyl formate: Formic acid, ethyl ester (8,9); (109-94-4)

CONVERSION OF AMINES TO PHOSPHO ESTERS:

DECYL DIETHYL PHOSPHATE

(Phosphoric acid, decyl diethyl ester)



Submitted by Nick Nikolaidis, Ioanna Schipor, and Bruce Ganem.¹

Checked by Susumu Saito and Hisashi Yamamoto.

1. Procedure

A. Diethyl decylphosphoramidate. An oven-dried (Note 1), three-necked, septum-capped, 250-mL, round-bottomed flask containing a 1-inch magnetic stirring bar is flushed with argon and charged with 10.0 mL (0.05 mol) of decylamine (Note 2) and 35 mL (0.25 mol) of triethylamine (Note 3). The solution is cooled to 0°C in an ice bath with stirring. Using a 10-mL, gas-tight syringe, 7.4 mL (0.05 mol) of diethyl chlorophosphate (Note 4) is added dropwise, whereupon a voluminous white precipitate forms. Upon completion of addition, vigorous stirring is maintained for 30 min at 0°C. The mixture is diluted with 100 mL of ice-cold, anhydrous diethyl ether (Note 5) and filtered through a sintered glass funnel (Note 6) layered with ca. 1 in. of Celite. The solid residue is washed with ca. 50 mL of fresh, cold ether, and the filtrate is concentrated by rotary evaporation (room temperature under aspirator pressure) to give a cloudy white suspension. Another aliquot of cold ether (50 mL) is added and the process of filtration through Celite is repeated at least three times (Note 7). Concentration by rotary evaporation followed by drying under reduced pressure for 1

hr at 0.1 mm provides 14.0-14.5 g (95-99% yield) of a clear, pale yellow oil (Note 8). This compound is stored under argon until used in part B.

B. Decyl diethyl phosphate. An oven-dried (Note 1), three-necked, septum-capped, 250-mL, round-bottomed flask containing a 1-in. magnetic stirring bar is flushed with argon and charged with 14 g (0.048 mol) of diethyl decylphosphoramidate and 125 mL of dichloromethane (Note 9). Using a 20-mL gas-tight syringe, 31.9 mL (0.24 mol) of isoamyl nitrite (Note 10) is added successively in two portions (20 mL, 11.9 mL) at 33°C (oil bath) and stirring is continued for 18 hr. At this time, nitrogen evolution is no longer observed and thin layer chromatography (eluting with 3:2 hexanes:ethyl acetate, Note 11) indicates the complete disappearance of starting phosphoramidate ($R_f = 0.1$) and the appearance of a major product spot ($R_f = 0.3$). The solvent is removed by rotary evaporation (40-50°C under aspirator pressure) to produce 17 g (>100%) of a viscous yellow oil that still contains traces of isoamyl nitrite and other impurities. The crude product is redissolved in 20 mL of ethyl acetate, loaded onto a 1" x 6" column of Silica Gel 60 (Note 12) and eluted under pressure (Note 13) with 150 mL of ethyl acetate into a 500-mL, round-bottomed flask. The solvent is removed by rotary evaporation (room temperature under aspirator pressure), the product is transferred to an ammonia-washed (Note 14), oven-dried, 50-mL, round-bottomed flask and distilled under vacuum to yield 7.7-8.8 g (54-60%) of the phospho triester as a clear, colorless oil (bp 95-105°C/0.15 mm) (Notes 15 and 16).

2. Notes

1. All glassware was oven-dried for at least 24 hr at 130°C, assembled hot, and cooled under a stream of argon.²

2. Decylamine was obtained from Aldrich Chemical Company, Inc., and was distilled under reduced pressure prior to use (bp 70°C at 1.9 mm).

3. Reagent grade triethylamine was obtained from Mallinckrodt Inc. and distilled from barium oxide immediately prior to use (bp 87°C at 1 atm).

4. Diethyl chlorophosphate (97%) was obtained from Aldrich Chemical Company, Inc., and distilled before use (bp 58-60°C at 2 mm). This material is a highly toxic acetylcholinesterase inhibitor and must be handled with caution.

5. Diethyl ether was distilled from sodium benzophenone ketyl immediately before use.

6. A grade D (10-20 m) sintered glass funnel from Ace Glass Corporation was used.

7. Insufficient filtrations led to solid precipitates after rotary evaporation.

8. The product exhibits the following spectral properties: IR (film) cm^{-1} : 3220, 2970, 2880, 1470, 1240, 1060, 1040; ^1H NMR (300 MHz, CDCl_3) δ : 0.78 (t, 3 H, $\text{J} = 6.4$, CH_3), 1.17-1.25 (m, 20 H, $-\text{[CH}_2\text{]}_7-\text{OCH}_2\text{CH}_3$), 1.39 (m, 2 H, $\text{CH}_2\text{CH}_2\text{N}$), 2.79 (m, 3 H, NH , CH_2N), 3.96 (m, 4 H, OCH_2CH_3); CIMS (isobutane) m/z 294 ($\text{M}+1$, 100%).

9. Dichloromethane was dried and distilled over calcium hydride immediately prior to use.

10. Isoamyl nitrite (97%) was obtained from either Aldrich Chemical Company, Inc., or Fluka AG and used without further purification. Five equivalents of isoamyl nitrite were optimal for complete consumption of starting phosphoramidate. Use of three equivalents of isoamyl nitrite necessitated much longer reaction times (2-3 days) and resulted in incomplete conversions.

11. ACS reagent grade hexanes and ethyl acetate were obtained from Aldrich Chemical Company, Inc. Thin layer chromatography was performed on Silica Gel 60 F-254 precoated plates. Chromatograms were visualized with phosphomolybdic acid reagent from Aldrich Chemical Company, Inc.

12. Silica Gel 60 (230-400 mesh) was obtained from Merck & Company, Inc.

13. The published procedure of flash chromatography was employed.³

14. The distillation flask was rinsed with 28% ammonium hydroxide solution to neutralize the acidic glass surface, then placed directly in the oven (i.e., with no aqueous rinse).

15. The product exhibits the following spectral properties: IR (film) cm^{-1} : 2940, 2860, 1470, 1395, 1275, 1040, 755; ^1H NMR (300 MHz, CDCl_3) δ : 0.82 (t, 3 H, $\text{J} = 6.8$, CH_3), 1.24-1.33 (m, 20 H, $-\text{[CH}_2\text{]}_7-\text{OCH}_2\text{CH}_3$), 1.63 (m, 2 H, $\text{CH}_2\text{CH}_2\text{OP}$), 3.96-4.13 (m, 6 H, OCH_2-); CIMS (isobutane) m/z 295 ($\text{M}+1$, 50%), 155 (100%).

16. The checkers isolated decyl isoamyl ether as a side-reaction product in 2.0-2.3 g (18-20%) yield. This product exhibits the following spectral properties: ^1H NMR (200 MHz, CDCl_3) δ : 0.80-1.05 (m, 9 H, $\text{C[CH}_3\text{]}_2$, $-\text{CH}_3$), 1.12-1.80 (m, 19 H, $[\text{CH}_2]_8$, $-\text{OC-CH}_2\text{CH}_2$), 3.41 (q, 4 H, $\text{J} = 6.6$, OCH_2); (bp 80-85°C/0.5 mm).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Phospho esters are important components of nucleic acids, lipids, and other biologically significant substances. Most existing phospho ester syntheses rely on the direct phosphorylation of alcohols.⁴ Here, a general procedure for the conversion of amines into phospho esters is described,⁵ based on the well-known thermal decomposition of N-nitroso carboxamides to carboxylic esters, that represents one of the few useful synthetic methods for replacing an amine group with oxygen-based functionality.⁶⁻⁸ Besides complementing existing methods for synthesizing phospho triesters, the nitrosation of phosphoramidates makes available unnatural phosphates

derived from naturally-occurring amino sugars, alkaloids, and amino acids. Phospho monoesters may similarly be prepared by hydrogenolysis of the corresponding alkyl dibenzyl phosphates.⁹

1. Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, NY 14853-1301
2. Techniques for handling air-sensitive compounds are reviewed in Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. "Organic Syntheses via Boranes"; Wiley: New York, 1975: Technical data on air-sensitive compounds is also available in Lane, C. F.; Kramer, G. W. *Aldrichemica Acta* **1977**, *10*, 11-16.
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8. For alternative methods, see (a) Katritzky, A.R. *Tetrahedron* **1980**, *36*, 679; (b) DeChristopher, P. J.; Adamek, J.P.; Klein, S. A.; Lyon, G. D.; Baumgarten, R. J. *J. Org. Chem.* **1975**, *40*, 3288; (c) White, E. H.; Maskill, H.; Woodcock, D. J.; Schroder, M. A. *Tetrahedron Lett.* **1969**, 1713; (d) Moss, R. A. *Chem. Eng. News* **1971**, *49*, 28-36
9. Luo, J.; Ganem, B. *Tetrahedron Lett.* **1991**, *32*, 3145.

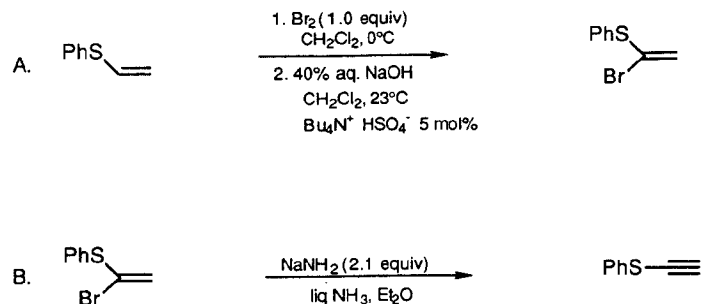
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Decyl diethyl phosphate: Phosphoric acid, decyl diethyl ester (9); (20195-16-8)
 Diethyl decylphosphoramidate: Phosphoramidic acid, decyl-, diethyl ester (9); (53246-96-1)
 Decylamine (8); 1-Decanamine (9); (2016-57-1)
 Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)
 Diethyl chlorophosphate: Phosphorochloridic acid, diethyl ester (8,9); (814-49-3)
 Isoamyl nitrite: Nitrous acid, isopentyl ester (8); Nitrous acid, 3-methylbutyl ester (9); (110-46-3)

PHENYLTHIOACETYLENE

(Benzene, (ethynylthio)-)



Submitted by Plato A. Magriotis and John T. Brown.¹

Checked by Armin Walser, Carl Mason, and David L. Coffen.

1. Procedure

Caution! These operations involve reagents and solvents with potentially harmful vapors (Br_2 , NH_3) and therefore should be conducted in an efficient hood. The use of disposable gloves is highly recommended.

A. 1-Bromovinyl phenyl sulfide. A 1-L, round-bottomed flask is equipped with a 1.5-in egg-shaped magnetic stirring bar and a 100-mL, pressure-equalizing, addition funnel fitted with a Claisen adapter that contains a drying tube and stopper. The flask is charged with 40.8 g (0.30 mol) of phenyl vinyl sulfide (Note 1) and 250 mL of dichloromethane (Note 2). The resulting solution is cooled to 0°C and 49.6 g (0.31 mol) of bromine (Note 3) is added dropwise over approximately 1 hr through the funnel, until a bright red color persists. The intermediate product, phenylthio-1,2-

dibromoethane (Note 4), is then treated at 0°C with 250 mL of aqueous 40% sodium hydroxide followed by 5.1 g (15 mmol, 5 mol%) of the phase-transfer catalyst tetrabutylammonium hydrogen sulfate. Vigorous stirring is continued at ambient temperature for 2-3 hr until TLC (10% benzene, 90% hexane) indicates that dehydrobromination is complete (Note 5). The organic layer is separated and the aqueous layer is extracted with two, 200-mL portions of dichloromethane. The combined organic extracts are washed with a saturated solution of sodium bisulfite (250 mL), water (250 mL), and brine (250 mL) and dried over sodium sulfate. Excess dichloromethane is removed under reduced pressure on a rotary evaporator and the resulting dark brown oil is distilled under vacuum (1.5 mm) to provide 51.5-58.0 g (80-90%) of pure 1-bromovinyl phenyl sulfide as a pale yellow liquid, bp 76-78°C (Notes 6 and 7).

B. Phenylthioacetylene. An oven-dried, 2-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer (Note 8), an acetone-dry ice condenser with a drying tube containing potassium hydroxide pellets, and a gas inlet. The flask is placed in an acetone-dry ice bath (-40°C, bath temperature) and 450 mL of anhydrous ammonia (Note 9) is condensed into the flask. Upon addition of a small piece of sodium metal (ca. 0.6 g) to the liquid ammonia the characteristic deep blue color develops. A catalytic amount of anhydrous ferric chloride (0.25 g, 1.5 mmol; 0.3 mol%) is added with continued stirring (Note 10) and the color of the reaction mixture turns gray. The remaining sodium metal (10.0 g, 0.46 g-atom total) is added in 0.6-g pieces over ca. 1 hr, since the blue color must be discharged before each new addition of sodium. A gray suspension of sodium amide is obtained upon completion of this addition. The temperature of the cooling bath is adjusted to -50°C and the gas inlet is replaced with a 250-mL, pressure-equalizing addition funnel containing 49.5 g (0.23 mol) of 1-bromovinyl phenyl sulfide in 100 mL of anhydrous ether (Note 11). This solution is added dropwise to the freshly generated sodium amide over 20 min, while

the temperature of the acetone-dry ice bath is maintained at -50°C . Stirring is continued (Note 8) at this temperature for 0.5 hr, the brown-red reaction mixture is allowed to warm to reflux temperature (-33°C) during 1 hr, and then is recooled to -60°C (bath temperature). Solid ammonium chloride is added slowly (Note 12) to quench the sodium phenylthioacetylide, the cooling bath is removed, and the ammonia is allowed to evaporate. During evaporation, 400 mL of anhydrous ether (Note 13) is added dropwise through the addition funnel to replace ammonia. The resulting mixture is filtered at ambient temperature and reduced pressure through a coarse, Celite-packed, fritted-glass filter to remove the inorganic salts that are subsequently washed three times with 50 mL of anhydrous ether. The combined ethereal filtrate and washes are concentrated on a rotary evaporator and the dark brown residue (Note 14) is transferred to a 100-mL, round-bottomed flask fitted with a short-path distillation head. Pure product (Note 15) is distilled at 1.5 mm pressure (bp $48-50^{\circ}\text{C}$, Note 16) into an ice-cooled receiver. In this way, 21.6-24.7 g (70-80% yield) of phenylthioacetylene (Note 17) is obtained as a pale yellow liquid, which turns brown-red upon storage at -10°C (freezer) within a few hours (Note 18). Phenylthioacetylene stored under these conditions is stable for several months.

2. Notes

1. Phenyl vinyl sulfide is prepared from thiophenol and 1,2-dibromoethane according to the procedure described by Paquette and Carr; see: *Org. Synth.* **1985**, *64*, 157. An earlier, three-step synthesis employing 2-chloroethanol instead of 1,2-dibromoethane is available.²

2. Dichloromethane (A.C.S. certified) was obtained from Fisher Scientific Company and used as received.

3. Bromine (A.C.S. certified) was purchased from Aldrich Chemical Company Inc., used as received, and measured with a 50-mL graduated cylinder in the hood.

4. At this point crude phenylthio-1,2-dibromoethane can be isolated by separation of the organic phase, extraction of the aqueous layer with dichloromethane, washing of the combined extracts with saturated sodium bisulfite solution, drying (MgSO_4), and concentration (95% crude yield): ^1H NMR (270 MHz, CDCl_3) δ : 3.75 (dd, 1 H, $J = 11.0, 8.6$), 3.94 (dd, 1 H, $J = 11.0, 5.5$), 5.39 (dd, 1 H, $J = 8.6, 5.5$), 7.20-7.70 (m, 5 H). This dibromide is relatively unstable giving rise to a streak on silica gel TLC (10% benzene, 90% hexanes; R_f of the streak front is ca. 0.35, anisaldehyde detection). It has been reported that a 2:1-3:1 ratio of cis- and trans-2-bromovinyl phenyl sulfide is obtained upon distillation of the above dibromide.²

5. Neither a streak nor any significant by-product is detected (UV and anisaldehyde) by TLC analysis (Merck 0.25-mm thickness silica gel plates with 254 nm UV indicator).

6. Assay of this material by GC/MS (HP 5970 Mass Selective Detector equipped with a 50-m HP-1 capillary column) shows it to be ca. 96% pure ($R_t = 3.6$ min; $80-280^{\circ}\text{C}$, $20^{\circ}\text{C}/\text{min}$). The spectral and analytical properties are as follows: ^1H NMR (270 MHz, CDCl_3) δ : 5.83 (d, 1 H, $J = 2.2$), 5.93 (d, 1 H, $J = 2.2$), 7.35-7.55 (m, 5 H); MS m/e (relative intensity) 216 (M^+ , 17), 214 (16), 135 (100), 109 (15). Anal. Calcd for $\text{C}_8\text{H}_7\text{BrS}$: C, 44.67; H, 3.28; S, 14.91. Found: C, 44.30; H, 3.46; S, 15.23.

7. The literature boiling point is reported as $70-73^{\circ}\text{C}$ (2 mm). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) in ether has been employed to effect this elimination.³ However, the procedure reported here is more amenable to large scale preparation because of its lower cost.

8. The stirring blade should be glass because sodium in ammonia solution attacks Teflon.

9. Commercial anhydrous ammonia is employed without further drying.

10. Stirring is maintained at a rate such that splattering of the reaction mixture on the upper parts of the flask's side-wall is minimized (see also ref 4, Chapter I, pp 1-4).

11. Ether is distilled from sodium-benzophenone ketyl under argon just prior to use.

12. A total of 35 g of solid ammonium chloride is added in portions of ca. 1 g with a spatula.

13. Anhydrous ether (A.C.S. certified) was obtained from Fisher Scientific Company and used as received.

14. TLC analysis (10% benzene, 90% hexanes) of the crude reaction mixture (95% yield) indicates complete conversion of vinyl bromide ($R_f = 0.5$) to phenylthioacetylene ($R_f = 0.6$). A minor product, which can be purified by flash column chromatography and identified as *cis*-1,2-bis(phenylthio)ethylene,⁵ is also detected ($R_f = 0.3$) in variable amounts (5-15% yield) depending on the run.

15. Assay of this material by GC/MS shows it to be >98% pure ($R_t = 3.0$ min; 80-280°C, 15°C/min).

16. Four literature boiling points are reported: 78-79°C (7 mm),^{5b} 86-88°C (14 mm),² 61-62°C (5 mm),² and 48°C (0.8 mm).^{6a}

17. Spectral and analytical properties for phenylthioacetylene are as follows: IR (neat) cm^{-1} : 3285, 2040, 1585; ^1H NMR (270 MHz, CDCl_3) δ : 3.26 (s, 1 H), 7.20-7.50 (m, 5 H), ; ^{13}C NMR (67.8 MHz, CDCl_3) δ : 70.0, 87.0, 126.5, 126.7, 129.2 131.4; MS m/e (relative intensity) 134 (M^+ , 100), 90 (24), 89 (26), 51 (44). Anal. Calcd for $\text{C}_8\text{H}_6\text{S}$: C, 71.60; H, 4.51; S, 23.89. Found: C, 71.77; H, 4.63; S, 24.31.

18. It has been reported that methyl phenyl sulfide acts as a stabilizer; phenylthioacetylene did not tend to darken in its presence.^{5b}

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academy Press; Washington, DC, 1983.

3. Discussion

Phenylthioacetylene has been prepared by elimination of thiophenol and dehydrobromination of *cis*-1,2-bis(phenylthio)ethylene⁵ and *cis*-1-bromo-2-phenylthioethylene,^{2,7} respectively. The latter was obtained by addition of thiophenol to propiolic acid in ethanol and subsequent one-pot bromine addition, decarboxylative dehalogenation, and careful distillation to remove the *trans* isomer.^{2,7} On the other hand, *cis*-1,2-bis(phenylthio)ethylene was prepared by double addition of thiophenol to *cis*-1,2-dichloroethylene.^{5a-d} Although these procedures can provide useful amounts of phenylthioacetylene, they were found to be somewhat less satisfactory in our hands as far as operation and/or overall yields are concerned. Furthermore, we have encountered problems with regard to the reproducibility of one-pot dehydrobrominations of phenylthio-1,2-dibromoethane.⁶ However, the stepwise execution of the double dehydrobromination, as described in the modified procedure reported here, provides preparatively useful quantities of phenylthioacetylene in a practical manner.

A reported procedure based on lithium diisopropylamide induced double elimination of ethanol from bromoacetaldehyde diethyl acetal also was not very effective for the large scale preparation of phenylthioacetylene.⁸ Another more recent synthesis of the title compound relies on the reaction of dimethyl(chloroethynyl)carbinol with an alkali metal phenylthiolate, followed by

elimination of acetone under basic conditions.⁹ Finally, synthesis of phenylthioacetylene has been achieved by the reaction of lithium trimethylsilyl acetylide with either phenylsulfinyl chloride¹⁰ or the relatively expensive (>\$10/l g, Fluka Chemical Corp.) phenyl benzenethiosulfonate^{6d,11} and subsequent desilylation.

A large variety of phenylthio-substituted alkynes can be conveniently prepared from phenylthioacetylene as the nucleophilic component (Table I).¹² This type of construction is more flexible than the one based on nucleophilic substitution of a terminal alkali metal acetylide on phenyl benzenethiosulfonate, phenyl sulfinyl chloride, and/or diphenyl disulfide.^{4,13} Regio- and stereoselective syntheses of functionalized vinyl sulfides¹⁴ are accomplished by Pd(0)-catalyzed hydrostannation,^{12c} hydroboration,¹⁵ treatment with low-valent tantalum,¹⁶ and stannylcupration^{6d,17} of 1-phenylthio-1-alkynes. In turn, vinyl sulfides are very useful intermediates in organic synthesis not only as carbonyl-masking moieties,¹⁸ but also in a variety of other transformations,¹⁹ including the Ni(0)-catalyzed cross-coupling reactions with alkyl, aryl, and alkenyl Grignard reagents.²⁰ The important role of the phenylthio group and its higher oxidation states in activating and directing olefins in cycloaddition reactions²¹ has been reviewed.^{21a}

Finally, useful stereoselectivities have been recorded for the heteroconjugate addition of organometallic reagents to 1-silyl substituted vinyl sulfones.²² The synthesis of such sulfones can be achieved starting from phenylthioacetylene.^{6d,11,23} The synthesis of the dicobalt hexacarbonyl complex²⁴ and the polymerization of phenylthioacetylene²⁵ have been described.

Table I
Preparation of Phenylthio Alkynes from Phenylthioacetylene

Entry	Phenylthioalkyne ^a	Electrophile ^b	%Yield ^c
1.		1. HCHO 2. t-BuMe ₂ SiCl	82
2.		HCHO	86
3.		MeI	89
4.		1. 2. NaBH ₄ /CeCl ₃	70
5.		1. HCHO 2.	78
6.		ClCO ₂ Et	85
7.			75
8.		PhI	73
9.		BuI	80
10.		Me ₃ SiCl	90

^aAll phenylthio alkyne products exhibited spectral properties (¹H NMR, IR, and GC/MS) in accord with the assigned structures. ^bThe electrophile employed in entries 4 and 7 was prepared from glycolic acid by reaction of its bis(*tert*-butyldimethylsilyl) derivative with oxalyl chloride followed by N,O-dimethylhydroxylamine hydrochloride.²⁶ Entry 8 involved Pd(0)- and Cu(I)-catalyzed coupling. ^cIsolated yield after preparative TLC, sg flash chromatography, or short-path distillation.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Phenylthioacetylene: Sulfide, ethynyl phenyl (8); Benzene, (ethynylthio)- (9);
(6228-98-4)

1-Bromovinyl phenyl sulfide: Benzene, [(1-bromoethenyl)thio]- (10); (80485-53-6)

Phenyl vinyl sulfide: Sulfide, phenyl vinyl (8); Benzene, (ethenylthio)- (9); (1822-73-7)

Bromine (8,9); (7726-95-6)

Tetrabutylammonium hydrogen sulfate: Ammonium, tetrabutyl-, sulfate (1:1) (8);

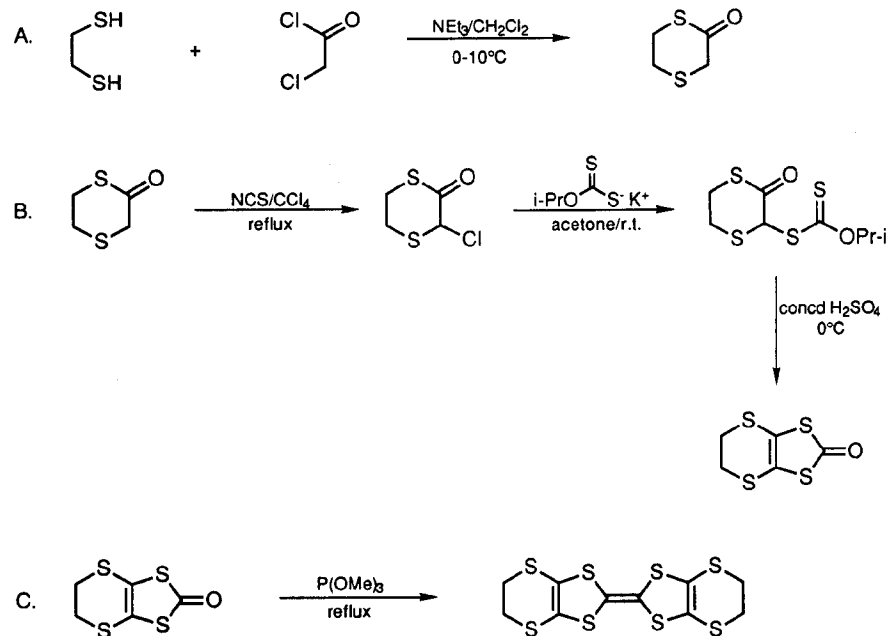
1-Butanaminium, N,N,N-tributyl-, sulfate (1:1) (9); (32503-27-8)

Ammonia (8,9); (7664-41-7)

Sodium (8,9); (7440-23-5)

2,2'-BI-5,6-DIHYDRO-1,3-DITHIOLO[4,5-b][1,4]DITHIINYLIDENE (BEDT-TTF)

(1,3-Dithiolo[4,5-b][1,4]dithiin, 2-(5,6-dihydro-1,3-dithiolo-
[4,5-b][1,4]dithiin-2-ylidene)-5,6-dihydro-)



Submitted by Jan Larsen¹ and Christine Lenoir.²

Checked by Mathew Carson and David L. Coffen.

1. Procedure

Caution! This preparation should be conducted in an efficient hood because of the obnoxious odor of 1,2-ethanedithiol.

A. 2-Oxo-1,4-dithiane. A 4-L, four-necked, round-bottomed flask equipped with a mechanical stirrer, 500-mL pressure-equalizing dropping funnel, thermometer, and reflux condenser provided with a calcium chloride drying tube, is charged with 1 L of dichloromethane, 1,2-ethanedithiol (102 mL, 1.2 mol) (Note 1), and triethylamine (336 mL, 2.4 mol). The mixture is cooled while it is stirred in an ice-acetone bath to 0-10°C while a solution of chloroacetyl chloride (96 mL, 1.2 mol) (Note 2) in 400 mL of dichloromethane is added over a period of 1.5 hr, during which time a thick white precipitate of triethylamine hydrochloride is formed. After the addition is complete, stirring is continued for another 2 hr at ambient temperature. To the stirred mixture is added 500 mL of ice water. During the addition all the precipitated triethylamine hydrochloride is dissolved and a two-phase system is formed. The organic phase is washed with four, 200-mL portions of water and dried over anhydrous magnesium sulfate (MgSO_4). The drying agent is removed by filtration, and the dichloromethane is evaporated using a rotary evaporator at ca. 13 mm. The residue is distilled at 0.7 mm using an oil bath with the temperature set at 120-130°C (Note 3) and 2-oxo-1,4-dithiane is distilled at 92-93°C; yield, 96 g (60%) (Notes 4, 5).

B. 3-Chloro-2-oxo-1,4-dithiane. A 250-mL, round-bottomed flask, equipped with a magnetic stirring bar and a reflux condenser provided with a nitrogen bubbler, is flushed with nitrogen and charged with 150 mL of carbon tetrachloride (CCl_4), 2-oxo-1,4-dithiane (10.0 g, 0.075 mol), and N-chlorosuccinimide (11.0 g, 0.083 mol) (Notes 6, 7). The mixture is refluxed for 30 min. After cooling to 0°C the precipitated succinimide is removed by filtration and washed with 20 mL of CCl_4 (Note 8). The solution is filtered directly into a 1-L, conical, flask equipped with a magnetic stirring

bar, charged with a suspension of potassium O-(2-propyl) dithiocarbonate (13.1 g, 0.075 mol) (Note 9) in 300 mL of dry acetone, and stirred at ambient temperature for 0.5 hr. The precipitate is removed by filtration and the solvent is evaporated at ambient temperature using a rotary evaporator at ca. 13 mm. 2-Oxo-3-(2-propoxythiocarbonylthio)-1,4-dithiane is obtained in quantitative yield as a slightly brown oil and used in the following step without further purification (Note 10).

2-Oxo-5,6-dihydro-1,3-dithiolo[4,5-b][1,4]dithiin. A 1-L, conical flask, equipped with a magnetic stirring bar, is charged with 500 mL of concentrated sulfuric acid (H_2SO_4), and cooled to 0°C; 45 mL of ether is added dropwise. 2-Oxo-3-(2-propoxythiocarbonylthio)-1,4-dithiane is added in a thin stream during 10 min using an additional 5 mL of ether to complete the transfer. During the addition the sulfuric acid becomes dark. After 1.5 hr the reaction mixture is poured onto 3 kg of ice, at which time a sticky mass appears. The mixture is filtered by suction through a sintered glass funnel (D = 10 cm) charged with a layer of 2 cm of Celite. The Celite is washed with four, 150-mL portions of water. A first crop is obtained by combining the water phase and leaving it for 5-7 days at room temperature. During this time the solution first becomes turbid and then clear, at which time 2-oxo-5,6-dihydro-1,3-dithiolo[4,5-b][1,4]dithiin has separated as slightly yellow crystals. The water is removed by filtration, the product is washed with four, 50-mL portions of water, and with two, 20-mL portions of methanol, and dried under reduced pressure at ambient temperature.

The gummy mass isolated on the Celite is dissolved by washing with four, 100-mL portions of dichloromethane. The organic phase is washed with three, 100-mL portions of water and dried over anhydrous MgSO_4 . The drying agent is removed by filtration and the solvent is evaporated using a rotary evaporator at ca. 13 mm. The residue is purified by filtration on silica gel (Note 11) with toluene. Toluene is evaporated using a rotary evaporator at ca. 13 mm. The residue is combined with the first crop and purified by recrystallization from absolute ethanol to yield 2-oxo-5,6-

dihydro-1,3-dithiolo[4,5b][1,4]dithiin as white crystals 7.8-9.4 g (yield, 50-60% based on 2-oxo-1,4-dithiane); mp 126-127°C (Note 12).

C. *2,2'-Bi-5,6-dihydro-1,3-dithiolo[4,5-b][1,4]dithiinylidene (BEDT-TTF)*. A 250-mL, round-bottomed flask equipped with a magnetic stirring bar and reflux condenser provided with a nitrogen bubbler is charged with 100 mL of freshly distilled trimethyl phosphite and 2-oxo-5,6-dihydro-1,3-dithiolo[4,5-b][1,4]dithiin (5.0 g, 0.024 mol). The solution is heated to reflux by immersing the flask in an oil bath preheated to 125°C (Note 13) for 2-3 hr. During this time bright orange-red crystals of product precipitate. The mixture is cooled to room temperature and the solid is filtered, and washed with four, 20-mL portions of methanol and with four, 20-mL portions of ether and dried under reduced pressure at ambient temperature to provide BEDT-TTF. Recrystallization from 300 mL of chlorobenzene affords 4.3 g (93%) of BEDT-TTF as bright red needles; mp 245-247°C (dec).

2. Notes

1. 1,2-Ethanedithiol (99%) is available from Aldrich Chemical Company, Inc., and is used without further purification.

2. Chloroacetyl chloride (98%) is available from Aldrich Chemical Company, Inc., and is used without further purification.

3. The use of an electric heating mantle results in local overheating of the initially formed poly- or oligomeric products giving red, foul-smelling products instead. The product distills rather slowly (2-4 hr).

4. The product was pure by NMR spectroscopy. ^1H NMR (CDCl_3/TMS) δ : 3.2 (m); ^{13}C NMR (CDCl_3/TMS) δ : 25.82 (CH_2), 31.02 (CH_2), 35.25 (CH_2), 197.11 ($\text{C}=\text{O}$).

5. 2-Oxo-1,4-dithiane can be stored for a long time at -20°C, at which temperature the product crystallizes.

6. N-Chlorosuccinimide (98%) is available from Aldrich Chemical Company, Inc., and is used without further purification.

7. The use of N-bromosuccinimide instead of N-chlorosuccinimide affords a dark, tarry mass.

8. 3-Chloro-2-oxo-1,4-dithiane can be obtained by removing the solvent at ambient temperature using a rotary evaporator at ca. 13 mm. The product was pure by NMR spectroscopy. ^1H NMR (CDCl_3/TMS) δ : 3.2 (m, 4 H, CH_2), 5.37 (s, 1 H, CH); ^{13}C NMR (CDCl_3/TMS) δ : 24.52 (CH_2), 30.18 (CH_2), 61.91 (CH), 188.27 ($\text{C}=\text{O}$). The product becomes black in a few days, even when stored at -20°C.

9. Potassium O-(2-propyl) dithiocarbonate can be prepared in the following manner: With heating, 42 g (0.75 mol) of potassium hydroxide is dissolved in 400 mL of 2-propanol. The solution is then cooled in an ice bath, and the temperature is kept below 10°C while carbon disulfide (46 mL, 0.75 mol) is added dropwise with stirring. The potassium xanthate is collected by suction filtration and washed with four, 100-mL portions of ether and dried under reduced pressure at ambient temperature; yield 111 g (85%).

10. The product was pure by NMR spectroscopy. ^1H NMR (CDCl_3/TMS) δ : 1.40 (d, 6 H, CH_3), 3.41 (m, 4 H, CH_2), 5.62 (s, 1 H, CH), 5.70 (sept, 1 H, CH); ^{13}C NMR (CDCl_3/TMS) δ : 21.00 (CH_3), 27.70 (CH_2), 31.74 (CH_2), 54.17 (CH), 79.53 (CH), 191.58 ($\text{C}=\text{O}$), 207.71 ($\text{C}=\text{S}$).

11. Silicagel 60, 55 g, was used on a 5-cm column.

12. The product showed the following NMR data: ^1H NMR (CDCl_3/TMS) δ : 3.43 (s, 4 H, CH_2); ^{13}C NMR (CDCl_3/TMS) δ : 31.08 (CH_2), 113.41 ($\text{C}=\text{C}$), 188.72 ($\text{C}=\text{O}$).

13. It is essential that the mixture be heated rapidly, otherwise the yield decreases dramatically.

3. Discussion

BEDT-TTF [Bis(ethylenedithio)tetrathiafulvalene] has been synthesized by a variety of methods, mostly by reduction of carbon disulfide with alkali metals,^{3,4,5} or electrochemically,⁶ followed by alkylation of the formed disodium 4,5-dimercapto-1,3-dithiole-2-thione with 1,2-dibromoethane,^{3,4,5} The thione is converted to 2-oxo-5,6-dihydro-1,3-dithiolo[4,5-b][1,4]dithiin by oxidation with mercuric acetate.⁴ Finally coupling with triethyl phosphite,^{4,7,8} or direct coupling of the thione with triethyl phosphite^{5,9,10} or with triethyl phosphite under photochemical conditions¹¹ or with triethyl phosphite under high pressure¹² yields BEDT-TTF. Coupling has also been effected by alkylating the thione followed by electrochemical reduction of the formed 2-alkylthio-1,3-dithiolium salt.¹³ Pyrolysis then yields the final product.

BEDT-TTF was also obtained by selective ring opening of 1,3,4,6-tetrathiapentalen-2,6-dione and alkylation with 1,2-dibromoethane followed by coupling with triethyl phosphite.^{7,8}

The present procedure, which is based on those of Schumaker⁸ and Larsen and Lenoir,¹⁴ is simple and avoids the use of the troublesome and sometimes hazardous reduction of carbon disulfide with alkali metals. On several occasions a violent explosion has occurred in our laboratories during this reaction.

The present method gives high yields of BEDT-TTF in excellent purity. Actual investigation of super-conducting salts of BEDT-TTF show that BEDT-TTF made by the present route gives material of superior purity.¹⁵ Also by the present method BEDT-TTF is obtained from readily available starting materials.

1. Department of General and Organic Chemistry, H. C. Ørsted Institute, Universitetsparken 5, DK-2100 Copenhagen, Denmark.
2. Laboratoire de Physique des Solides, Université Paris-Sud, Bât. 510, F-91405 Orsay France.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2,2'-Bi-5,6-dihydro-1,3-dithiolo[4,5-b][1,4]dithiinylidene (BEDT-TTF): 1,3-Dithiolo[4,5-b][1,4]dithiin, 2-(5,6-dihydro-1,3-dithiolo-[4,5-b][1,4]dithiin-2-ylidene)-5,6-dihydro- (10); (66946-48-3)

2-Oxo-1,4-dithiane: 1,4-Dithian-2-one (10); (74637-14-2)

1,2-Ethanedithiol (8,9); (540-63-6)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

Chloroacetyl chloride: Acetyl chloride, chloro- (8,9); (79-04-9)

3-Chloro-2-oxo-1,4-dithiane: 1,4-Dithiane-2-one, 3-chloro- (11); (88682-21-7)

Carbon tetrachloride (8); Methane, tetrachloro- (9); (56-23-5)

N-Chlorosuccinimide: Succinimide, N-chloro- (8); 2,5-Pyrrolidinedione, 1-chloro- (9); (128-09-6)

Potassium O-(2-propyl) dithiocarbonate: Carbonic acid, dithio-, O-isopropyl ester, potassium salt (8); Carbonodithioic acid, O-(1-methylethyl) ester, potassium salt (9); (140-92-1)

2-Oxo-3-(2-propoxythiocarbonylthio)-1,4-dithiane: Carbonodithioic acid, O-(1-methylethyl) S-(3-oxo-1,4-dithian-2-yl) ester (12); (120627-40-9)

2-Oxo-5,6-dihydro-1,3-dithiolo[4,5-b][1,4]dithiin: 1,3-Dithiolo[4,5-b][1,4]dithiin-2-one, 5,6-dihydro- (10); (74962-29-1)

Trimethyl phosphite: Phosphorous acid, trimethyl ester (8,9); (121-45-9)

Unchecked Procedures

Accepted for checking during the period May 2, 1992 through August 1, 1993. An asterisk (*) indicates that the procedure has been subsequently checked.

Previously, *Organic Syntheses* has supplied these procedures upon request. However, because of the potential liability associated with procedures which have not been tested, we shall continue to list such procedures but requests for them should be directed to the submitters listed.

- 2658* Synthesis of Enantiomerically Pure β -Amino Acid from 2-*tert*-Butyl-1-carbomethoxy-2,3-dihydro-4(1H)-pyrimidinone: (S)- β -Tyrosine-O-methyl Ether.
F. J. Lakner, K. S. Chu, G. R. Negrete, and J. P. Konopelski, Department of Chemistry & Biochemistry, University of California, Santa Cruz, Santa Cruz, CA 90564
- 2659 Regio- and Stereoselective Intramolecular Hydrosilation of α -Hydroxy Enol Ethers: 2,3-syn-2-Methoxymethoxy-1,3-nonanediol.
K. Tamao, Y. Nakagawa, Y. Ito, Department of Synthetic Chemistry, Kyoto University, Yoshida Sakyo-Ku, Kyoto 606, Japan
- 2665 Asymmetric Synthesis of trans-2-Aminocyclohexanecarboxylic Acid Derivatives from Pyrrolobenzodiazepine-5,11-diones.
A. G. Schultz and Carlos W. Alva, Department of Chemistry, Rensselaer Polytechnic Institute, Troy, NY 12180-3590
- 2669 Synthesis of 2-Oxocyclopentaneacetaldehyde.
E. Baciocchi, A. B. Paolobelli, and R. Ruzziconi, Dipartimento di Chimica, Universita di Perugia, 06100 Perugia, Italy
- 2670 Preparation of 3-Methyl-4H-1,2-Benzoxazine and Its Reactivity as a Precursor of o-Benzoquinone Methide.
T. Ohwada, K. Okabe, M. Yato, T. Ohta, and K. Shudo, Faculty of Pharmaceutical Sciences, University of Tokyo, 7-3-1-Hongo, Bunkyo-ku, Tokyo 113, Japan
- 2671 2-Cyclohexene-1,4-dione.
M. Oda, T. Kawase, T. Okada, and T. Enomoto, Department of Chemistry, Faculty of Science, Osaka University, Toyonaka, Osaka 560, Japan
- 2672R* An Improved Preparation of 3-Bromo-2(H)-pyran-2-one: An Ambiphilic Diene for Diels-Alder Cycloadditions.
G. H. Posner, K. Afarinkia, and H. Dai, Department of Chemistry, Johns Hopkins University, Baltimore, MD 21218-2685
- 2673 2,3-Dibromo-1-(phenylsulfonyl)-1-propene as a Versatile Reagent for the Synthesis of Furans and Cyclopentenones.
Z. Ni, S. S. Murphree, and A. Padwa, Department of Chemistry, Emory University, Atlanta, GA 30322
- 2676 Bis-(trifluoroethyl)-2-carboethoxyethylphosphonate.
C. Patois, P. Savignac, E. About-Jaudet, and N. Collignon, Hétéroatomes et Coordination, URA 1499 du CNRS, DCPH Ecole Polytechnique, 91128 Palaiseau Cedex, France

- 2677 1,3,5-Cyclooctatriene.
M. Oda, T. Kawase, and H. Kurata, Department of Chemistry, Faculty of Science, Osaka University, Toyonaka, Osaka 560, Japan
- 2679* 3-Pyrroline.
A. I. Meyers, J. S. Warmus, and G. J. Dille, Department of Chemistry, Colorado State University, Fort Collins, CO 80523
- 2680 The Dess-Martin Periodinane.
R. K. Boeckman, Jr. and Joseph J. Mullins, Department of Chemistry, The University of Rochester, River Station, Rochester, NY 14627
- 2681R (1R,5S)-(-)-6,6-Dimethyl-3-oxabicyclo[3.1.0]hexan-2-one. Highly Enantioselective Intramolecular Cyclopropanation Catalyzed by Dirhodium(II) Tetrakis[methyl 2-pyrrolidone-5(R)-carboxylate].
M. P. Doyle, W. R. Winchester, M. N. Protopopova, A. P. Kazala, and L. J. Westrum, Department of Chemistry, Trinity University, San Antonio, TX 78212-7299
- 2682 Diethyl (2S,3R)-2-(N-*t*-Butoxycarbonyl)amino-3-hydroxysuccinate.
S. Saito, K. Komada, and T. Moriwake, Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushima, Okayama, 700 Japan
- 2683 Synthesis of 4-(2-Bromo-2-Propenyl)-4-Methyl- γ -Butyrolactone by the Reaction of Ethyl Levulinate with (2-Bromoallyl)diisopropoxyborane Prepared by Haloboration of Allene.
S. Hara and A. Suzuki, Department of Applied Chemistry, Faculty of Engineering, Hokkaido University, Sapporo 060, Japan
- 2684 (4R)-(+)-*t*-Butyldimethylsiloxy-cyclopentenone.
L. A. Paquette, M. J. Earle, and G. F. Smith, Department of Chemistry, The Ohio State University, Columbus, OH 43210
- 2685 (4S)-(-)-*t*-Butyldimethylsiloxy-cyclopentenone.
L. A. Paquette and T. M. Heidelbaugh, Department of Chemistry, The Ohio State University, Columbus, OH 43210
- 2687 4-Keto-Undecanoic Acid.
M. A. Tschantz, L. B. Burgess, and A. I. Meyers, Department of Chemistry, Colorado State University, Fort Collins, CO 80523
- 2688 S(-)-5-n-Heptylpyrrolidinone. Chiral Bicyclic Lactams as Templates to Pyrrolidines and Pyrrolidinones.
M. A. Tschantz, L. B. Burgess, and A. I. Meyers, Department of Chemistry, Colorado State University, Fort Collins, CO 80523

- 2689 Synthesis of (+)-(2R,8aS)-[(8,8-Dimethoxycamphoryl)-sulfonyl]oxaziridine and (+)-(2R,8a)-[(8,8-Dichloro-camphoryl)sulfonyl]oxaziridine.
B.-C. Chen, C. K. Murphy, A. Kumar, R. Thimma Reddy, C. Clark, P. Zhou, B. M. Lewis, D. Gala, I. Mergelsberg, D. Scherer, J. Buckley, D. DiBenedetto, and F. A. Davis, Department of Chemistry, Drexel University, Philadelphia, PA 19104
- 2690 Double Hydroxylation Reaction for Construction of Corticoid Side Chain: Synthesis of 16 α -Methylcortexolone.
Y. Horiguchi, E. Nakamura, and I. Kuwajima, Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan
- 2693 Palladium Catalyzed Coupling of Arylboronic Acids: Methyl 5-(3-Nitrophenyl)nicotinate.
W. J. Thompson, A. K. Ghosh, and S. P. McKee, Department of Medicinal Chemistry, Merck Research Laboratories, W26-410, West Point, PA 19486
- 2695 Terminal Alkynes: Ethynylferrocene.
J. Polin and H. Schottenberger, Institut für Anorganische und Analytische Chemie, Universität Innsbruck, Innrain 52a, A-6020 Innsbruck, Austria

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- 3) Literature reference or enclose preprint if available.
- 4) Proposed sequence.
- 5) Best current alternative(s) (ref.):
- 6)
 - a. Proposed scale, final product:
 - b. Overall yield:
 - c. Method of isolation and purification:
 - d. Purity of product (%):
 - e. How determined?
- 7) Any unusual apparatus or experimental technique:
- 8) Any hazards?
- 9) Source of starting material?
- 10) Utility of method or usefulness of product.

**ORGANIC
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With Volume 62, the Editors of *Organic Syntheses* began a new presentation and distribution policy to shorten the time between submission and appearance of an accepted procedure. The soft cover edition of this volume is produced by a rapid and inexpensive process, and is sent at no charge to members of the Organic Divisions of the American and French Chemical Society, The Perkin Division of the Royal Society of Chemistry, and The Society of Synthetic Organic Chemistry, Japan. The soft cover edition is intended as the personal copy of the owner and is not for library use. A hard cover edition is published by John Wiley and Sons Inc. in the traditional format, and differs in content primarily in the inclusion of an index. The hard cover edition is intended primarily for library collections and is available for purchase through the publisher. Annual Volumes 65-69 have been incorporated into a new five-year version of the collective volumes of *Organic Syntheses* which has appeared as *Collective Volume Eight* in the traditional hard cover format. It is available for purchase from the publishers. The Editors hope that the new *Collective Volume* series, appearing twice as frequently as the previous decennial volumes, will provide a permanent and timely edition of the procedures for personal and institutional libraries. The Editors welcome comments and suggestions from users concerning the new editions.

The procedures in this text are intended for use only by persons with prior training in the field of organic chemistry. In the checking and editing of these procedures, every effort has been made to identify potentially hazardous steps and to eliminate as much as possible the handling of potentially dangerous materials; safety precautions have been inserted where appropriate. If performed with the materials and equipment specified, in careful accordance with the instructions and methods in this text, the Editors believe the procedures to be very useful tools. However, these procedures must be conducted at one's own risk. Organic Syntheses, Inc., its Editors, who act as checkers and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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Both common and systematic names of compounds are used throughout this volume, depending on which the Editor-in-Chief felt was more appropriate. The *Chemical Abstracts* indexing name for each title compound, if it differs from the title name, is given as a subtitle. Systematic *Chemical Abstracts* nomenclature, used in both the 9th and 10th Collective Indexes for the title compound and a selection of other compounds mentioned in the procedure, is provided in an appendix at the end of each preparation. Registry numbers, which are useful in computer searching and identification, are also provided in these appendixes. Whenever two names are concurrently in use and one name is the correct *Chemical Abstracts* name, that name is preferred.

SUBMISSION OF PREPARATIONS

Organic Syntheses welcomes and encourages submission of experimental procedures which lead to compounds of wide interest or which illustrate important new developments in methodology. The Editorial Board will consider proposals in outline format as shown below, and will request full experimental details for those proposals which are of sufficient interest. Tear-out copies of this form may be found at the back of this volume. Submissions which are longer than three steps from commercial sources or from existing *Organic Syntheses* procedures will be accepted only in unusual circumstances.

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Proposals will be evaluated in outline form, again after submission of full experimental details and discussion, and, finally by checking experimental procedures. A form that details the preparation of a complete procedure (Notice to Submitters) may be obtained from the Secretary.

Additions, corrections, and improvements to the preparations previously published are welcomed; these should be directed to the Secretary. However, checking of such improvements will only be undertaken when new methodology is involved. Substantially improved procedures have been included in the Collective Volumes in place of a previously published procedure.

ACKNOWLEDGMENT

Organic Syntheses wishes to acknowledge the contributions of Hoffmann-La Roche, Inc. and Merck & Co. to the success of this enterprise through their support, in the form of time and expenses, of members of the Boards of Directors and Editors.

HANDLING HAZARDOUS CHEMICALS

A Brief Introduction

General Reference: *Prudent Practices for Handling Hazardous Chemicals in Laboratories*, National Academy Press, Washington, D.C. 1983

Physical Hazards

Fire. Avoid open flames by use of electric heaters. Limit the quantity of flammable liquids stored in the laboratory. Motors should be of the nonsparking induction type.

Explosion. Use shielding when working with explosive classes such as acetylides, azides, ozonides, and peroxides. Peroxidizable substances such as ethers and alkenes, when stored for a long time, should be tested for peroxides before use. Only sparkless "flammable storage" refrigerators should be used in laboratories.

Electric Shock. Use 3-prong grounded electrical equipment if possible.

Chemical Hazards

Because all chemicals are toxic under some conditions, and relatively few have been thoroughly tested, it is good strategy to minimize exposure to all chemicals. In practice this means having a good, properly installed hood; checking its performance periodically; using it properly; carrying out most operations in the hood; protecting the eyes; and, since many chemicals can penetrate the skin, avoiding skin contact by use of gloves and other protective clothing.

a. Acute Effects. These effects occur soon after exposure. The effects include burn, inflammation, allergic responses, damage to the eyes, lungs, or nervous system (e.g., dizziness), and unconsciousness or death (as from overexposure to HCN). The effect and its cause are usually obvious and so are the methods to prevent it. They generally arise from inhalation or skin contact, so should not be a problem if one follows the admonition "work in a hood and keep chemicals off your hands". Ingestion is a rare route, being generally the result of eating in the laboratory or not washing hands before eating.

b. Chronic Effects. These effects occur after a long period of exposure or after a long latency period and may show up in any of numerous organs. Of the chronic effects of chemicals, cancer has received the most attention lately. Several dozen chemicals have been demonstrated to be carcinogenic in man and hundreds to be carcinogenic to animals. Although there is no simple correlation between carcinogenicity in animals and in man, there is little doubt that a significant proportion of the chemicals used in laboratories have some potential for carcinogenicity in man. For this and other reasons, chemists should employ good practices.

The key to safe handling of chemicals is a good, properly installed hood, and the referenced book devotes many pages to hoods and ventilation. It recommends that in a laboratory where people spend much of their time working with chemicals there should be a hood for each two people, and each should have at least 2.5 linear feet (0.75 meter) of working space at it. Hoods are more than just devices to keep undesirable vapors from the laboratory atmosphere. When closed they provide a protective barrier between chemists and chemical operations, and they are a good containment device for spills. Portable shields can be a useful supplement to hoods, or can be an alternative for hazards of limited severity, e.g., for small-scale operations with oxidizing or explosive chemicals.

Specialized equipment can minimize exposure to the hazards of laboratory operations. Impact resistant safety glasses are basic equipment and should be worn at all times. They may be supplemented by face shields or goggles for particular operations, such as pouring corrosive liquids. Because skin contact with chemicals can lead to skin irritation or sensitization or, through absorption, to effects on internal organs, protective gloves are often needed.

Laboratories should have fire extinguishers and safety showers. Respirators should be available for emergencies. Emergency equipment should be kept in a central location and must be inspected periodically.

DISPOSAL OF CHEMICAL WASTE

General Reference: *Prudent Practices for Disposal of Chemicals from Laboratories*, National Academy Press, Washington, D.C. 1983

Effluents from synthetic organic chemistry fall into the following categories:

1. Gases

- 1a. Gaseous materials either used or generated in an organic reaction.
- 1b. Solvent vapors generated in reactions swept with an inert gas and during solvent stripping operations.
- 1c. Vapors from volatile reagents, intermediates and products.

2. Liquids

- 2a. Waste solvents and solvent solutions of organic solids (see item 3b).
- 2b. Aqueous layers from reaction work-up containing volatile organic solvents.
- 2c. Aqueous waste containing non-volatile organic materials.
- 2d. Aqueous waste containing inorganic materials.

3. Solids

- 3a. Metal salts and other inorganic materials.
- 3b. Organic residues (tars) and other unwanted organic materials.
- 3c. Used silica gel, charcoal, filter aids, spent catalysts and the like.

The operation of industrial scale synthetic organic chemistry in an environmentally acceptable manner* requires that all these effluent categories be dealt with properly. In small scale operations in a research or academic setting, provision should be made for dealing with the more environmentally offensive categories.

*An environmentally acceptable manner may be defined as being both in compliance with all relevant state and federal environmental regulations *and* in accord with the common sense and good judgement of an environmentally aware professional.

- 1a. Gaseous materials that are toxic or noxious, e.g., halogens, hydrogen halides, hydrogen sulfide, ammonia, hydrogen cyanide, phosphine, nitrogen oxides, metal carbonyls, and the like.
- 1c. Vapors from noxious volatile organic compounds, e.g., mercaptans, sulfides, volatile amines, acrolein, acrylates, and the like.
- 2a. All waste solvents and solvent solutions of organic waste.
- 2c. Aqueous waste containing dissolved organic material known to be toxic.
- 2d. Aqueous waste containing dissolved inorganic material known to be toxic, particularly compounds of metals such as arsenic, beryllium, chromium, lead, manganese, mercury, nickel, and selenium.
3. All types of solid chemical waste.

Statutory procedures for waste and effluent management take precedence over any other methods. However, for operations in which compliance with statutory regulations is exempt or inapplicable because of scale or other circumstances, the following suggestions may be helpful.

Gases:

Noxious gases and vapors from volatile compounds are best dealt with at the point of generation by "scrubbing" the effluent gas. The gas being swept from a reaction set-up is led through tubing to a (large!) trap to prevent suck-back and on into a sintered glass gas dispersion tube immersed in the scrubbing fluid. A bleach container can be conveniently used as a vessel for the scrubbing fluid. The nature of the effluent determines which of four common fluids should be used: dilute sulfuric acid, dilute alkali or sodium carbonate solution, laundry bleach when an oxidizing scrubber is needed, and sodium thiosulfate solution or diluted alkaline sodium borohydride when a reducing scrubber is needed. Ice should be added if an exotherm is anticipated.

Larger scale operations may require the use of a pH meter or starch/iodide test paper to ensure that the scrubbing capacity is not being exceeded.

When the operation is complete, the contents of the scrubber can be poured down the laboratory sink with a large excess (10-100 volumes) of water. If the solution is a large volume of dilute acid or base, it should be neutralized before being poured down the sink.

Liquids:

Every laboratory should be equipped with a waste solvent container in which *all* waste organic solvents and solutions are collected. The contents of these containers should be periodically transferred to properly labeled waste solvent drums and arrangements made for contracted disposal in a regulated and licensed incineration facility.**

Aqueous waste containing dissolved toxic organic material should be decomposed *in situ*, when feasible, by adding acid, base, oxidant, or reductant. Otherwise, the material should be concentrated to a minimum volume and added to the contents of a waste solvent drum.

Aqueous waste containing dissolved toxic inorganic material should be evaporated to dryness and the residue handled as a solid chemical waste.

Solids:

Soluble organic solid waste can usually be transferred into a waste solvent drum, provided near-term incineration of the contents is assured.

Inorganic solid wastes, particularly those containing toxic metals and toxic metal compounds, used Raney nickel, manganese dioxide, etc. should be placed in glass bottles or lined fiber drums, sealed, properly labeled, and arrangements made for disposal in a secure landfill.** Used mercury is particularly pernicious and small amounts should first be amalgamated with zinc or combined with excess sulfur to solidify the material.

Other types of solid laboratory waste including used silica gel and charcoal should also be packed, labeled, and sent for disposal in a secure landfill.

Special Note:

Since local ordinances may vary widely from one locale to another, one should always check with appropriate authorities. Also, professional disposal services differ in their requirements for segregating and packaging waste.

** If arrangements for incineration of waste solvent and disposal of solid chemical waste by licensed contract disposal services are not in place, a list of providers of such services should be available from a state or local office of environmental protection.

PREFACE

Organic Syntheses endeavors to collect synthetic methods, reagents and compounds appearing at the leading edge of organic chemical research and, through presentation as sound, reliable procedures, facilitate their "reduction to practice". In keeping with this tradition, Volume 72 provides 32 checked and edited procedures addressing some of the most significant new methods and new chemical entities to emerge in recent years from the unending evolution of organic synthesis.

This collection starts with a group of nine procedures whose principal affinity lies in the use of naturally derived starting materials to produce important chiral intermediates in enantiomerically pure form. Procedures for both glyceraldehydes in their acetonide protected form are provided. **L-(S)-GLYCERALDEHYDE ACETONIDE** is obtained from an ascorbic acid-derived gulonolactone derivative and **D-(R)-GLYCERALDEHYDE ACETONIDE** from D-mannitol. Companion procedures exemplify their utility. **(3S,4S)-3-AMINO-1(3,4-DIMETHOXY-BENZYL)-4-[(R)-2,2-DIMETHYL-1,3-DIOXOLAN-4-YL]-2-AZETIDINONE**, a highly functionalized β -lactam with three chiral centers is prepared diastereospecifically by the 2+2 ketene-imine cycloaddition method using a Schiff base of L-glyceraldehyde. The D-glyceraldehyde is applied to a diastereoselective preparation of **2-O-BENZYL-3,4-ISOPROPYLIDENE-D-ERYTHROSE** using a 2-(trimethylsilyl)thiazole-based aldehyde homologation procedure. A Grignard reaction with methyl mandelate leads to **(R)-(+)-2-HYDROXY-1,2,2-TRIPHENYLETHYL ACETATE** and the C,O-dianion of this hydroxy ester shows a high level of chiral auxiliary type enantioselectivity in its reactions with aldehydes, as illustrated in a procedure for **(R)-3-HYDROXY-4-METHYLPENTANOIC ACID**. Procedures for preparing **(2S,4S)-2,4,5-TRIHYDROXPENTANOIC ACID 4,5-ACETONIDE METHYL ESTER** from D-xylose, for preparing **(1R,5R)-(+)-**

VERBENONE from (+)- α -pinene, and for preparing **(S)-2-METHYLPROLINE** from (S)-proline complete this group.

The next four procedures are based on some recent advances in catalysis. The first of these, an asymmetric hydrogenation of an allylic alcohol, illustrates yet another facet of the versatility of BINAP-ligated platinum group metals with a preparation of **(S)-(-)-CITRONELLOL** from geraniol. An asymmetrically catalyzed Diels-Alder reaction is used to prepare **(1R)-1,3,4-TRIMETHYL-3-CYCLOHEXENE-1-CARBOXALDEHYDE** with an (acyloxy)borane complex derived from L-(+)-tartaric acid as the catalyst. A high-yield procedure for the rearrangement of epoxides to carbonyl compounds catalyzed by **METHYLALUMINUM BIS(4-BROMO-2,6-DI-tert-BUTYLPHENOXIDE)** is demonstrated with a preparation of **DIPHENYL-ACETALDEHYDE** from stilbene oxide. A palladium/copper catalyst system is used to prepare **(Z)-2-BROMO-5-(TRIMETHYLSILYL)-2-PENTEN-4-YNOIC ACID ETHYL ESTER**. The coupling of vinyl and aryl halides with acetylenes is a powerful carbon-carbon bond-forming reaction, particularly valuable for the construction of such enyne systems.

The next three procedures provide useful synthetic intermediates. A stereospecific synthesis of **ETHYL (Z)-3-BROMO-2-PROPENOATE** affords an alternative vinyl bromide partner for the coupling chemistry in the preceding procedure. A very simple but elegant illustration of the flash vacuum pyrolysis technique is used to prepare **BENZOCYCLOBUTENONE** from o-toluoyl chloride. Another member of the functionalized indole family of synthetic intermediates is presented in a four-step procedure for **5-METHOXYINDOLE-2-ACETIC ACID METHYL ESTER**.

Eight procedures highlighting some recent and practical developments in organometallic chemistry form the next group. Highly reactive calcium prepared by reduction of dissolved calcium bromide with lithium biphenylide affords access to the

calcium equivalent of Grignard reagents. Their superiority over classical Grignards in certain instances is illustrated in a preparation of **1-(1-ADAMANTYL)-CYCLOHEXANOL** from 1-bromoadamantane and cyclohexanone. Lithium-tellurium organometallic exchange reactions provide **N,N-DIETHYLCARBAMOYL-LITHIUM**, which reacts as a nucleophile with a variety of carbonyl compounds. Its reaction with 3-phenylpropanal gives **N,N-DIETHYL-2-HYDROXY-4-PHENYL-BUTANAMIDE**. Yields in the conjugate addition of Grignard reagents to enones show marked improvement when manganese and copper are used as co-catalysts, presumably with participation of organomanganese intermediates. The method is illustrated with a preparation of **2-(1,1-DIMETHYLPENTYL)-5-METHYL-CYCLOHEXANONE** from pulegone and butylmagnesium chloride. Directed ortho metalation confers powerful regiochemical control on the generation of aryl lithium reagents by deprotonation. This method of constructing contiguously trisubstituted aromatics is presented in a preparation of **7-METHOXYPHTHALIDE**. Lithium 4,4'-di-*t*-butylbiphenylide effects reductive cleavage of epoxides to form lithium β -lithioalkoxides. When combined with aldehydes, these reagents give facile access to 1,3-glycols, as shown in the preparation of **2,5-DIMETHYL-2,4-HEXANEDIOL**. The next procedure illustrates the preparation of vinyl chromium reagents from vinyl triflates and their nickel-catalyzed reactions with aldehydes (specifically) to provide allylic alcohols. The preparation of **2-HEXYL-5-PHENYL-1-PENTEN-3-OL** exemplifies this method. Organic tin compounds constitute a rich and growing area of organometallic-based synthetic methods. A TiCl_4 -driven intramolecular reaction of stannane and aldehyde functions is the key reaction in a preparation of **2-OXO-5-METHOXYSPIRO[5.4]-DECANE**. The last procedure in this group provides details for the preparation of a water soluble tin hydride, **TRIS(3-(2-METHOXYETHOXY)PROPYL)STANNANE**. This reagent expands the scope of tin hydride mediated free radical chemistry into aqueous solutions.

Organic fluorine compounds and methods for their preparation are the central topic of the next four procedures. Much of the synthetic versatility of methyl phenyl sulfone is embodied in **FLUOROMETHYL PHENYL SULFONE** and the fluoro Pummerer reaction of methyl phenyl sulfoxide with DAST is a key step in its preparation. The utility of this fluoromethyl sulfone in the preparation of fluoroalkenes is demonstrated in a companion procedure for **Z-[2-(FLUOROMETHYLENE)-CYCLOHEXYL]BENZENE**, a procedure with several prominent stereoselective features. Geminal difluoroalkenes are featured in the following procedure. **(3,3-DIFLUOROALLYL)TRIMETHYLSILANE** is prepared by a method in which the radical addition of dibromodifluoromethane to alkenes and the selective reduction of α -bromoalkylsilanes are key steps. A procedure for nucleophilic introduction of the trifluoromethyl group completes this set. The key reagent, **(TRIFLUOROMETHYL)-TRIMETHYLSILANE** is obtained by reductive coupling of TMS chloride and bromotrifluoromethane. Liberation of a CF_3^- equivalent with fluoride ion in the presence of cyclohexanone affords **1-TRIFLUOROMETHYL-1-CYCLOHEXANOL**.

Volume 72 concludes with procedures for four important organophosphorus and organosulfur compounds. α -Formylalkylphosphonates, reagents for the synthesis of α,β -unsaturated aldehydes via Wittig-Horner-Emmons chemistry, are readily made from triethylphosphate by sequential treatment with alkyl lithium reagents and ethyl formate, as illustrated with the preparation of **DIETHYL 1-PROPYL-2-OXOETHYL-PHOSPHONATE**. Long-chain alkyl phosphates can be conveniently prepared from amines using a phosphoramidate equivalent of the N-nitrosocarboxamide to carboxylic ester rearrangement. **N-DECYL DIETHYLPHOSPHATE** is used to illustrate this chemistry. **PHENYLTHIOACETYLENE**, by virtue of its facile introduction into other molecules via the corresponding acetylide and the wide range of subsequent synthesis options, is an intermediate with broad utility. Its preparation

proceeds from phenyl vinyl sulfide via **1-BROMOVINYL PHENYL SULFIDE**. The final procedure provides details for a straightforward preparation of **2,2'-BI-5,6-DIHYDRO-1,3-DITHIOLO[4,5-b][1,4]DITHIINYLIDENE**, otherwise known as **BEDT-TTF** and an important member of the tetrathiafulvalene-based class of organic conductors.

The meticulous care that goes into the selection, preparation, and checking of these procedures entails a very substantial effort on the part of the Editorial Board members and their coworkers and first (by a long shot) among equals in this group is Professor Jeremiah Freeman. Jerry's enormous contributions to Organic Syntheses ensure continued fruition of all our endeavors. Special appreciation must also be extended to Assistant Editor Theodora Greene for her invaluable participation in the editorial process.

This volume, like others in this series, is in some respects a microcosm of the entire science of organic chemistry. Its vitality and diversity are reflected in the wide range of topics addressed by these thirty-two procedures and by the fact that they come from laboratories in ten different countries.

Nutley, New Jersey

August 1993

David L. Coffen



MELVIN S. NEWMAN

March 10, 1908 - May 30, 1993

Mel Newman was born on March 10, 1908 in New York City and raised in New Orleans. With his passing on May 30, 1993, organic chemistry lost one of its foremost investigators, strongest proponents, and unusually engaging personalities. Professor Newman's love for laboratory research is legendary. His mastery and love of the game of golf was almost as equally impressive. Fortunately, he was able to pursue both activities well beyond his formal retirement date, virtually to the point when death came.

Professor Newman was educated at Yale University, receiving his B.S. degree *magna cum laude* in 1929 and his Ph.D. in 1932. He subsequently embarked on postdoctoral stints at Yale, Columbia, and Harvard. The last of these was spent in the

laboratories of Louis Fieser, from whom he inherited an insatiable curiosity for the chemistry of polycyclic benzenoid hydrocarbons. Mel joined the Ohio State University Chemistry Department in 1936, where he was to remain scientifically active for more than 55 years. During his distinguished career, he directed the theses of over 110 students and enjoyed equally well his mentorship of many postdoctoral fellows. These students have been enriched by his character and philosophy, and organic chemistry has profited handsomely from the 350 publications that have emanated from the Newman group.

Mel always felt highly privileged to live in a society that paid him to teach and practice organic chemistry. And he excelled in these arenas of activity. Frustrated by the inability on the part of students to understand and fully appreciate stereochemistry, he developed his Newman projection formulas that gained him instant fame and prominence since the appearance of his seminal paper in 1952. A high point of his scientific career was reached when hexahelicene was prepared and resolved into its antipodes. Also notable was his development of the chemistry of esters and pseudoesters, of unique methodology for the generation and capture of unsaturated carbenes, and of sterically-strained compounds and reagents.

Professor Newman's extraordinary zeal carried over to the area of steric effects, this intense interest culminating in the publication of the landmark book *Steric Effects in Organic Chemistry* in 1956. His philosophy of how to teach an undergraduate laboratory course is clearly spelled out in a later text entitled *An Advanced Organic Laboratory Course* (1976). Mel was never irreverent, but did hold strong opinions on how certain activities should be carried out. For example, his writing style was notably terse and his lectures were characteristically to the point, except for the joke or two that he had inevitably to interject.

Mel served on the editorial boards of the *Journal of the American Chemical Society*, the *Journal of Organic Chemistry*, *Organic Syntheses*, and *Synthetic*

Communications. He had been a Fulbright Lecturer and a Guggenheim Fellow. He was a member of the National Academy of Sciences. He received many honors for his scientific work including the Roger Adams Award from the American Chemical Society, the Morley Medal from the Cleveland ACS section, the Columbus Section Award, the Cross Medal from Yale University, and the Sullivant Medal from The Ohio State University. Professor Newman also held honorary degrees from the University of New Orleans, Bowling Green State University and The Ohio State University.

Professor Newman exhibited a great fondness for jazz, undoubtedly a result of his exposure to such music in his formative years. This brought Mel into a close friendship with Louis Armstrong whom he introduced to Bob Woodward at a time when both were simultaneously in Columbus. As the story goes, Mel said to Louie: "Bob is to organic chemistry what you are to jazz." A party overhearing this responded "Dr. Woodward, you must be a hell of a chemist."

He is survived by his wife Beatrice (née Crystal), by their four children, and six grandchildren. Mel was a person of many facets. For us who remember him with affection and admiration, it gives great satisfaction to recognize that he served as a role model that will never be easy to overlook.

July 21, 1993

Leo A. Paquette



PETER YATES

August 26, 1924 - November 16, 1992

Peter Yates was well endowed with what one of his University of Toronto colleagues, Keith Yates, calls the old-fashioned virtues: fierce loyalty to his students and colleagues; stoicism in the face of adversity, such as his poor eyesight and other physical problems; fairness in all his dealings; and scholarliness, whether in chemistry (his life) or mathematics and bridge (his pastimes). To this list of admirable qualities, those of us who worked with him as an *Organic Syntheses* editor would add the Churchillian wittiness with which he enlivened several editorial dinners in the sixties.

Peter was born in Essex, England, in 1924 and received a B.Sc. from the University of London in 1946. He gained a Ph.D. from Yale in 1951 and was on the faculty of Harvard in 1952-1960. He then became a Professor of Chemistry at the

University of Toronto, where he remained for the rest of his career except for visiting professorships at Yale in 1966 and Princeton in 1977.

Professor Yates' research, reported in over 200 papers, covered a remarkably wide range. He established the structures of complex natural products, such as mangostin, shellolic acid, haplophytine, and the fecapentaenes. He was successful in synthesizing such complex natural products as gambogic acid, various bridged-ring steroids, and cedrene.

Professor Yates made important contributions to organic photochemistry, mechanistic organic chemistry, synthetic methods, and spectroscopy of organic compounds. His most important work in photochemistry was discovery of the photorearrangement of cyclic ketones to oxacarbenes. His studies of alpha-diazoketones led to syntheses of novel nitrogen and sulfur heterocycles. Among his many contributions to synthetic methodology was his discovery that some Diels-Alder reactions can be accelerated by Lewis acids.

Professor Yates was an early user and advocate of infrared spectroscopy to elucidate structures in organic chemistry. He published one of the first books on this subject, and it was widely used by practicing organic chemists for many years.

Professor Yates' chemical achievements were recognized by, for example, the Centennial Medal of the Government of Canada in 1967 and Fellowship in the Royal Society of Canada in 1970. He was active in the International Union of Pure and Applied Chemistry for over a decade, serving as President of its organic Division in the late 70's. He was editor of the *Canadian Journal of Chemistry* for many years.

Peter was active in research to the very end. Although hospitalized in considerable discomfort, he held a research review with an associate in his hospital room three days before his death.

May 22, 1993

Blaine C. McKusick

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