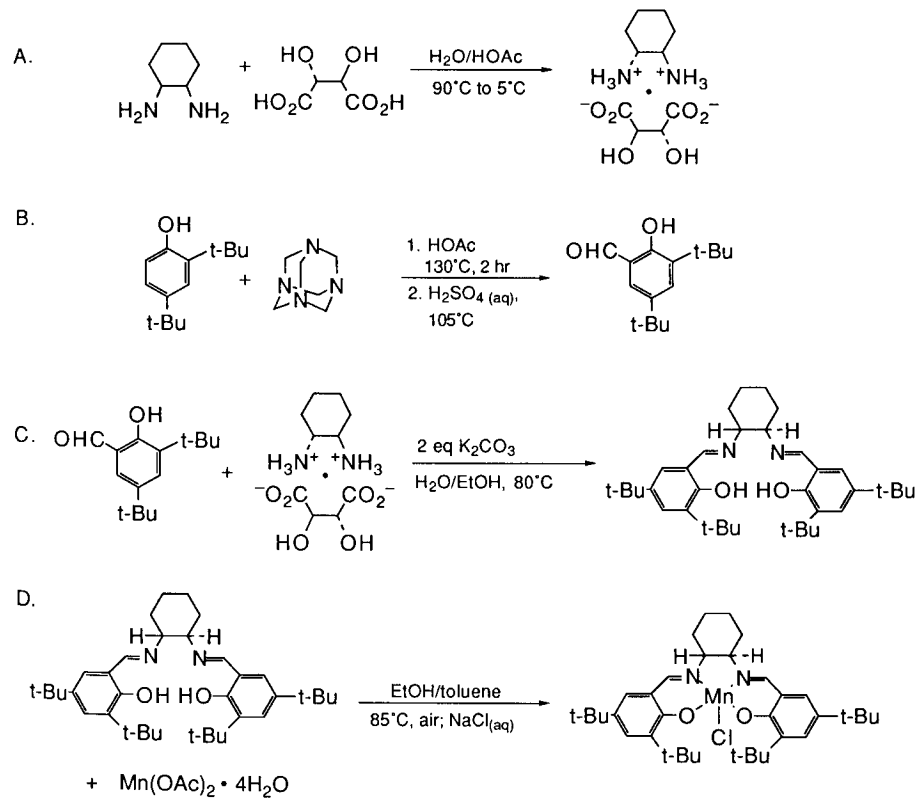# (R,R)-N,N'-BIS(3,5-DI-tert-BUTYLSALICYLIDENE)-1,2-CYCLOHEXANEDIAMINO MANGANESE(III) CHLORIDE, A HIGHLY ENANTIOSELECTIVE EPOXIDATION CATALYST

(Manganese, chloro[[2,2'-[1,2-cyclohexanediylbis(nitrilomethylidyne)]-bis[4,6-bis(1,1-dimethylethyl)phenalato]](2-)-N,N',O,O']-, [SP-5-13-(1R-trans-]-)

A.

B.

C.

D.

1

Submitted by Jay F. Larrow and Eric N. Jacobsen.[1]

Checked by Chris H. Senanayake, Ji Liu, and Ichiro Shinkai.

1. Procedure

A. *(R,R)-1,2-Diammoniumcyclohexane mono-(+)-tartrate* (Note 1). A 1-L beaker assembled with a mechanical overhead stirrer and a thermometer is charged with 250 mL of distilled or deionized water. L-(+)-Tartaric acid (75 g, 0.5 mol) is added with stirring in one portion (Note 2). The solution is stirred as 114 g (120 mL, 1 mol) of racemic trans-1,2-diaminocyclohexane is added carefully in one portion (Note 3). A slurry is formed initially but complete dissolution is observed once addition is complete. Glacial acetic acid (50 mL) is then added in one portion (Note 4). Product begins to precipitate during the addition, and continues to precipitate while the reaction mixture is allowed to cool from 90°C to 5°C, with stirring, over 3 to 4 hr. The temperature is maintained at 5°C for an additional hour and the product is isolated by filtration. The filter cake is washed with 50 mL of cold (5°C) water followed by 4 x 50-mL portions of ambient temperature methanol (Note 5). The enantiomeric excess of the derivatized diamine is determined by sampling the top and bottom of the filter cake using the procedure below (Note 6). The product is dried at 40-45°C under reduced pressure to give 105-110 g (80-83%) of the (R,R)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt as a white powder. (R,R)-1,2-Diaminocyclohexane obtained from this salt exhibits >98.0% enantiomeric excess (Note 7).

Derivatization and enantiomeric excess determination of 1,2-diaminocyclohexane: A 13 x 100-mm test tube is charged with 25 mg of the diammonium tartrate salt, 1.5 mL of methylene chloride (CH_2Cl_2), and 0.5 mL of 4 N aqueous sodium hydroxide. The two phases are mixed thoroughly for 30 sec using a vortex mixer, then m-toluoyl chloride (50 µL) is added and the two phases are mixed

for an additional 30 sec. The phases are allowed to separate and a 250-µL sample of the lower organic layer is removed. The sample is diluted to 10 mL with isopropyl alcohol and the resultant solution (10 µL) is analyzed by HPLC. The enantiomers are separated using a Pirkle covalent L-Leucine-DNB column and eluting with hexane/isopropyl alcohol (90:10; v/v) at a flow rate of 1.0 mL/min and at ambient temperature. The enantiomers are detected by measuring the absorbance of the eluent at 254 nm (Note 8).

B. *3,5-Di-tert-butylsalicylaldehyde* (Note 9). A 2-L, three-necked, round-bottomed flask equipped with a mechanical overhead stirrer, reflux condenser, and thermometer is charged with 125 g (0.60 mol) of 2,4-di-tert-butylphenol, 170 g (1.20 mol, 2 eq) of hexamethylenetetramine, and 300 mL of glacial acetic acid (Note 10). Complete dissolution results within minutes after stirring is initiated. The reaction mixture is heated to 130°C over a period of 60 min or less, and the temperature is diligently maintained within a range of 125-135°C for 2 hr as stirring is continued (Note 11). The reaction mixture is then cooled to 75-80°C and aqueous sulfuric acid [300 mL of 33% (w/w)] is added with stirring while the temperature is maintained below 100°C (Note 12). After the resulting mixture is heated to reflux (105-110°C) for 30-60 min, the reaction mixture is cooled to 75-80°C and transferred to a 1-L separatory funnel wrapped with electrical heating tape (Note 13). The phases are allowed to separate while the temperature is maintained at 75-80°C; the lower aqueous phase (650 to 750 mL; pH 4-5) is drawn off (Note 14). The organic layer is transferred to an Erlenmeyer flask and cooled to 50°C, at which point methanol (100 mL) is added with stirring. The mixture is cooled to room temperature, then to ≤5°C with an ice bath and maintained at that temperature for 1 hr with continued stirring. The product is collected by vacuum filtration and the solid is washed with 30 mL of cold (≤5°C) methanol. Air is pulled through the filter cake for not less than 30 min to remove most of the solvent (Note 15). The crude product is suspended in methanol (approximately 1:1; w/v) and

the mixture is heated to 50-55°C for 30 min with stirring (Note 16). The solution is cooled to ≤5°C over a 1-hr period and this temperature is maintained for another hour. The product is collected by vacuum filtration and washed with 20 mL of cold methanol. The product is allowed to air dry and is isolated as a free-flowing yellow solid, mp ≥52°C (Notes 17 and 18).

C. *(R,R)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine.* A 2-L, three-necked, round-bottomed flask equipped with a mechanical overhead stirrer, reflux condenser, and an addition funnel is charged with 29.7 g of (R,R)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt (0.112 mol), 31.2 g of potassium carbonate (0.225 mol, 2 eq), and 150 mL of water. The mixture is stirred until dissolution is achieved, and 600 mL of ethanol is added. The cloudy mixture is heated to reflux with a heating mantle and a solution of 53.7 g (0.229 mol, 2.0 eq) of 3,5-di-tert-butylsalicylaldehyde in 250 mL of ethanol is then added in a slow stream over 30 min (Note 19). The addition funnel is rinsed with 50 mL of ethanol and the mixture is stirred at reflux for 2 hr before heating is discontinued. Water, 150 mL, is added and the stirred mixture is cooled to ≤5°C over 2 hr and maintained at that temperature for another hour. The yellow solid is collected by vacuum filtration and washed with 100 mL of ethanol. After the solid is air dried, it is dissolved in 500 mL of methylene chloride. The organic solution is washed with 2 x 300 mL of water, followed by 300 mL of saturated aqueous sodium chloride. The organic layer is dried over sodium sulfate, and filtered to remove the drying agent. The solvent is removed by rotary evaporation to yield the product as a yellow solid, mp 200-203°C (Notes 20 and 21).

D. *(R,R)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamino manganese(III) chloride.* A 2-L, three-necked, round-bottomed flask equipped with a mechanical overhead stirrer, reflux condenser, and a 500-mL addition funnel is charged with 67.2 g (0.27 mol; 3 eq) of manganese acetate tetrahydrate (Mn(OAc)$_2$·4H$_2$O) and 500 mL of ethanol. Stirring is begun and the solution is heated to reflux (75-80°C) with a heating mantle. A solution of 50.0 g (0.09 mol, 1 eq) of (R,R)-N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine in 250 mL of toluene is added in a slow stream over 45 min and the funnel is rinsed with 50 mL of toluene (Notes 22 and 23). The reaction mixture is stirred at reflux for 2 hr, at which time the addition funnel is replaced by a gas dispersion tube connected to an air source (Notes 24 and 25). Air is bubbled through the refluxing reaction mixture for 1 hr, and the reaction is monitored for complete ligand consumption by thin layer chromatography (Note 26). When ligand consumption is complete, heating and air addition are discontinued and 100 mL of saturated aqueous sodium chloride is added. The reaction mixture is cooled to room temperature then transferred to a 2-L separatory funnel. The flask is rinsed into the funnel with 300 mL of toluene (Note 27) and the organic solution is washed with 3 x 600-mL portions of water followed by 500 mL of saturated aqueous sodium chloride. The organic layer is dried over anhydrous sodium sulfate, then filtered to remove the drying agent. Most of the toluene is removed by low pressure distillation followed by rotary evaporation of the residual solvent. The dark brown solid is dissolved in 300 mL of methylene chloride in a 1-L, round-bottomed flask. Heptane (300 mL) is added (Note 28), and the methylene chloride is removed by reduced pressure rotary evaporation. After complete removal of the methylene chloride, the brown slurry is stirred for 1 hr at ≤5°C in an ice bath. The brown solid is collected by vacuum filtration and allowed to air dry. Heating of the solid at 50-60°C under high vacuum removes any residual solvent to yield the desired product, mp 324-326°C (Notes 29, 30 and 31).

2. Notes

1. This procedure is a modification of that described by Galsbøl, et al.[2]

2. For all procedures, the submitters employed reagents (Aldrich Chemical Company, Inc., or Spectrum Chemical Mgf. Corp.) and solvents as supplied from commercial suppliers without purification.

3. The addition of the diamine is exothermic and the reaction temperature rises to approximately 70°C by the end of addition. The temperature should not exceed 90°C.

4. The addition of acetic acid is also exothermic and the reaction temperature should rise to, but not exceed, 90°C.

5. The aqueous filtrates may be combined and saved for isolation of (S,S)-1,2-diaminocyclohexane as the bis-(+)-tartrate salt using an alternate procedure.[2] The methanol washes can be discarded.

6. The enantiomeric excess of the two samples should be >98.0% for the (R,R)-enantiomer and within 0.2% enantiomeric excess of each other. Otherwise, the product should be washed with more methanol to remove the undesired enantiomer. If this procedure fails to yield product of acceptable enantiomeric purity, the product can be further purified by recrystallization of the salt from water (1:10, w/v). This affords product in 60-70% overall yield and >99.5% ee.

7. The (S,S)-diamine can be obtained as the mono-(–)-tartrate salt by using the same procedure with D-(–)-tartaric acid.

8. The column employed by the submitters had 25 cm x 4.6-mm (ID) dimensions and was purchased from Regis International (Morton Grove, IL). The (S,S)-derivative elutes first (9 min) followed by the (R,R)-derivative (12 min).

9. This procedure is an adaptation of the Duff reaction.[3]

10. The order of addition does not seem to be important. If the sequence that is described is employed, a slight exotherm is observed upon addition of the acetic acid.

11. Extreme care should be taken to maintain the reaction mixture temperature within the stated limits. Heating too slowly results in increased formation of side products and decreased product yield, as does allowing the reaction temperature to increase above 135°C. A mild exotherm is exhibited once the reaction reaches about 110°C, and the upper temperature limit can be exceeded if the rate of heating is not carefully monitored.

12. Addition of the sulfuric acid solution is exothermic and can cause vigorous evolution of steam. The acid solution should be cooled to (or below) room temperature before addition.

13. The checkers used a 1-L resin kettle (Kontes #614010-1000) with a temperature controller and preheated at 80°C.

14. It is important that sufficient time be allowed for proper partitioning between the phases. The heating tape maintains the temperature in the desired range, preventing the precipitation of solids and allowing for better separation. The phases should be allowed to separate for at least 15 min. If a small amount of solids is observed, this should not interfere with the separation and the solids may be discarded with the aqueous phase.

15. The typical yield for the crude aldehyde is 71-85 g (50-60%).

16. Any solids remaining in the mixture after 30 min at 50-55°C should be removed by filtration. The amount of solid is typically less than 1 g.

17. The typical yield of the recrystallized product is 50.0-64.3 g (35-45%). The literature[4] melting point of the product is 58-60°C, but high purity samples (≥ 98% by GC) generally have melting points in the given range.

18. The spectral properties of the product are as follows: ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.33 (s, 9 H), 1.43 (s, 9 H), 7.35 (d, 1 H, J = 2.4), 7.59 (d, 1 H, J = 2.4), 9.87

(s, 1 H), 11.65 (s, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 29.4, 31.4, 34.3, 35.1, 120.2, 127.8, 131.9, 137.8, 141.7, 159.2, 197.2; IR (KBr) cm^{-1}: 1653, 1612, 1373, 1322, 1265, 1170.

19. Gentle heating may be required to dissolve all of the aldehyde. The reaction mixture immediately turns bright yellow upon addition of the aldehyde and precipitation of the ligand occurs as addition proceeds.

20. The typical yield of the ligand is 58.2-60.6 g (95-99%). If further purification is required, the product can be recrystallized in two crops from boiling acetone (1:20; w/v) with 86-93% recovery as a fluffy yellow solid.

21. The spectral properties of the product are as follows: ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.27 (s, 18 H), 1.32-1.54 (m, 2 H), 1.4-2.0 (m, 6 H), 1.46 (s, 18 H), 3.31-3.70 (m, 2 H), 7.02 (d, 2 H, J = 2.2), 7.34 (d, 2 H, J = 2.2), 8.34 (s, 2 H), 13.76 (s, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 24.4, 29.5, 31.5, 33.3, 34.1, 35.0, 72.4, 117.9, 126.1, 126.8, 136.4, 139.9, 158.1, 165.9; IR (KBr) cm^{-1}: 2960, 2869, 1631, 1595, 1468, 1439, 1362, 1271, 1174, 829.

22. The ligand is only moderately soluble in toluene and complete dissolution is often achieved with the aid of sonication and gentle warming.

23. The pinkish-brown solution turns to a dark brown heterogeneous mixture immediately upon addition of the ligand.

24. After 2 hr at reflux the dark solution should appear homogeneous.

25. The submitters employed a commercial aquarium pump, although any device used to supply low pressure air for flash chromatography should be suitable. The flow rate should be 10-30 mL/min.

26. TLC was performed on silica (Merck silica gel 60 F-254; 0.25-mm thickness) with EtOAc/hexanes (1:4). The complex remains at the baseline (R$_f$ = 0), while the ligand has an R$_f$ = 0.85. If ligand consumption is not complete, bubbling of air through the solution and heating are continued while the reaction is monitored every 20 min

until completion. A small amount of 3,5-di-tert-butylsalicylaldehyde may be detected because of ligand decomposition.

27. The presence of an insoluble residue is common and this may be left in the reaction flask.

28. The catalyst may or may not precipitate upon addition of the heptane, but the end result is the same and isolation of the product is not affected.

29. The yield of this reaction is typically 54.9-57.2 g (95-99%).

30. Elemental analysis can be used to establish purity, although a melting point ≥320°C is generally a sufficient criterion of product purity. The complex does not exhibit a readily interpretable NMR spectrum because of the paramagnetic nature of the complex.

31. A procedure for the large-scale (>100 g) production of the complex as a DMF adduct has also been described.[5]

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The product of this preparation is the most enantioselective catalyst developed to date for asymmetric epoxidation of a broad range of unfunctionalized olefins.[6] The procedure includes a highly efficient resolution of trans-1,2-diaminocyclohexane as well as a convenient analytical method for the determination of its enantiomeric purity. This method is general for the analysis of chiral 1,2-diamines. The Duff formylation described in Step B is a highly effective method for the preparation of 3,5-di-tert-

butylsalicylaldehyde, and it circumvents the use of hazardous or sensitive materials, such as tin chloride (SnCl$_4$), which were employed in previously reported syntheses.[6d] The Duff reaction is applicable to the preparation of other 3,5-substituted salicylaldehydes,[5] which in turn can be used to prepare chiral (salen)Mn, [N,N'-bis(salicylideneamino)ethane]Mn, epoxidation catalysts with sterically- and electronically-tuned reactivities.[7] As such, a wide range of (salen)metal complexes can be prepared by adaptation of the procedure described above, by variation of the diamine, the salicylaldehyde, or the metal center.

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Appendix

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

(R,R)-N,N'-Bis-(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamino manganese(III) chloride: Manganese, chloro[[2,2'-[1,2-cyclohexanediylbis(nitrilomethylidyne)]bis[4,6-bis(1,1-dimethylethyl)phenolato]](2-)-N,N',O,O']-[SP-5-13-(1R-trans)] (12); (138124-32-0]

(R,R)-1,2-Diammoniumcyclohexane mono-(+)-tartrate: 1,2-Cyclohexanediamine, (1R-trans)-, [R-(R*,R*)-2,3-dihydroxybutanedioate (1:1) (9); (39961-95-0)

L-Tartaric acid: Tartaric acid, L- (8); Butanedioic acid, 2,3-dihydroxy-, [R-(R*,R*)]- (9); (87-69-4)

(±)-trans-1,2-Diaminocyclohexane: 1,2-Cyclohexanediamine, trans- (8,9); (1121-22-8)

m-Toluoyl chloride (8); Benzoyl chloride, 3-methyl- (9); (1711-06-4)

3,5-Di-tert-butylsalicylaldehyde: Benzaldehyde,3,5-bis(1,1-dimethylethyl)-2-hydroxy- (9); (37942-07-7)

2,4-Di-tert-butylphenol: Phenol, 2,4-di-tert-butyl- (8); Phenol, 2,4-bis(1,1-dimethylethyl)- (9); (96-76-4)

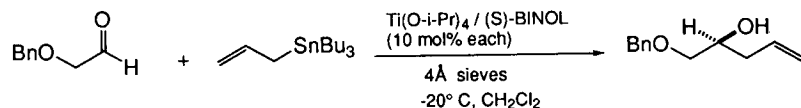Hexamethylenetetramine (8); 1,3,5,7-Tetraazatricyclo[3.3.1.1^{3,7}]decane (9); (100-97-0)

Manganese acetate tetrahydrate: Acetic acid, manganese (2+ salt), tetrahydrate (8,9); (6156-78-1)

(R,R)-N,N'-Bis-(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine: Phenol, 2,2'-[1,2-cyclohexanediylbis(nitrilomethylidyne)]bis[4,6-bis(1,1-dimethylethyl)- [1R-(1a(E),2b(E)]]- (12); (135616-40-9]

CATALYTIC ASYMMETRIC ALLYLATION REACTIONS:

(S)-1-(PHENYLMETHOXY)-4-PENTEN-2-OL

(4-Penten-2-ol, 1-(phenylmethoxy)-, (S)-)

$$BnO \overset{O}{\underset{H}{\bigvee}} + \bigvee SnBu_3 \xrightarrow[\substack{4\text{Å sieves} \\ -20°\text{ C, CH}_2\text{Cl}_2}]{\substack{Ti(O\text{-}i\text{-}Pr)_4 / (S)\text{-BINOL} \\ (10 \text{ mol\% each})}} BnO \overset{H_{\cdots}}{\bigvee} \overset{OH}{\bigvee}$$

Submitted by Gary E. Keck[1] and Dhileepkumar Krishnamurthy.

Checked by William R. Roush and Melissa L. Reilly.

1. Procedure

A 250-mL, round-bottomed flask (Note 1) equipped with a stirring bar and a rubber septum is charged with (S)-(-)-1,1'-bi-2-naphthol [(S)-BINOL] (1.14 g, 4.0 mmol) (Note 2) and methylene chloride (Note 3) (40 mL). The suspension is stirred until the binaphthol is completely dissolved. Powdered 4 Å molecular sieves (16.0 g) (Note 4) are then added. To the resultant suspension is added a 1 M methylene chloride solution of titanium tetraisopropoxide (4.0 mL, 4.0 mmol) (Note 5) by syringe at ambient temperature. The resulting orange-red suspension is heated at reflux for 1 hr (Note 6). The red-brown mixture is cooled to ambient temperature and a methylene chloride (6 mL) solution of benzyloxyacetaldehyde (Note 7) (6.0 g, 40 mmol) is injected via syringe. The resulting mixture is stirred for 5 min at ambient temperature, then cooled to -78°C. To the reaction mixture is added allyltributylstannane (Note 8) (15.9 g, 14.9 mL, 48 mmol) via syringe. The resulting reaction mixture is then kept in a freezer at -20°C for 60 hr without stirring. Even after 60 hr a small amount of unreacted aldehyde is detected (TLC analysis) (Note 9). The reaction mixture is quenched with saturated aqueous sodium hydrogen carbonate solution (50 mL), diluted with methylene chloride (50 mL), and stirred at ambient temperature for 2 hr. The molecular sieves are removed by filtration through a pad of Celite, and the aqueous layer is extracted with methylene chloride (2 x 25 mL). The combined organic extracts are dried over sodium sulfate and evaporated under reduced pressure. Chromatography over silica gel (Note 10) gives 6.16-6.69 g (80-87%) of (S)-1-(phenylmethoxy)-4-penten-2-ol (Notes 11, 12, 13). The enantiomeric purity is 94-96% ee by HPLC analysis using a chiral column (Notes 14, 15).

2. Notes

1. The reaction flask, needles, and syringes were stored in an oven at 120°C overnight prior to use.

2. S-(-)-1,1'-Bi-2-naphthol is purchased from the Aldrich Chemical Company, Inc.

3. Methylene chloride is distilled from calcium hydride before use.

4. Powdered 4 Å molecular sieves are purchased from the Aldrich Chemical Company, Inc., and activated by storing in an oven at 120°C for several days.

5. Titanium tetraisopropoxide [titanium(IV) isopropoxide] is purchased from the Aldrich Chemical Company, Inc.

6. The reaction mixture is refluxed gently using an oil bath.

7. Benzyloxyacetaldehyde is purchased from the Aldrich Chemical Company Inc., and distilled under vacuum before use.

8. Allyltributylstannane is commercially available (Aldrich Chemical Company Inc.) or can be easily prepared following an *Org. Synth.* procedure.[2]

9. Thin layer chromatography is performed on Merck Kieselgel silica gel 60 F-254 plates eluting with 30% acetone/hexanes, visualized by a 254-nm UV lamp and

stained with an ethanolic 12-phosphomolybdic acid solution followed by heating at ca. 250°C on a hot plate. Observed R_f's were 0.30 for aldehyde and 0.38 for product.

10. A 25 x 17-cm silica gel (Davisel 633) column is used. Initially, hexanes are used as eluant to elute recovered allyltributylstannane, then 9 : 1 hexane:acetone is used as eluant to isolate the product. Further elution of the column with 8 : 2 hexane:acetone gives 0.9 g (80%) of crude recovered BINOL which can be further purified by chromatography over silica gel to give 0.8 g (70%) of pure BINOL.

11. The submitters obtained 6.79 g (88%) of product.

12. The optical rotations for the R- and S- isomers of this compound have been reported in the literature with the same (-) sign.[3a,b] The submitters established the absolute stereochemistry of this compound using the Mosher method,[3c] and for the S-isomer measured $[\alpha]_D^{23}$ 1.96° (CHCl$_3$, c 2.3). The optical rotation determined by the checkers for the S isomer is $[\alpha]_D^{23}$ -1.87° (CHCl$_3$, c 2.3). Thus the same situation was encountered in the present case. Upon exchange of samples, the submitters measured a *positive* rotation for the checker's sample. The discrepancy was traced to the chloroform (CHCl$_3$) used: The submitters used EM Science Spectral Grade CHCl$_3$, which does not contain ethanol (EtOH) as a stabilizer, while the checkers used Mallinckrodt CHCl$_3$ which contained 0.75% EtOH as stabilizer. The submitters measured $[\alpha]_D^{23}$ -2.9° (c 2.5) in absolute ethanol; other experiments that involved adding small amounts of EtOH to the EM Science CHCl$_3$ showed that the presence of small amounts of EtOH affected the rotation quite markedly. This is clearly a case where the measured rotations are so small as to be of limited value in making unambiguous assignments.

13. (S)-1-(Phenylmethoxy)-4-penten-2-ol prepared by this procedure gave the following spectroscopic data: ^{1}H NMR (400 MHz, CDCl$_3$) δ: 2.28 (m, 2 H), 3.38 (dd, 1 H, J = 9.43, 7.55), 3.52 (dd, 1 H, J = 9.43, 3.46), 3.88 (m, 1 H), 4.58 (s, 2 H), 5.11 (m, 2 H), 5.82 (m, 1 H), 7.34 (m, 5 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 37.9, 69.7, 73.4, 73.9,

117.6, 127.68, 127.73, 128.4, 134.2, 138.0; IR spectrum (neat) cm^{-1}: 3450, 3080, 3041, 2979, 2920, 1648, 1461, 1268, 1105, 1065; mass spectrum (low resolution, DCI/NH$_3$) 192 m/z.

14. CHIRALCEL OD-H is available from Chiral Technologies Inc. The checkers used a 15-cm column, with a 97 : 3 hexane/2-propanol mixture as eluant, a flow rate of 0.5 mL/min, and detection by RI detector. The t_R of the R-isomer (17.0 min) is shorter than that of the major S-isomer (17.8 min). The submitters used a 25-cm column with a 94 : 6 mixture of hexane/2-propanol as eluant and a flow rate of 0.5 mL/min. Under the latter conditions, the t_R's of the R- and S-isomers are 17.9 min and 19.4 min, respectively.

15. The submitters reported the enantiomeric purity of the product as 94% e.e.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.
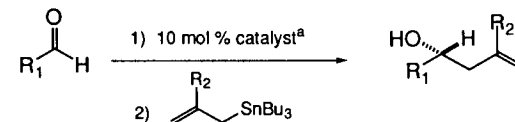
3. Discussion

This procedure describes the preparation and use of an effective chiral catalyst for the asymmetric allylation of aldehydes. A previous synthesis of optically pure 1-(phenylmethoxy)-4-penten-2-ol requires seven steps from D-mannitol.[4] This procedure has been employed successfully with other aldehydes,[5] and also with methallyltributylstannane[5] (see Table). Catalysts prepared from (R)- or (S)-BINOL and Ti(O-i-Pr)$_4$ at 2:1 stoichiometry have also proven useful in these reactions.[6,7] The olefinic products may be regarded as latent aldol products between aldehydes and the enolate of acetaldehyde or acetone. In all cases examined thus far, enantioselectivity

is consistent with the observation that (R)-BINOL gives R-product with benzaldehyde. Thus addition occurs to the *re* face of substrate with this catalyst prepared using (R)-BINOL.

1. Department of Chemistry, University of Utah, Salt Lake City, Utah 84112.

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TABLE

CATALYTIC ASYMMETRIC ALLYLATION REACTIONS WITH OTHER ALDEHYDES

R_1	R_2	T, °C (time, hr)	Yield,[b] %	ee,[c] %
C_6H_5	H	-20 (70)	88	95
	CH_3	-20 (60)	75	91
c-C_6H_{11}	H	-20 (70)	66	94
	CH_3	-20 (48)	50	84
(E)-$C_6H_5CH=CH$	H	-20 (70)	42	89
	CH_3	-20 (12)	68	87
$C_6H_5CH_2CH_2$	H	-20 (70)	93	96[d]
	CH_3	-20 (40)	97	98
i-C_3H_7	H	-20 (70)	89	96
furyl	H	-20 (70)	73	96
	CH_3	-20 (12)	99	99
p-$CH_3OC_6H_4$	CH_3	-20 (48)	61	93
p-$CH_3OC_6H_4CH_2OCH_2$	H	-20 (70)	81	96[d]

[a]See experimental procedure for catalyst preparations. [b]Isolated yields of the product. [c]Determined by ^{1}H NMR with Eu(hfc)$_3$. [d]Determined by ^{19}F NMR of the Mosher ester.

ASYMMETRIC SYNTHESIS OF DIETHYL (R)-(-)-(1-AMINO-3-METHYLBUTYL)PHOSPHONATE

(Phosphonic acid, (1-amino-3-methylbutyl)-, diethyl ester, (R)-)

Submitted by Amos B. Smith, III, Kraig M. Yager, Barton W. Phillips, and Carol M.
Taylor.[1]

Checked by Martha Huntington, Edward G. Corley, Andrew S. Thompson, and
Ichiro Shinkai.

1. Procedure

A. *(R)-(-)-1-Amino-1-phenyl-2-methoxyethane* (**2**).[2] A solution of (R)-(-)-2-phenylglycinol (**1**) (25.0 g, 182.2 mmol) (Note 1) in anhydrous tetrahydrofuran (THF) (370 mL) (Note 2) is added dropwise via an oven-dried, 500-mL, pressure-equalizing addition funnel to an oven-dried, 2-L, round-bottomed flask containing a stirred (Note 3) suspension of potassium hydride (7.82 g, 195 mmol) (Note 4) in anhydrous THF (150 mL) at 25°C under an argon atmosphere. The resultant pale yellow mixture is stirred overnight and then treated dropwise with a solution of methyl iodide (25.2 g, 177.6 mmol) (Note 5) in THF (220 mL) over 2 hr at room temperature. The resultant mixture is stirred for an additional 3 hr, poured into cold (~5°C) saturated aqueous sodium chloride solution (1.5 L) and extracted with anhydrous diethyl ether (4 x 250 mL); the combined organic extracts are dried over anhydrous sodium sulfate (Note 6). Filtration and rotary evaporation gives 39.2 g of yellow oil that is purified by vacuum distillation (bp 47-50°C, 0.2 mm) to yield 25.3 g (94%) of **2** as a colorless oil (Note 7).

B. *Diethyl (R)-(-)-[1-((N-(R)-(1-phenyl-2-methoxyethyl)amino)-3-methylbutyl)]-phosphonate* (**4**). To an oven-dried, 1-L, round-bottomed flask containing a magnetic stirring bar (Note 3) are added isovaleraldehyde (**3**) (9.4 g, 109 mmol) (Note 8) and dry toluene (100 mL) (Note 9) under an argon atmosphere. The solution is cooled to 0°C (ice bath) and a solution of (R)-(-)-1-amino-1-phenyl-2-methoxyethane (**2**) (16.5 g, 109 mmol) in dry toluene (160 mL) is introduced dropwise over 45 min via a 250-mL, pressure-equalizing addition funnel. The cooling bath is removed and the mixture is allowed to warm to room temperature. The resultant turbid solution is treated with anhydrous sodium sulfate (125 g, 0.88 mol), stirred for 1 hr, and then filtered through a fritted glass funnel, washing the residue with toluene (150 mL). The filtrate is concentrated, first by rotary evaporation and then at ≤1 mm for 1 hr, yielding 23.3 g of the imine as a slightly yellow oil.

To the 1-L, round-bottomed flask containing the above imine are added a magnetic stirring bar and dry THF (180 mL) under an argon atmosphere. To this stirring solution is added lithium diethyl phosphite (Note 10) via a 12-gauge cannula. After 20 hr at ambient temperature the reaction mixture is quenched by addition of water (200 mL) and most of the THF is removed by rotary evaporation. The aqueous layer is then saturated with sodium chloride and extracted with ethyl acetate (3 x 300 mL) (Note 11), and the combined organic phases are dried over anhydrous sodium sulfate. Filtration and rotary evaporation furnish 39-45 g of a pale yellow oil that is dissolved in 50% ethyl acetate-hexane (50 mL) and purified by flash chromatography [9-cm column, 800 g of Silica Gel 60 (Note 12), eluting with 1.2 L of 50% ethyl acetate-hexane followed by 6 L of 60% ethyl acetate-hexane, 35 mL/min, 125-mL fractions after a 2-L forerun; product R_f = 0.5, 2:1 ethyl acetate-hexane]. Concentration via rotary evaporation furnishes 30.5 g (85%) of **4** as a colorless oil (Notes 13 and 14).

C. *Diethyl (R)-(-)-(1-amino-3-methylbutyl)phosphonate* (**5**). A 1-L, round-bottomed flask is equipped with a magnetic stirring bar and charged with **4** (30.5 g, 85.4 mmol) and absolute ethanol (600 mL). To this solution is added 20% palladium hydroxide on carbon (35.5 g) (Note 15), and the flask is connected to an atmospheric-pressure hydrogenation apparatus equipped with a graduated burette containing water or mercury to monitor uptake of hydrogen (Note 16). The suspension is thoroughly degassed (aspirator pressure), backfilled twice, with hydrogen and stirred vigorously for 16 hr. The mixture is then degassed (aspirator pressure) and filtered through a pad of Celite (Note 17). The filter pad is washed with absolute ethanol (3 x 75 mL), the filtrate concentrated under reduced pressure, and the residual oil purified by flash chromatography (9-cm column, 580 g of Silica Gel 60, eluting with 150 mL of dichloromethane, 1.5 L of 2% methanol-dichloromethane and 2 L of 5% methanol-dichloromethane, 50 mL/min, 125-mL fractions; product R_f = 0.25, 5% methanol-

dichloromethane). Concentration of the fractions gives 15.5 g (82%) of **5** as a pale yellow oil (Notes 18 and 19).

2. Notes

1. (R)-(-)-2-Phenylglycinol (≥98% ee), purchased from Aldrich Chemical Company, Inc., was used as received.

2. Tetrahydrofuran was distilled from sodium/benzophenone ketyl at atmospheric pressure under an argon atmosphere.

3. A large (7 cm long, 4 cm diameter) football-shaped magnetic stirring bar was required to ensure efficient mixing of the heterogeneous mixture.

4. Potassium hydride, 35% by weight in mineral oil, was purchased from Aldrich Chemical Company, Inc., and washed with dry pentane prior to use. *Note that potassium hydride is a pyrophoric solid and must be handled with extreme care.*

5. Methyl iodide was purchased from Aldrich Chemical Company, Inc., and used as received.

6. Anhydrous, powdered sodium sulfate, purchased from Aldrich Chemical Company, Inc., was used as received.

7. Analytical data for **2** are as follows: $[\alpha]_D^{25}$ -49.4° (benzene, *c* 6.3); IR (CHCl$_3$) cm^{-1}: 3380 (w), 3040 (w), 3000 (w), 2900 (m), 2240 (m), 1580 (m), 1460 (m), 1200 (m), 1120 (s), 905 (s), 700 (s); ^{1}H NMR (500 MHz, CDCl$_3$) δ: 1.75 (br s, 2 H), 3.39 (t, 1 H, J = 9.1), 3.41 (s, 3 H), 3.53 (dd, 1 H, J = 9.3, 3.9), 4.21 (dd, 1 H, J = 8.7, 3.9), 7.30 (m, 1 H), 7.35 (t, 2 H, J = 7.3), 7.40 (dd, 2 H, J = 8.7, 1.6); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 55.4, 58.8, 78.9, 126.7, 127.3 (2 C), 128.3, 142.6 (2 C); high resolution mass spectrum (CI, CH$_4$) m/z 152.1069 [(M+H)$^+$; calcd for C$_9$H$_{14}$NO: 152.1075].

8. Isovaleraldehyde was purchased from Aldrich Chemical Company, Inc., and distilled at atmospheric pressure before use.

9. Toluene was distilled from sodium spheres at atmospheric pressure under an argon atmosphere. The checkers report that reagent grade toluene stored over 4 Å molecular sieves proved satisfactory.

10. An oven-dried, 250-mL, conical flask is charged with freshly distilled diethyl phosphite (29.3 g, 212.1 mmol) (Note 20) and dry THF (110 mL) under an argon atmosphere. The solution is cooled to 0°C (ice bath) and treated dropwise over 20 min with a solution of butyllithium (1.6 M in hexane; 63.0 mL, 100.8 mmol) (Note 21). After an additional 0.5 hr the mixture is warmed to room temperature and used immediately.

11. Reagent-grade ethyl acetate and hexanes were purchased from commercial sources and distilled before use.

12. EM Science Silica Gel 60 (230-400 mesh ASTM) was purchased from Bodman Industries (Aston, PA). The checkers recommend 36 g of silica gel/1 g of crude product.

13. Analytical data for **4** are as follows: $[\alpha]_D^{25}$ -118.4° (CHCl$_3$, *c* 2.07); IR (CHCl$_3$) cm^{-1}: 3340 (br, w), 2985 (s), 2960 (s), 2940 (s), 1460 (m), 1390 (w), 1370 (w), 1230 (s), 1050 (s), 1030 (s), 970 (s), 700 (m); ^{1}H NMR (500 MHz, CDCl$_3$) δ: 0.51 (d, 3 H, J = 6.5), 0.88 (d, 3 H, J = 6.8), 1.37 (m, 6 H, J = 7.0), 1.41 (q, 2 H, J = 7.6), 1.95 (m, 1 H), 2.12 (br s, 1 H), 2.69 (ddd, 1 H, J$_{HP}$ = 9.1, J$_{HH}$ = 7.9, 6.7), 3.38 (t, 1 H, J = 3.9), 3.40 (s, 3 H), 3.46 (t, 1 H, J = 9.6), 4.09-4.19 (m, 4 H), 4.54 (dt, 1 H, J = 9.4, 3.9), 7.27 (m, 1 H), 7.30 (t, 2 H, J = 7.6), 7.40 (d, 2 H, J = 7.2); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 16.5 (d, J$_{CP}$ = 6), 16.6, 20.7 (d, J$_{CP}$ = 6), 23.6 (d, J$_{CP}$ = 5), 23.7, 40.5 (d, J$_{CP}$ = 7), 49.4, 58.4, 59.5 (d, J$_{CP}$ = 138), 61.4 (d, J$_{CP}$ = 7), 61.8, 77.7, 127.6 (d, J$_{CP}$ = 7), 128.2 (2 C), 128.3, 140.3 (2 C); high resolution mass spectrum (CI, CH$_4$) m/z 358.2132 [(M+H)$^+$; calcd for C$_{18}$H$_{33}$NO$_4$P: 358.2147]. Anal. Calcd for C$_{18}$H$_{32}$NO$_4$P: C, 60.49; H, 9.02; N, 3.92. Found: C, 60.70; H, 9.21; N, 3.80.

14. The minor (R,S) diastereomer is present in the crude reaction mixture to the extent of approximately 0.9% as determined by capillary gas-liquid chromatographic analysis performed on a Hewlett-Packard 5790A gas chromatograph equipped with a Hewlett-Packard 3390A integrator and HP-1 methylsilicone gum column (25 m x 0.2 mm x 0.33 μm film thickness). The checkers found that HPLC analysis (Zorbax SB-Phenyl column 25 cm x 4.6 mm, 40:60 MeCN/0.1% aqueous phorphoric acid, 1.5 mL/min, 250 nm detection) provided satisfactory resolution of the R,R- and R,S-diastereomers. The minor diastereomer is hardly discernible by ^{1}H NMR (500 MHz) after purification by flash chromatography.

15. Palladium hydroxide on carbon (moist, Pd content 20%, dry weight basis, moisture content ≤50%) was purchased from Aldrich Chemical Company, Inc., and used as received.

16. The checkers found the use of a Parr shaker (2 PSIG hydrogen, 16 hr, ambient temperatures) satisfactory for the hydrogenolysis step, and distillation (bp 108°C/2.5 mm, 89.9-91% yield) for purification.

17. The filter pad was prepared by compressing Celite (4 cm) onto a layer of sand (1.5 cm) in a fritted glass funnel (10-cm diameter).

18. Analytical data for **5** are as follows: $[\alpha]_D^{25}$ -20.8° (CHCl$_3$, c 1.6); IR (CHCl$_3$) cm^{-1}: 3690 (br, w), 3000 (s), 2940 (m), 1470 (w), 1390 (m), 1230 (s), 1040 (s), 965 (s), 780 (m) ; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 0.90 (d, 3 H, J = 6.7), 0.96 (d, 3 H, J = 6.7), 1.34 (td, 6 H, J$_{HH}$ = 7.0, J$_{HP}$ = 1.8), 1.50 (m, 2 H), 1.56 (br s, 2 H), 1.91 (m, 1 H, J = 1.4), 3.04 (ddd, 1 H, J$_{HP}$ = 10.8, J$_{HH}$ = 10.8, 3.7), 4.16 (m, 4 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 16.5, 21.0, 23.5 (d, 2 C, J$_{CP}$ = 5), 24.1, 39.9 (d, J$_{CP}$ = 13), 46.7 (d, J$_{CP}$ = 148), 62.0 (d, J$_{CP}$ = 7), 62.1 (d, J$_{CP}$ = 7); high resolution mass spectrum (CI, CH$_4$) m/z 224.1419 [(M+H)$^+$; calcd for C$_9$H$_{23}$NO$_3$P: 224.1415]. Anal. Calcd for C$_9$H$_{22}$NO$_3$P: C, 48.42; H, 9.93; N, 6.28. Found: C, 48.60; H, 9.93; N, 6.23.

19. α-Aminophosphonate **5** is obtained in >99% enantiomeric excess as determined by ^{1}H NMR (500 MHz) analysis of the derived S-Mosher amide.[3]

20. Diethyl phosphite, purchased from Aldrich Chemical Company, Inc., was vacuum distilled just prior to use (bp 50-51°C, 2 mm).

21. Butyllithium, purchased from Aldrich Chemical Company, Inc., was standardized by titration with diphenylacetic acid. Butyllithium solutions with concentrations less than 1.5 M may result in drastically reduced diastereomeric excesses and should be avoided.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

α-Aminophosphonic acids and esters, also referred to as α-aminophosphonates, represent an important class of organic compounds by virtue of their analogy to α-aminocarboxylic acids. Several synthetic derivatives of α-aminophosphonates have significant biological activities including inhibition of proteolytic enzymes[4] and of bacterial growth,[5] and they have also been found in nature as components of hypertensive tripeptides.[6] Currently, α-aminophosphonates are also serving as transition-state mimics in haptens for catalytic antibody research.[7] It is not surprising that their biological properties are strongly influenced by the absolute configuration at the α carbon.[5]

Several methods have been devised for the preparation of racemic α-aminophosphonates; in 1972 the first optically active example was synthesized.[8]

Since then, optically active α-aminophosphonates have been obtained by a variety of methods including resolution, asymmetric phosphite additions to imine double bonds and sugar-based nitrones, condensation of optically active ureas with phosphites and aldehydes, catalytic asymmetric hydrogenation, and 1,3-dipolar cycloadditions. These approaches have been discussed in a comprehensive review by Dhawan and Redmore.[9] More recent protocols involve electrophilic amination of homochiral dioxane acetals,[10] alkylation of homochiral imines derived from pinanone[11] and ketopinic acid,[12] and alkylation of homochiral, bicyclic phosphonamides.[13]

The method described here takes advantage of the chelating ability of homochiral imines typified by 6 to achieve high levels of asymmetric induction during the addition of phosphite anion to the C-N double bond.[14] Coordination of the lithium counterion by the ether oxygen and imine nitrogen is believed to generate a rigid, five-membered-ring transition state; addition occurs anti to the phenyl ring, leading predominantly to the R,R-diastereomers with de values typically exceeding 96%. The α-aminophosphonates are then generated with ee values of 71 to 99% by catalytic hydrogenolysis of the chiral directing group. As illustrated in Table I, this strategy is widely applicable. Moreover, the enantiomer of 1 is also commercially available, providing ready access to the corresponding S-α-aminophosphonates.[15,16,17,18]

1. Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104.

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phosphoalanine diethyl ester, $[\alpha]_D^{25}$ +7.3° (CHCl$_3$, c 1.3); (S)-(+)-phosphoserine diethyl ester, $[\alpha]_D^{25}$ +9.0° (CHCl$_3$, c 1.0).

16. (R)-(-)-Phospholeucine, mp 288-291°C; $[\alpha]_D^{25}$ -28° (1 M NaOH, c 1): Lejczak, B.; Kafarski, P.; Mastalerz, P. *J. Chromatogr.* **1985**, *324*, 455; this work: mp 281-283°C (dec); $[\alpha]_D^{25}$ -24.7° (1 M NaOH, c 0.7). (S)-(-)-Phosphomethionine, $[\alpha]_D^{25}$ -40.4° (0.25 M NaOH, c 1.0): Kupczk-Subotkowska, L.; Mastalerz, P. *Int. J. Pepti. Protein Res.* **1983**, *21*, 485; this work: (R)-(+)-Phosphomethionine, mp 248-251°C (dec); $[\alpha]_D^{25}$ +39.1° (0.25 M NaOH, c 1.1). (R)-(-)-Phosphoglutamic acid, mp 183-184°C; $[\alpha]_D^{25}$ -20° (1 M NaOH, c 1): Lejczak, B.; Kafarski, P.; Mastalerz, P. *J. Chromatogr.* **1985**, *324*, 455; this work: mp 175-177°C; $[\alpha]_D^{25}$ -7° (1 M NaOH, c 0.7). (R)-(-)-Phospho(phenylglycine), $[\alpha]_D^{25}$ +18° (1 M NaOH, c 2): Glowiak, T.; Sawka-Dobrowolska, W.; Kowalik, J.; Mastalerz, P.; Soroka, M.; Zon J. *Tetrahedron Lett.* **1977**, 3965; this work: mp 282-284°C (dec); $[\alpha]_D^{25}$ +16.6° (1 M NaOH, c 0.42).

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Appendix

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

Diethyl (R)-(-)-(1-amino-3-methylbutyl)phosphonate: Phosphonic acid, (1-amino-3-methylbutyl)-, diethyl ester, (R)- (13); (159171-46-7)

(R)-(-)-1-Amino-1-phenyl-2-methoxyethane: Benzenemethanamine, α-(methoxymethyl)-, (R)- (10); (64715-85-1)

(R)-(-)-2-Phenylglycinol: Benzeneethanol, β-amino-, (R)- (9); (56613-80-0)

Potassium hydride (8,9); (7693-26-7)

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

Diethyl (R)-(-)-[1-((N-(R)-(1-phenyl-2-methoxyethyl)amino)-3-methylbutyl)]phosphonate: Phosphonic acid, [1-(2-methoxy-1-phenylethyl)amino]-3-methylbutyl]-, diethyl ester, [R-(R*,R*)]- (13); (159117-09-6)

Isovaleraldehyde (8); Butanal, 3-methyl- (9); (590-86-3)

Diethyl phosphite: Phosphonic acid, diethyl ester (8,9); (762-04-9)

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

TABLE I

PREPARATION OF α-AMINOPHOSPHONATES

$$MeO\text{-}\underset{Ph}{\overset{NH_2}{|}} \xrightarrow[\text{PhH, Na}_2\text{SO}_4]{\text{RCHO}} MeO\text{-}\underset{Ph}{\overset{N=}{|}}R \xrightarrow[\text{THF, 25°C, 18 hr}]{\text{BuLi, HPO}_3\text{Et}_2} MeO\text{-}\overset{H}{N}\text{-}\overset{O}{\overset{||}{P}}(OEt)_2 \xrightarrow[\text{EtOH, 25°C}]{\text{H}_2, \text{Pd(OH)}_2} H_2N\text{-}\overset{O}{\overset{||}{P}}(OEt)_2$$

0° to 25°C, 1 hr   **2**   **6**   **7** +   **8**   18 hr   **9**
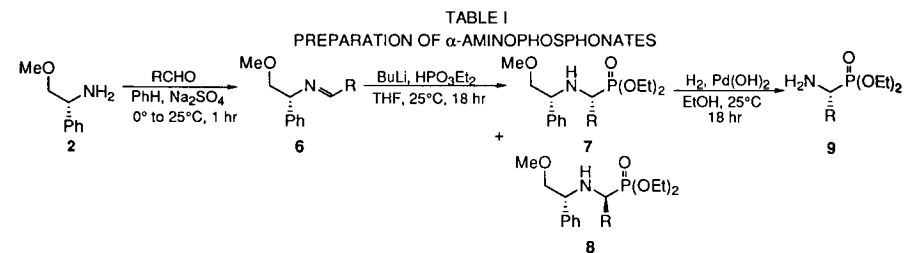
Entry	R	Yield 6 (%)[a]	7:8 Ratio	de (%)	Yield 7,8 (%)[b]	Yield 9 (%)[b]	9 $[\alpha]_D^{25}$	ee 9 (%)[c]
a	(cyclohexylmethyl)	90	49:1[d]	96.0	68	94	-52.2° (c 1.2, Me₂CO)	96
b	(cyclohexylethyl)	89	114:1[e]	98.3	70[f]	87	-20.9° (c 0.6, CHCl₃)	≥99
c	(isopropylmethyl)	82	55:1[e]	96.5	82	86	-0.8°[15] (c 1.3, CHCl₃)	97
d	(isobutylmethyl)	84	>114:1[e]	>98.3	81[f]	89	-20.8°[16] (c 1.6, CHCl₃)	≥99
e	Me—	90	41:1[e]	95.2	77[f]	99	-5.4°[15] (c 1.8, CHCl₃)	≥99
f	(hexyl)	95	49:1[d]	96.0	78	98	-12.2° (c 1.1, CHCl₃)	≥98
g	MeS—	84	55:1[e]	96.5	69	89[g,h]	-21.6°[16] (c 0.6, CHCl₃)	75
h[16]	BnO—	92	49:1[d]	96.0	36	100[i]	-10.6°[15] (c 1.5, CHCl₃)	≥98
i[17]	t-BuO₂C—	95	49:1[d]	96.0	37	83	-14.3°[16] (c 0.7, CHCl₃)	96
i	(phenylethyl)	82	7.3:1[d]	76	90[j]	88	-13.3°[16] (c 1.9, CHCl₃)	71

[a] Crude yield. [b] After chromatography. [c] Determined by 500 MHz ¹H NMR analysis of the derived S-Mosher amides. [d] Determined by ¹H NMR (500 MHz) analysis of crude material. [e] Determined by capillary gas-liquid chromatographic analysis of crude material. [f] Trace **8** detectable. [g] Based on recovered starting material. [h] Pd-black (5 equiv), H₂, AcOH, 48 hr. [i] R = CH₂OH. [j] Reaction time of 48 hr.

ETHYL (R)-2-AZIDOPROPIONATE

(Propanoic acid, 2-azido-, ethyl ester, (R)-)

$$\underset{O}{\overset{OH}{\text{CH}_3\text{CH(OH)CO}_2\text{Et}}} \xrightarrow[\text{DBU/THF}]{\text{(PhO)}_2\text{PON}_3} \underset{O}{\overset{N_3}{\text{CH}_3\text{CH(N}_3)\text{CO}_2\text{Et}}}$$
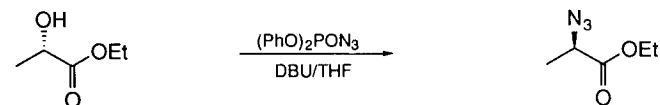
Submitted by Andrew S. Thompson, Frederick W. Hartner, Jr., and Edward J. J. Grabowski.[1]

Checked by Christopher L. Lynch and Stephen F. Martin.

1. Procedure

Ethyl (R)-2-azidopropionate. An oven-dried, 500-mL, three-necked flask is equipped with an overhead stirrer, nitrogen inlet, and an immersion thermometer (Note 1). The flask is charged with ethyl S-(-)-lactate (19.2 mL, 0.169 mol) (Note 2), tetrahydrofuran (175 mL) (Note 3), and diphenylphosphoryl azide (40 mL, 0.185 mol) (Note 4). The mixture is cooled to 2°C in an ice-water bath. To the mixture is added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (24 mL, 0.157 mol) (Note 5) dropwise via syringe. *(Caution: The DBU addition causes an exotherm. The reaction temperature is maintained below 5°C by carefully controlling the rate of addition. For this reaction the addition required 35 min).* A thick white precipitate forms during the DBU charge. The reaction is stirred at 1°C for 1 hr, and then it is warmed to room temperature and stirred under nitrogen for 24 hr (Note 6). The resulting homogeneous reaction is diluted with methyl tert-butyl ether (MTBE, 170 mL), and water (100 mL) is added. After the water layer is removed, the organic phase is washed with water (100 mL) and 0.5 M citric acid monohydrate (100 mL). The organic layer is dried (Na₂SO₄) and concentrated under reduced pressure to ca. 40-50 g of a pale yellow oil (Note 7). The product is

purified by simple distillation to afford 12.84 g (57%) of a clear, colorless oil, bp 83-88°C/50mm (Notes 8, 9 and 10).

2. Notes

1. A Teflon-coated thermocouple of the J-type attached to an Omega model 650 digital thermometer can be substituted for the immersion thermometer.

2. Ethyl lactate was purchased from Aldrich Chemical Company, Inc., and used without further purification. The water content was 0.8 mg/mL by Karl Fisher titration (Metrohm model 684 KF coulometer).

3. Tetrahydrofuran was purchased from Fisher Scientific Company and dried over 4 Å molecular sieves for 18 hr prior to use. The water content was less than 0.05 mg/mL by Karl Fisher titration.

4. Diphenylphosphoryl azide was 98% as purchased from Aldrich Chemical Company, Inc., and the water content was less than 0.01 mg/mL by Karl Fisher titration.

5. DBU was 98% as purchased from Aldrich Chemical Company, Inc., and the water content was 0.5 mg/mL by Karl Fisher titration. The amount of DBU was calculated to be 0.93 equiv of the ethyl lactate charge by assuming a purity of 98% for DBU and 100% purity for ethyl lactate. Amounts of base over 1 equiv resulted in product epimerization.

6. The reaction typically requires 16-24 hr. The progress of the reaction was monitored by capillary GC after diluting a 0.1-mL sample with 1 mL of methyl tert-butyl ether. GC conditions: Hewlett-Packard 5890 series II GC using an Alltech Econo-cap column (30 M x 0.32 mm x 0.25 μM, catalog # 19646). [The submitters used an HP-5 column (25 M x 0.32 mm x 0.52 mm, HP part # 19091J-112)]. Start oven at 50°C, then increase to 250°C at 10°C per min. The reaction was considered complete after 90% conversion; starting material R_t 4.3 min, product R_t 7.0 min.

7. The vacuum was deliberately bled to maintain 120-130 mm to minimize product losses due to volatility.

8. The yield was based on the DBU charge. The product was contaminated with 4-8% of starting material that codistilled with the product. The following characterization data was obtained: ethyl (R)-(+)-2-azidopropionate: $[\alpha]_D^{25}$ +14.8° (hexane, c 1.00); ^{1}H NMR (250 MHz, CDCl$_3$) δ: 1.28 (t, 3 H, J = 7.2), 1.43 (d, 3 H, J = 7.1), 3.89 (q, 1 H, J = 7.1), 4.21 (q, 2 H, J = 7.2); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 14.1, 16.7, 57.3, 61.8, 170.9; IR (thin film) cm^{-1}: 2120, 1743.

9. Optical purity can be quantitatively assayed by HPLC after reducing a sample to the amine with triphenylphosphine. A 50-mg sample was diluted with 10:1 THF:water (1 mL in a screw cap vial) and treated with triphenylphosphine (190 mg). Gas evolution begins within 5 min; once this subsides the reaction is sealed and placed in an oil bath at 50°C for 30 min. The mixture is diluted with HClO$_4$ (pH 1.0, 1 mL) and washed with dichloromethane (2 x 1 mL). The acidic water phase contains the salt of the amine. A 200-μL sample was diluted to 1 mL and assayed by HPLC using a Crownpak CR(+) column (Diacel Chemical Industries): HPLC conditions; aqueous pH 1.0 HClO$_4$, flow 0.5 mL/min, UV detection at 210 nm. The product had an enantiomeric excess of 96%, major enantiomer, R_t 3.4 min, and minor enantiomer, R_t 5.0 min.

10. The product from the distillation was analyzed by drop weight testing and differential scanning calorimetry (DSC). The drop weight test indicated that the product was not shock sensitive. By DSC, there was a 400 cal/g release of energy which initiated at 135°C. The pot residue showed a slow release of energy which was estimated to be ca. 100 cal/g and initiated at 150°C.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Asymmetric introduction of azide to the α-position of a carbonyl has been achieved by several methods. These include amine to azide conversion by diazo transfer,[2] chiral enolate azidation,[3] and displacement of optically active trifluoromethanesulfonates,[4] p-nitrobenzenesulfonates,[5] or halides.[6] Alkyl 2-azidopropionates have been prepared in optically active form by diazo transfer,[2] p-nitrobenzenesulfonate displacement,[5] and the Mitsunobu displacement using zinc azide.[7] The method presented here is the simplest of the displacement methods since alcohol activation *and* displacement steps occur in the same operation. In cases where the α-hydroxy esters are available, this would be the simplest method to introduce azide.

In addition to α-hydroxy carbonyl compounds, the method can be generally applied for alcohol to azide displacements. This method has been successfully demonstrated on fourteen optically active alcohols.[8] Mechanistically, this reaction proceeds in two stages. The first is alcohol activation via formation of the corresponding phosphate, and the second stage is the azide displacement step. The method is most useful for azide displacements of alcohols which tend to racemize using highly reactive groups for activation (e.g., sulfonate formation or Mitsunobu conditions[9]). When diphenylphosphoryl azide and DBU are used, the alcohol is only mildly activated for displacement as a phosphate. Use of the phosphate thus provides access to azide displacements of alcohols that are too sensitive using standard activation techniques. However, since the phosphate is only mildly activating, the alcohol undergoing displacement should be benzylic, allylic, or as in the present case, α to a carbonyl.

Certain classes of compounds are too reactive for the present method. Ethyl mandelate produced a racemic, protected phenyl glycine derivative. Benzylic alcohols with two methoxy groups (directly conjugating in the 2 and 4 positions) gave azide of 50% e.e.

Other classes of alcohols are unreactive. Ethyl 3-hydroxybutyrate (a β-hydroxy ester) went to the phosphate stage, but would not undergo azide displacement. In this example about 30% of the crotonate was formed because of β-elimination.

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Appendix

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

Ethyl (R)-2-azidopropionate: Propanoic acid, 2-azido-, ethyl ester, (R)- (12); (124988-44-9)

Ethyl (S)-(-)-lactate: Lactic acid, ethyl ester, L- (8); Propanoic acid, 2-hydroxy-, ethyl ester, (S)- (9); (687-47-8)

Diphenylphosphoryl azide: Phosphorazidic acid, diphenyl ester (8, 9); (26386-88-9)

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)

Methyl tert-butyl ether: Ether, tert-butyl methyl (8); Propane, 2-methoxy-2-methyl- (9); (1634-04-4)

Citric acid monohydrate (8); 1, 2, 3-Propanetricarboxylic acid, 2-hydroxy-, monohydrate (9); (5949-29-1)

ETHYL GLYCIDATE FROM (S)-SERINE:

ETHYL (R)-(+)-2,3-EPOXYPROPANOATE

(Oxiranecarboxylic acid, ethyl ester, (R)-)
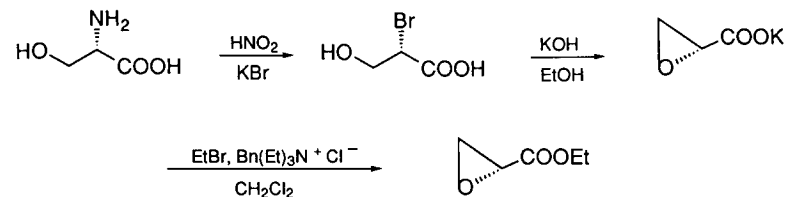
Submitted by Y. Petit and M. Larchevêque.[1]

Checked by Barry C. Peterson and William R. Roush.

1. Procedure

(S)-(-)-2-Bromo-3-hydroxypropanoic acid. L-Serine (Note 1) (52.5 g, 0.5 mol) and potassium bromide, KBr, (200 g, 1.7 mol) (Note 2) are dissolved in water (400 mL). Hydrobromic acid (48%,123 mL, 1.09 mol) is added at room temperature and the mixture is cooled to -13°C with stirring (Note 3). Nitrogen, N_2, is bubbled through the solution and sodium nitrite (42.8 g, 0.62 mol) is slowly added in small portions (ca. 5 g every 15 min) (Note 4). After each addition, the reaction mixture turns brown and then the color slowly fades, but the solution does not decolorize entirely. The total time required for addition of all the sodium nitrite is approximately 2.5 hr. The solution is then allowed to warm to 0°C, the N_2 purge is stopped, and the mixture is stirred for 6 hr. Excess nitrogen oxides are removed by bubbling N_2 through the solution for 1 hr. The pale green solution is then extracted with ether (6 x 300 mL). The combined organic extracts are concentrated to 0.5 L by rotary evaporation and dried over

anhydrous magnesium sulfate. After filtration, the ether is evaporated and the residual solvent is removed under reduced pressure (0.1 mm). The pale yellow or green oil (74-75 g, 87-89%) is used immediately in the next reaction without purification (Notes 5, 6, 7).

Potassium (R)-(+)-2,3-epoxypropanoate (Potassium glycidate). The crude acid from the preceding step (74.5 g, 0.44 mol) is dissolved in absolute ethanol (300 mL) and cooled to -20°C. Under N_2, a filtered solution of potassium hydroxide (86%, 55.5 g, 0.85 mol) in absolute ethanol (300 mL) is slowly added. After 2 hr, the mixture is allowed to warm to 0°C and stirred at this temperature for 14 hr. The solution is filtered to remove precipitated salts. Half of the solvent is removed by rotary evaporation without warming and an additional crop of salt (2-4 g) is isolated by filtration. The combined salts are dried under vacuum to give 105 g of a 1 : 1 mixture of KBr and potassium glycidate.

One third of this mixture (35 g) is extracted by refluxing in a mixture of 585 mL of absolute ethanol and 15 mL of water in a 1-L flask with good stirring for 45 min (Note 8). After filtration of the hot suspension, the glycidate crystallizes from the filtered solution to give 12-13 g of product. Another third of the 1 : 1 KBr-potassium glycidate mixture is heated at reflux with stirring in the mother liquors for 45 min. After the second batch of crystalline potassium glycidate is isolated by filtration, the procedure is repeated with the last portion of the KBr-glycidate mixture. The solids collected from the three hot filtrations are combined and extracted a fourth time with the same solution, then crystallized to give additional product. After drying, the total weight of recrystallized potassium glycidate is 47-50 g. This salt contains 9.5-13% of KBr, and the yield is thus 74-80% (corrected for KBr content) (Notes 9, 10).

Ethyl (R)-(+)-2,3-epoxypropanoate (Ethyl glycidate). A suspension of dry potassium glycidate (26 g of an 90.5:9.5 potassium glycidate:KBr mixture, 0.186 mol), benzyltriethylammonium chloride (42.4 g, 0.186 mol), and ethyl bromide (76 g, 0.7

mol) in methylene chloride, CH_2Cl_2, (300 mL) is heated at reflux for 16 hr with good stirring (Note 11). The solvent and excess ethyl bromide are then slowly removed by rotary evaporation without warming, and the resulting viscous solid is triturated with anhydrous diethyl ether (3 x 100 mL) to extract the ethyl glycidate. The combined ethereal extracts are filtered and dried over anhydrous magnesium sulfate. The solvent is slowly removed by rotary evaporation (without warming) and the residue is distilled at 40°C (2.4 mm) with 0°C water circulated through the condenser to afford 17.6 g of ethyl glycidate (81%) (Notes 12, 13).

Notes

1. L- or D-Serine are available from chemical suppliers such as Aldrich Chemical Company, Inc., Fisher Scientific Company, Fluka Chemical Corp., Acros Organics. In Europe, they may be obtained in bulk quantities from Degussa (Germany) and Rexim (France).

2. The excess of potassium bromide allows the required reaction temperature to be achieved; moreover, a high concentration of bromide ion suppresses the formation of the corresponding α-hydroxy acid.

3. An ice-sodium chloride mixture is used.

4. The exhaust gas is very acidic (pH ≤ 1 using wet pH paper), and therefore should be scrubbed by bubbling through a solution of potassium hydroxide.

5. The checkers obtained 74.5-78 g (88-92% yield) of product with $[\alpha]_D^{20}$ -10.2° (MeOH, c 5.1).

6. (S)-(-)-2-Bromo-3-hydroxypropanoic acid was characterized as follows: $[\alpha]_D^{20}$ -12.8° (MeOH, c 5.6); ^{1}H NMR (400 MHz, D_2O) δ: 3.76 (d, 2 H, J = 6.0), 4.29 (t, 1 H, J = 6.0); ^{13}C NMR (100 MHz, d_6-acetone) δ: 46.1, 64.2, 170.1; IR (neat) cm^{-1}: 3400-3000, 2960, 2660, 1735, 1465, 1410, 1260, 1200, 1170, 1080, 1040, 945, 850; MS

m/z 169 (M+H); HRMS (CI, CH$_4$) for C$_3$H$_6$BrO$_3$ [M+H] calcd 168.9500, found 168.9499; Anal. Calcd for C$_3$H$_5$BrO$_3$: C, 21.33; H, 2.98. Found: C, 21.66; H, 2.92.

7. The checkers found that the product partially decomposed when stored for a day at ambient temperature. Therefore it is recommended that the bromo acid be used immediately in the next step.

8. The success of this extraction is highly dependent on the efficiency of the stirring; best results are obtained with a good magnetic stirrer at 1200 rpm using an egg-shaped magnetic stir bar (40 x 13 mm).

9. The amount of potassium bromide remaining in the recrystallized potassium glycidate is determined by potentiometric titration using a silver electrode.

10. An analytical sample was generated by an additional recrystallization from EtOH: mp 180°C (dec); $[\alpha]_D^{20}$ +32.1° (H$_2$O, c 20); ^{1}H NMR (400 MHz, D$_2$O) δ: 2.64-2.66 (m, 1 H), 2.79-2.82 (m, 1 H), 3.22-3.24 (m, 1 H); ^{13}C NMR (100 MHz, d$_6$-DMSO/D$_2$O) δ: 46.0, 50.3, 174.7; IR (KBr) cm^{-1}: 1620 (br), 1440, 1240, 915, 860, 820, 770, 680.

11. A 50°C oil bath was used to maintain gentle reflux.

12. The purity of the ethyl glycidate prepared according to this procedure was ≥97% as measured by gas chromatography (BP5 capillary column from SGE). The enantiomeric purity was greater than 99% ee as determined by chiral gas chromatography on a 50-m CYDEX-B capillary column (β-cyclodextrin stationary phase) from SGE: bp 68-69°C (15 mm); bp 40°C (2.4 mm); $[\alpha]_D^{20}$ +15.8° (neat); $[\alpha]_D^{20}$ +12.3° (MeOH, c 5.0); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.24 (t, 3 H, J = 7.2), 2.87 (A of ABX, 1 H, J$_{AB}$ = 6.6, J$_{A,X}$ = 4.2), 2.89 (B of ABX, 1 H, J$_{AB}$ = 6.6, J$_{BX}$ = 2.4), 3.36 (X of ABX, 1 H, J$_{AX}$ = 4.2, J $_{BX}$ = 2.4), 4.16 (B of AB as q, 1 H, J$_{BA}$ = 10.8, J$_{B,Me}$ = 7.2), 4.19 (A of AB as q, 1 H, J$_{AB}$ = 10.8, J$_{A,Me}$ = 7.2); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 13.9, 46.1, 47.2, 61.5, 169.1; IR (neat) cm^{-1}: 2995, 1752, 1417, 1392, 1298, 1260, 1211, 1040,

922, 866, 760; MS m/z 117 (M+H); HRMS (CI, CH$_4$) for C$_5$H$_9$O$_3$ [M+H] calcd 117.0552, found 117.0551. Anal. Calcd for C$_5$H$_8$O$_3$: C, 51.72; H, 6.94. Found: C, 51.59; H, 6.90.

13. Ethyl glycidate is a rather sensitive compound (it cannot be chromatographed on silica gel) and distillation at low temperature under high vacuum (0.1-2 mm) avoids the formation of undistillable residues resulting from polymerization. The product should be stored at 5°C (or lower) and is perfectly stable at this temperature.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This procedure describes an efficient method for the synthesis of ≥99% enantiomerically pure ethyl glycidate from L-serine. Although preparation of potassium glycidate via cyclization of 3-bromo-2-hydroxypropionic acid,[2] and from 3-chloro-2-hydroxypropionic acid (obtained by microbial reduction of chloropyruvic acid)[3] was previously reported, the corresponding ethyl ester was never described. An enantioselective synthesis of the 2,3-epoxy acid by oxidation of 2,3-epoxypropanol has also been reported.[4]

Ethyl 2,3-epoxypropanoate is a very interesting chiron. It may be opened by various organometallic compounds such as dialkyl, diaryl, and divinyl lithium cuprates, dialkylmagnesium cuprates, trialkylalanes and aluminum acetylides.[5,6] The epoxide ring is attacked regiospecifically at the β-position and produces α-hydroxy esters exclusively without racemization. The same result is observed with

heteronucleophiles such as azide anion. However, thiolates afford a mixture of α and β opening.

After protection, the α-hydroxy esters can be reduced by DIBAL-H into O-protected α-hydroxyaldehydes that are very useful synthetic intermediates (e.g., leukotrienes,[7-9] ionophore antibiotics,[10] insect pheremones,[11] etc.). The secondary hydroxyl group of the α-hydroxy esters may also be substituted with inversion of configuration after activation as triflates of nosylates (p-nitrobenzenesulfonates) to give α-alkyl esters[12] or α-amino esters.[13]

Methyl 2,3-epoxypropanoate can be prepared by reaction of potassium glycidate with dimethyl sulfate and one equivalent of benzyltriethylammonium chloride in methylene chloride at room temperature (65% yield).[14] The reactions of this ester with organolithium or organomagnesium reagents at low temperature afford optically pure epoxy ketones[14] that may be transformed via reductive amination to anti amino epoxides.[15]

Using benzyl bromide as the alkylation agent, the corresponding benzyl glycidate is obtained in 60% yield.[5,16] In contrast with ethyl glycidate, this compound is not stable to distillation; however, it can be purified by chromatography on silica gel.

The preparation of cis-methyl or ethyl 2,3-epoxybutanoate from threonine can also be accomplished using the procedure described here.[17]

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Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

Ethyl glycidate: Oxiranecarboxylic acid, ethyl ester, (R)- (12); (111058-33-4)

(S)-Serine: L-Serine (8,9); (56-45-1)

(S)-(-)-2-Bromo-3-hydroxypropanoic acid: Propanoic acid, 2-bromo-3-hydroxy-,

(S)- (10); (70671-46-4)

Potassium bromide (8,9); (7758-02-3)

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

Sodium nitrite: Nitrous acid, sodium salt (8,9); (7632-00-0)

Potassium (R)-(+)-2.3-epoxypropanoate: Oxiranecarboxylic acid, potassium salt, (R)-

(11); (82044-23-3)

Benzyltriethylammonium chloride: Ammonium, benzyltriethyl-, chloride (8);

Benzenemethanaminium, N,N,N-triethyl-, chloride (9); (56-37-1)

(4R,5S)-4,5-DIPHENYL-3-VINYL-2-OXAZOLIDINONE

(2-Oxazolidinone, 3-ethenyl-4,5-diphenyl-, (4R-cis)-)
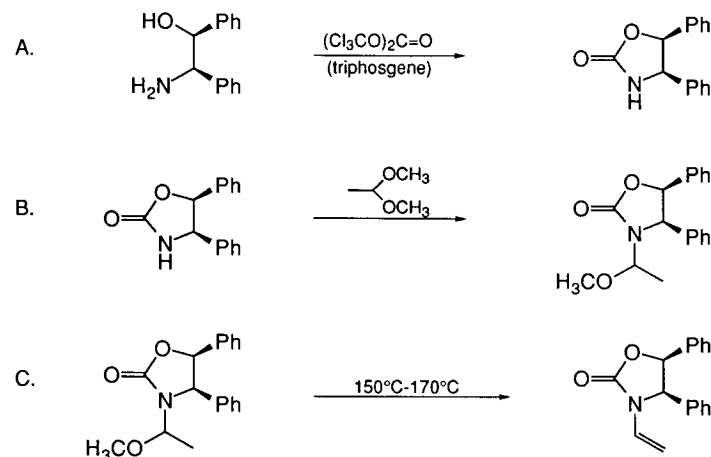
Submitted by T. Akiba,[1] O. Tamura,[2] and S. Terashima.[3]

Checked by Brian Brown and Louis S. Hegedus.

1. Procedure

Caution! Step A should be performed with gloves in an efficient hood in order to avoid contact with the toxic phosgene derivative.

A. *(4R,5S)-4,5-Diphenyl-2-oxazolidinone.* A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, thermometer, reflux condenser, and a dropping funnel is charged with (1S,2R)-(+)-2-amino-1,2-diphenylethanol (20.0 g, 94 mmol) (Note 1) and dichloromethane, CH$_2$Cl$_2$, (140 mL), and cooled in an ice-water bath. After addition of triethylamine (28.4 mL, 204 mmol), a solution of triphosgene [bis

(trichloromethyl) carbonate] (9.8 g, 33 mmol) (Note 2) in dichloromethane (20 mL) is added dropwise with a dropping funnel over 1 hr, keeping the temperature below 10°C (Note 3). After the addition is over, the mixture is stirred for 2 hr at the same temperature (Note 4). Water (40 mL) and methanol (20 mL) are added to the resulting suspension, and the mixture is stirred for 30 min. The mixture is concentrated under reduced pressure on a rotary evaporator. Water (100 mL) is poured onto the residue and the suspension is stirred vigorously for several minutes. The resulting precipitate is collected by filtration, and washed with 1 M hydrochloric acid (10 mL) and water (50 mL) to give (4R,5S)-4,5-diphenyl-2-oxazolidinone as colorless crystals (Note 5). The combined organic extracts are washed with brine, then evaporated under reduced pressure. A small amount of water is added to the residue, and the precipitate is collected by filtration and washed with a small amount of water to obtain additional (4R,5S)-4,5-diphenyl-2-oxazolidinone as colorless crystals. The two lots of crystals are air-dried, then completely dried in a desiccator over phosphorus pentoxide (P_2O_5) under reduced pressure for 24 hr. The (4R,5S)-4,5-diphenyl-2-oxazolidinone (22.3 g, 99.2%) (Note 6) obtained is used for the next step without further purification.

B.   *(4R,5S)-3-(1-Methoxyethyl)-4,5-diphenyl-2-oxazolidinone.* A 2-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, thermometer, and a reflux condenser is charged with (4R,5S)-4,5-diphenyl-2-oxazolidinone (20.0 g, 84 mmol), (±)-10-camphorsulfonic acid (9.7 g, 42 mmol) (Note 7), and acetaldehyde dimethyl acetal (700 mL) (Note 8). The mixture is heated at gentle reflux in an oil bath (bath temperature 80°C) for 5 hr (Note 9). The mixture is allowed to cool to ambient temperature, then concentrated under reduced pressure on a rotary evaporator (Note 10). Ethyl acetate (100 mL) is added to the residue, and the ethyl acetate solution is transferred to a beaker. The solution is neutralized with saturated sodium bicarbonate solution (100 mL) (Note 11), and transferred into a separatory funnel. The two layers are separated, and the lower aqueous layer is extracted with ethyl acetate (100 mL).

The organic layers are combined, washed with brine, dried over anhydrous sodium sulfate, filtered, then concentrated under reduced pressure on a rotary evaporator. The residue is stirred with 2-propanol-hexane (1 : 1, 60 mL) for several minutes. The solid product is collected by filtration. The filtrate is concentrated on a rotary evaporator, and the residue is again stirred with 2-propanol-hexane (1 : 1, 5 mL). The precipitate is collected by filtration. The two lots of the products are dried in a desiccator over phosphorus pentoxide (P_2O_5) under reduced pressure for 12 hr. (4R,5S)-3-(Methoxyethyl)-4,5-diphenyl-2-oxazolidinone (22.2 g, 89.3%) (Note 12) is obtained as a diastereomeric mixture. In some runs, small amounts of impurities remained after trituration. These impurities can be carried through the next step without a problem although final yields will be reduced.

C.   *(4R,5S)-4,5-Diphenyl-3-vinyl-2-oxazolidinone.* A 500-mL filter flask is charged with (4R,5S)-3-(1-methoxyethyl)-4,5-diphenyl-2-oxazolidinone (8.9 g, 30 mmol) and solid ammonium chloride, NH_4Cl (0.32 g, 6.0 mmol). The flask is stoppered and heated behind a blast shield in a sand bath to 150°C - 170°C under reduced pressure via a water aspirator (ca. 11 mm) for 3 hr. The crude material is dissolved in CH_2Cl_2 and run through silica gel with CH_2Cl_2 (40 g of SiO_2, 250 mL of CH_2Cl_2) to afford the product as a white solid (6.68 g, 84.2%) (Note 13). (A second treatment with silica is sometimes required to give completely clean product.)

2. Notes

1. (1S,2R)-(+)-2-Amino-1,2-diphenylethanol and its enantiomer were purchased from Aldrich Chemical Company, Inc. These compounds are also available from Tokyo Kasei Kogyo Co., Ltd.

2. Triphosgene[4] was purchased from Tokyo Kasei Kogyo Co., Ltd. This is also available from Aldrich Chemical Company, Inc. The submitters recommend the use of

triphosgene which is more convenient to handle than diphosgene (trichloromethyl chloroformate).

3. This is an extremely exothermic reaction.

4. TLC analysis on Merck silica gel 60 F254 plates (dichloromethane : methanol 10 : 1) showed formation of the product, Rf 0.63 (visualized with phosphomolybdic acid in ethanol). If starting material (Rf 0.36) remains, further amounts of triethylamine (2.7 mL) and triphosgene (0.98 g) are added.

5. The submitters extracted the combined filtrates with CH_2Cl_2; the checkers omitted this operation after finding it made less than 1% difference in the yield of final product.

6. A pure sample can be obtained by recrystallization (toluene). The spectral and physical properties are as follows: mp 232.5-233.5°C; $[\alpha]_D^{20}$ +60.6° (MeOH, c 0.86); IR (CHCl$_3$) cm^{-1}: 3580, 1765, 1540; ^{1}H NMR (CDCl$_3$): 5.20 (d, 1 H, J = 8.0), 5.85 (br, 1 H), 5.96 (d, 1 H, J = 8.0), 6.8-7.6 (m, 10 H); MS (m/z): 239 (M$^+$), 108, 107. Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.86. Found: C, 75.09; H, 5.38; N, 5.86.

7. (±)-10-Camphorsulfonic acid was purchased from Tokyo Kasei Kogyo Co., Ltd. (±)-10-Camphorsulfonic acid could be reduced to 0.1 equiv of the starting material with prolonged reaction time. The checkers used (±)-10-camphorsulfonic acid purchased from Aldrich Chemical Company, Inc.

8. Acetaldehyde dimethyl acetal was purchased from Tokyo Kasei Kogyo Co., Ltd. It is also available from Aldrich Chemical Company, Inc.

9. TLC analysis on Merck silica gel 60 F254 plates (hexane : ethyl acetate 1 : 1) showed clean formation of the diastereomeric products, Rf 0.69, and Rf 0.61 (cf. the starting material, Rf 0.45, visualized with phosphomolybdic acid in ethanol). The checkers found Rf 0.32 for the oxazolidinone starting material and Rf 0.50 and 0.61 for the diastereomeric products in 1:1 ethyl acetate:hexane.

10. Excess acetaldehyde dimethyl acetal can be recovered by distillation.

11. The pH of the aqueous layer was 7-8. Care should be taken because of foaming on neutralization.

12. The spectral properties of the diastereomeric mixture are as follows: IR (CHCl$_3$) cm^{-1}: 3000, 1750, 1410, 1100, 1055; ^{1}H NMR (CDCl$_3$) δ: 0.96 (d, 3 H x 2/3, J = 6.2), 1.46 (d, 3 H x 1/3, J = 6.2), 3.25 (s, 3 H x 1/3), 3.46 (s, 3 H x 2/3), 5.0-6.1 (m, 3 H), 6.6-7.5 (m, 10 H); MS (m/z): 297 (M$^+$), 238, 222, 165, 59.

13. A pure sample can be obtained by vacuum distillation or recrystallization (hexane-ethyl acetate), but some decomposition occurs under drastic conditions. The spectral and physical properties are as follows: mp 170-171°C; $[\alpha]_D^{20}$ +21.7° (CHCl$_3$, c 0.78); IR (CHCl$_3$) cm^{-1}: 1760, 1640, 1540, 1382, 1364; ^{1}H NMR (C$_6$D$_6$): 3.88 (dd, 1 H, J = 1.0 and 16.0), 4.10 (dd, 1 H, J = 1.0 and 9.2), 4.42 (d, 1 H, J = 8.1), 5.08 (d, 1 H, J = 8.1), 6.5-6.9 (m, 10 H), 7.13 (dd, 1 H, J = 9.2 and 16.0); MS (m/z): 265 (M$^+$), 180, 132, 131, 104. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.80; H, 5.65; N, 5.25.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Optically active 2-oxazolidinones and 2-thiazolidinones are versatile compounds as chiral auxiliaries.[5a,b] (4R,5S)-4,5-Diphenyl-2-oxazolidinone has been used for the synthesis of optically active amines[6] because of its high stereoselectivity and easy deprotection by hydrogenolysis after the reaction. Compared with several preparations[7a-c] of (4R,5S)-4,5-diphenyl-2-oxazolidinone reported so far, this method,

which makes use of triphosgene, seems to have the following advantages: simple and easy procedure, mild reaction conditions, and quantitative chemical yield. This procedure can also be used for preparing 2-oxazolidinones from various 2-amino-ethanol derivatives.

Hegedus and co-workers[8] reported the synthesis of (4S,5R)-4,5-diphenyl-3-vinyl-2-oxazolidinone (the enantiomer of the compound prepared here) via the chromium carbene complex in a fair yield. This is an interesting method, but the procedure is complicated (e.g., low temperature, argon atomsphere) and the chromium waste must be disposed of in an appropriate way. On the other hand, this procedure, consisting of transacetalization[9] and pyrolysis,[10] is simple and safe. Optically active 3-vinyl-2-oxazolidinone is also used for the synthesis of (1R,2S)-2-fluorocyclopropylamine[11a,b] that is the key intermediate for novel antibacterial quinolonecarboxylic acids.

1. Chemical Technology Research Laboratories, Daiichi Pharmaceutical Co., Ltd., Kita-Kasai, Edogawa, Tokyo 134, Japan.

2. Meiji College of Pharmacy, Nozawa, Setagaya, Tokyo 154, Japan.

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

(4R,5S)-4,5-Diphenyl-3-vinyl-2-oxazolidinone: 2-Oxazolidinone, 3-ethenyl-4,5-diphenyl-, (4R-cis)- (13); (143059-81-8)

(4R,5S)-4,5-Diphenyl-2-oxazolidinone: 2-Oxazolidinone, 4,5-diphenyl-, (4R-cis)- (11); (86286-50-2)

(1S,2R)-(+)-2-Amino-1,2-diphenylethanol: Ethanol, 2-amino-1,2-diphenyl-, L-erythro-(+)- (8); Benzeneethanol, β-amino-α-phenyl-, [S-(R*,S*)]- (9); (23364-44-5)

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

Triphosgene: Carbonic acid, bis(trichloromethyl) ester (8,9); (32315-10-9)

(4R,5S)-3-(1-Methoxyethyl)-4,5-diphenyl-2-oxazolidinone: 2-Oxazolidinone, 3-(1-methoxyethyl)-4,5-diphenyl-, [4R-[3(R*),4a,5a]]- (13); 142977-52-4)

Camphorsulfonic acid monohydrate: Bicyclo[2.2.1]heptane-1-methanesulfonic acid,

7,7-dimethyl-2-oxo-, (±)- (9); (5872-08-2)

Acetaldehyde dimethyl acetal (8); Ethane, 1,1-dimethoxy- (9); (534-15-6)

Ammonium chloride (8,9); (12125-02-9)

(4S,5R)-4,5-Diphenyl-3-vinyl-2-oxazolidinone: 2-Oxazolidinone, 3-ethenyl-4,5-

diphenyl-, (4S-cis)- (12); (128947-27-3)

SYNTHESIS OF UNSYMMETRICAL BIARYLS USING A MODIFIED SUZUKI CROSS-COUPLING: 4-BIPHENYLCARBOXALDEHYDE ([1,1'-Biphenyl]-4-carboxaldehyde)
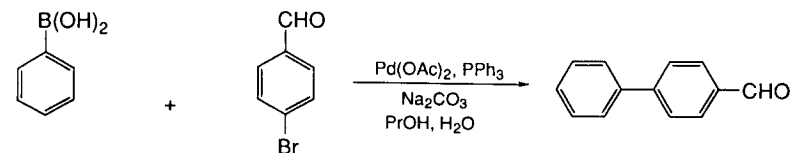
Submitted by Bret E. Huff, Thomas M. Koenig, David Mitchell, and Michael A. Staszak.[1]

Checked by Steven Wenglowsky and Louis S. Hegedus.

1. Procedure

A 2-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, condenser, and a nitrogen gas inlet is charged with 50.0 g (0.270 mol) of 4-bromobenzaldehyde, 34.6 g (0.284 mol, 1.05 equiv) of benzeneboronic acid, and 485 mL of 1-propanol under a nitrogen purge. The mixture is stirred at room temperature for 30 min, allowing the solids to dissolve. The resulting solution is treated with 0.182 g (0.811 mmol, 0.003 equiv) of palladium acetate, 0.638 g (2.43 mmol, 0.009 equiv) of triphenylphosphine, 162 mL of 2 M sodium carbonate (Na_2CO_3) (0.324 mol, 1.20 equiv), 95.0 mL of deionized water and heated to reflux under a nitrogen atmosphere (Note 1).

After 45 min at reflux, a reaction aliquot checked by ^{1}H NMR indicates that the reaction is complete (Notes 2, 3 and 4). The heat source is removed and 350 mL of water is added while the mixture is still hot. The nitrogen gas source is removed and

the reaction is allowed to stir open to the atmosphere for 2.5 hr while cooling to room temperature (Note 5). The darkened mixture is diluted with 500 mL of ethyl acetate and transferred to a 2-L separatory funnel (Note 6). The two phases are separated and the aqueous layer is back-extracted with two additional 250-mL portions of ethyl acetate. The combined organic layers are washed with 250 mL of aqueous 5% sodium bicarbonate ($NaHCO_3$) followed by saturated brine, 2 x 250 mL (Note 7). The organic solution is placed in a 2-L Erlenmeyer flask with a magnetic stirring bar, treated with 25.0 g of Darco G-60 (Note 8) and stirred at room temperature for 30 min. To the mixture is added 50.0 g of sodium sulfate (Na_2SO_4) (Note 9) and stirring is continued for an additional 30 min.

A 2-L filter flask is equipped with an 11-cm Büchner funnel with filter paper. The funnel is charged with Celite to a depth of 1 cm (Note 10) and 50.0 g of Florisil is spread evenly on top of the Celite. The above mixture is filtered through this pad of filter aid (Note 11). The filter cake is rinsed with ethyl acetate, 2 x 100 mL. The resulting pale yellow filtrate is concentrated under reduced pressure to yield 47.3 g (96.2%) of pale yellow crystals (Note 12).

The crude solids are treated with 189 mL of hexanes (4 mL/g) and slurried at room temperature for 10 min before heating to reflux (Note 13). The resulting hazy solution is treated with 47.3 mL of methanol (1 mL/g), which clarifies the mixture (Note 14). Crystallization is induced by removing the heat source and allowing the mixture to cool slowly to room temperature over 2 hr. The flask is placed in a freezer to chill overnight. The thick slurry of crystals is filtered, rinsed with cold hexanes, 2 x 40 mL, and vacuum dried at room temperature to afford 42.5 g of pale yellow crystals (86.3% overall yield) (Notes 15 and 16).

2. Notes

1. 4-Bromobenzaldehyde and triphenylphosphine were purchased from Aldrich Chemical Company, Inc. Benzeneboronic acid and palladium acetate were obtained from Lancaster Synthesis. Sodium carbonate was purchased from EM Science and deionized water was used to prepare the 2 M solution. Reagent grade 1-propanol is available from Mallinkrodt Inc. All reagents and solvents are used without purification or degassing. There was no need to dry the glassware rigorously.

2. Upon dissolution of all the solids, the reaction mixture is pale yellow. The solution undergoes a sequence of color changes from yellow to orange (t~10 min) to red (t~20 min) to dark red/black (t~30 min). This color change is generally indicative of reaction completeness in all of the coupling reactions performed here. These color changes were not observed by the checker in any of the runs. Instead, the organic portion was brown to dark brown for the duration of the reaction.

3. The reaction is monitored by ^{1}H NMR with sample preparation as follows: A 0.3-mL aliquot of the reaction mixture is removed and concentrated under reduced pressure for 10 min. The resulting residue is dissolved in 0.5 mL of methyl sulfoxide-d (DMSO-d_6) (Cambridge Isotope Labs) and filtered through a pipette with a glass wool plug directly into an NMR tube. The sample is checked on a Bruker ARX-500 MHz instrument. The checker used a Bruker 300 MHz instrument, which sufficed.

4. Reaction completeness is determined by observing the ^{1}H NMR signals of the aldehyde protons at 300-500 MHz. The starting material has an aldehydic proton signal at δ 10.00 while the product aldehyde signal is cleanly separated at δ 10.06. The 30-min sample showed no starting material remaining. This was confirmed by spiking the NMR tube with 3 mg of 4-bromobenzaldehyde and reanalyzing the sample.

5. During the 2.5-hr stir time, the reaction mixture darkens considerably and a thin, black emulsion forms. Open air stirring is required to force formation of the

emulsion layer early in the workup and thus prevent its formation during the recrystallization stage.

6. HPLC grade ethyl acetate is available from Mallinkrodt Inc.

7. During the washes, the thin, black emulsion that forms is taken with the organic layer on each separation until the final brine wash. The material is then discarded with the brine layer, aiding the subsequent purification steps.

8. Darco G-60, a 100-mesh activated carbon, is available from Aldrich Chemical Company, Inc.

9. Sodium sulfate is available from EM Science.

10. Celite is available from Aldrich Chemical Company, Inc.

11. 200 Mesh Florisil is available from Aldrich Chemical Company, Inc.

12. ^{1}H NMR (DMSO-d_6) is consistent with the desired structure, but does indicate the presence of low levels of benzeneboronic acid and other aromatic impurities.

13. Reagent grade hexanes are available from Mallinkrodt Inc.

14. Reagent grade anhydrous methanol is available from Mallinkrodt Inc.

15. The recrystallized 4-biphenylcarboxaldehyde exhibits the following physical properties: mp 58-59°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.45 (t, 1 H, J = 7.4), 7.52 (t, 2 H, J = 7.4), 7.77 (d, 2 H, J = 7.4), 7.91 (d, 2 H, J = 8.1), 8.01 (d, 2 H, J = 8.1), 10.06 (s, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 127.9, 128.2, 129.4, 129.9, 131.0, 135.9, 139.6, 146.7, 193.5; FD MS m/z: 182.2; IR (neat) cm^{-1}: 1700, 1680, 1606, 1170, 839; Anal. Calcd for $C_{13}H_{10}O$: C, 85.69; H, 5.53. Found: C, 85.60; H, 5.62.

16. On a smaller scale, crude 4-biphenylcarboxaldehyde can be purified by flash chromatography using 93/7 hexanes/ethyl acetate (R_f = 0.3). Recoveries are typically 90-95%.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Although a variety of methods are available for preparing unsymmetrical biaryls, many of them suffer from the use of harsh conditions, the need for special apparatus and handling operations, or the employment of stoichiometric levels of zinc or tin reagents.[2] The classic Suzuki cross-coupling between boronic acids and aryl halides uses palladium catalysis under mildly basic conditions to obviate a number of these problems.[3] The increased availability of boronic acid derivatives along with the development of alternatives to the use of tetrakis(triphenylphosphine)palladium(0) has resulted in one of the most useful methods for forming carbon-carbon bonds between aromatic rings.[4]

The procedure described here incorporates a number of modifications to the Suzuki coupling that result in a sound, efficient and scaleable means of synthesizing biaryls. First, the catalytic use of palladium acetate and triphenylphosphine to generate palladium(0) eliminates the need for the expensive air and light sensitive tetrakis(triphenylphosphine)palladium(0). No purification of reagents is necessary, no special apparatus is required, and rigorous exclusion of air from the reaction mixture is not necessary. Furthermore, homo-coupled products are not present in significant levels (as determined by 500 MHz ^{1}H NMR).

Further improvements to the cross-coupling process are observed by employing 1-propanol as solvent. The water miscibility of 1-propanol allows reaction mixtures to remain homogeneous in the presence of aqueous base. The 1-propanol/water ratio

can be varied for each derivative to adjust for the solubility characteristics of starting materials, coupled products, and salt by-products. The reasonably high boiling point of 1-propanol (97°C; 88°C azeotrope with water) affords rate advantages over reactions normally run in tetrahydrofuran or ethanol.[5] Reactions run in 1-propanol are typically complete within 30 min at reflux. Furthermore, additives (LiCl) or stronger bases [Ba(OH)$_2$, TlOH] are not necessary to obtain high yields.[6]

The Table lists the results of applying these modified conditions to a number of biaryl derivatives, including recent examples from the literature. With the exception of entry 6, that employs a non-reactive aromatic chloride, all the cross-couplings result in excellent yields and are indicative of the generality of this procedure.

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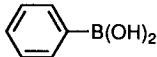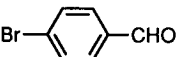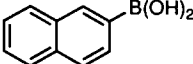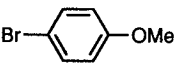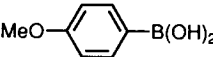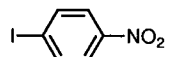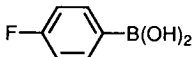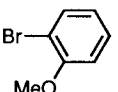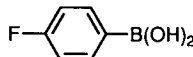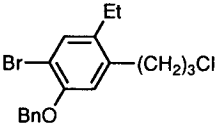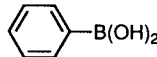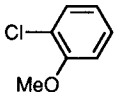
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Appendix
Chemical Abstract Nomenclature (Collective Index Numbers); (Registry Number)

4-Biphenylcarboxaldehyde (8); [1,1'-Biphenyl]-4-carbcxaldehyde (9); (3218-36-8)

4-Bromobenzaldehyde: Benzaldehyde, 4-bromo- (9); (1122-91-4)

Benzeneboronic acid (8); Boronic acid, phenyl- (9); (98-80-6)

1-Propanol: Propyl alcohol (8); 1-Propanol (9); (71-23-8)

Palladium acetate: Acetic acid, palladium(2+) salt (8,9); (3375-31-3)

Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)

TABLE
Preparation of Biaryls via Pd(0) Catalyzed
Cross-Coupling of Boronic Acids with Aryl Halides[a]

Entry	Boronic Acid	Aryl Halide	Purified Yield (%)	Ref.
1	⟨⟩—B(OH)$_2$	Br—⟨⟩—CHO	86.3	7
2	naphthyl-B(OH)$_2$	Br—⟨⟩—OMe	82.7	8
3	MeO—⟨⟩—B(OH)$_2$	I—⟨⟩—NO$_2$	83.4	9,10
4	F—⟨⟩—B(OH)$_2$	Br—⟨⟩ MeO	96.8	
5	F—⟨⟩—B(OH)$_2$	Br—⟨⟩(Et)(CH$_2$)$_3$Cl, BnO	91.1	11
6	⟨⟩—B(OH)$_2$	Cl—⟨⟩ MeO	< 10	

[a]With the exception of entry 1 (270-mmol scale), all reactions were performed on a 25-mmol scale and the products were purified by flash chromatography using varying ratios of hexanes/ethyl acetate to effect an R_f value of 0.3 for the desired compound.

ACCELERATED SUZUKI COUPLING VIA A LIGANDLESS PALLADIUM CATALYST: 4-METHOXY-2'-METHYLBIPHENYL
(1,1'-Biphenyl, 4'-methoxy-2-methyl-)

$$ \text{o-tolylB(OH)}_2 + \text{I—C}_6\text{H}_4\text{—OCH}_3 \xrightarrow[\text{H}_2\text{O}]{\substack{\text{Pd(OAc)}_2 \\ \text{K}_2\text{CO}_3, \text{acetone}}} \text{4-methoxy-2'-methylbiphenyl} $$
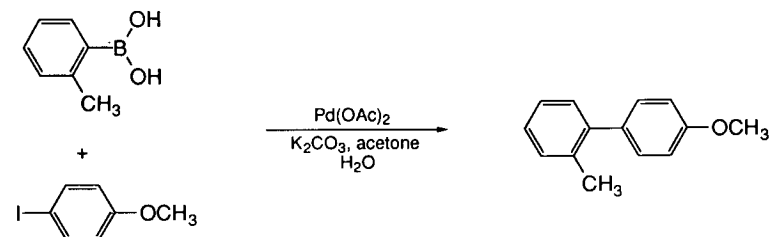
Submitted by Felix E. Goodson, Thomas I. Wallow,[1] and Bruce M. Novak.[2]
Checked by Ingrid M. Fellows and Stephen F. Martin.

1. Procedure

4-Methoxy-2'-methylbiphenyl. o-Tolylboronic acid, 10.0 g (73.6 mmol) (Note 1), 16.8 g (71.8 mmol) of 4-iodoanisole (Note 2), and 200 mL of acetone (Note 3) are combined in a 1-L, three-necked flask equipped with an efficient stirbar, two stoppers, and a reflux condenser attached to a gas-flow adapter with a stopcock. Potassium carbonate, 25.0 g (0.180 mol), is dissolved in 200 mL of water (Note 4) in a separate 250-mL Schlenk flask. In a third flask (25-mL Schlenk flask) 3.30 mg (0.02 mmol, 0.2%) of palladium acetate (Note 5) is dissolved in 10 mL of acetone. All three flasks are then thoroughly degassed by four freeze-pump-thaw cycles. Under an argon back flow, one of the stoppers on the three-necked flask is replaced with a rubber septum, and the carbonate and catalyst solutions are added via cannula to form a biphasic mixture. The top layer turns brown upon addition of the catalyst. The septum is

replaced with the glass stopper and three additional freeze-pump-thaw cycles are applied. The flask is then backfilled with argon, and the reaction is brought to reflux under a positive argon pressure. After 2 hr at reflux the heat source is removed and the reaction is allowed to cool. By this time the brown color has faded and the reaction is a triphasic mixture with copious amounts of palladium black floating between the layers. The reaction is transferred to a 1-L separatory funnel and extracted into diethyl ether (3 x 100 mL). The organic layers are combined, washed with water (1 x 100 mL) saturated with sodium chloride, and dried over magnesium sulfate. Solvent is removed with a rotary evaporator to yield a yellow oil which is distilled (125-130°C, 0.10 mm) to give 12.8 g of 4-methoxy-2'-methylbiphenyl as a colorless oil (90.3% yield) (Note 6).

2. Notes

1. o-Tolylboronic acid is used as received from Aldrich Chemical Company, Inc. The reagent is listed as 95% pure, but NMR analysis reveals that the predominant impurity is o-tolylboronic anhydride that reverts back to the acid in the presence of water. In one bottle there was a slight brownish impurity as well, but the presence of this impurity did not affect the reaction. The slight excess of this reagent is to ensure complete conversion of the 4-iodoanisole, which is difficult to separate from the final product.

2. Commercial 4-iodoanisole (Aldrich Chemical Company, Inc.) is sublimed immediately prior to use.

3. Commercial reagent grade acetone (Fisher Scientific Company) is used without further purification.

4. Commercial HPLC grade water (Sigma Chemical Company) is used without further purification.

5. Palladium acetate (99.99+%) is used as received from Aldrich Chemical Company, Inc.

6. The spectral properties are as follows: ^{1}H NMR (200 MHz, CDCl$_3$) δ: 2.26 (s, 3 H), 3.80 (s, 3 H), 6.94 (d, 2 H, J = 8.7), 7.20-7.25 (m, 6 H); ^{13}C NMR (200 MHz, CDCl$_3$) δ: 20.5, 55.2, 113.5, 125.7, 126.9, 129.9, 130.2, 134.4, 135.4, 141.5, 158.5; mass spectrum (CI) m/z 199.1118 (M+1 requires 199.1122).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The palladium-mediated cross-coupling reaction of an aryl halide with an arylboronic acid, (Suzuki coupling), is a versatile method for synthesizing unsymmetrical biaryls.[3] Traditionally, these reactions have been carried out using phosphine-based palladium catalysts. The primary advantage of the ligandless[4] methodology presented here is that it eliminates two phosphine related side reactions, aryl-aryl exchange,[5] and phosphonium salt formation,[6] that plague the traditional phosphine-based systems. The first of these side reactions equilibrates the aryl group bound to the palladium in the ArPdL$_2$I catalyst intermediate with the aryl groups bound to the phosphorus atoms, allowing the ligand-bound phenyl groups to enter the cross-coupling cycle in lieu of the aryl-halide derived aryl moieties. This, in turn, can sometimes introduce substantial amounts of phenylated by-products into the product mixture.[7] The second side reaction is the palladium-catalyzed formation of tetraarylphosphonium iodides from iodoarenes and triarylphosphines.[6] To the degree

that this occurs during cross-coupling, it represents a nonproductive consumption of aryl halides. A second key advantage of the ligandless methodology is a marked improvement in reaction efficiency, allowing for shorter reaction times, milder conditions and greater catalytic turnovers. Indeed, on small scale reactions, as little as 0.02% catalyst is required for complete conversion.[8] Electron-rich, sterically hindered aryl boronates and heteroaromatic boronates in particular are known to be troublesome substrates for Suzuki couplings under standard conditions because of their enhanced susceptibility toward base-catalyzed protodeboronation.[9] Increased catalytic efficiency represents one of the few tools available for minimizing this side reaction.

To investigate the scope and limitations of this procedure, small-scale couplings were carried out on a variety of substrates using different catalysts and solvents (1 mmol halide, 1.05 equiv of boronic acid precursor, 2.5 mL of solvents). The results are summarized in Table I. (Some of these results were presented in the submitters' earlier publication.[8]) Electron withdrawing and electron donating substituents on either the aryl halide or boronic acid have no effect on the ability of the ligandless catalyst to promote this reaction to completion. Aryl bromides undergo coupling as well as aryl iodides, but the required reaction times are longer (2-4 hr). When aryl iodides are used, increased steric hindrance on either substrate also has no detrimental effect on conversion. On aryl bromides, however, increased steric hindrance does hinder quantitative product formation. Palladium acetate (**1**), tris(dibenzilideneacetone)dipalladium [Pd$_2$(dba)$_3$] (**2**), and allylpalladium chloride (**3**) all serve as satisfactory ligandless catalyst precursors. However, as the first is the most air, light, and heat stable, it is the most convenient to use. Although the ligandless methodology is relatively insensitive to the above parameters, the choice of solvent is critical. Of the solvents screened, only acetone and tetramethylurea promote quantitative conversion to the biphenyl, even after prolonged reaction times. In general, the reaction is facilitated by more polar solvents, but the failure of dimethyl sulfoxide to produce quantitative product formation suggests that this generalization is not universal. If a Suzuki coupling reaction must be carried out in a less polar solvent because of solubility, substrate compatibility, etc., the submitters suggest the addition of two catalyst equivalents of the bulky tri(o-tolyl)phosphine ligand. This phosphine is known to suppress the formation of by-products derived from aryl-aryl transfer in palladium-mediated couplings.[10] Furthermore, palladium complexes of tri(o-tolyl)phosphine have also found use in the formation of aryl amines from aryl halides and tin amides[11] or secondary amines.[12]

1. Current address: AT&T Bell Laboratories, 600 Mountain Ave., Murray Hill, NJ 07974.

2. Department of Polymer Science and Engineering, University of Massachusetts, Amherst, MA 01003.

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

4-Methoxy-2'-methylbiphenyl: 1,1'-Biphenyl, 4'-methoxy-2-methyl- (11); (92495-54-0)

o-Tolylboronic acid: o-Tolueneboronic acid (8,9); (16419-60-6)

4-Iodoanisole: Anisole, p-iodo- (8); Benzene, 1-iodo-4-methoxy- (9); (696-62-8)

Palladium acetate: Acetic acid, palladium (2+) salt (8,9); (3375-31-3)

TABLE

SYNTHESIS OF BIPHENYLS VIA SUZUKI COUPLING REACTIONS
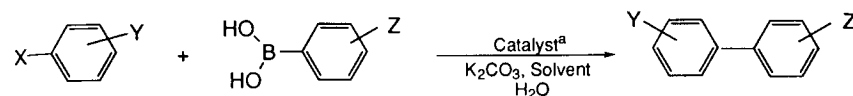
X	Y	Z	Catalyst[a]	% Cat.	Solvent	Time (h)	100% Conv.[b]
I	4-CH$_3$	H[c]	1	0.2	Acetone	12[d]	Yes
I	4-NO$_2$	H[c]	1	0.2	Acetone	0.67	Yes
I	4-OCH$_3$	4-CF$_3$[e]	1	0.2	Acetone	0.67	Yes
I	4-CF$_3$	4-OCH$_3$[e]	1	0.2	Acetone	0.67	Yes
I	2-CH$_3$	4-OCH$_3$[e]	1	0.2	Acetone	0.67	Yes
I	4-OCH$_3$	2-CH$_3$[e]	1	0.2	Acetone	0.67	Yes
Br	4-OCH$_3$	4-CF$_3$[e]	1	0.2	Acetone	4	Yes
Br	2-CH$_3$	4-OCH$_3$[e]	1	0.2	Acetone	3-16	No
I	4-NO$_2$	H[c]	2	0.2	Acetone	0.75	Yes
I	4-NO$_2$	H[c]	3	0.2	Acetone	1	Yes
I	4-CH$_3$	H[c]	1	0.2	THF	12	No
I	4-CH$_3$	H[c]	1	1	THF	12	No
I	4-CH$_3$	H[c]	1	1+1[f]	THF	24	No
I	4-CH$_3$	H[c]	2	0.2	Acetone	12[d]	Yes
I	4-CH$_3$	H[c]	2	0.2	THF	12	No
I	4-CH$_3$	H[c]	2	0.2	DME[g]	12	No
I	4-CH$_3$	H[c]	2	0.2	Anisole	12	No
I	4-CH$_3$	H[c]	2	0.2	NBZ[h]	12	No
I	4-CH$_3$	H[c]	2	0.2	TMU[i]	12[d]	Yes
I	4-CH$_3$	H[c]	2	0.2	DMSO	12	No
I	4-CH$_3$	H[c]	2+2 OTP[j]	0.2	Toluene	40[d]	Yes
I	4-CH$_3$	H[c]	2+2 OTP[j]	0.2	THF	12[d]	Yes

[a]1, Palladium acetate; **2**, tris(dibenzilidene acetone)dipalladium [Pd$_2$(dba)$_3$]; **3**, allylpalladium chloride. [b]As determined by NMR and/or thin layer chromatography. [c]Phenylboronic anhydride was used as the boronic acid precursor. [d]The exact time of reaction completion was not determined. [e]The ethylene glycol boronic ester was used as the boronic acid precursor. [f]1% catalyst was added at the beginning of the reaction, and again 12 hr into the reaction. [g]Dimethoxyethane. [h]Nitrobenzene. [i]Tetramethylurea. [j]Tri(o-tolyl)phosphine.

2-(4-METHOXYPHENYL)-2-CYCLOHEXEN-1-ONE:

PREPARATION OF 2-IODO-2-CYCLOHEXEN-1-ONE AND SUZUKI

COUPLING WITH 4-METHOXYPHENYLBORONIC ACID

(2-Cyclohexen-1-one, 2-(4-methoxyphenyl)- and

2-Cyclohexen-1-one, 2-iodo-)
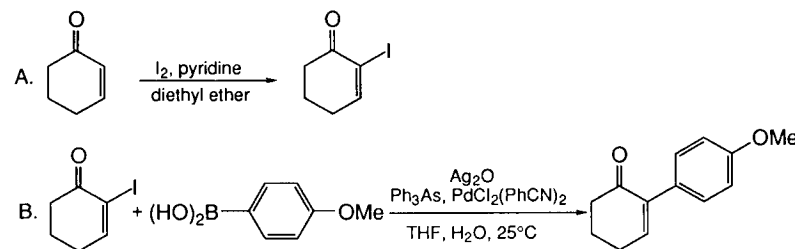
Submitted by Frederic S. Ruel, Matthew P. Braun, and Carl R. Johnson.[1]
Checked by Alain Zakarian and David J. Hart.

1. Procedure

Caution! This procedure involves volatile and toxic reagents and should be conducted in an efficient fume hood.

A. *2-Iodo-2-cyclohexen-1-one.* A 500-mL, three-necked, round-bottomed flask equipped with a 1.5-in. Teflon-coated magnetic stirring bar, glass stopper, 50-mL addition funnel, and a reflux condenser is charged with a 1:1 mixture of 75 mL of anhydrous diethyl ether (Note 1) and 75 mL of pyridine. With vigorous stirring, 53 g (0.21 mol) of iodine (Note 2) is added slowly. At the completion of the addition, the dark brown mixture is stirred an additional 10-20 min until complete dissolution is obtained.

The addition funnel is charged with 9.53 mL (9.46 g, 98.4 mmol) of 2-cyclohexen-1-one (Note 3). After addition of approximately 2 mL of the enone, the flask is quickly immersed in an ice bath (Note 4) and the remainder of the enone is added dropwise to the cooled, stirred, dark-brown solution over a 10-min period. At the completion of the addition, the ice bath is removed and the mixture is stirred an additional 2.5 hr. The reaction mixture is poured into a 1-L separatory funnel and the round-bottomed flask is washed with two 200-mL portions of diethyl ether that are added to the separatory funnel. The mixture is washed successively with two 150-mL portions of 2N hydrochloric acid to remove pyridine (Note 5), three 150-mL portions of aqueous 20% sodium thiosulfate ($Na_2S_2O_3$) (Note 6) and 100 mL of brine. The resulting organic phase is dried over anhydrous magnesium sulfate, filtered, and evaporated at reduced pressure to give a yellow-orange solid.

This material is recrystallized from diethyl ether/pentane (2:1) to give 15.1 g (69%) of 2-iodo-2-cyclohexen-1-one as a pale yellow solid, mp 48.5-49°C (Note 7). If desired, an additional 2.4 g (11%; mp 48-49°C) can be isolated by concentration of the mother liquor, column chromatography of the residue on 40 g of silica gel eluting with a mixture of 10% ethyl acetate in petroleum ether, and recrystallization of the collected iodoenone from pentane.

B. *2-(4-Methoxyphenyl)-2-cyclohexen-1-one.* A 500-mL, round-bottomed flask, equipped with a 1.5-in. Teflon-coated magnetic stirring bar and an argon inlet adaptor, is charged with 10.02 g (45.1 mmol) of 2-iodo-2-cyclohexen-1-one, 10.69 g (70.4 mmol, 1.56 eq) of 4-methoxyphenylboronic acid (Note 8), 16.72 g (72.1 mmol, 1.6 eq) of silver(I) oxide (Ag_2O) (Note 9), 0.85 g (2.8 mmol, 6 mol %) of triphenylarsine (Note 10), 0.53 g (1.4 mmol, 3 mol %) of palladium(II) bis(benzonitrile)dichloride (Note 11), 200 mL of tetrahydrofuran (THF) and 25 mL of water (Note 12). The reaction mixture, flushed with argon, is stirred for 1 hr and then quenched by the addition of 125 mL of saturated aqueous ammonium chloride. After the solution is stirred for 1 hr, the resulting two-phase mixture is poured into a 2-L separatory funnel. The upper (organic) and lower (aqueous) phases are separated. The aqueous phase is extracted twice with 300-mL portions of diethyl ether. The combined organic phases are washed successively with two 500-mL portions of water and 200 mL of brine. The resulting organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure to give a pale yellow solid.

The resulting product is purified by column chromatography on 90 g of silica gel eluting with a mixture of 30% ethyl acetate in petroleum ether (Note 13). The chromatographed material is further purified by recrystallization from diethyl ether/pentane (2:1) to give 7.1 g (78%) of 2-(4-methoxyphenyl)-2-cyclohexen-1-one as a pale yellow solid, mp 58-59°C (Note 14). An additional 1.6 g (18%; mp 58-59°C) can be isolated by concentration of the mother liquor and column chromatography of the residue on 30 g of silica gel eluting with a mixture of 10% ethyl acetate in petroleum ether.

2. Notes

1. Unless otherwise indicated, the solvents are reagent grade and are used without further purification.

2. Iodine certified A.C.S. was purchased from Fisher Scientific Company.

3. 2-Cyclohexen-1-one (97%) was purchased from Aldrich Chemical Company, Inc. *Caution! This chemical is highly toxic; glove protection is recommended.*

4. The reaction is exothermic. The first addition of 2 mL of the enone is necessary to avoid formation of aggregates that occurs if the mixture is cooled before this initial addition is made.

5. These first washes are very important; less acidic washes can promote reversal of the reaction from pyridine left in the medium.

6. These washes remove the brown color of the upper (organic) phase. The aqueous solution of sodium thiosulfate is 20% by weight.

7. Spectral data for 2-iodo-2-cyclohexen-1-one follow: ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.07 (quint, 2 H, J = 6.3), 2.43 (dt, 2 H, J = 5.4, 5.8), 2.64 (apparent t, 2 H, J = 6.3), 7.76 (t, 1 H, J = 4.5); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ: 22.7, 29.8, 37.1, 103.7, 159.5, 192.1.

8. 4-Methoxyphenylboronic acid can be purchased from Aldrich Chemical Company, Inc.

9. Silver(I) oxide, 99+%, was purchased from Aldrich Chemical Company, Inc.

10. Triphenylarsine, 97%, was purchased from Aldrich Chemical Company, Inc.

11. Palladium(II) bis(benzonitrile)dichloride was purchased from Aldrich Chemical Company, Inc.

12. The dissolution of all solid chemicals may be slightly exothermic but this does not cause any build-up of pressure.

13. Insoluble by-products could be removed by hot filtration but with a significant loss of product. Chromatography is advised to optimize the isolated yield.

14. This material gave a satisfactory combustion analysis. Characterization data for 2-(4-methoxyphenyl)-2-cyclohexen-1-one follow: ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.09 (quint, 2 H, J = 6.3), 2.5-2.6 (m, 4 H), 3.80 (s, 3 H), 6.88 (d, 2 H, J = 8 Hz), 6.98 (t, 1 H, J = 4.5), 7.26 (d, 2 H, J = 8 Hz); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ: 22.9, 26.5, 39.0, 55.2, 113.4, 128.9, 129.7, 139.6, 146.9, 159.0, 198.2; Anal. calcd for C$_{13}$H$_{14}$O$_2$: C, 77.20; H, 6.97. Found: C, 77.09; H, 7.01.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Cycloalkenones are ubiquitous as reactive intermediates and bioactive materials. Modification of a simple cycloalkenone by addition of a carbon substituent at the α-position should be a useful transformation, but one that is not readily accomplished by conventional enone chemistry. α-Substituted cycloalkenones could of themselves be of interest, but perhaps, of more general importance would be their use as intermediates for the production of substituted cycloalkanones or α,β-disubstituted cycloalkanones by a subsequent conjugate addition procedure.[2] These strategies avoid many of the limitations attendant to the trapping of enolates with carbon electrophiles. The method of Kim involving treatment of enones with the combination of a dimethyl acetal, pyridine and trimethylsilyl triflates results in α-(1-methoxyalkyl)enones.[3] The metallation of α-bromoenones masked as ketals for α-functionalizations has been developed by Smith.[4]

This preparation illustrates an efficient two-step process for the transformation of a cycloalkenone to the corresponding α-substituted derivative. The first step involves the installation of an α-iodo substituent by a process thought to involve nucleophilic addition of pyridine, iodine capture of the resulting enolate, and pyridine-promoted elimination of pyridine.[5] The resulting vinyl iodides are superior to other vinyl halides as participants in a variety of transition-metal catalyzed coupling reactions, illustrated here by the Suzuki coupling with an arylboronic acid. Other coupling partners that

have been investigated in the laboratories of the submitters include alkenes, vinyl metals,[6] arylstannanes,[7] and alkyl-9-BBN's.[2]

Prior to our original report[7] on this method, acceptable and general preparative routes to α-iodocycloalkenones had not been described. Treatment of a β-substituted cycloalkenone with trimethylsilyl azide and a mixture of iodine and pyridine sequentially in dichloromethane has now been reported as a method for the preparation of β-substituted-α-iodocycloalkenones.[8] The combination of iodine and pyridinium dichromate has also been reported to provide α-iodoenones from enones[9] as well as from ethynyl carbinols.[9,10] Some successes have also been achieved with enones and iodine azide (IN_3)[11] and iodine/ceric ammonium nitrate.[12-14] The submitters' first variant[5] of the present procedure used carbon tetrachloride as a solvent. In this procedure this solvent has been replaced with the more benign diethyl ether.

The Suzuki coupling of 2-iodo-2-cyclohexen-1-one and 4-methoxy-phenylboronic acid is achieved using silver(I) oxide as a suspension in aqueous THF as the base. Unlike earlier reports,[15-17] in which up to 6 equiv of Ag_2O were used, we have found that 1.6 equiv is completely effective. Under these mild conditions, rapid conversion can be achieved at room temperature for a large variety of sensitively functionalized partners in near quantitative yields (see Table).[18]

TABLE

2-ARYL-2-CYCLOALKENONES FROM 2-IODO-2-CYCLOALKENONES

97 %　　　97 %　　　98 %　　　100 %

TBS = *t*-butyldimethylsilyl　　TIPS = triisopropylsilyl
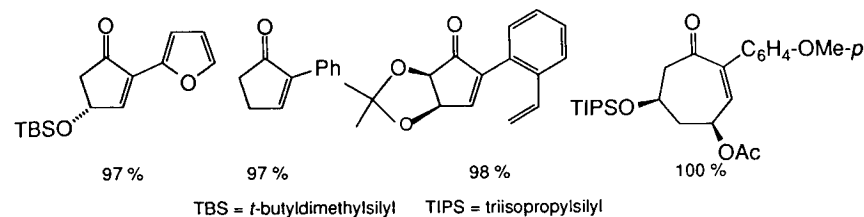
1. Department of Chemistry, Wayne State University, Detroit, MI 48202-3489.

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18. The development of this procedure was made possible by a grant from the National Science Foundation.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number)

(Registry Number)

2-(4-Methoxyphenyl)-2-cyclohexen-1-one: 2-Cyclohexen-1-one, 2-(4-methoxyphenyl)- (10); (63828-70-6)

2-Iodo-2-cyclohexen-1-one: 2-Cyclohexen-1-one, 2-iodo- (8,9); (33948-36-6)

4-Methoxyphenylboronic acid: Benzeneboronic acid, p-methoxy- (8), Boronic acid, (4-methoxyphenyl)- (9); (5720-07-0)

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

Iodine (8,9); (7553-56-2)

2-Cyclohexen-1-one, HIGHLY TOXIC (8,9); (930-68-7)

Sodium thiosulfate: Thiosulfuric acid, disodium salt (8,9); (7772-98-7)

Silver(I) oxide: Silver oxide (8); Silver oxide (Ag$_2$O) (9); (20667-12-3)

Triphenylarsine: Arsine, triphenyl- (8,9); (603-32-7)

Palladium(II) bis(benzonitrile)dichloride: Palladium, bis(benzonitrile)dichloro- (8,9); (14220-64-5)

SYNTHESIS OF CHIRAL (E)-CROTYLSILANES: [3R- AND 3S-]-(4E)-METHYL 3-(DIMETHYLPHENYLSILYL)-4-HEXENOATE

(4-Hexenoic acid, 3-(dimethylphenylsilyl)-, methyl ester, [(R)-, and (S)-(E)-]-)
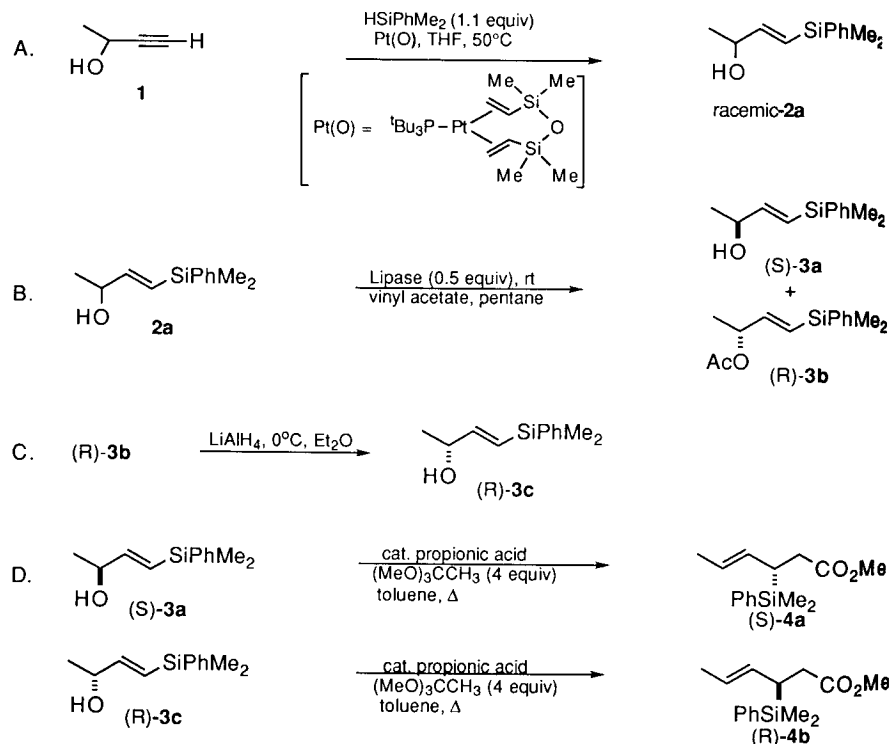
Submitted by Richard T. Beresis, Jason S. Solomon, Michael G. Yang, Nareshkumar F. Jain, and James S. Panek.[1]

Checked by Pradeep Madan and Steven Wolff.

1. Procedure

A. (±)-1-(Dimethylphenylsilyl)-1-buten-3-ol (**2a**). A solution of 10.0 g (0.143 mol) of racemic 3-butyn-2-ol (Note 1) dissolved in 255 mL of tetrahydrofuran (THF, Note 2) in a 1-L, round-bottomed flask equipped with a reflux condenser and nitrogen atmosphere is prepared. Dimethylphenylsilane (21.4 g, 0.157 mol) (Note 3) and a small piece of sodium metal (ca. 5 mg) (Note 4) are placed in the reaction mixture. The solution is stirred for 15 min and 12 mg (2.05×10^{-5} mol) of bis(η-divinyltetramethyldisiloxane)tri-tert-butylphosphineplatinum(0) (Note 5) is added. The reaction mixture is then heated under reflux for 12 hr. The orange solution is cooled to ambient temperature, and the solvent is removed under reduced pressure to yield a crude orange residue containing **2a**. The oil is subjected to column chromatography on silica gel (Note 6) (gradient elution 5, 10, 20, 35% EtOAc/hexanes) providing 25.4 g (123.23 mmol, 86%) of pure **2a** as a yellow oil (Note 7).

B. (3S)-1-(Dimethylphenylsilyl)-1-buten-3-ol (**3a**) *and (3R)-1-(dimethylphenylsilyl)-1-buten-3-ol acetate* (**3b**). A 400-mL pentane solution of 20.0 g (97.08 mmol) of the racemic secondary allylic alcohol **2a** in a 500-mL, round-bottomed flask is prepared. A crude preparation of 10.0 g of lipase Amano AK (Note 8) is added along with 24.8 mL (269.1 mmol) of freshly distilled vinyl acetate (Note 9). The heterogeneous mixture is stirred vigorously at 25°C for 4 hr (Note 10) before being filtered through a sintered glass funnel to recover the enzyme extract. The extract is washed with ether (Et$_2$O) (2 x 20 mL). The solvent is removed under reduced pressure and the products are purified by column chromatography on silica gel: gradient elution 4% EtOAc/hexanes affords 11.56 g of acetate (R)-**3b** (46.59 mmol, 48%), and gradient elution 20->35% EtOAc/hexanes affords 9.3 g of alcohol (S)-**3a** (45.12 mmol, 46%), as faint yellow oils (Notes 6, 11 and 12).

C. (3R)-1-(Dimethylphenylsilyl)-1-buten-3-ol (**3c**). Acetate (R)-**3b** (9.0 g, 36.27 mmol) is dissolved under a nitrogen atmosphere in a cooled (0°C), 1-L, round-bottomed flask containing 120 mL of anhydrous Et_2O (Note 13). To this stirred mixture is slowly added over 10 min 1.81 g (47.79 mmol, 1.3 eq) of lithium aluminum hydride ($LiAlH_4$). After 15 min, aqueous 5% hydrochloric acid is added dropwise until bubbling ceases (Note 13). The resulting suspension is further diluted with a total volume of 100 mL of the acidic solution. The layers are separated, and the aqueous layer is extracted with 100 mL of Et_2O. The combined organic extracts are washed with an aqueous saturated solution of sodium chloride and dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum, to yield 6.27 g (30.42 mmol, 83%) of the (R)-alcohol **3c**. No additional purification is performed (Note 14).

D. (3S, 4E)-Methyl 3-(dimethylphenylsilyl)-4-hexenoate (**4a**). A stirred solution of 6.0 g (29.11 mmol) of alcohol **3a** and 60 mL of dry toluene in a 200-mL flask equipped with a reflux condenser is treated with 15 mL (116.89 mmol) of trimethyl orthoacetate and 0.15 mL (2.01 mmol, 0.07 equiv) of propionic acid (Note 15). The reaction mixture is heated under reflux for 48 hr and then allowed to cool to room temperature. Solvents and volatile material are removed under reduced pressure to leave the crude (E)-crotylsilane **4a** as a yellow oil. The crude residue is chromatographed on silica gel (gradient elution 5% EtOAc/hexanes). The eluant (Note 6) affords 6.58 g (25.1 mmol, 86%) of pure **4a** as a faint yellow, viscous oil (Notes 6, 16 and 17).

2. Notes

1. 3-Butyn-2-ol, 99%, is purchased from Aldrich Chemical Company, Inc.

2. Tetrahydrofuran is freshly distilled from sodium and benzophenone.

3. Dimethylphenylsilane is purchased from United Chemical Technologies, Inc (formerly Hüls Petrarch Inc.).

4. In the Pt(0)-catalyzed hydrosilation, the addition of a catalytic amount of Na(0) appears to be necessary to achieve high levels of regioselectivity (cf., 1,1- vs 1,2-disubstituted vinylsilane). Without the inclusion of Na(0), the reaction yields a minor regioisomer, (±)-2-(dimethylphenylsilyl)-1-buten-3-ol, **2b**, in a ratio of 10-15:1. The checkers found that the reaction was considerably faster and higher-yielding with 60 mg of the catalyst, bis(η-divinyltetramethyldisiloxane)tri-tert-butylphosphine-platinum(0).

5. The platinum catalyst is prepared according to the procedure of Chandra and Lo.[2] Chloroplatinic acid, H_2PtCl_6, (5.0 g, 12.22 mmol) and 0.6 mL of water are added to 61.71 mL (268.84 mmol) of 1,3-divinyltetramethyldisiloxane. The heterogeneous solution is heated to 55°C in an oil bath for 4 hr. The now homogeneous solution is cooled to room temperature and 5.0 g of sodium bicarbonate is added. The solid is filtered, and the resulting yellow solution is treated with 3.33 mL (13.44 mmol) of tri-tert-butylphoshine[(tert-Bu)$_3$P]. The catalyst precipitates as 4.8 g (67%) of a white solid that is filtered and washed with 1,3-divinyltetramethyldisiloxane (25 mL), and dried under vacuum. The checkers found that the mixture remained heterogeneous after 4 hr. Heating was continued for 18 hr.

6. Flash chromatography is performed on E. Merck silica gel 230-400 mesh: 250 g of silica gel is loaded on a 16- x 2-in size column using a minimum amount of hexanes as loading solvent.

7. The hydrosilylation product **2a** is sufficiently pure for use as starting material in procedure B. The spectral properties are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.38 (s, 6 H), 1.30 (d, 3 H, J = 6.5), 4.34 (m, 1 H), 5.99 (dd, 1 H, J = 1.3, 18.7), 6.22 (dd, 1 H, J = 4.9, 18.7), 7.28-7.56 (m, 5 H); ^{13}C NMR (67.5 MHz) δ: -2.7(2C), 22.8, 70.4, 125.9, 126.6, 127.6, 128.9, 133.8, 151.3; IR (neat) cm^{-1}: 3380, 3080, 2960, 1730,

1620, 1430, 1250, 1110, 860; CIHRMS M + NH$_4^+$ (calcd for C$_{12}$H$_{22}$NOSi): 224.1470, (found): 224.1416.

8. The amount of enzyme extract is roughly calculated to be 0.5 wt equiv. The crude enzyme preparation may be purchased from Amano Enzyme U.S.A. Co., Ltd., Rt. 2, Box 1475, Troy, VA 22974.

9. A marked increase in reaction rate is noted when vinyl acetate is freshly distilled.

10. Reaction progress is monitored by ^{1}H NMR (CDCl$_3$); 0.5-mL of sample is withdrawn periodically (at 30-min intervals after 3 hr), filtered through a cotton plug, and the solvent is removed under reduced pressure. The intergration ratio of proton 4.34 (m, 1 H) (S)-**3a**, and 5.38 (m, 1 H) (R)-**3b** is measured and the reaction is terminated when the integration ratio is 1:1.

11. The enantiomeric purity of vinylsilane (S)-**3a** and (R)-**3c** are determined to be >95% ee by ^{1}H-NMR (400 MHz) on the derived mandelate ester, obtained by a DCC-promoted coupling to (R)-O-acetylmandelic acid, and absolute stereochemical assignment is accomplished by ^{1}H NMR analysis of the derived (R)-O-acetyl-mandelate esters. For details of this procedure see the published method of Trost.[3]

12. The spectral properties are as follows: (S)-**3a**: ^{1}H NMR (400 MHz, CDCl$_3$) δ: 0.38 (s, 6 H), 1.30 (d, 3 H, J = 6.5), 4.34 (m, 1 H), 5.99 (dd, 1 H, J = 1.3, 18.7), 6.22 (dd, 1 H, J = 4.9, 18.7), 7.28-7.56 (m, 5 H); ^{13}C NMR (67.5 MHz) δ: -2.7 (2C), 22.8, 70.4, 125.9, 126.6, 127.6, 128.9, 133.8, 151.3; IR (neat) cm^{-1}: 3380, 3080, 2960, 1730, 1620, 1430, 1250, 1110, 860; CIMS (NH$_3$), m/e (relative intensity): 224 (M+NH$_4^+$, 100), 206 (M, 44); CIHRMS (NH$_3$), m/e M+NH$_4^+$ (calcd for C$_{12}$H$_{22}$NOSi): 224.1470, (found): 224.1416; $[\alpha]_D^{23}$ +4.3° (CHCl$_3$, c 0.8); (R)-**3b**: ^{1}H NMR (400 MHz, CDCl$_3$) δ: 0.37 (s, 6 H), 1.32 (d, 3 H, J = 6.5), 2.08 (s, 3 H), 5.38 (m, 1 H), 5.9 (dd, 1 H, J = 1.33, 18.8), 6.1 (dd, 1 H, J = 4.64, 18.8), 7.3-7.5 (m, 5 H); ^{13}C NMR δ: -2.7 (2C), 19.8, 21.3, 72.1, 127.7, 127.8, 128.0, 129.0, 133.8, 146.6, 170.2; IR (neat) cm^{-1}: 3040, 2950,

1740, 1430, 1570, 1240, 1110, 1040, 830, 740; CIMS (NH$_3$), m/e (relative intensity) 209 (33), 179 (24), 171 (68), 135 (100), 117 (97); CIHRMS (NH$_3$), m/e M$^+$(calcd for C$_{14}$H$_{20}$O$_2$Si): 248.1233, (found): 248.1299; $[\alpha]_D^{23}$ +58.3° (CHCl$_3$, c 0.5).

13. Ether is freshly distilled from sodium and benzophenone. Lithium aluminum hydride is purchased from Aldrich Chemical Company, Inc., and used as supplied.

14. The specific rotation of alcohol (R)-**3c** obtained from LiAlH$_4$ reduction of acetate (R)-**3b** is $[\alpha]_D^{23}$ -3.8° (CHCl$_3$, c 0.8).

15. Toluene is freshly distilled from calcium hydride. Trimethyl orthoacetate, 99%, and propionic acid, 99%, are purchased from Aldrich Chemical Company, Inc., and used as supplied.

16. The determination of enantiomeric excess (96% ee) of the Claisen rearrangement products **4a** and **4b** is accomplished by a Mosher ^{1}H NMR analysis of the (R)-O-acetylmandelate esters that are derived from the primary alcohols. For example, **4a** is reduced with LiAlH$_4$ (1.0 equiv/THF/0°C) followed by esterification of the resulting primary alcohol with (R)-O-acetylmandelic acid (DCC, 1.5 equiv/cat. DMAP/CH$_2$Cl$_2$) to afford the mandelate ester in 91% yield (two steps).[3]

17. The spectral properties are as follows: ^{1}H NMR (400 MHz, CDCl$_3$) δ: 0.28 (s, 6 H), 1.64 (d, 3 H, J = 4.7), 2.20 (m, 1 H), 2.27 (dd, 1 H, J = <1.0, 14.5), 2.33 (dd, 1 H, J = 6.3, 14.5), 3.57 (s, 3 H), 5.28 (m, 2 H), 7.35-7.49 (m, 5 H); ^{13}C NMR (67.5 MHz) δ: -5.5, -4.5, 18.1, 28.7, 34.3, 51.4, 123.8, 127.7, 129.1, 129.8, 133.9, 136.8, 173.9; CIMS (NH$_3$), m/e (relative intensity) 280 (M+NH$_4^+$, 48), 263 (M$^+$, 39), 184 (100), 151 (40); CIHRMS (NH$_3$), m/e M+NH$_4^+$ (calcd for C$_{15}$H$_{26}$NO$_2$Si): 280.1733, (found): 280.1734; $[\alpha]_D^{23}$ -11.4° (CHCl$_3$, c 0.5) and $[\alpha]_D^{23}$ -15.4° (CH$_2$Cl$_2$, c 1.4) for [(R)-**4b** derived from Claisen rearrangement of (R)-**3c**. For (S)-**4a** $[\alpha]_D^{23}$ +11.9° (CHCl$_3$, c 0.5) and $[\alpha]_D^{23}$ +15.9° (CH$_2$Cl$_2$, c 1.6).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Functionalized chiral (E)-crotylsilanes **4a** and **4b** and related silane reagents have recently been used as carbon nucleophiles in highly diastereo- and enantioselective crotylation reactions.[4] Of particular interest are enantioselective transformations, including an asymmetric [3 + 2] cyclopentane annulation through a conjugate addition and subsequent cyclization. The condensation between the chiral silane reagent and in situ generated N-acylimines affords the homoallylic N-acylamines[5] and functionalized homoallylic ether formation via a three-component, in situ generation and trapping the derived oxonium ion.[6] A subsequent silyl group-directed alkylation of the derived lithium enolate produces a silane reagent bearing functionalization α to the methyl ester which has been employed in the in situ asymmetric crotylsilation producing homoallylic ethers.[7] Equations 1 - 3 illustrate representative examples of the Lewis acid-promoted enantioselective transformations of the silane reagent.

• Asymmetric [3 +2] Cyclopentane Annulation

(1)

93%, Diastereoselection >30:1
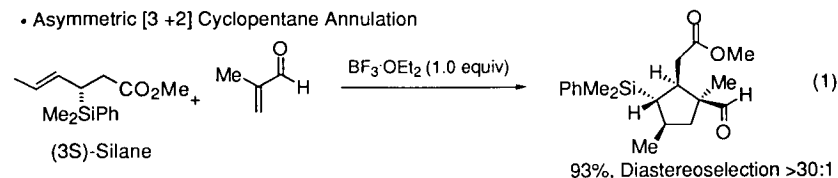
• In Situ N-Acylimine generation and trapping

(2)

94%, Diastereoselection >30:1
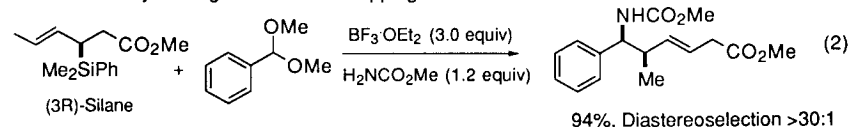
• In Situ oxonium ion generation and trapping

(3)

94%, Diastereoselection >30:1
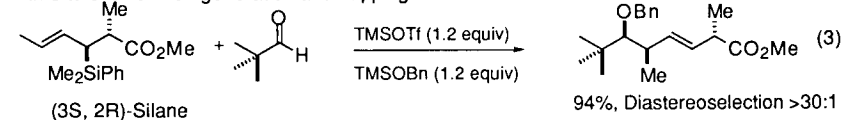
The three-step procedure described for the preparation of the illustrated crotylsilanes is initiated with the hydrosilation of rac-3-butyn-2-ol. This procedure is significantly improved with respect to the positional selectivity of the hydrosilation resulting in exclusive formation of the racemic (E)-vinylsilane, and as a result the present procedure is much more amenable to scale-up than those previously described in the literature.[8] The enzymatic resolution of the racemic secondary allylic alcohol (vinylsilane) has also been reported using commercially available lipase extracts. The use of a Johnson ortho ester Claisen rearrangement affords the (E)-crotylsilanes **4** in nearly enantiomerically pure form.

1. Department of Chemistry, Metcalf Center for Science and Engineering, Boston University, Boston, MA 02215.

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Appendix

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

(3R)-(4E)-Methyl 3-(dimethylphenylsilyl)-4-hexenoate: 4-Hexenoic acid, 3-(dimethylphenylsilyl)-, methyl ester, [R-(E)]- (12); (136174-52-2)

(3S)-(4E)-Methyl 3-(dimethylphenylsilyl)-4-hexenoate: 4-Hexenoic acid, 3-(dimethylphenylsilyl)-, methyl ester, [S-(E)]- (12); (136314-66-4)

(±)-1-(Dimethylphenylsilyl)-1-buten-3-ol: 3-Buten-2-ol, 1-(dimethylphenylsilyl)-, (E)-(±)- (12); (137120-08-2)

3-Butyn-2-ol: 3-Butyn-2-ol, (±)- (10); (65337-13-5)

Dimethylphenylsilane: Silane, dimethylphenyl- (8,9); (766-77-8)

Sodium (8,9); (7440-23-5)

Bis(η–divinyltetramethyldisiloxane)tri-tert-butylphosphineplatinum(0): Platinum, [1,3-bis(η^2-ethenyl)-1,1,3,3-tetramethyldisiloxane][tris(1,1-dimethylethyl)phosphine]- (11); (104602-18-8)

(3S)-1-(Dimethylphenylsilyl)-1-buten-3-ol: 3-Buten-2-ol, 4-(dimethylphenylsilyl)-, [S-(E)]- (12); (133398-24-0)

(3R)-1-(Dimethylphenylsilyl)-1-buten-3-ol acetate: 3-Buten-2-ol, 4-(dimethylphenylsilyl)-, acetate, [R-(E)]- (12); (129921-47-7)

Vinyl acetate: Acetic acid vinyl ester (8); Acetic acid ethenyl ester (9); (108-05-4)

(3R)-1-(Dimethylphenylsilyl)-1-buten-3-ol: 3-Buten-2-ol, 1-(dimethylphenylsilyl)-, [R-(E)]- (12); (133398-25-1)

Trimethyl orthoacetate: Orthoacetic acid, trimethyl ester (8); Ethane, 1,1,1-trimethoxy- (9); (1445-45-0)

Propionic acid (8); Propanoic acid (9); (79-09-4)

1,3-Divinyltetramethyldisiloxane: Disiloxane, 1,1,3,3-tetramethyl-1,3-divinyl- (8);

Disiloxane, 1,3-diethenyl-1,1,3,3-tetramethyl- (9); (2627-95-4)

Chloroplatinic acid hexahydrate: Platinate (2-), hexahydro-, dihydrogen (8); Platinate

(2-), hexachloro-, dihydrogen, (OC-6-11)- (9); (16941-12-1)

Tri-tert-butylphosphine: Phosphine, tri-tert-butyl- (8); Phosphine,

tris(1,1-dimethylethyl)- (9); (13716-12-6)

3-CHLORO-2-(CHLOROMETHYL)-1-PROPENE

(1-Propene, 3-chloro-2-(chloromethyl)-)

A. $C(CH_2OH)_4 \xrightarrow[\text{2. SOCl}_2]{\text{1. pyridine}} HOCH_2C(CH_2Cl)_3$

B. $HOCH_2C(CH_2Cl)_3 \xrightarrow{\text{HNO}_3} HOCC(CH_2Cl)_3$ (carbonyl O on the C)

C. $HOCC(CH_2Cl)_3 \xrightarrow{\text{200 - 215°C}} CH_2=C(CH_2Cl)_2$ (carbonyl O on the C)
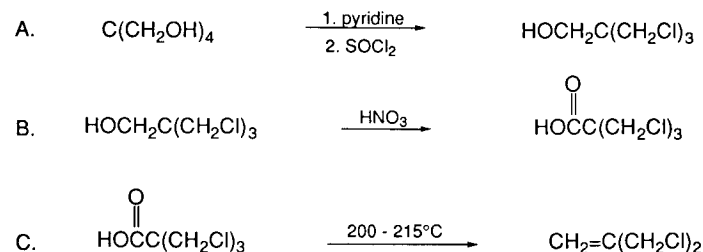
Submitted by Kathleen Mondanaro Lynch and William P. Dailey.[1]

Checked by Rajib Pal, Yan Dong, Peter Belica, and Steven Wolff.

1. Procedure

A. Pentaerythrityl trichlorohydrin: 3-Chloro-2,2-bis(chloromethyl)propan-1-ol.
A dry, 5-L, four-necked, round-bottomed flask equipped with an efficient mechanical
stirrer, addition funnel, thermometer adapter, and a condenser is charged with 417 g
(3.06 mol) of pentaerythritol (Note 1) and 730 g (9.24 mol) of pyridine (Note 2). A
Drierite drying tube is attached to the condenser, and the addition funnel is closed with
a glass stopper after being charged with 1.134 kg (9.53 mol) of thionyl chloride (Note
3). The reaction flask is placed inside a bucket to which an ice/water mixture may be
added in the event that the reaction becomes too exothermic. Thionyl chloride is
added dropwise with vigorous stirring to the slurry so that the white mist that appears
in the flask does not rise up into the condenser. Thionyl chloride is added as rapidly
as possible over 4-5 hr so that the temperature of the yellow-orange reaction mixture is
maintained between 65-95°C (Note 4). When the addition is complete, the drying tube

is removed, and the ice bucket is replaced with a heating mantle. The resulting orange-yellow reaction mixture is heated to 120-130°C until no more sulfur dioxide is evolved (Note 5). As the heating continues, the reaction mixture turns from dark orange to brown, and gas evolution becomes evident. After gas evolution ceases, the flask is cooled slightly and 2 L of cold water is added with stirring. The brown-yellow product precipitates, is filtered, and washed with 2-3 L of water. The dried, crude product (461 g) is approximately a 1:2.8 mixture of pentaerythrityl tetrachloride (131 g) and pentaerythrityl trichlorohydrin (330 g, 57% yield) (Note 6). This crude material may be used directly in the next step (Note 7).

B. *Tris(chloromethyl)acetic acid: 3-Chloro-2,2-bis(chloromethyl)propanoic acid.* *(Caution: Nitrogen oxides are highly toxic. This procedure should be carried out in a well-ventilated hood!)* The crude mixture (461 g) of pentaerythrityl tetrachloride and pentaerythrityl trichlorohydrin obtained from the above reaction is transferred to a 3-L, four-necked, round-bottomed flask that is equipped with an efficient mechanical stirrer, reflux condenser, thermometer adapter, and an addition funnel. The transfer is most easily accomplished by melting the solid over a steam bath and pouring the mixture through a funnel directly into the reaction flask. The flask and its contents are heated to 70-80°C with a heating mantle (Note 8), and a small portion (10-15 mL) of concentrated nitric acid (Note 9) is added with vigorous stirring to initiate the reaction (Note 10). As the reaction begins, a large amount of dark orange-brown vapors appears. Stirring is continued, and the addition of nitric acid is resumed after the initial exothermic reaction subsides (usually within 15 min). The remaining nitric acid (660-680 mL) is added in 20-30-mL aliquots over 30 to 60 min so that nitrogen oxides are continually evolved but the reaction does not become violent. After the addition is complete, the addition funnel is carefully removed and left in the hood to air out and is replaced by a glass stopper. The reaction mixture is heated at 70-80°C until the evolution of nitrogen oxides is no longer evident (Note 11). At this point, the biphasic

reaction mixture is a cloudy yellow or white liquid. The warm reaction mixture is poured into a 4-L beaker and 2 L of cold water is added is to precipitate the tetrachloride/carboxylic acid product mixture. The beaker and its contents are allowed to stand for several hours at room temperature to ensure complete precipitation of the product; then the crude product mixture is filtered, washed with water, and the carboxylic acid is extracted as follows. The solid is pulverized, transferred to a 4-L beaker, and 2.5 L of 1 M sodium hydroxide is added with stirring (Note 12). The liquid reaction mixture instantly becomes bright yellow, and the insoluble, white tetrachloride clumps on the sides of the beaker. Stirring is continued for 30-60 min whereupon the insoluble material is filtered and washed well with water. The combined washings and yellow, aqueous filtrate are acidified to pH 1 with concentrated hydrochloric acid (~250 mL). The carboxylic acid precipitates as a white solid that is easily filtered using two pieces of filter paper. The filtered and dried product thus obtained is a fine white powder (230 g, 65% yield). The aqueous filtrate is extracted with methylene chloride; the extracts are dried with magnesium sulfate and concentrated to provide an additional 50-60 g of the desired acid. The crude, combined product (75% yield) can be used directly in the next step (Note 13). Over several runs, the yield varies from 65-80%.

C. *3-Chloro-2-(chloromethyl)-1-propene.* Tris(chloromethyl)acetic acid (205 g, 1.00 mol) is transferred to a 500-mL, two-necked, round-bottomed flask. On top of the powdery acid, which nearly fills the flask, is placed a football magnetic stir bar (1.25 x 0.5 in.). The neck of the flask to be clamped is wrapped well with aluminum foil and is fitted with a glass stopper. A standard taper 24/40 short path still head, to which is attached a Drierite drying tube, is attached at the second neck. The upper flask and short path column are wrapped with aluminum foil, and the flask is immersed in a high temperature oil bath (Note 14) that has been preheated to a stable 210°C. As the solid melts, the reaction mixture becomes yellow, and the oil bath temperature drops (10-

20°C). If after 10-15 min, the temperature does not rise to between 205-215°C, it may be necessary to adjust the heating to maintain the oil bath temperature between 205-215°C (Note 15). Moderate stirring is maintained throughout the reaction (Note 16). Within 30 to 60 min, gas evolution becomes apparent, the reaction mixture turns brown, then black, and the product begins to distill. As the reaction proceeds, a black, tarry residue begins to build up on the bottom and sides of the flask. The product begins to distill, slowly at first, then quite steadily, at which point the head temperature rises to 138°C (Note 17). The reaction time varies (Note 17), but heating is continued until just before dryness. The product (115 g, 92% yield) thus obtained is a clear, colorless liquid (bp 136-138°C) that is > 98% pure by GLC and ^{1}H NMR analysis (Note 18). Over several runs, the yield varies from 88-99%.

2. Notes

1. Pentaerythritol (98%) was purchased from Aldrich Chemical Company, Inc., and was used without further purification.

2. Pyridine (> 99%) was purchased from Fisher Scientific Company. Only freshly opened or recently distilled (CaH$_2$) pyridine was used.

3. Thionyl chloride (97%, technical) was purchased from Aldrich Chemical Company, Inc. Only freshly opened or recently distilled reagent was used.

4. An addition rate of 2-3 drops per second is adequate to maintain the desired reaction temperature. The submitters have experienced several problems if the reaction temperature is below 60°C. The reaction mixture solidifies, leading to a potentially exothermic situation. In the event that the mixture does become solid, increasing the rate of addition creates enough heat to melt the solid.

5. Gas evolution generally ceases in 8 to 10 hr of heating, but the mixture is allowed to heat overnight.

6. Extraction of the initial filtrate (prior to washing) with toluene provides an additional 94 g of material that is approximately a 1:15 mixture of pentaerythrityl tetrachloride and pentaerythrityl trichlorohydrin. Thus, the yield may be improved by up to 10%. It is important to remove all the toluene prior to oxidation. This may be done by prolonged rotary evaporation or by distillation as described in Note 7. Some residual pyridine has not been a problem in the oxidation.

7. Pentaerythrityl trichlorohydrin may be separated from pentaerythrityl tetrachloride by fractional distillation under reduced pressure with a heated Vigreux column. The column (6 in. x 1 in.) is preheated to 100°C using a heating tape. Steam is run through the condenser as necessary to prevent the distillate from solidifying. Pentaerythrityl tetrachloride is collected from 95-120°C at 10-12 mm. It may be recrystallized from cyclohexane to yield small white crystals, mp 95-96°C; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 3.65 (s). Pentaerythrityl trichlorohydrin is collected from 125-130°C at 10-12 mm. It may be recrystallized from cyclohexane to obtain long, fine, white needles, mp 63-65°C; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 2.0 (br, 1 H), 3.66 (s, 6 H), 3.75 (s, 2 H). The ratio of pentaerythrityl tetrachloride to pentaerythrityl trichlorohydrin was determined by GLC analysis. Pentaerythrityl tetrachloride has a shorter retention time than the trichlorohydrin.

8. It is important that the starting materials be melted prior to the addition of nitric acid. Heating above 85°C during the reaction causes the product to sublime on the sides of the flask and in the condenser, potentially clogging it and leading to pressure build-up in the reaction flask. The sublimed acid may be melted back into the reaction mixture with judicious use of a heat gun.

9. Concentrated nitric acid (specific gravity ~1.42) was purchased from Fisher Scientific Company and used without further purification.

10. Initiation of the reaction is usually evident within 10 min. More nitric acid may be added, if necessary, but care should be taken to avoid adding more than 100

mL before the reaction is obviously progressing. The initial reaction may be quite exothermic and large amounts of nitrogen oxides are generated.

11. Heating overnight is usually sufficient, but up to 24 hr may be required. Near the end of the reaction, (i. e., after heating overnight), the condenser and glass stopper may be removed to facilitate escape of the nitrogen oxides.

12. A long magnetic stir bar (2 in. x 0.25 in.) was found to be useful.

13. The crude product (mp 107-109°C) may be recrystallized from cyclohexane to yield long white crystals; mp 111-112°C, or directly used in the next reaction; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 3.85 (s, 6 H), 10.87 (br 1 H); ^{13}C (500 MHz, CDCl$_3$) δ: 42.7, 55.3, 175.5; IR (CDCl$_3$ soln) cm^{-1}: 3400-2700 (br), 2990 sharp, 1730, 1445, 1220. In one run, the checkers isolated the tris(chloromethyl)acetic acid solely by extraction with dichloromethane, rather than by precipitating some and extracting the remainder according to the procedure. In this manner, the amount of water that co-distills with the product in Step C is minimized.

14. Thomas Scientific 6428-R25 Silicone Fluid SF 96/50 was used.

15. Heating to higher temperatures (e.g., >225°C.) leads to a significant decrease in yield as more tar is produced and the carboxylic acid distills. If some acid distills, it may be filtered away from the alkene.

16. Using a Thermolyne Type 7200 magnetic stir plate, a setting of 5-6 was used to control the stirring.

17. The total reaction time has varied greatly over several runs from 2-6 hr. The head temperature during the reaction rises slowly and appears to depend on how steadily the product distills. Occasionally, the head temperature has reached only 70°C, but the purity of the product was >98% by GC and ^{1}H NMR analysis. In three attempts, the checkers found the distillation to be long, in no instance less than 5 hr and once 9 hr. Users should heed the precaution in Note 15.

18. Occasionally, the product has a pale yellow color. The purity as determined by GLC and ^{1}H NMR appears to be unaffected. If desired, the product can be further purified by simple distillation which gives a sharp bp at 137-138°C; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 4.18 (s, 4 H), 5.30 (s, 2 H).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The present procedure represents a modification of two previously published procedures,[2,3] and results in a safer, more convenient preparation of the title compound. In Step A, the ratio of reagents has been adjusted to allow for the formation of only pentaerythrityl tetrachloride and trichlorohydrin; none of the dichlorinated product is produced. Thus work up of the reaction is easier: the product can be filtered rather than extracted, so minimal solvent is used, and the crude products are used in Step B, thus avoiding a tedious distillation. Step B has also been modified to make it safer and more convenient. The crude material from Step A is used, and addition of nitric acid over a longer period reduces the hazards of this step. Previously, it was noted that after the nitric acid was added in one portion and the mixture was heated, "a reaction became apparent, whereupon the flask was lowered rapidly into a waiting cold bath and the operator withdrew".[2] Step C is a more detailed modification of the procedure reported by the Russian workers[3] as an improvement to the original method of Mooradian and Cloke.[2] The latter used quinoline to catalyze the conversion of tris(chloromethyl)acetic acid to 3-chloro-2-(chloromethyl)propene.

Gafarov, et al.[3] reported that heating neat tris(chloromethyl)acetic acid to a higher temperature cleanly affords the final product, 3-chloro-2-(chloromethyl)-1-propene. The present procedure allows for the pyrolysis of the crude material obtained in Step B to be used in Step C, thus eliminating the use of large amounts of solvents for recrystallization.

The best alternative preparation of 3-chloro-2-(chloromethyl)-1-propene involves the direct chlorination of 3-chloro-2-methyl-1-propene using elemental chlorine.[4] This method leads to a mixture of products that must be purified by a tedious spinning band distillation, and only yields 34% of the desired product.

3-Chloro-2-(chloromethyl)-1-propene is commercially available but is very expensive (>$45/g for 10 g, Aldrich Chemical Company, 1996). It is commonly used in the synthesis of natural products,[5] polymers,[6] cryptands and crown ethers,[7] compounds of biological and medical importance,[8] and is the starting material for the Szeimies synthesis of [1.1.1]propellane.[9]

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

3-Chloro-2-(chloromethyl)-1-propene: 1-Propene, 3-chloro-2-(chloromethyl)- (8,9); (1871-57-4)

Pentaerythrityl trichlorohydrin: 1-Propanol, 3-chloro-2,2-bis(chloromethyl)- (8,9) (813-99-0)

Pentaerythritol (8); 1,3-Propanediol, 2,2-bis(hydroxymethyl)- (9); (115-77-5)

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

Thionyl chloride (8.9); (7719-09-7)

Pentaerythrityl tetrachloride: Propane, 1,3-dichloro-2,2-bis(chloromethyl)- (8,9); (3228-99-7)

Tris(chloromethyl)acetic acid: Propionic acid, 3-chloro-2,2-bis(chloromethyl)- (9); (17831-70-8)

Nitric acid (8,9); (7697-37-2)

[1.1.1]PROPELLANE

(Tricyclo[1.1.1.0^{1,3}]pentane)
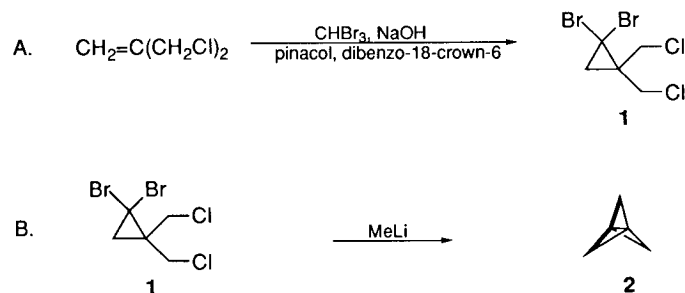
A. $CH_2=C(CH_2Cl)_2$ $\xrightarrow[\text{pinacol, dibenzo-18-crown-6}]{\text{CHBr}_3,\ \text{NaOH}}$ **1**

B. **1** $\xrightarrow{\text{MeLi}}$ **2**

Submitted by Kathleen Mondanaro Lynch and William P. Dailey.[1]

Checked by Rajib Pal, Peter Belica, and Steven Wolff.

1. Procedure

A. 1,1-Dibromo-2,2-bis(chloromethyl)cyclopropane (**1**). Into a 1-L, three-necked, round-bottomed flask, equipped with an efficient mechanical stirrer, a thermometer, and a condenser equipped with a potassium hydroxide drying tube, are placed 54.1 g (0.403 mol) of 3-chloro-2-(chloromethyl)propene (Note 1), 212 g (0.805 mol) of bromoform (Note 2), 1.70-2.00 g (14.4-16.9 mmol) of pinacol (Note 3), and 1.45 g (3.94 mmol) of dibenzo-18-crown-6 (Note 4). With very vigorous stirring (Note 5), 312 g of an aqueous 50% sodium hydroxide solution that has been cooled to 15°C is added in one portion. The reaction mixture turns orange, then brown, then black within 5 min, and the temperature of the reaction mixture begins to rise. Within 20 min, the internal reaction temperature is 49-50°C at which point the reaction flask is cooled with a room-temperature water bath, and the reaction temperature decreases to ca.

20°C. After 1 hr, the bath is removed and the reaction mixture is heated to 40°C (internal temperature) with an oil bath. The vigorously stirred mixture is maintained at this temperature for 4 days (Note 6). The reaction mixture is cooled to room temperature, diluted with 500 mL of water, and filtered through a pad of Celite on a glass-fritted funnel (pore size C), using a water aspirator (Note 7). Up to an additional 1-L of water is used to rinse the thick black reaction mixture from the flask. The resulting golden-yellow filtrate is discarded (Note 8). The black, solid residue in the frit, and any material remaining in the reaction flask are transferred to a 1-L beaker with pentane, acetone, and a glass rod, and the solution is vigorously stirred with an additional 500 mL of a 1:1 (v/v) solution of acetone and pentane for 30 min. This mixture is filtered through a glass-fritted funnel using a minimal layer of Celite. The Celite pad is washed thoroughly with 1:1 pentane/acetone solution, and the resulting brown filtrate is dried over magnesium sulfate. Concentration using a rotary evaporator, followed by distillation under reduced pressure (bp 75-85°C/0.4 mm), and low temperature (ca. -20°C) recrystallization from pentane (ca. 1 mL/g of product), provide 70-95 g (60-80% yield) of the product as small, white crystals (mp 47.5-50°C) (Notes 9 and 10).

B. [1.1.1]Propellane (**2**). A 500-mL, three-necked, round-bottomed flask that has been flame dried under reduced pressure and purged with argon, is equipped with a vacuum adapter equipped with an argon balloon, an efficient mechanical stirrer, and a pressure-equalizing, 150-mL addition funnel equipped with a rubber septum. The flask is charged with a 25-g (0.085 mol) portion of material obtained from part A, and 25 mL of pentane (Note 11). A diethyl ether solution of methyllithium, 132 mL of a 1.4 M (0.185 mol) solution (Note 12), is transferred to the addition funnel via cannula under a flow of argon. The reaction flask is cooled to -78°C and the methyllithium is added over 15 min with vigorous stirring. The reaction mixture is maintained at -78°C for 10 - 15 min; then the -78°C cooling bath is replaced with an ice-water bath (0°C),

and the addition funnel is replaced with a rubber septum equipped with an argon balloon. Stirring is continued for an additional hour; then the volatile materials are transferred under reduced pressure to a flame-dried flask that is cooled to -196°C (Note 13). Based on the recovery of the thiophenol adduct, the yield of [1.1.1]propellane is between 75 and 88%.

Determination of the yield of propellane. Wiberg and Waddell have shown that propellane reacts spontaneously in normal room light with thiophenol to yield bicyclo[1.1.1]pentyl phenyl sulfide in 98% yield.[2] A slight modification of their method provides a good estimate of the yield of propellane. Thus, a 3.0-mL portion of the propellane solution is transferred via a gas-tight syringe to a tared, flame-dried, argon-purged, 10-mL, round-bottomed flask equipped with a stirring bar and maintained under a static atmosphere of argon. Thiophenol is added in slight excess via syringe and the mixture is stirred under room light for 15 min. Concentration of the solution provides a mixture of thiophenol and bicyclo[1.1.1]pentyl phenyl sulfide. The ratio of compounds may be determined by ^{1}H NMR or GLC, and the yield of propellane calculated (Note 14). Alternatively, the mixture may be diluted with pentane, washed with 1 M sodium hydroxide, dried with magnesium sulfate, and concentrated to provide bicyclo[1.1.1]pentyl phenyl sulfide from which the yield of propellane is calculated. The reaction of thiophenol with propellane is assumed to be quantitative; thus yields for bicyclo[1.1.1]pentyl sulfide are 75 to 88% based on 1.

Wiberg and Waddell also noted that propellane reacts with iodine in 88% yield.[2] Alber and Szeimies report a somewhat lower yield (61%) when an ethereal solution of propellane is treated with a solution of iodine in ether/pentane while being irradiated.[3] Thus, titration of a portion of the resulting propellane solution with iodine provides an estimate of the minimum yield. A 3.0-mL portion of the propellane solution is transferred as noted above. Small pieces of iodine are added with stirring under room light over 10 min until just before the dark color persists. Concentration of the solution provides 1,3-diiodobicyclo[1.1.1]pentane from which the minimal concentration of the propellane solution and minimal yield of propellane may be estimated if iodine is not added in excess. Alternatively, a solution of iodine in diethyl ether/pentane may be added instead of neat iodine.

2. Notes

1. 3-Chloro-2-(chloromethyl)propene was prepared according to the method of Lynch and Dailey.[4] Percent purity was determined by GLC, and 0.400 mol of starting material was calculated accordingly. A typical experiment used ca. 54 g of alkene that was 92-93% pure by GLC

2. Bromoform (96%) stabilized with 1-3% ethanol, was purchased from the Aldrich Chemical Company, Inc., and used without further purification.

3. Pinacol was purchased from the Aldrich Chemical Company, Inc., and used without further purification.

4. Dibenzo-18-crown-6 (98%) was purchased from the Aldrich Chemical Company, Inc., and used without further purification.

5. A Glas Col GT-21 mechanical stirrer was used at maximum speed.

6. In some runs, the internal temperature varied between 37-43°C over the 4-day period without a significant change in yield.

7. Aspirator filtration through a pad of Celite was beneficial to prevent small particulate matter from clogging the fritted funnel. However, it was necessary to break up the pad of Celite to allow for effective filtration.

8. Pentane extraction of the primarily aqueous filtrate provides only an additional 4 g (3%) of product.

9. If solvents have not been evaporated completely, a forerun may be recovered with bp up to 50°C/0.5-1 mm. This should be trapped with a dry ice-acetone

bath. If the sample is evaporated well prior to distillation, crystallization of the product will occur upon standing. Stirring a pentane solution of the crude product with decolorizing carbon, followed by filtration, and low temperature (ca. -20°C) recrystallization gives material that is suitable for many applications (mp 44-45°C); ^{1}H NMR (CDCl$_3$) δ: 1.80 (s, 2 H), 3.19 (s, 4 H); ^{13}C NMR (CDCl$_3$) δ: 32.02 (s), 33.89 (t), 35.20 (s), 47.58 (t).

10. Reactions that were stirred for up to 5 or 6 days had slightly higher yields (up to 80%) and needed minimum purification. Reactions that were stirred for less than 3 days or more than 6 days had slightly lower yields (60% after recrystallization). The checkers found that distilled 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane was sufficiently pure (^{1}H NMR and mp) for the subsequent step and did not require recrystallization. The procedure has been carried out on a 1-mol scale with comparable results.

11. High purity grade pentane was purchased from Fisher Scientific Company or Burdick and Jackson Inc. and was used without further purification. Recently opened solvent was always used.

12. Methyllithium (1.4 M, low halide) in diethyl ether, was purchased from the Aldrich Chemical Company, Inc., and was used without further purification. Titration using the method of Watson and Eastham[5] was used to determine the molarity. The best and most reproducible results (ca. 88% yield) were obtained when freshly opened methyllithium was used. The yield was severely depressed when 0.86 M methyllithium was used (< 33%). The checkers used a recently purchased, freshly opened bottle of methyllithium and did not determine its molarity by titration.

13. The volatile materials are transferred under essentially static conditions. Bulb-to-bulb vacuum transfer may be accomplished with a standard 24/40 short path distillation apparatus. The reaction flask may be warmed slightly (40°C) with a water bath and the receiving flask is cooled in a liquid nitrogen bath. Vacuum is applied

intermittently to allow for effective transfer of the volatile material. It is helpful to continue stirring the reaction flask during the transfer.

14. Integration and normalization of the ^{1}H NMR peaks for the acidic proton of thiophenol (d 3.4 ppm) and the bicyclo[1.1.1]pentyl group (d 1.96 ppm) were used to calculate the yield of propellane; ^{13}C NMR (125 MHz, CDCl$_3$) δ: 1.0 and 74.2.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This preparation of 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane is a modification of the method reported by Szeimies and co-workers,[6] and represents a significant improvement in both the convenience of the workup and the yield of the reaction. In the present method, dilution and filtration of the reaction mixture leave behind a mostly solid residue from which the product is easily obtained. Most significantly, the problematic emulsion that forms in the Szeimies method is effectively eliminated.

The cocatalytic effects of pinacol in the phase transfer catalysis (PTC) of dihalocarbene additions to alkenes were noted by Dehmlow and co-workers who showed that pinacol accelerates the PTC deprotonation of substrates up to pKa 27.[7] Dehmlow also studied the effects of various crown ethers as phase transfer catalysts in the addition of dibromocarbene to allylic bromides.[8] In Dehmlow's study, elevated temperature (40°C) and dibenzo-18-crown-6 did not give the highest ratio of addition/substitution to allyl bromide. However, the submitters' use of pinacol,

dibenzo-18-crown-6, and heat in the addition of dibromocarbene to 3-chloro-2-(chloromethyl)propene lead to good yields and a procedure with a significantly more facile work-up. In the course of the submitters' work in this area, Della and Taylor also reported an improvement in the synthesis of 1;[9] however, the submitters were unable to reproduce their results, even with several attempts.

The synthesis of [1.1.1]propellane from 1 is essentially as reported by Michl and co-workers,[10] with only a slight modification in the process of transferring the crude propellane solution. As a result of the submitters' improvements in the preparation of 3-chloro-2-(chloromethy)propene[4] and 1,1-dibromo-2,2-bis(chloromethyl)cyclo-propane, many of the difficulties in the Szeimies route to [1.1.1]propellane have been eliminated.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

[1.1.1]Propellane: Tricyclo[1.1.1.0^{1,3}]pentane (9); (35634-10-7)

1,1-Dibromo-2,2-bis(chloromethyl)cyclopropane: Cyclopropane, 1,1-dibromo-2,2-bis(chloromethyl)- (11); (98577-44-7)

3-Chloro-2-(chloromethyl)-1-propene: 1-Propene, 3-chloro-2-(chloromethyl)- (8,9); (1871-57-4)

Bromoform: Methane, tribromo- (8,9); (75-25-2)

Pinacol: 2,3-Butanediol, 2,3-dimethyl- (8,9); (76-09-5)

Dibenzo-18-crown-6: Dibenzo[b,k][1,4,7,10,13,16]hexaoxacyclooctadecin, 6,7,9,10,17,18,20,21- (8,9); (14187-32-7)

Methyllithium: Lithium, methyl- (8,9); (917-54-4)

Bicyclo[1.1.1]pentyl phenyl sulfide: Bicyclo[1.1.1]pentane, 1-(phenylthio)- (11); (98585-81-0)

Thiophenol: Benzenethiol (8,9); (108-98-5)

Iodine (8,9); (7553-56-2)

1,3-Diiodobicyclo[1.1.1]pentane: Bicyclo[1.1.1]pentane,1,3-diiodo- (1); (105542-98-1)

N-BENZYL-2,3-AZETIDINEDIONE

(2,3-Azetidinedione, 1-(phenylmethyl)-)

A. CH_3CHO + (structure: COOMe) $\xrightarrow[CH_3OH]{DABCO}$ (structure: OH, COOMe)

B. (structure: OH, COOMe) + $C_6H_5CH_2NH_2$ $\xrightarrow{CH_3OH}$ (structure: OH, COOMe, NHCH$_2$C$_6$H$_5$)

C. (structure: OH, COOMe, NHCH$_2$C$_6$H$_5$) $\xrightarrow[THF]{t\text{-}BuMgCl}$ (structure: OH, azetidinone, CH$_2$C$_6$H$_5$)

D. (structure: OH, azetidinone, CH$_2$C$_6$H$_5$) $\xrightarrow[\substack{CH_2Cl_2 \\ 2.\ DBU}]{1.\ CH_3SO_2Cl, (C_2H_5)_3N}$ (structure: azetidinone, CH$_2$C$_6$H$_5$)

E. (structure: azetidinone, CH$_2$C$_6$H$_5$) $\xrightarrow[\substack{NaIO_4 \\ CH_3OH,\ H_2O}]{OsO_4}$ (structure: dione azetidinone, CH$_2$C$_6$H$_5$)
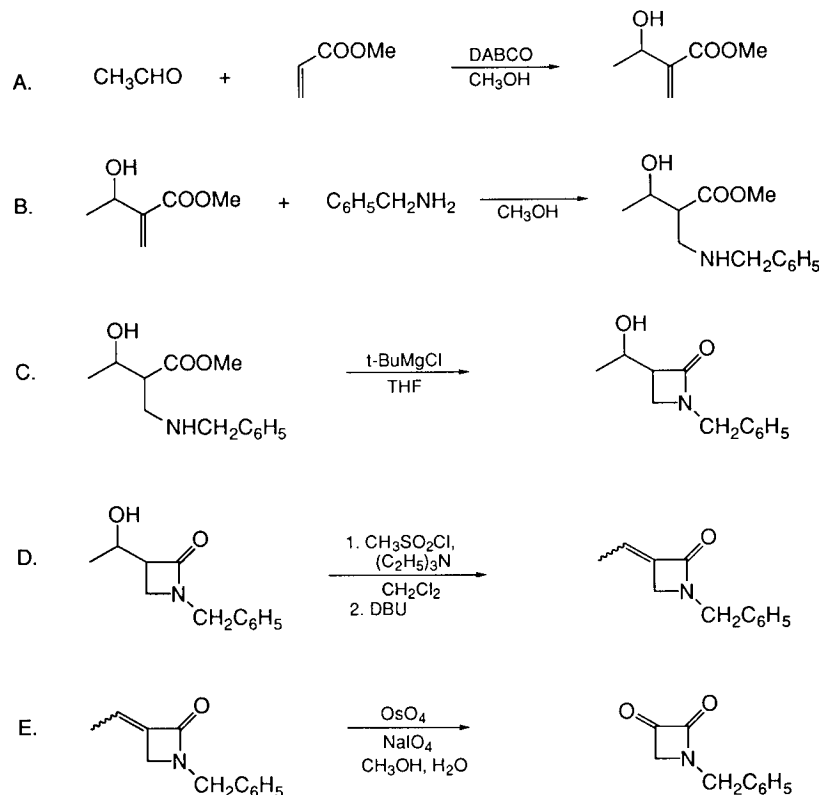
Submitted by Carsten Behrens and Leo A. Paquette.[1]
Checked by Kei Manabe and Kenji Koga.

1. Procedure

A. Methyl 3-hydroxy-2-methylenebutanoate. A 500-mL, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 90.05 mL (1.0 mol) of methyl acrylate, 80 mL (1.43 mol) of acetaldehyde, 11.22 g (0.1 mol) of 1,4-diazabicyclo[2.2.2]octane and 4.0 mL (0.1 mol) of methanol (Note 1). The flask is sealed with a rubber septum and stirred at room temperature for 48 hr. The resulting oil is taken up in ethyl acetate (300 mL) and washed once with water (200 mL). The aqueous layer is back-extracted with ethyl acetate (200 mL) and the combined organic phases are dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the resulting clear oil is fractionally distilled to give 102.1 g (79%) of methyl 3-hydroxy-2-methylenebutanoate as a colorless liquid, bp 62-63°C (1 mm) (Note 2).

B. Methyl 2-(benzylamino)methyl-3-hydroxybutanoate. A dried, 2-L, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 68.7 g (0.53 mol) of methyl 3-hydroxy-2-methylenebutanoate and 800 mL of anhydrous methanol. After the addition of 57.7 mL (0.53 mol) of benzylamine (Note 1), the mixture is stirred at room temperature for 48 hr (Note 3). The methanol is removed under reduced pressure to leave 125.6 g (100%) of the amino ester as a clear oil, essentially pure by ^{1}H NMR analysis (Note 4).

C. N-Benzyl-3-(1-hydroxyethyl)azetidin-2-one. Into a flame-dried, 1-L, three-necked, round-bottomed flask fitted with a condenser, addition funnel, and a large magnetic stirring bar, is placed 12.24 g (0.50 mol) of magnesium turnings and 400 mL of dry tetrahydrofuran (Note 5). tert-Butyl chloride (60.0 mL, 0.55 mol) (Note 6) is placed in the addition funnel and slowly added to the magnesium turnings as the reaction mixture spontaneously begins to reflux. When the addition is completed, heating is continued for 1 hr more (Note 7). A solution of 30.0 g (0.13 mol) of methyl 2-

(benzylamino)methyl-3-hydroxybutanoate in 100 mL of anhydrous tetrahydrofuran is slowly added dropwise to the well stirred Grignard solution (Note 8) over a period of 3 hr at room temperature. The mixture is then carefully neutralized with 300 mL of saturated ammonium chloride solution (Note 8) and the separated aqueous phase is extracted with diethyl ether (2 x 300 mL). The combined organic layers are washed with brine (500 mL), dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The resulting orange oil is purified by passing it down a short silica gel column (elution with 5% methanol in dichloromethane). The appropriate fractions are pooled and freed of solvent under reduced pressure to give 19.45-21.85 g (73-82%) of N-benzyl-3-(1-hydroxyethyl)azetidin-2-one as a yellowish oil (Note 9).

D. N-Benzyl-3-(Z/E)-ethylideneazetidin-2-one. Into a dry, 250-mL, one-necked, round-bottomed flask, fitted with a magnetic stirring bar, is placed 9.60 g (0.047 mol) of N-benzyl-3-(1-hydroxyethyl)azetidin-2-one, 125 mL of dry dichloromethane (Note 10), and 13.0 mL (0.093 mol) of triethylamine. The solution is cooled in an ice bath before 4.0 mL (0.052 mol) of methanesulfonyl chloride (Note 11) is introduced. The mixture is stirred at 0°C for 1 hr, transferred to a separatory funnel, and washed with saturated sodium bicarbonate solution (2 x 150 mL) and brine (200 mL). The organic phase is dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to leave 14.3 of orange oil (Note 12).

The oil is immediately dissolved in 200 mL of dry benzene and transferred to a 500-mL, one-necked, round-bottomed flask to which is added 7.73 g (0.051 mol) of 1,8-diazabicyclo[5.4.0]undec-7-ene, DBU (Note 13). The flask is fitted with a condenser, heated at reflux for 8 hr, allowed to cool to room temperature, and washed with 200 mL of water and 200 mL of brine. The organic phase is dried over anhydrous magnesium sulfate, filtered, and evaporated to leave a dark brown oil. This material is chromatographed on silica gel (elution with 30% ethyl acetate in hexanes) (Notes 14 and 15) to give 7.02 g (79.9% for the two steps) as a very pale yellow oil.

E. N-Benzylazetidine-2,3-dione. N-Benzyl-3-(Z/E)-ethylideneazetidin-2-one (5.0 g, 26.7 mmol) is dissolved in 150 mL of methanol and 100 mL of water contained in a 500-mL, one-necked, round-bottomed flask. Sodium metaperiodate (14.3 g, 67.0 mmol) (Note 16) is introduced, followed by approximately 40 mg of osmium tetraoxide (Note 17). The reaction mixture is stirred vigorously for 12 hr under nitrogen, treated with Celite (6 g), and agitated for an additional hour prior to filtration. The filtrate is concentrated to 1/3 of its volume under reduced pressure, then extracted with ethyl acetate (2 x 200 mL). The combined organic phases are washed once with brine, dried, and concentrated to leave a dark brown oil. This oil is flushed through a short pad of silica gel (8 cm x 8 cm) using dichloromethane as eluant (900 mL). The pure fractions are pooled and evaporated to give a clear pale yellow oil, which crystallizes on prolonged standing at 5°C. The yield of N-benzylazetidine-2,3-dione is 3.12-3.64 g (66.7-77.9%) (Note 18).

2. Notes

1. Methyl acrylate, acetaldehyde, 1,4-diazabicyclo[2.2.2]octane, and benzyl-amine were purchased from the Aldrich Chemical Company, Inc. The first two reagents were distilled before use and the last two were used without further purification.

2. The product exhibits the following spectroscopic properties; IR (CHCl$_3$) cm^{-1}: 3500, 1720, 1635; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.33 (d, 3 H, J = 6.5), 2.80 (br s, 1 H), 3.74 (s, 3 H), 4.57 (q, 1 H, J = 6.5), 5.79 (s, 1 H), 6.16 (s, 1 H).

3. The progress of this reaction can be conveniently monitored by ^{1}H NMR spectroscopy. A small aliquot is evaporated to dryness and the disappearance of the vinyl protons at δ 5.79 and 6.16 (CDCl$_3$ solution) is followed.

4. The spectroscopic properties of this diastereomeric mixture are as follows: ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.14-1.20 (two sets of doublets, 3 H, J = 6.3), 2.43-2.49 (m, 2 H), 2.98-3.04 (m, 2 H), 3.66 (s, 3 H), 3.74 (s, 2 H), 4.15-4.19 (m, 1 H), 7.25 (m, 5 H).

5. Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl.

6. tert-Butyl chloride was purchased from J. T. Baker Inc. and distilled prior to use.

7. If unreacted magnesium remains at this time, more tert-butyl chloride is introduced in order to achieve complete conversion to the Grignard reagent.

8. It is essential to have good stirring during this step. If the reaction mixture becomes significantly turbid, a change to mechanical stirring is advisable.

9. This compound has the following properties: R$_f$ = 0.3 (5% ethanol in dichloromethane; IR (CHCl$_3$) cm^{-1}: 3500-3300, 1740; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.24 (d, 3 H, J = 6.3), 2.65 (br s, 1 H), 3.14-3.22 (m, 3 H), 4.17 (m, 1 H), 4.37 (m, 2 H), 7.22-7.36 (m, 5 H).

10. Dichloromethane was distilled from calcium hydride.

11. Methanesulfonyl chloride was obtained from the Mallinckrodt Company and distilled under reduced pressure before use.

12. This product is unstable and should be used without delay. It exhibits the following ^{1}H NMR spectrum: (80 MHz, CDCl$_3$) δ: 1.5 (m, 3 H), 3.0 (s, 3 H), 3.3 (m, 3 H), 4.4 (s, 2 H), 5.0 (m, 1 H), 7.3 (s, 5 H).

13. DBU (96%) was obtained from the Aldrich Chemical Company, Inc., and distilled under reduced pressure before use.

14. The Z- and E-isomers have quite different R$_f$ values in 3:1 hexane-ethyl acetate (0.25 and 0.10, respectively) and can easily be separated if desired. ^{1}H NMR for the Z-isomer (300 MHz, CDCl$_3$) δ is as follows: 2.03 (d, 3 H, J = 7.1), 3.52 (s, 2 H), 4.46 (s, 2 H), 5.58 (q, 1 H, J = 7.1), 7.53 (s, 5 H); for the E-isomer (300 MHz, CDCl$_3$) δ: 1.66 (d, 3 H, J = 7.0), 3.59 (s, 2 H), 4.45 (s, 2 H), 6.13 (q, 1 H, J = 7.0), 7.20-7.34 (m, 5 H).

15. The product can alternatively be purified by Kugelrohr distillation (165°C, 0.5-1.0 mm). However, the yield is significantly lower (52%).

16. Sodium metaperiodate was obtained from GFS Chemicals Inc., Columbus, OH.

17. Osmium tetraoxide was purchased from the Strem Chemicals Inc.

18. The spectral data are as follows: IR (CHCl$_3$) cm^{-1}: 1830, 1768; ^{1}H NMR (300 MHz, CD$_3$COCD$_3$) δ: 3.93 (s, 2 H), 4.79 (s, 2 H), 7.30-7.39 (m, 5 H); ^{13}C NMR (75 MHz, CD$_3$COCD$_3$) δ: 47.0, 59.9, 128.7, 129.1, 129.7, 135.8, 164.4, 195.6. The dione is stable for several weeks when kept in the dark at 5°C.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The previously reported preparations of N-benzyl-2,3-azetidinedione involve either high-pressure lactamization with carbon monoxide and lead(II) acetate, Pd(OAc)$_2$, in the presence of triphenylphosphine,[2] or construction of the β-lactam from an isoxazolidine precursor.[3] The present approach uses the readily available methyl

2-(benzylamino)methyl-3-hydroxybutanoate[4] to synthesize the lactam. Significantly, cyclization proceeds readily without prior protection of the hydroxyl group. Oxidative cleavage of the double bond in N-benzyl-3-ethylideneazetidin-2-one has previously been accomplished via ozonolysis.[3] However, this process results in concomitant competitive attack on the benzyl group when performed on a reasonable scale. The reaction mixture is very difficult to purify when this occurs. The osmium tetraoxide-mediated bond cleavage, on the other hand, is a clean reaction with an easy workup.

The method detailed here uses cheap starting materials and the sequence proceeds in high-yielding steps. Finally, it is noted that the title compound can exhibit high enol content depending on solvent.[2]

N-Benzyl-2,3-azetidinedione may be regarded as the most readily available of the unadorned α-keto-β-lactams. More complex analogs are of course known,[5] particularly derivatives of the penicillin[6] and cephalosporin antibiotics.[7] All members feature a high density of functionality in a small ring and consequently hold considerable synthetic potential. The transformations shown below have already been recorded.
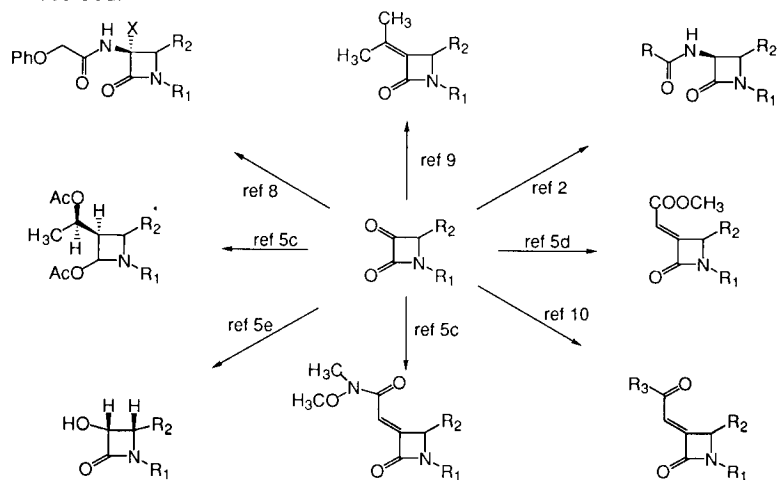
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

N-Benzyl-2,3-azetidinedione: 2,3-Azetidinedione, 1-(phenylmethyl)- (10); (75986-07-1)

Methyl 3-hydroxy-2-methylenebutanoate: Butyric acid, 3-hydroxy-2-methylene-, methyl ester (8): Butanoic acid, 3-hydroxy-2-methylene-, methyl ester (9); (18020-65-0)

Methyl acrylate: Acrylic acid, methyl ester (8); 2-Propenoic acid, methyl ester (9); (96-33-3)

Acetaldehyde (8,9); (75-07-0)

1,4-Diazabicyclo[2.2.2]octane [DABCO] (8,9); (280-57-9)

Benzylamine (8); Benzenemethanamine (9); (100-46-9)

Magnesium (8,9); (7439-95-4)

tert-Butyl chloride: Propane, 2-chloro-2-methyl- (8,9); (507-20-0)

N-Benzyl-3-(Z/E)-ethylideneazetidin-2-one: 2-Azetidinone, 3-ethylidene-1-(phenylmethyl)- (12); (115870-02-5)

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

Methanesulfonyl chloride (8,9); (124-63-0)

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)

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

Osmium tetroxide: Osmium oxide (8); Osmium oxide, (T-4)- (9); (20816-12-0)

Methyl 2-(benzylamino)methyl-3-hydroxybutanoate: Butanoic acid, 3-hydroxy-2-[[(phenylmethyl)amino]methyl]-, methyl ester (12); (R*,R*)- (118559-03-8); (R*,S*)- (118558-99-9)

N-Benzyl-3-(1-hyrdoxyethyl)azetidin-2-one: 2-Azetidinone, 3-(1-hydroxyethyl)-1-(phenylmethyl)-, (11); (R*,R*)- (89368-08-1); (R*,S*)- (89368-09-2)

SYNTHESIS OF β-LACTONES BY ALDOLIZATION OF KETONES WITH PHENYL ESTER ENOLATES:

3,3-DIMETHYL-1-OXASPIRO[3.5]NONAN-2-ONE

(1-Oxaspiro[3.5]nonan-2-one, 3,3-dimethyl-)
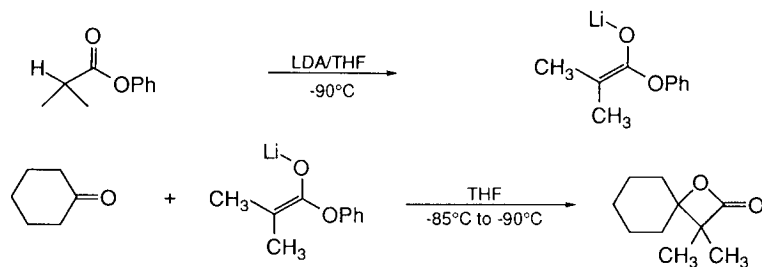
Submitted by Christine Wedler and Hans Schick.[1]
Checked by Rajib Pal, Peter Belica, and Steven Wolff.

1. Procedure

A 1-L, three-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirrer bar, a thermometer, an argon inlet/outlet adapter, and a 100-mL, pressure-equalizing dropping funnel with a cooling jacket (Note 1). The flask is charged with dry tetrahydrofuran (THF, 350 mL) (Note 2) and diisopropylamine (18.2 g, 25.3 mL, 0.180 mol) (Note 3). The mixture is cooled to -20°C in a bath filled with acetone and dry ice. At this temperature a 1.56 M solution of butyllithium in hexane (105.8 mL, 0.165 mol) is added dropwise over 5 min (Note 4). The mixture is allowed to warm up to room temperature within 15 min and is then cooled to -90°C in a bath charged with ethanol and liquid nitrogen (Note 5). A precooled solution of phenyl 2-methylpropanoate (27.09 g, 0.165 mol) in THF (50 mL) is added dropwise within 90 min from the dropping funnel (Notes 6 and 7), which is rinsed with THF (3 mL) (Note 8). During the addition the temperature in the reaction flask is maintained at -85°C to -90°C. The reaction mixture is stirred at this temperature for 20 min. Thereafter a precooled solution of cyclohexanone (14.72 g, 0.150 mol) (Note 9) in THF (50 mL) is added over a period of 60 min. After stirring for another 30 min at -90°C the mixture is allowed to warm up to ambient temperature. After standing overnight the reaction mixture is poured into a mixture of aqueous 1 N sodium hydroxide (200 mL) and diethyl ether (200 mL) and stirred for 10 min. The organic phase is separated and the aqueous phase is extracted with diethyl ether (2 x 100 mL). The combined organic phases are washed with 0.5 N aqueous sodium hydroxide (2 x 100 mL) and an aqueous saturated solution of sodium chloride (3 x 100 mL). Drying over anhydrous sodium sulfate, filtration, and removal of the solvent under reduced pressure in a rotary evaporator afford the crude β-lactone. After recrystallization from diethyl ether/hexane (Note 10) 3,3-dimethyl-1-oxaspiro[3.5]nonan-2-one is obtained in a yield of 91%. Other β-lactones have also been prepared by the submitters; these were not checked (Notes 11, 12).

2. Notes

1. The evacuated apparatus is dried with a flameless heat gun at 150°C and then flushed with dry argon. An atmosphere of dry argon is maintained during the course of the reaction. The jacket of the dropping funnel is charged with acetone and dry ice or with ethanol and liquid nitrogen.

2. Tetrahydrofuran dried over 4 Å molecular sieves was purchased from Fluka Chemical AG and purged with dry argon.

3. Diisopropylamine was purchased from Fluka Chemical AG. The product was distilled and stored over calcium hydride.

4. Butyllithium in hexane was purchased from E. Merck and titrated according to the method of Gilman.[2] The checkers used recently purchased material from Aldrich Chemical Company, Inc., without titration.

5. The checkers found that comparable yields could be obtained at -78°C. The submitters confirm this finding, but recommend the lower temperature especially when the β-lactone product is a liquid. Purification to remove small amounts of a β-keto ester by-product that forms at the higher temperature is more difficult with liquid products.

6. Phenyl 2-methylpropanoate was prepared by the following procedure:[3] A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer bar, thermometer, an argon inlet adapter, a reflux condenser, and a 100-mL pressure-equalizing dropping funnel is charged with toluene (350 mL), phenol (37.64 g, 0.400 mol), and concentrated sulfuric acid (0.5 mL). A solution of 2-methylpropanoyl chloride (42.62 g, 0.400 mol) in toluene (50 mL) is added dropwise at ambient temperature over a period of 45 min. The mixture is refluxed for 5 hr and then washed with an aqueous saturated sodium hydrogen carbonate solution (100 mL), an ice-cold 1 M aqueous sodium hydroxide solution (2 x 100 mL), and an aqueous saturated sodium chloride solution (75 mL). The organic phase is dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator to afford the crude ester as an oil. Fractionated distillation under reduced pressure affords phenyl 2-methylpropanoate (bp 89-91°C/13 mbar = 9.73 mm) in a yield of 90-95% with a purity of 98-99% (GLC).

7. The solution of phenyl 2-methylpropanoate in THF should be cooled in the dropping funnel to -70°C.

8. This portion of THF should be cooled to -70°C before adding it from the dropping funnel into the reaction flask.

9. Cyclohexanone was purchased from E. Merck and distilled prior to use.

10. Crude 3,3-dimethyl-1-oxaspiro[3.5]nonan-2-one was recrystallized from a mixture of diethyl ether (35 mL) and hexane (200 mL) to afford 20.60 g (82%) of colorless crystals, mp 110-112°C (the checkers obtained mp 100.5-103°C). The mother liquor is concentrated under reduced pressure and the residue is dissolved again in diethyl ether (4 mL) and hexane (20 mL) to afford another 2.27 g (9%) of colorless crystals, mp 100.5-103°C. If desired the procedure can be repeated again to provide another 0.45 g (1.8%) of colorless crystals. The compound exhibits the following analytical data: IR (CCl$_4$) cm^{-1}: 1820; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.31 (s, 6 H), 1.58-1.70 (m, 8 H), 1.94-1.97 (m, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 17.8, 22.4, 24.5, 32.0, 54.1, 84.9, 176.1. Anal. Calcd for C$_{10}$H$_{16}$O$_2$: Calcd. C, 71.39; H, 9.59. Found C, 71.53; H, 9.80.

11. Crude (±)-3-ethyl-1-oxaspiro[3.5]nonan-2-one, prepared from phenyl butanoate (27.09 g, 0.165 mol) and cyclohexanone (14.72 g, 0.150 mol), was purified by flash chromatography on silica gel (300 g, 230-400 mesh, E. Merck) using hexane/ethyl acetate (12:1, 2.6 L, 60 mL/min) as eluant. Fractions of 75 mL were taken. Fractions 10-21 afforded 23.97 g (95%) and fractions 22-25 afforded another 0.96 g (3.8%) of a colorless oil. The purity of these fractions determined by HPLC was 98 and 95%, respectively. The compound exhibits the following anlaytical data: IR (film) cm^{-1}: 1815; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.07 (t, 3 H, J = 7), 1.62-1.97 (m, 12 H), 2.97-3.03 (m, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 12.3, 17.5, 22.3, 23.0, 25.0, 31.2, 37.5, 59.9, 82.3, 172.4. Anal. Calcd for C$_{10}$H$_{16}$O$_2$: Calcd. C, 71.39; H, 9.59. Found C, 71.41; H, 9.81.

12. The crude 6:1 mixture of (3R*,4R*)- and (3R*,4S*)-4-isopropyl-4-methyl-3-octyl-2-oxetanone, prepared from phenyl decanoate (40.92 g, 0.165 mol) and 3-methylbutan-2-one (12.92 g, 0.150 mol), was purified by flash chromatography on silica gel (300 g, 230-400 mesh, E. Merck) using hexane/ethyl acetate (20:1, 2.6 L, 60 mL/min) as eluant. Fractions of 75 mL were taken. Fractions 8-22 afford 34.62 g

(96%) of a colorless oil. The purity of this fraction determined by HPLC was 97%. The compound exhibits the following analytical data: IR (film) cm^{-1}: 1815; ^{1}H NMR (300 MHz, CDCl$_3$), main diastereoisomer with (3R*,4R*)-configuration δ: 0.88 (t, 3 H, J = 7), 0.93 (d, 3 H, J = 7), 1.01 (d, 3 H, J = 7), 1.27-1.44 (m, 12 H), 1.36 (s, 3 H), 1.52-1.85 (m, 2 H), 1.99 (sept, 1 H, J = 7), 3.14 (t, 1 H, J = 8); minor diastereoisomer with (3R*,4S*)-configuration δ: 1.44 (s, 3 H), 2.16 (sept, 1 H, J = 7), additional signals are superimposed by signals of the main diastereoisomer; ^{13}C NMR (75 MHz, CDCl$_3$), main diastereoisomer with (3R*,4R*)-configuration δ: 14.1, 14.9, 16.6, 17.0, 22.7, 25.2, 27.6, 29.2, 29.3, 29.5, 31.9, 37.6, 56.3, 85.1, 171.9; minor diastereoisomer with (3R*,4S*)-configuration δ: 59.0, 84.8, 172.0 (additional signals are superimposed by signals of the main diastereoisomer). The configuration of the diastereoisomer was established by a NOESY experiment at 500 MHz. According to the integration of the septets at 1.99 and 2.16 ppm the ratio of the diastereoisomers was 6:1. Anal. Calcd for C$_{15}$H$_{28}$O$_2$: Calcd. C, 74.95; H, 11.74. Found C, 75.35; H, 11.94.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Decarboxylation of β-lactones to olefins,[4-6] stereoselective reactions of β-lactones with a variety of electrophiles,[6-9] and the regioselective fission of β-lactones by many different nucleophiles[10-12] make these highly reactive compounds versatile intermediates for organic syntheses.[13] Although several methods exist for the preparation of β-lactones, most β-lactones are now synthesized by [2+2] cycloaddition of carbonyl compounds to ketenes,[14] or by intramolecular cyclization of β-hydroxyalkanoic acids by means of benzenesulfonyl chloride in pyridine.[4]

The method described here belongs to a group of recently developed procedures comprising the spontaneous intramolecular acylation of active derivatives of metalated β-hydroxy alkanoates. These compounds are available by reactions of carbonyl compounds with ester enolates prepared from S-phenyl alkanethioates[6] or phenyl alkanoates,[15] as well as by Reformatsky[16] or Darzens[17] reactions of carbonyl compounds with phenyl α-halo alkanoates.

The method outlined here competes well with the method developed earlier by Danheiser, et al.[6,18] Its superiority is based on the fact that phenyl ester enolates give almost the same results as the S-phenyl thiolester enolates. However, handling the malodorous benzenethiol for the preparation of the active acid derivative and during workup of the β-lactone can be avoided. In addition, phenol is much cheaper than benzenethiol. The method is well suited for the preparation of β-lactones from symmetrical and unsymmetrical ketones. In addition to 3,3-dimethyl-1-oxaspiro[3.5]nonan-2-one, (±)-3-ethyl-1-oxaspiro[3.5]nonan-2-one and (3R*,4R*)- and (3R*,4S*)-4-isopropyl-4-methyl-3-octyl-2-oxetanone were prepared by this procedure in high yields (Notes 11 and 12). In the case of unsymmetrical ketones the less sterically crowded diasteroisomer is formed preferentially. With aldehydes as the carbonyl component the yields are unsatisfactory, because of the competitive formation of 1,3-dioxan-4-ones.[6]

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

3,3-Dimethyl-1-oxaspiro[3.5]nonan-2-one: 1-Oxaspiro[3.5]nonan-2-one, 3,3-dimethyl- (9); (22741-15-7)

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

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

Phenyl 2-methylpropanoate: Propanoic acid, 2-methyl-, phenyl ester (9); (20279-29-2)

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

Phenol: HIGHLY TOXIC (8,9); (108-95-2)

2-Methylpropanoyl chloride: Isobutyryl chloride (8); Propanyl chloride, 2-methyl- (9); (79-30-1)

EFFICIENT SYNTHESIS OF BROMIDES FROM CARBOXYLIC ACIDS
CONTAINING A SENSITIVE FUNCTIONAL GROUP:
DEC-9-ENYL BROMIDE FROM 10-UNDECENOIC ACID
(1-Decene, 10-bromo-)
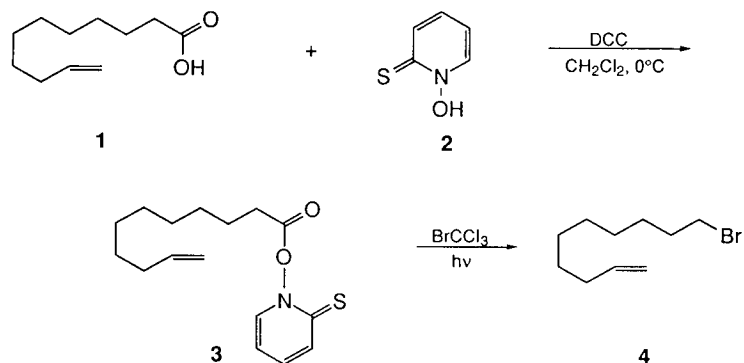
Submitted by Derek H. R. Barton,[1] John MacKinnon, Roland N. Perchet, and
Chi-Lam (Ivan) Tse.

Checked by Jessica E. Reed and Robert K. Boeckman, Jr.

1. Procedure

*Caution! Barton esters are light sensitive; therefore all procedures should be
carried out in the absence of light.*

N-(10-Undecenoyloxy)pyridine-2-thione (**3**). To an oven-dried, one-necked,
250-mL, round-bottomed flask equipped with a nitrogen inlet with gas bubbler, a
magnetic stirrer, and a dropping funnel are added 3.61 g (28.4 mmol) of N-
hydroxythiopyridone (**2**) (Note 1), 6.20 g (30.0 mmol) of dicyclohexylcarbodiimide

(Note 2), and 40 mL of methylene chloride (Note 3). The resulting homogeneous
solution is cooled to 0°C and 4.99 g (27.1 mmol) of 10-undecenoic acid (**1**) is added
dropwise (Note 4). Following the addition of the undecenoic acid, the ice bath is
removed and the reaction mixture is allowed to warm to room temperature and stirred
for a further 8 hr. The bright yellow suspension that results is filtered through a bed of
silica gel (Note 5). The solvent is removed under reduced pressure to give 8.06 g of
the crude Barton ester (**3**) (Notes 6 and 7).

Dec-9-enyl bromide (**4**). To an oven-dried, one-necked, 250-mL, round-
bottomed flask equipped with a nitrogen inlet with gas bubbler, magnetic stirrer and a
condenser are added 8.06 g (27.1 mmol) of the Barton ester (**3**), 100 mL of methylene
chloride (Note 3), and 3 mL (30.0 mmol) of bromotrichloromethane (Note 8). The
reaction mixture is photolyzed with a 250W tungsten lamp under reflux for 30 min
(Note 9). The color of the reaction mixture changes from bright yellow to pale yellow.
The reaction mixture is cooled to room temperature and the solvent is removed under
reduced pressure. The crude product is purified by flash column chromatography
(hexanes) until all the bromide **4** (Note 10) is eluted, affording 5.81 g of dec-9-enyl
bromide (98%) (Note 11).

2. Notes

1. N-Hydroxythiopyridone is purchased from the Olin Corp. as an aqueous
40% solution of sodium 2-pyridinethiol-1-oxide (sodium omadine). Sodium omadine
(1 L) is diluted with water (H_2O, 600 mL) and the solution cooled to 0°C. Hydrochloric
acid (350 mL) is added dropwise over a 20-min interval with continuous stirring and
cooling for a further 20 min. The resulting suspension containing N-hydroxythio-
pyridone is filtered and the solid is washed with H_2O (2 L). The N-hydroxythiopyridone
is dried over sodium hydroxide or potassium hydroxide under reduced pressure and

recrystallized from ethanol (250-300 mL). The product is finally dried over phosphorus pentoxide and stored at all times in a refrigerator. The checkers employed N-hydroxythiopyridone obtained from Aldrich Chemical Company, Inc.

2. Dicyclohexylcarbodiimide was purchased from the Aldrich Chemical Company, Inc., and used directly.

3. Dichloromethane is distilled from calcium hydride under argon immediately prior to use.

4. 10-Undecenoic acid was purchased from the Aldrich Chemical Company, Inc., and used after distillation under reduced pressure (bp 87°C / 2 mm Hg).

5. Using a medium size filter funnel, add enough silica gel to the depth of about 1.5" covered with sand. Prewash the silica gel with methylene chloride (CH_2Cl_2) under suction, discarding the filtrate. Add the reaction mixture and flush with CH_2Cl_2. Dicyclohexylurea remains at the top of the silica gel bed.

6. Spectral data for **3** are as follows: ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.22-1.45 (m, 10 H), 1.75-1.85 (m, 2 H), 1.99-2.06 (ddd, 2 H, J = 7.2, 6.9, 6.6), 2.70 (t, 2 H, J = 7.5) 4.89-5.02 (m, 2 H), 5.75-5.84 (m, 1 H), 6.62 (ddd, 1 H, J = 7.0, 6.5, 1.6), 7.19 (ddd, 1 H, J = 8.8, 7.0, 1.3), 7.53 (dd, 1 H, J = 6.5, 1.3), 7.68 (dd, 1 H, J = 8.8, 1.6); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 24.21, 28.78, 28.86, 28.93, 28.99, 29.13, 31.50, 33.68, 112.46, 114.10, 133.42, 137.36, 137.57, 139.07, 168.99, 175.86; IR (film) cm^{-1}: 3074, 1807, 1639, 1608, 1525, 1447, 1410, 1283.

7. The purity is estimated to be 98% by NMR. Crude material is obtained with a mass balance in excess of theoretical. Minor impurities can be detected by ^{13}C NMR having signals at δ: 24.61, 25.36, and 34.84 which may be due to the presence of a small amount of internal olefin in the 10-undecenoic acid.

8. Bromotrichloromethane was purchased from Aldrich Chemical Company, Inc., and used as received.

9. The 250W tungsten lamp generates a sufficient amount of heat to reflux the solution. The submitters used a 300W lamp. No other external source is required. The checkers observed the reaction to be complete in less than 30 min, although irradiation was carried out for the specified amount of time.

10. Spectral data for **4** are as follows: ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.32-1.46 (m, 10 H), 1.82-1.91 (m, 2 H), 1.96-2.09 (m, 2 H), 3.41 (t, 2 H, J = 6.8), 4.93-5.04 (m, 2 H), 5.81 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 28.15, 28.71, 28.86, 28.99, 29.27, 32.82, 33.75, 33.82, 114.16, 138.99; IR (film) cm^{-1}: 3075, 1640, 1463, 1438, 993, 791. The purity is estimated to be >98% by NMR.

11. This procedure is also suitable for large scale preparation.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described here allows for a convenient and efficient preparation in very high yields of large quantities of bromides from carboxylic acids containing an olefinic functionality. The Hunsdiecker reaction is traditionally accomplished by treating anhydrous silver carboxylates with bromine or iodine.[2] Heavy metal salts such as mercury,[3] lead,[4] and thallium[5] have also been used successfully as well as tert-butyl hypoiodite.[6] The major disadvantages associated with the above methods, such as use of heavy metal salts and non-tolerance towards olefins, has led to the development of a more versatile method using O-acyl thiohydroxamates.[7,8] The O-

acyl thiohydroxamates are neither strongly oxidizing nor strongly electrophilic species and have therefore a greater potential within organic synthesis.

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Appendix

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

Dec-9-enyl bromide: 1-Decene, 10-bromo- (10); (62871-09-4)

Undecenoic acid: 10-Undecenoic acid (8,9); (112-38-9)

N-(10-Undecenoyloxy)pyridine-2-thione: 2(1H)-Pyridinethione, 1-[(1-oxo-10-undecenyl)oxy]- (12); (114050-28-1)

N-Hydroxythiopyridone: 2(1H)-Pyridinethione, 1-hydroxy- (8,9); (1121-30-8)

Dicyclohexylcarbodiimide: HIGHLY TOXIC. Carbodiimide, dicyclohexyl- (8); Cyclohexanamine, N,N'-methanetetraylbis- (9); (538-75-0)

Bromotrichloromethane: Methane, bromotrichloro (8,9); (75-62-7)

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

(2(3H)-Furanone, 5-(2-bromo-2-propenyl)dihydro-5-methyl-)
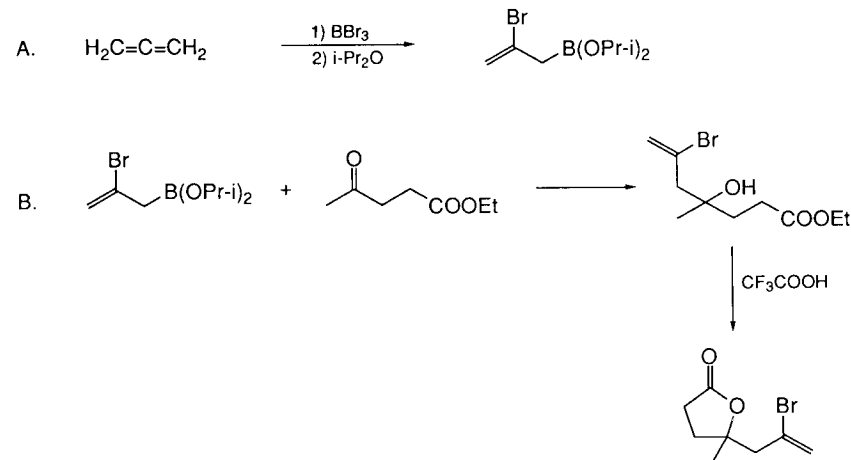
Submitted by Shoji Hara[1] and Akira Suzuki.[2]

Checked by Sherry R. Chemler and William R. Roush.

1. Procedure

Caution! Boron tribromide is moisture sensitive and decomposes in air with the evolution of hydrogen bromide. It should be used in an efficient hood.

A. *(2-Bromoallyl)diisopropoxyborane.* A flame-dried, 200-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, rubber septum, 125-mL

dropping funnel, and an Allihn-type condenser. To the top of the condenser, a 3-L bag (Note 1), water aspirator through a calcium chloride tube, and allene gas cylinder (Note 2) are connected with two three-way stopcocks as shown in Figure 1. The flask and the bag are evacuated twice using a water aspirator, and filled with allene gas each time (Note 3). The stopcock between the bag and the reaction flask is closed off (Note 4), and the flask is cooled to -20°C in a cooling bath made of dry ice and a 9 : 1 mixture of ethylene glycol and acetone. Boron tribromide, BBr_3 (25 g, 9.4 mL, 100 mmol) is introduced through the rubber septum via cannula (Note 5). The stopcock separating the bag from the reaction vessel is then opened. Gas absorption starts immediately and is complete within 10 min to give a dark red solution. When the allene is completely consumed, the gas cylinder is replaced by a nitrogen inlet tube and nitrogen is introduced into the flask. The mixture is stirred at -20°C for 30 min and then 30 mL of dry dichloromethane (Note 6) is added. Next, 33 mL (0.23 mol) of diisopropyl ether (Note 7) in 50 mL of dry dichloromethane is introduced from the dropping funnel over 1 hr (exothermic!). The mixture is stirred at -20°C for 30 min, then at room temperature for 2 hr, and finally under reflux for 1 hr. The mixture is cooled to room temperature and all volatile components are removed under reduced pressure using a water aspirator (Note 8). The vessel is filled with nitrogen, and the residue is transferred to a distillation flask via a cannula using nitrogen. Distillation of the residue under reduced pressure gives 16.4-17.1 g (66-69%) of (2-bromoallyl)diisopropoxy-borane as a clear liquid, bp 39-43°C (0.4 mm) (Notes 9-12).

B. *4-(2-Bromo-2-propenyl)-4-methyl-γ-butyrolactone.* A flame-dried, 200-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, rubber septum, nitrogen inlet adapter, and a 100-mL dropping funnel. The flask is purged with nitrogen and charged with (2-bromoallyl)diisopropoxyborane (16.2 g, 0.065 mol), prepared above, in 50 mL of dry tetrahydrofuran (Note 13). The flask is cooled in an ice bath, and ethyl levulinate (9.96 g, 0.069 mol) (Note 7) in 30 mL of dry

tetrahydrofuran is added dropwise over 1 hr from the dropping funnel. After the mixture is stirred at 0°C for 1 hr and then at room temperature overnight, it is poured into 50 mL of water and extracted three times with 50-mL portions of ether. The combined organic layers are dried over magnesium sulfate and concentrated using a rotary evaporator. The residue is diluted with 50 mL of dry dichloromethane, and 1 mL of trifluoroacetic acid (Note 7) is added. After the mixture is stirred at room temperature overnight, it is poured into water (50 mL) and the organic layer is separated. The aqueous layer is extracted twice with 100-mL portions of ether. The combined organic extracts are washed with 50 mL of saturated sodium bicarbonate and 50 mL of water, dried over magnesium sulfate, and concentrated using a rotary evaporator. The residue is distilled through a 15-cm Vigreux column under reduced pressure to give 9.22 g (65%) of 4-(2-bromo-2-propenyl)-4-methyl-γ-butyrolactone, bp 88-90°C (0.6 mm) (Notes 14, 15), plus 1.9 g of recovered ethyl levulinate, bp 48°C (0.6 mm), and a mixed fraction (0.8 g) containing ethyl levulinate and the product.

2. Notes

1. A Tedlar bag, made of polyvinyl fluoride, was used. These bags were purchased from SKC, Inc. (US).

2. Cylinders of allene were purchased from PCR (Japan) or Matheson Gas Products (US).

3. This step is very important. If all the air is not replaced by allene, the reaction with BBr_3 sometimes does not go to completion.

4. Allene must not be allowed to condense in the reaction vessel prior to the introduction of the BBr_3. Boron tribromide reacts rapidly and exothermically with liquid allene to give a black mixture that yields very little of the desired product. In one experiment in which the connection between the Tedlar bag and the reaction vessel

was not closed while the vessel was cooled to -20°C, the yield of (2-bromoallyl)-diisopropoxyborane was 9%.

5. BBr$_3$ (≥99.99% purity) was purchased in glass ampoules from Wako Pure Chemical Industries, Ltd., or Aldrich Chemical Company, Inc. The submitters transferred the reagent into a storage vessel equipped with septum inlets before use, as follows. The ampoule stem was scored with a file and broken off in a nitrogen-filled glove bag. A septum was then placed over the opening. While BBr$_3$ can be transferred by syringe, it is advisable to use a cannula to avoid problems with the plunger freezing. The beveled point of a 2-mm Teflon tube obtained from Nippon Rikagaku Kikai Co., Ltd. was inserted through the pre-punctured septum on the ampoule leaving the tip above the liquid level. The other end of the tube was inserted through a septum on the storage vessel that was vented through a bubbler. The tube was placed below the liquid level in the ampoule, and the BBr$_3$ was transferred into the storage vessel by applying a positive nitrogen pressure through a hypodermic needle. When all the liquid had been transferred, the Teflon tube and the bubbler vent were withdrawn from the ampoule and inserted into the measuring vessel. Graduated cylinders or centrifuge tubes with standard taper joints are excellent measuring vessels when fitted with a two-inlet adapter obtained from Aldrich Chemical Company, Inc. In the same way, the required amount of BBr$_3$ was transferred from the storage vessel to the measuring vessel, and then from the measuring vessel to the reaction flask. The submitters recommend that if the BBr$_3$ is not from a freshly opened ampoule, it should be distilled under nitrogen before use.[3] The checkers purchased 25-g lots of BBr$_3$ and used the entire ampoule in each run, thereby avoiding the need to store and redistill any excess, unused reagent. The checkers transferred the BBr$_3$ in a dry box under an atmosphere of dry nitrogen into a glass vessel, and then into the reaction vessel via cannula as specified by the submitters.

6. Dichloromethane was distilled from calcium hydride and stored over 4 Å molecular sieves.

7. Ethyl levulinate, diisopropyl ether, and trifluoroacetic acid were purchased from Wako Pure Chemical Industries, Ltd., or Aldrich Chemical Company, Inc., and distilled before use. The checkers distilled diisopropyl ether from calcium hydride.

8. A -78°C trap to collect all volatile materials should be placed between the aspirator and the reaction vessel during this evaporative distillation.

9. The submitters obtained 18.4 g of product (70%) starting from 26.5 g (10 mL, 106 mmol) of BBr$_3$.

10. As (2-bromoallyl)diisopropoxyborane is thermally labile, the distillation should be carried out below 100°C. It is not very sensitive to air but decomposes slowly. It is recommended that it be handled under an inert atmosphere and stored in a refrigerator. The spectral properties are as follows: ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 1.16 (d, 12 H, J = 6.0), 2.25 (br s, 2 H), 4.42 (septet, 2 H, J = 6.0), 5.31 (d, 1 H, J = 0.6), 5.48 (d, 1 H, J = 1.3); ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 24.4, 28-32 (br), 65.7, 116.3, 131.3; ^{11}B NMR (CDCl$_3$, 128 MHz) δ: 28.04; HRMS for C$_9$H$_{19}$BBrO$_2$ (M$^+$ + 1) calcd 249.0661, found 249.0667.

11. The checkers determined the purity of the reagent to be ca. 94% by manual integration (cut and weigh) of the three [11]B resonances observed in the sample: δ 17.42 (4.3 %), δ 28.04 (94.3 %) and δ 47.49 (1.4 %) respectively

12. The checkers found that the ^{1}H NMR spectrum of (2-bromoallyl)-diisopropoxyborane is concentration dependent. When the NMR spectrum was measured at a concentration of 20 μL of product in ca. 0.5 mL of CDCl$_3$, (2-bromo-allyl)diisopropoxyborane was observed along with a substantial amount of a second material that had ^{1}H resonances for the vinylic and allylic protons that were very similar in chemical shift to the vinylic and allylic resonances of the desired product. However, when the ^{1}H NMR spectrum of a much more concentrated solution (ca. 250

μL in 0.250 mL of CDCl₃) was measured, the resonances of the contaminant were barely apparent. The origin of this phenomenon has not been conclusively determined.

13. Tetrahydrofuran was distilled from benzophenone ketyl under nitrogen just before use.

14. The submitters obtained 11.6 g (72%) of product starting from 18.4 g of (2-bromoallyl)diisopropoxyborane and 10.7 g of ethyl levulinate. The checkers obtained yields of 65-69% in runs on several different scales.

15. The product contained traces of ethyl levulinate and was redistilled to give an analytical sample: ^{1}H NMR (CDCl₃, 400 MHz) δ: 1.47 (s, 3 H), 2.02-2.07 (m, 1 H), 2.09-2.48 (m, 1 H), 2.61 (d, 1 H, J = 8.5), 2.63 (dd, 1H, J = 7.6, J = 1.6), 2.85 (AB q, 2 H, J_{AB} = 15.0, Δυ = 16.0), 5.65 (d, 1 H, J = 1.9), 5.74 (t, 1 H, J = 0.9); ^{13}C NMR (CDCl₃, 100 MHz) δ: 26.3, 29.1, 32.4, 51.1, 85.1, 122.7, 125.9, 176.1; IR (neat) cm^{-1}: 1780 (C=O), 1635 (C=C); HRMS for $C_8H_{15}O_2NBr$ (M + NH₄⁺) calcd 236.0286, found 236.0287. Anal. Calcd. for $C_8H_{11}O_2Br$: C, 43.86; H, 5.06. Found: C, 43.57; H, 4.97.

3. Discussion

The haloboration reaction of 1-alkynes proceeds stereo- and regioselectively to give 2-halo-1-alkenylboranes that can be used for the stereoselective synthesis of haloalkenes and di- or trisubstituted alkenes.[4] Although isolated double bonds do not undergo the haloboration reaction with haloboranes,[5] allene[5] and conjugated dienes[6] give the 1 : 1 adducts. The bromoboration reaction of allene with tribromoborane proceeds very rapidly, but the resulting (2-bromoallyl)dibromoborane is difficult to isolate, because it readily polymerizes during distillation. On the other hand, this intermediate can be converted into dialkoxyborane derivatives by the reaction with ethers such as diisopropyl ether or anisole; the resulting (2-bromoallyl)-

dialkoxyboranes are stable and readily isolated by distillation. Alcohols have also been used for the conversion of bromoboranes to the corresponding alkoxyboranes.[7] However, the reaction with ethers is preferred because evolution of hydrogen bromide is avoided. This method is especially effective when the product is sensitive to acids, as in the case reported here. Diisopropoxyborane derivatives have the same reactivity as that of the diphenoxyborane derivatives described in a previous paper;[8] however, diisopropoxyborane derivatives are easier to isolate because of their lower boiling points. As described here, (2-bromoallyl)diisopropoxyborane can be prepared by the bromoboration reaction of allene with tribromoborane, followed by addition of isopropyl ether. Isopropyl bromide thus generated does not cause any problems and can be removed readily.

(2-Bromoallyl)diisopropoxyborane reacts with aldehydes and ketones under mild conditions to give the corresponding 2-bromohomoallylic alcohols in good yields. The resulting 2-bromohomoallylic alcohols are useful intermediates for the synthesis of α-methylene-γ-lactones.[9] 2-Bromohomoallylic alcohols have also been prepared from carbonyl compounds via reaction with 2,3-dibromo-1-propene in the presence of tin,[10] and the reaction with 2-bromo-3-(trimethylsilyl)propene in the presence of a Lewis acid.[11] However, (2-bromoallyl)diisopropoxyborane reacts with carbonyl compounds under very mild conditions, even at -78°C in some cases, and the reaction proceeds smoothly without the addition of any other reagents such as metals or Lewis acids. The ketone functional group of ethyl levulinate reacts selectively with (2-bromoallyl)diisopropoxyborane to give the hydroxy ester that partially cyclizes to the lactone under the reaction conditions. The hydroxy ester is completely converted into the lactone by treatment with trifluoroacetic acid.

Although (2-bromoallyl)diisopropoxyborane can be stored under nitrogen in a refrigerator for a few months, it is recommended that the reagent be redistilled if stored for a longer time.

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

4-(2-Bromo-2-propenyl)-4-methyl-γ-butyrolactone: 2(3H)-Furanone, 5-(2-bromo-2-propenyl)dihydro-5-methyl- (13); (138416-14-5)

Ethyl levulinate: Levulinic acid, ethyl ester (8); Pentanoic acid, 4-oxo-, ethyl ester (9); (539-88-8)

Allene (8); 1,2-Propadiene (9); (463-49-0)

Boron tribromide: Boron bromide (8); Borane, tribromo- (9); (10294-33-4)

Trifluoroacetic acid: Acetic acid, trifluoro- (8,9); (76-05-1)

Figure 1
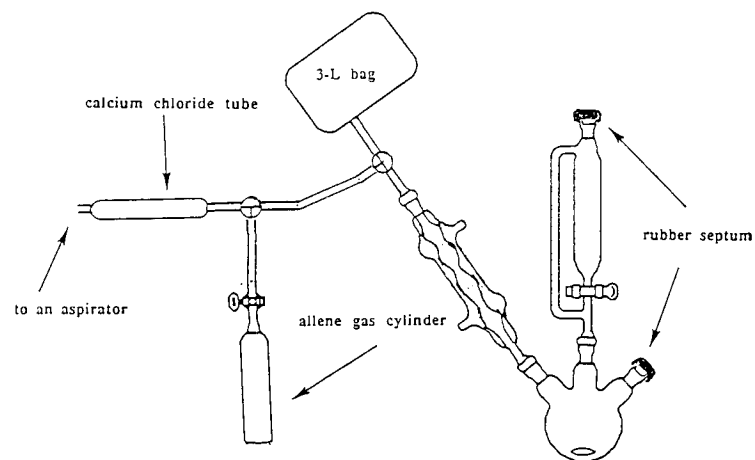
PHOTOINDUCED-ADDITION OF METHANOL TO (5S)-(5-O-tert-BUTYLDIMETHYLSILOXYMETHYL)FURAN-2(5H)-ONE: (4R,5S)-4-HYDROXYMETHYL-(5-O-tert-BUTYLDIMETHYLSILOXYMETHYL)FURAN-2(5H)-ONE

(2(5H)-Furanone, 5-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-, (S)- and D-erythro-Pentonic acid, 2,3-dideoxy-5-O-[(1,1-dimethylethyl)dimethylsilyl]-3-(hydroxymethyl)-, γ-lactone)

R = TBDMS
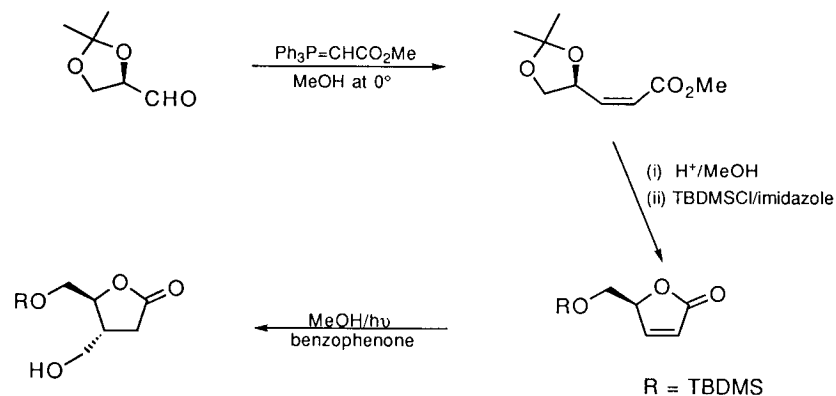
Submitted by John Mann and Alexander C. Weymouth-Wilson.[1]

Checked by Robert E. Koehler, Steven Wolff, and David L. Coffen.

1. Procedure

(5S)-(5-O-tert-Butyldimethylsiloxymethyl)furan-2(5H)-one (Note 1). An oven-dried, 500-mL, round-bottomed flask is charged with 35.5 g (0.27 mol) of 2,3-O-isopropylidene-D-glyceraldehyde (Note 2) and 250 mL of methanol. The flask is cooled in an ice bath during the portionwise addition of 96 g (0.28 mol) of methyl

(triphenylphosphoranylidene)acetate (Note 3), and the resultant mixture is stirred for 1 hr at 0°C. The solvent is removed on a rotary evaporator and the residue is refluxed for 30 min with a mixture of ether:petroleum ether (3:7, 100 mL). The process is repeated three times, the combined extracts are filtered, and the filtrate is concentrated to yield a colorless oil. The oil is purified by silica chromatography [1 kg of silica, 8.5-cm x 43-cm column eluting with ethyl acetate:petroleum ether (3:7)] to yield 39.5 g (78%) of methyl (4S)-4,5-O-isopropylidenepent-(2Z)-enoate, and 4.8 g (10%) of the corresponding trans-isomer, both as colorless oils (Notes 4, 5).

A solution of 39.0 g (0.21 mol) of the cis-alkene in 100 mL of methanol is treated with concd sulfuric acid (ca. 0.8 mL of 30%), and the mixture is stirred for 2 hr at room temperature. Evaporation of the solvent and purification of the residue by silica chromatography (1 kg of silica, 8.5-cm x 43-cm column with ethyl acetate as eluant) yield 22.3 g (93%) of (S)-5-hydroxymethylfuran-2(5H)-one as a white crystalline solid, mp 40-41°C and $[\alpha]_D^{20}$ -150.8° (water, c 2.1) (Note 6).

A solution of 22.0 g of the alcohol (0.19 mol) and 17.6 g (0.26 mol) of imidazole in dichloromethane (Note 7) (100 mL) is cooled in an ice bath, and 36.2 g (0.24 mol) of tert-butyldimethylsilyl chloride (Note 8) is added in one portion. The mixture is stirred for 15 min at 0°C and for a further 20 min at room temperature. Water (200 mL) is then added, and the organic layer is separated. The aqueous layer is extracted with dichloromethane (3 x 50 mL), and the combined organic extracts are dried over sodium sulfate prior to evaporation of the solvent. Purification of the residue by silica chromatography [1 kg of silica, 8.5-cm x 43-cm column eluting with ethyl acetate:petroleum ether (3:7)] yields 45 g (ca. ~ 100%) of (5S)-(5-O-tert-butyldimethyl-siloxymethyl)furan-2(5H)-one as a colorless solid, mp 31°C and $[\alpha]_D^{20}$ -146° (in chloroform, c 0.2) (Note 9).

(4R,5S)-4-Hydroxymethyl-(5-O-tert-butyldimethylsiloxymethyl)furan-2(5H)-one.
A 1-L Pyrex vessel is charged with 29.5 g (0.13 mol) of (5S)-(5-O-tert-butyldimethylsiloxymethyl)furan-2(5H)-one, 23.7 g (0.13 mol) of benzophenone (Note 10) and 800 mL of methanol. The vessel is placed in a water-cooled, immersion-irradiation apparatus (Note 11), and the solution is degassed for 1 hr in a stream of nitrogen. It is then irradiated using two 125-watt, 350-nm lamps; the reaction is complete after 48 hr (Note 12). The solvent is evaporated and the residue is purified by silica chromatography [1 kg of silica, 8.5-cm x 43-cm column with a gradient elution from ethyl acetate:petroleum ether (1:1) to neat ethyl acetate]. This yields 18.5 g (55%) of the title compound, 18.3 g (77%) of recovered benzophenone, 3.6 g of benzpinacol, and 1.56 g (3%) of the photoadduct (4R,5S)-4-diphenylhydroxymethyl-5-tert-butyldimethylsiloxymethylfuran-2(5H)-one. The title photoadduct is an oil with $[\alpha]_D^{20}$ +3.2° (in chloroform, c 2.0) (Note 13).

2. Notes

1. (5S)-(5-O-tert-Butyldimethylsiloxymethyl)furan-2(5H)-one has been prepared by a number of groups.[2] They report mp of 31-32°C and 31°C, and $[\alpha]_D^{20}$ of -141° and -139°.

2. 2,3-O-Isopropylidene-D-glyceraldehyde was prepared as described in *Org. Synth.* **1995**, *72*, 6.

3. This compound was purchased from Aldrich Chemical Company, Inc.

4. The submitters report that they currently use two 500-g columns run consecutively. After the first column is used, it is washed with methanol, all traces of solvent flushed through with compressed air, reequilibrated with eluant, then those fractions (from the first column) that contain a mixture of cis- and trans-alkenes are rechromatographed.

5. The cis-alkene has the following spectral features: IR (thin film) cm^{-1}: 1725, 1650, 1210, 1065; ^{1}H NMR (220 MHz, CDCl$_3$) δ: 1.40 and 1.46 (2 s, 6 H, 2 x Me), 3.65 (dd, 1 H, J$_{gem}$ 8.5, J$_{4,5}$ 7, 5-H), 3.75 (s, 3 H, OMe), 4.40 (dd, 1 H, J$_{4,5}$ 7, 5-H), 5.52 (m, 1 H, 4-H), 5.88 (dd, 1 H, J$_{2,3}$ 11.5, J$_{2,4}$ 1.5, 2-H), 6.39 (dd, 1 H, J$_{2,3}$ 11.5, J$_{3,4}$ 6.5, 3-H).

6. (S)-5-Hydroxymethylfuran-2(5H)-one has the following spectral data: IR (KBr disc) cm^{-1}: 3420, 1790, 1605, 1170, 1115, 1080, 1060, 865; ^{1}H NMR (200 MHz, CDCl$_3$) δ: 3.70-4.06 (m, 3 H, 5-H and OH), 5.19 (m, 1 H, 4-H), 6.20 (dd, 1 H, J$_{2,3}$ 5.5, J$_{2,4}$ 2, 2-H), 7.56 (dd, 1 H, J$_{2,3}$ 5.5, J$_{3,4}$ 1.5, 3-H). This compound is available from Aldrich Chemical Company, Inc., and has been prepared by a number of other groups.^{3} They report mp ranging from 39° to 42°C, and [α]$_D^{20}$ values from -140° to -154.5°.

7. Dichloromethane was dried over phosphorus pentoxide.

8. tert-Butyldimethylsilyl chloride was purchased from Aldrich Chemical Company, Inc.

9. Spectral data for the silyl ether are as follows: IR (nujol mull) cm^{-1}: 1747, 1605, 1473, 1331, 1135, 1016, 888; ^{1}H NMR (250 MHz, CDCl$_3$) δ: 0.02 (s, 3 H, Me), 0.03 (s, 3 H, Me), 0.83 (s, 9 H, tert-Bu), 3.76 (dd, 1 H, J$_{gem}$ 10.8, J$_{4,5}$ 5, 5-H), 3.86 (dd, 1 H, J$_{4,5}$ 5-H), 5.04 (m, 1 H, 4-H), 6.11 (dd, 1 H, J$_{2,3}$ 5.7 J$_{2,4}$ 1.95, 2-H), 7.49 (dd, 1 H, J$_{2,3}$ 5.7, J$_{3,4}$ 1.4, 3-H).

10. Use of less than one equivalent of benzophenone increases the photolysis time.

11. The checkers employed a Hanovia 450W medium-pressure mercury arc lamp with an uranium glass filter, a Pyrex immersion well, and a 1-L irradiation vessel (all available from Ace Glass).

12. Use of larger wattage lamps decreases the photolysis time.

13. Spectral data for the photoadduct are as follows: IR cm^{-1}: 3430, 1760, 1470, 1410, 1380, 1258, 1121, 1020, 940, 875, 838, 778; ^{1}H NMR (400 MHz, CDCl$_3$)

δ: 0.04 (s, 3 H, Me), 0.05 (s, 3 H, Me), 0.86 (s, 9 H, tert-Bu), 2.29 (dd, 1 H, J$_{gem}$ 17, J$_{3,4}$ 4.6, 3-H), 2.63 (m, 2 H, 4-H and OH), 2.69 (dd, 1 H, J$_{3,4}$ 9.4, 3-H), 3.60 (dd, 1 H, J$_{gem}$ 10.5, J$_{4,7}$ 6.6, 7-H), 3.66 (dd, 1 H, J$_{4,7}$ 5.2, 7-H), 3.72 (dd, 1 H, J$_{gem}$ 11.2, J$_{5,6}$ 2.9, 6-H), 3.83 (dd, 1 H, J$_{5,6}$ 3.7, 6-H), 4.39 (dt, 1 H, J$_{5,6}$ 3.7, J$_{4,5}$ 3.2, 5-H).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The photoinduced-addition of alcohols to cycloalkenones has been investigated by Fraser-Reid and co-workers,[4] by Paquette,[5] and was used as the key step in the synthesis of the prostaglandin endoperoxide analogue (15S)-hydroxy-9α,11α–epoxymethanoprosta-(5Z,13E)-dienoic acid,[6] and for the recent synthesis of 2',3'-dideoxy-3'-hydroxymethyl-5'-carbanucleosides.[7] No work (other than our own) has been reported on the photoinduced-addition of alcohols to 5-substituted furan-2(5H)-ones.

The reaction appears to be general and the additions are regiospecific and stereoselective. The product from the reaction with 2-propanol has been used for the synthesis of cis-chrysanthemic acid,[8] and the product with methanol has been used for the construction of novel 2',3'-dideoxy-3'-hydroxymethylnucleosides.[9] In addition, ethane-1,2-diol provides the expected photoadduct as a 1:1 mixture of the two possible diastereoisomers, and these can be easily separated as their acetonides, to provide compounds with three contiguous chiral centers emanating from furan-ones with only one chiral center.[9] More recently, we have shown that photoinduced-

additions also occur with cyclic amines[10] and these reactions provide access to the skeletons of the pyrrolizidine and indolizidine alkaloids in a concise and stereochemically efficient fashion.

These photoinduced reactions proceed in fair to good yields (50-80%) and tolerate a variety of protecting groups at C-6, e.g., acetate, benzoate, methyl, and benzyl.

1. Department of Chemistry, University of Reading, Whiteknights, P.O. Box 224, Reading, RG6 6AD, England.

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

(5S)-(5-O-tert-Butyldimethylsiloxymethyl)furan-2(5H)-one: 2(5H)-Furanone, 5-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-, (S)- (11); (105122-15-4)

(4R,5S)-4-Hydroxymethyl-(5-O-tert-butyldimethylsiloxymethyl)furan-2(5H)-one: D-erythro-Pentonic acid, 2,3-dideoxy-5-O-[(1,1-dimethylethyl)dimethylsilyl]-3-hydroxymethyl-, γ-lactone (13); (164848-06-0)

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

Methyl (triphenylphosphoranylidene)acetate: Acetic acid, (triphenylphosphoranylidene), methyl ester (8); Propanoic acid, 2-(triphenylphosphoranylidene)-, methyl ester (9); (2605-67-6)

Methyl (4S)-4,5-O-isopropylidenepent-(2Z)-enoate: 2-Propenoic acid, 3-(2,2-dimethyl-1,3-dioxolan-4-yl)-, methyl ester, [S-(Z)]- (11); (81703-94-8)

(S)-5-Hydroxymethylfuran-2(5H)-one: 2(5H)-Furanone, 5-(hydroxymethyl)-, (S)- (10); (78508-96-0)

tert-Butyldimethylsilyl chloride: Silane, chloro(1,1-dimethylethyl)dimethyl- (9); (18162-48-6)

Benzophenone (8); Methanone, diphenyl- (9); (119-61-9)

PREPARATION OF CYANOALKYNES: 3-PHENYL-2-PROPYNENITRILE

(2-Propynenitrile, 3-phenyl-)
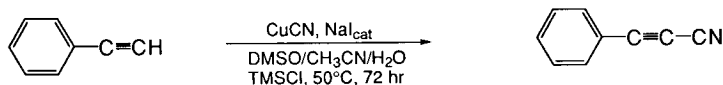
Submitted by Fen-Tair Luo, May-Wen Wang, and Ren-Tzong Wang.[1]

Checked by Christopher S. Brook, Wenqing Yao, and Amos B. Smith, III.

1. Procedure

3-Phenyl-2-propynenitrile. A 1-L, two-necked flask, fitted with a 100-mL addition funnel, 2-cm stir bar, and a thermometer, is charged with dimethyl sulfoxide (DMSO) (240 mL), acetonitrile (CH_3CN) (80 mL), and water (4.3 mL, Note 1). To this rapidly stirring solution (Note 2) is added cuprous cyanide (CuCN) (43.0 g, 0.48 mol, Note 3), sodium iodide (2.4 g, 0.016 mol), and phenylacetylene (17.6 mL, 0.16 mol, Note 4). Chlorotrimethylsilane (TMSCl) (60.6 mL, 0.48 mol, Note 5) is added to the reaction mixture dropwise over a 2-hr period, via the addition funnel, and the reaction mixture is heated at 50°C (internal temperature) for 72 hr (Note 6). The mixture is cooled to room temperature, 100 mL of water is added, and it is extracted with ether (5 x 200 mL). The combined organic layers are washed with saturated sodium bicarbonate (500 mL), brine (500 mL), dried over magnesium sulfate, and concentrated (Note 7). The crude residue is dissolved in pentane (100 mL), filtered through a silica plug (50 gm), and the precipitate is washed with pentane (2 x 100 mL). The filtrate is concentrated and reduced pressure distillation (Note 8) yields 9.8 g (48% yield) of 3-phenyl-2-propynenitrile (Note 9) as a yellow solid at room temperature.

2. Notes

1. The optimum ratio for $DMSO:CH_3CN$ is 3:1.

2. Cuprous cyanide must be added slowly to the rapidly stirring solution in order to obtain a fine suspension and avoid clumping.

3. Cuprous cyanide was used as purchased from Aldrich Chemical Company, Inc. Trace amounts of copper(II) may cause dimerization of the phenylacetylene.

4. Phenylacetylene (98%) was used as purchased from Aldrich Chemical Company, Inc.

5. Chlorotrimethylsilane (redistilled, 99+%) was used as purchased from Aldrich Chemical Company, Inc. The optimum ratio for NaI:CuCN:phenyl-acetylene:TMSCl is 0.1:3:1:3.

6. The reaction was monitored by TLC using Whatman K6F 60 Å silica gel TLC plates; $R_f = 0.55$ (hexane : chloroform = 4 : 1).

7. The checkers found it very important to use low boiling solvents (e.g., ether, pentane) and not to heat the rotary evaporator water bath when removing the solvent. If the bath is heated, a fair amount of the product is observed in the rotary evaporator trap.

8. The product was collected as a dark yellow liquid, bp 140-145°C at 60 mm.

9. The physical properties of 3-phenyl-2-propynenitrile are as follows: mp 37-38°C; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.41 (t, 2 H, J = 7.2), 7.53 (t, 1 H, J = 7.6), 7.60 (d, 2 H, J = 7.2); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 62.9, 82.9, 105.3, 117.4, 128.7, 128.8, 131.8, 133.3, 133.4; IR ($CHCl_3$) cm^{-1}: (C≡N) 2272; HRMS calcd for C_9H_5N: 127.0422. Found 127.0417.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Cyanoalkynes are important in both synthetic and mechanistic studies.[2] Several synthetic methods have already been developed such as the reaction of metallated acetylides with toxic cyanogen chloride,[3] pyrolysis of β-ketoalkylidenephosphoranes,[4] dehydration of acetylenic carboxamides,[5] or the reaction of acetylenic bromides with cuprous cyanide.[6] The drawback to the last three reactions is that they require preparation of precursors: β-ketoalkylidene-phosphoranes, acetylenic carboxamides, and acetylenic bromides, respectively. Recently, the reaction of phenylacetylene with CuCN/bis(trimethylsilyl) peroxide to give cyanoalkynes has been described by Ricci, et al.[7] However, the formation of acetylenic dimer in 30% yield severely limits its applicability to the preparation of other cyanoalkynes. This procedure describes the cyanation of terminal acetylenes with cuprous cyanide in the presence of chlorotrimethylsilane, water, and a catalytic amount of sodium iodide in DMSO/CH$_3$CN to provide a general procedure for preparing cyanoalkynes in fair to good yields as shown in Table I. A wide range of terminal acetylenes bearing various kinds of functional groups can undergo this cyanation reaction. The use of DMSO with CH$_3$CN as the co-solvent is critically important in this cyanation process. Dimerization can be minimized to less than 4% when the volume ratio of DMSO and CH$_3$CN is 3 to 1. While increasing the amount of CH$_3$CN in the reaction can further minimize the dimerization, yield of the desired product is sacrificed. When DMSO is used alone as the solvent, the reaction gave the desired and dimerized products in 11% and 22% yields, respectively. Under the same conditions, the use of other solvent systems such as CH$_3$CN, THF, THF + HMPA (10%), and benzene led to recovering the starting material after 72 hr at 50°C. The addition of a catalytic amount of sodium iodide (NaI) can facilitate and accelerate the cyanation process.[8] On the other hand, the addition of a stoichiometric amount of NaI in the reaction gave low yields of the desired product along with one unidentified product. In the absence of iodide the desired products were formed in only low yields. For comparison with halide ion as catalyst, various salts were used in the reaction. Most iodide salts such as CuI, ZnI$_2$, LiI and KI may also be employed as the catalyst in the cyanation reaction to give comparable results, but only low yields of the desired product were obtained when salts such as NaCl or NaBr were used in the reaction. In the absence of either TMSCl or H$_2$O no cyanation reaction occurred.

TABLE I

CYANOALKYNES VIA IODIDE-CATALYZED CYANATION OF TERMINAL ACETYLENES WITH CUPROUS CYANIDE IN THE PRESENCE OF TMSCl AND H_2O IN DMSO/CH_3CN[9]

Entry	R in RC≡CH	Time (hr)	Product[a]	Isolated Yield (%
1	Ph	60	Ph-C≡C-CN	58
2	Me-⟨C₆H₄⟩- (p-tolyl)	72	Me-⟨C₆H₄⟩-C≡C-CN	76
3	o-(Me)C₆H₄-	72	o-(Me)C₆H₄-C≡C-CN	72
4	MeO-⟨C₆H₄⟩- (p)	60	MeO-⟨C₆H₄⟩-C≡C-CN	84
5	o-(OMe)C₆H₄-	60	o-(OMe)C₆H₄-C≡C-CN	78
6	Cl-⟨C₆H₄⟩- (p)	60	Cl-⟨C₆H₄⟩-C≡C-CN	51
7	o-(CO_2Me)C₆H₄-	60	o-(CO_2Me)C₆H₄-C≡C-CN	74
8	n-C_5-	72	n-C_5-C≡C-CN	56
9	n-C_6-	72	n-C_6-C≡C-CN	53

[a]All new compounds have been fully characterized by ^{1}H and ^{13}C NMR, IR or MS spectroscopy.

1. Institute of Chemistry, Academia Sinica, Nankang, Taipei, Taiwan, ROC.

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Appendix

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

3-Phenyl-2-propynenitrile: Propiolonitrile, phenyl- (8); 2-Propynenitrile, 3-phenyl- (9); (935-02-4)

Dimethyl sulfoxide: Methyl sulfoxide (8); Methane, sulfinylbis- (9); (67-68-5)

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

Cuprous cyanide: Copper cyanide (8,9); (544-92-3)

Phenylacetylene: Benzene, ethynyl- (8,9); (536-74-3)

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

WITTIG OLEFINATION OF PERFLUOROALKYL CARBOXYLIC ESTERS; SYNTHESIS OF 1,1,1-TRIFLUORO-2-ETHOXY-5-PHENYLPENT-2-ENE AND 1-PERFLUOROALKYL EPOXY ETHERS: 1,1,1-TRIFLUORO-2-ETHOXY-2,3-EPOXY-5-PHENYLPENTANE

(Oxirane, 2-ethoxy-3-(2-phenylethyl)-2-(trifluoromethyl)-, cis-(±)-)
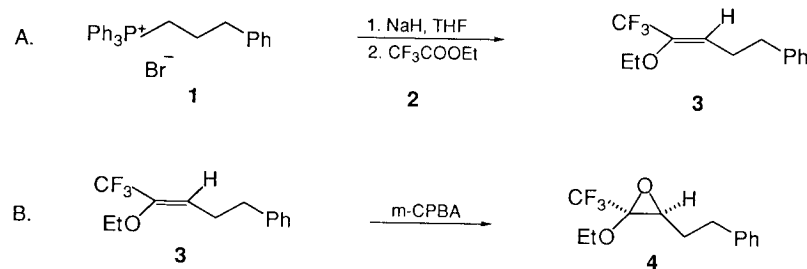
Submitted by Jean-Pierre Bégué, Danièle Bonnet-Delpon, and Andrei Kornilov.[1]
Checked by Yugang Liu and Robert K. Boeckman, Jr.

1. Procedure

A. (Z)-1,1,1-Trifluoro-2-ethoxy-5-phenyl-2-pentene (**3**). A dry, 250-mL, three-necked, round-bottomed flask (Note 1), equipped for magnetic stirring and with a rubber septum, argon inlets, and calcium chloride drying tube, is flushed with dry argon (Note 2) and charged with 2.31 g (77 mmol) of an 80% suspension of sodium hydride (NaH) in mineral oil (Note 3). The suspension is washed free of oil with two portions of dry pentane. The flask is then charged with 100 mL of tetrahydrofuran (Note 4), and 32.3 g (70 mmol) of 3-phenylpropyltriphenylphosphonium bromide (**1**) (Note 5), and equipped with a condenser bearing the calcium chloride drying tube. The reaction mixture is stirred under reflux for 5 hr and then cooled to ~ 0°C with an ice

bath (Note 6). By syringe, 10.0 g (70 mmol) of ethyl trifluoroacetate (**2**) is slowly added through the septum inlet to the stirred reaction mixture (Note 7). After the addition is complete, the ice bath is removed and the reaction mixture is heated at reflux for 1 hr, cooled, and diluted with 300 mL of pentane. The supernatant liquid from the resulting suspension is decanted and filtered through a short silica gel column (Note 8). The residual solids are washed twice with 50 mL of pentane, and the combined pentane solutions are passed through the same column. The column is then eluted with 200 mL of a 5:1 (v/v) mixture of pentane-diethyl ether. Evaporation of the solvents from the combined eluates under reduced pressure and bulb-to-bulb vacuum distillation of the residual liquid (oven temperature 120-130°C at 10 mm) provides 12.0-12.8 g (70-75%) of 97% pure (by gas chromatography) (Z)-1,1,1-trifluoro-2-ethoxy-5-phenyl-2-pentene (**3**) as a clear, colorless liquid, bp 80°C (10 mm) (Note 9).

B. 1,1,1-Trifluoro-2-ethoxy-2,3-epoxy-5-phenylpentane (**4**). A 250-mL, round-bottomed flask, equipped for magnetic stirring and with a condenser fitted with a calcium chloride drying tube, is charged with 9.76 g (40 mmol) of 1,1,1-trifluoro-2-ethoxy-5-phenyl-2-pentene (**3**), and a solution of 14.79 g (60 mmol) of 70% meta-chloroperoxybenzoic acid in 170 mL of dichloromethane (Notes 10 and 11). The resulting mixture is heated under reflux with stirring for 20 hr (Note 12), cooled, and concentrated to 50-60 mL under reduced pressure. The residual liquid is diluted with 200 mL of pentane and the supernatant liquid from the resulting suspension is passed through a short silica gel column (Note 8). The residual solids are washed twice with 50 mL of a 10:1 mixture (v/v) of pentane-diethyl ether, and the wash solutions are passed through the same column. The column is then eluted with 100 mL of a 5:1 (v/v) mixture of pentane-diethyl ether. The combined eluants are concentrated under reduced pressure and the residual liquid is purified by bulb-to-bulb vacuum distillation (oven temperature 120-130°C at 10 mm) to provide 9.36-9.88 g (90-95%) of pure

1,1,1-trifluoro-2-ethoxy-2,3-epoxy-5-phenylpentane (**4**) as a clear, colorless liquid, bp 90°C (10 mm) (Note13).

2. Notes

1. All of the glassware used in the preparation of enol ether (**3**) was dried for at least 10 min at 200°C, assembled hot, and allowed to cool under an atmosphere of argon.

2. A slight positive pressure of argon is maintained throughout the reaction.

3. An 80% suspension of NaH was obtained from Alfa Inorganics Inc.

4. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.

5. 3-Phenylpropyltriphenylphosphonium bromide (**1**) was prepared using the following procedure: A solution of 1 equiv of 1-bromo-3-phenylpropane and 1.05 equiv of triphenylphosphine (both obtained from Aldrich Chemical Company, Inc.) in dry toluene is heated at reflux for 50 hr. The resulting solids are collected by vacuum filtration, washed on the filter three times with dry pentane, and dried at 100°C/1 mm for 6 hr affording **1** in 87-92% yield.

6. The color of the reaction mixture became yellow after 10 min of reflux, and then orange after 2-3 hr. A catalytic amount of hexamethyldisilane can be added to accelerate the formation of the phosphorane.

7. Ethyl trifluoroacetate (**2**), obtained from Aldrich Chemical Company, Inc., is distilled and stored over sodium bicarbonate before use.

8. A 50-g portion of silica gel 60 (70-200 microns) was used for this procedure.

9. 1,1,1-Trifluoro-2-ethoxy-5-phenyl-2-pentene (**3**) displays the following spectral properties: IR (neat) cm^{-1}: 1670 (vC=C); ^{19}F NMR δ: -68.0; ^{1}H NMR (300 MHz) δ: 1.30 (t, 3 H, J = 7), 2.53 (m, 2 H), 2.75 (t, 2 H, J = 7.3), 3.81 (q, 2 H, J = 7), 5.70

(t, 1 H, J = 7), 7.20-7.35 (m, 5 H); ^{13}C NMR δ: 15.1, 26.5, 34.7, 69.4, 121.3 (q, ^{1}J = 275), 126.0, 128.2 (2C), 128.5, 140.7, 143.1 (q, ^{2}J = 32).[3]

10. Reagent grade dichloromethane obtained from J. T. Baker Inc. was used.

11. A solution of 14.79 g of crude commercial meta-chloroperoxybenzoic acid (Aldrich Chemical Company, Inc., or Janssen Chimica, approximately 70%) in 150 mL of dichloromethane is dried over magnesium sulfate (MgSO$_4$), filtered, and the MgSO$_4$ is washed twice with 10 mL of dichloromethane.

12. The process was monitored by GC analysis (SGE 25QC3, BPX5, 25 m x 0.32μ capillary column, 0.25μ film thickness); the retention time was 10.4 min for the enol ether (3) and 1.1 min for the epoxide (4).

13. 1,1,1-Trifluoro-2-ethoxy-2,3-epoxy-5-phenylpentane (4) displays the following spectral properties: ^{19}F NMR δ: -76.6; ^{1}H NMR (300 MHz) δ: 1.32 (t, 3 H, J = 7, CH$_3$), 2.07 (m, 2 H), 2.88 (m, 2 H), 3.36 (t, 1 H, J = 6.1), 3.80 (m, 2 H), 7.28 (m, 3 H), 7.39 (m, 2 H); ^{13}C NMR (75 MHz) δ: 14.9, 28.2, 31.6, 61.0, 63.5, 81.5 (q, ^{2}J$_{CF}$ = 27.2), 122.0 (q, ^{1}J$_{CF}$ = 272), 126.0, 128.1, 128.3, 140.3.[4]

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described here illustrates a general and inexpensive two-step method for the stereoselective preparation of new, variously substituted 1-CF$_3$ epoxy ethers from ethyl trifluoroacetate.[2,3,4] The first step of this procedure is a Wittig olefination of ethyl trifluoroacetate in which sodium hydride is used for the generation

of the ylide in order to obtain the best yield of desired enol ether (3). The base used to prepare the phosphorane strongly influences the nature and yield of the resulting products.[3] Enol ethers (3) with different substituents were obtained by this procedure. The reaction is successful with other alkyl perfluorinated alkanoates, where R$_F$ can be different perfluoroalkyl substituents (C$_2$F$_5$, n-C$_3$F$_7$, etc.), R$_1$ can be a variety of aryl or alkyl substituents, and R$_2$ can be various primary alkyl or silyl groups.[2,3] All enol ethers are colorless liquids, stable to distillation under reduced pressure and storage in the refrigerator. 1-Perfluoroalkyl enol ethers (3) have been used in the preparation of homoallylic fluorinated ketones,[5] vinyl bromides,[6] and trisubstituted trifluoromethyl alkenes.[6]
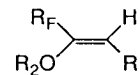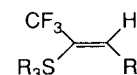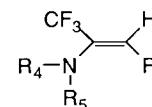
Corresponding vinyl sulfides (5)[7] and enamines (6)[8] are accessible by the same Wittig reaction with alkyl thiotrifluoroacetates and disubstituted-trifluoroacetamides respectively.

The second step of the procedure reported here is the usual epoxidation by meta-chloroperoxybenzoic acid. We have obtained the cis-epoxides (4) with different perfluoroalkyl (R$_F$) and aryl or alkyl (R) substituents:[4]
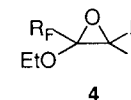
Recently 1-perfluoroalkyl epoxy ethers have been useful starting synthons for the preparation of various perfluoroalkylated organic compounds. For example, in the

reaction with magnesium bromide (MgBr$_2$), α-bromoalkyl perfluoroalkyl ketones **7** were obtained;[4] reaction with secondary amines led to α-amino ketones and β-amino alcohols **8**;[9,10] and treatment with sodium thiolates provided α-thioalkyl trifluoromethyl ketones **9**.[11] Chlorohydrins, α-alkoxy aldehydes **10** and 2-hydroxytetralins could be prepared by the treatment with Lewis acids.[12]
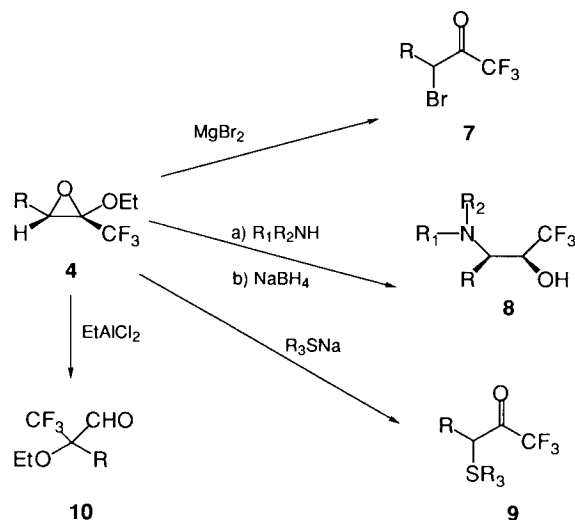
1. BIOCIS CNRS, Faculté de Pharmacie de Chatenay-Malabry, Rue J.B. Clément, 92296 Chatenay-Malabry, France.

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12. Bégué, J.-P.; Benayoud, F.; Bonnet-Delpon, D.; *J. Org. Chem.* **1995**, *60*, 5029-5036.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

1,1,1-Trifluoro-2-ethoxy-2,3-epoxy-5-phenylpentane: Oxirane, 2-ethoxy-3-(2-phenylethyl)-2-(trifluoromethyl)-, cis-(±)- (13); (141937-91-9)

(Z)-1,1,1-Trifluoro-2-ethoxy-5-phenyl-2-pentene: Benzene, (4-ethoxy-5,5,5-trifluoro-3-pentenyl)-, (Z)- (13); (141708-71-6)

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

3-Phenylpropyltriphenylphosphonium bromide: Phosphonium, triphenyl(3-

phenylpropyl)-, bromide (8 ,9); (7484-37-9)

Ethyl trifluoroacetate: Acetic acid, trifluoro-, ethyl ester (8,9); (383-63-1)

m-Chloroperoxybenzoic acid: Peroxybenzoic acid, m-chloro- (8); Benzocarboperoxoic

acid, 3-chloro- (9); (937-14-4)

1-Bromo-3-phenylpropane: Benzene, (3-bromopropyl)- (8,9); (637-59-2)

Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)

2-TRIMETHYLSILYLETHANESULFONYL CHLORIDE (SES-Cl)

(Ethanesulfonyl chloride, 2-(trimethylsilyl)-)
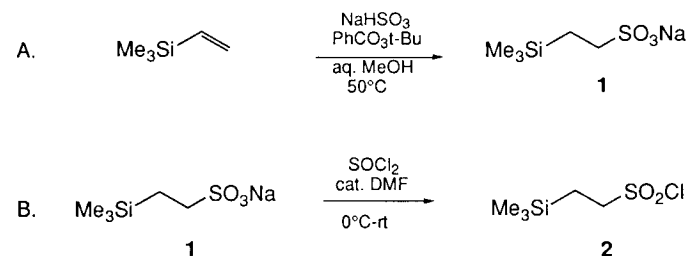
Submitted by Steven M. Weinreb,[1] Charles E. Chase,[1] Peter Wipf,[2] and Srikanth Venkatraman.[2]

Checked by Geoffrey R. Heintzelman and Robert K. Boeckman, Jr.

1.   Procedure

Caution!   Although tert-butyl perbenzoate is one of the safest peresters/peroxides to handle, one should remain aware of the inherent shock sensitivity and instability of these compounds. Users should exercise appropriate caution during concentration procedures.

A. Sodium β-trimethylsilylethanesulfonate (1). To a 500-mL, round-bottomed flask (Note 1) flushed with argon and equipped with a magnetic stirring bar is added vinyltrimethylsilane (28.0 mL, 18.2 g, 181 mmol), methanol (70 mL), and tert-butyl perbenzoate (0.70 mL, 0.70 g, 3.6 mmol) (Notes 2 - 4). To this solution is added a solution of sodium bisulfite, $NaHSO_3$, (36.1 g, 347 mmol) in 70 mL of water (Notes 5 - 7). The flask is equipped with a Claisen adapter bearing an immersion thermometer and reflux condenser, and the resulting suspension is heated in an oil bath at 50°C

under argon for 48 hr (Note 8). The suspension is concentrated on a rotary evaporator (Notes 9 and 10) followed by azeotropic removal of the residual water with methanol (2 x 25 mL). Methanol (200 mL) is added to the resulting white solid, and the resulting suspension is stirred vigorously for 10 min. The mixture is filtered through a pad of Celite into a 500-mL, round-bottomed flask, and the filtrate is concentrated on a rotary evaporator (Note 11). The filter cake is resuspended in 200 mL of methanol and stirred vigorously for 10 min, filtered into the vessel containing the original filtrate, and further concentrated (Note 11). The preceding operations are repeated again on the filter cake. After the final concentration of the combined filtrates (Note 11), the resulting white solid is dried (100°C and 0.1 mm) for 12 hr (Note 12) to give 29.0-31.9 g (~78-86%) of crude sodium β-trimethylsilylethanesulfonate as white flakes with mp >310°C (Note 13).

B. 2-Trimethylsilylethylsulfonyl chloride (2). The 500-mL, round-bottomed flask containing sulfonate salt **1** (29.0 g) is equipped with a magnetic stirring bar and a pressure-equalizing addition funnel fitted at the top with a silicone oil bubbler connected through a rubber septum. The apparatus is purged with argon. The sodium sulfonate is cooled to 0°C in an ice-water bath and the addition funnel is charged with 80 mL (1.10 mol) of thionyl chloride ($SOCl_2$) (Note 14). The slow, dropwise addition of $SOCl_2$ to **1** is accompanied by generation of sulfur dioxide, SO_2 (Note 15). After addition of the $SOCl_2$ is complete, the addition funnel is removed, and the flask is fitted with a rubber septum and bubbler. N,N-Dimethylformamide (DMF) (0.40 mL, 0.38 g, 5.2 mmol) (Note 16) is slowly added via syringe resulting in a substantial increase in the evolution of SO_2 (Note 17). The solution is stirred for an additional 20 min at 0°C during which time evolution of SO_2 ceases. The reaction mixture is warmed to room temperature and stirred overnight, resulting in a white precipitate (Note 18). The reaction flask is fitted with a short path distillation head and excess $SOCl_2$ is distilled off at reduced pressure (Note 19). Twice the resulting white

paste is diluted with 50 mL of hexanes and the residual $SOCl_2$ and hexanes are removed under reduced pressure. The resulting pale tan slurry is once again diluted with 50 mL of hexanes and the slurry is filtered through a pad of Celite. The filter cake is washed with an additional 50 mL of hexanes and the combined filtrate and washings are concentrated to afford 23.5 g of a light brown oil (Note 20). Short path distillation of the crude oil using an oil bath as heat source (70-75°C at 0.2 mm) affords 19.3 - 22.0 g (~68-77% yield, or 53-66% overall yield from vinyltrimethylsilane) of the sulfonyl chloride **2** (Notes 21 and 22) as a pale tan oil.

2. Notes

1. The submitters employed a 250-mL flask. The checkers found that use of a larger vessel (500 mL) minimized problems associated with bumping during removal of volatile material (see Note 10 below).

2. Vinyltrimethylsilane was purchased from Aldrich Chemical Company, Inc., and used without further purification.

3. Spectrophotometric grade methanol was purchased from Fisher Scientific Company and used without further purification.

4. tert-Butyl perbenzoate (98%) was purchased from Aldrich Chemical Company, Inc., and used without further purification.

5. Increasing the concentration of both the methanolic and aqueous solutions results in a 20-30% decrease in the yield of sodium salt **1**.

6. Increasing the ratio of $NaHSO_3$: vinyltrimethylsilane from 1.9:1 to 4:1 results in lower yields of **1**.

7. A fine suspension of $NaHSO_3$ forms immediately. Although the reactants are soluble in 22% (*v/v*) aqueous methanol, no improvement in the yield of **1** is observed.

8. *The reaction should be conducted behind appropriate shielding.* Maintaining the internal temperature of the reaction mixture at 50°C is imperative in order to obtain good yields of **1** [the bp of vinyltrimethylsilane (55°C) should not be exceeded]. Alternatively, the submitters employed a sand bath and the whole assembly was insulated with glass wool. The checkers found that temperature control was more easily achieved with an oil bath and did not employ glass wool insulation.

9. *Caution!* Peroxides may be present. The checkers observed a negative test for peroxides on the filtrate using acidified starch/iodide test paper prior to the final concentration and drying. The checkers recommend testing for peroxides prior to the final concentration and drying.

10. The mixture tends to bump upon concentration.

11. Do not concentrate to dryness. After the third extraction, removing the last 25 mL of methanol on a rotary evaporator at atmospheric pressure and 70°C prevents bumping.

12. The 500-mL flask should be tared in advance, and after breaking up the large chunks of salt **1**, the product can be dried sufficiently in the flask by placing the flask in a vacuum oven, or by applying heat directly to the flask with a sand bath at the same temperature and pressure.

13. NMR spectral data for **1** are as follows: ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: -0.05 (s, 9 H), 0.76-0.82 (m, 2 H), 2.25-2.31 (m, 2 H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ: -1.6, 12.1, 46.6.

14. SOCl$_2$ was purchased from Aldrich Chemical Company, Inc., and used without further purification.

15. The addition is carried out at a rate that maintains the reaction temperature between 0-10°C (20-30 min). If the temperature is increased beyond this range prior to dissolution of **1**, substantial formation of the sulfonyl anhydride occurs.

16. DMF was purchased from J. T. Baker Inc. and used without further purification.

17. *Caution!* Do not add DMF to the reaction mixture through the pressure equalizing addition funnel.

18. The reaction can be monitored by ^{1}H NMR spectroscopy by removing 0.1-mL aliquots, filtering through glass wool, and diluting with CDCl$_3$. The diagnostic peaks are: δ 3.55-3.63 (m, 2 H) (**2**); 3.42-3.51 (m, 4 H) (sulfonic anhydride); 2.26-2.35 (m, 2 H) (salt **1**).

19. Using a water aspirator and a warm water bath is sufficient. Recovered SOCl$_2$ can be recycled.

20. ^{1}H NMR spectrum indicates that the crude product is comprised of a mixture of the sulfonyl chloride **2** and the sulfonic anhydride in an 11:1 ratio. Pure sulfonyl chloride **2** is obtained by distillation. Alternatively, the crude sulfonyl chloride can be chromatographed (60 g of silica gel per 1 g of sulfonyl chloride) eluting with hexane to provide pure **2** in equivalent yields.

21. *Caution!* If a sufficiently high vacuum is not maintained, the increased temperature (pot temperatures >100-110°C) required for distillation may cause thermal decomposition of **2** and evolution of hydrogen chloride. The checkers observed that **2** had bp 95-100°C at 0.5 mm. Kugelrohr distillation (85-100°C at 0.3-0.5 mm) of the product in two batches can also be employed.

22. NMR spectral data for **2** are as follows: ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.13 (s, 9 H), 1.30-1.36 (m, 2 H), 3.60-3.66 (m, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ: -2.3, 11.7, 63.2.

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Sodium sulfonate **1** has previously been prepared from $NaHSO_3$ and vinyltrimethylsilane using sodium nitrite/sodium nitrate as the radical initiator.[3] In the submitters hands this protocol resulted in salt **1** as a pale tan powder in only 15-53% yield if 50% (v/v) aqueous methanol is employed as solvent. The yield of **1** could be increased to 63% if 22% (v/v) aqueous methanol is employed. An advantage of this method is the elimination of a potentially explosive perester as radical initiator. However, lower yields of **1** and the subsequent lower yield of the sulfonyl chloride **2** (53% for the sulfonylation, 35% overall from vinyltrimethylsilane) make this procedure less desirable than the method presented. The use of tert-butyl perbenzoate as the radical initiator[4] not only provides **1** in a higher yield, but the subsequent conversion to **2** also proceeds in better yield.

Sulfonyl chloride **2** has previously been prepared from salt **1** and phosphorus pentachloride, PCl_5 in carbon tetrachloride, CCl_4.[5] The disadvantage of this procedure is the difficulty in avoiding sulfonic anhydride formation. Using this method, the ^{1}H NMR spectrum of the crude reaction mixture prior to distillation indicates a 2-4:1 mixture of **2** and the corresponding sulfonic anhydride. Although the sulfonic anhydride can also serve as an efficient sulfonylating agent (sulfonylation of ammonia resulted in the corresponding sulfonamide in 99% yield), and for most purposes the crude mixture of **2** and the sulfonic anhydride can be used directly, limiting the formation of the sulfonic anhydride is economically desirable. Sulfonyl chloride **2** can be synthesized from β-trimethylsilylethanesulfonic acid (obtained from salt **1** by ion exchange chromatography) and PCl_5 in CCl_4, although there seems to be no advantage in using the acid.[3] Both sodium salt **1** and the corresponding triethylammonium salt, when treated with triphenylphosphine, PPh_3, and SO_2Cl_2, provide **2** in 62% and 79% yields, respectively.[6] Sulfonyl chloride **2** has also been prepared from β-trimethylsilylethylmagnesium chloride and sulfuryl chloride in 50% yield.[3]

The use of a catalytic amount of DMF in $SOCl_2$ here is based on the work of Bosshard.[7] The advantage of this procedure is the ability to minimize the formation of the sulfonic anhydride. At 0°C **1** is reasonably soluble and unreactive in $SOCl_2$, thereby minimizing local high salt concentrations. Upon slow addition of DMF to the mixture, the resulting Vilsmeier-Haack reagent efficiently catalyzes the formation of **2** from **1**. Sulfonyl chloride **2** can be stored in a freezer at -15°C for months without any significant decomposition.

Sulfonyl chloride **2** is used to protect primary and secondary amines as the corresponding sulfonamide.[8] The SES-protected amines are stable compounds that can be readily cleaved by fluoride sources to regenerate the parent amine.
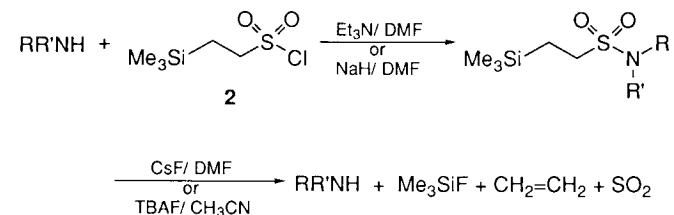
1. Department of Chemistry, The Pennsylvania State University, University Park, PA 16802.

2. Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

2-Trimethylsilylethanesulfonyl chloride: Ethanesulfonyl chloride, 2-(trimethylsilyl)- (12); (106018-85-3)

tert-Butyl perbenzoate: Peroxybenzoic acid, tert-butyl ester (8); Benzenecarboperoxoic acid, 1,1-dimethylethyl ester (9); (614-45-9)

Sodium β-trimethylsilylethanesulfonate: Ethanesulfonic acid, 2-(trimethylsilyl)-, sodium salt (9); (18143-40-3)

Vinyltrimethylsilane: Silane, trimethylvinyl- (8); Silane, ethenyltrimethyl- (9); (754-05-2)

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

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

(1'S,2'S)-METHYL-3O,4O-(1',2'-DIMETHOXYCYCLOHEXANE-1',2'-DIYL)-α-D-MANNOPYRANOSIDE

(α-D-Mannopyranoside, methyl 3,4-O-(1,2-dimethoxy-1,2-cyclohexanediyl)-, [3[S(S)]]-)

A.

$(MeO)_3CH, H_2SO_4$ / MeOH

B.

MeOH, CSA, $(MeO)_3CH$
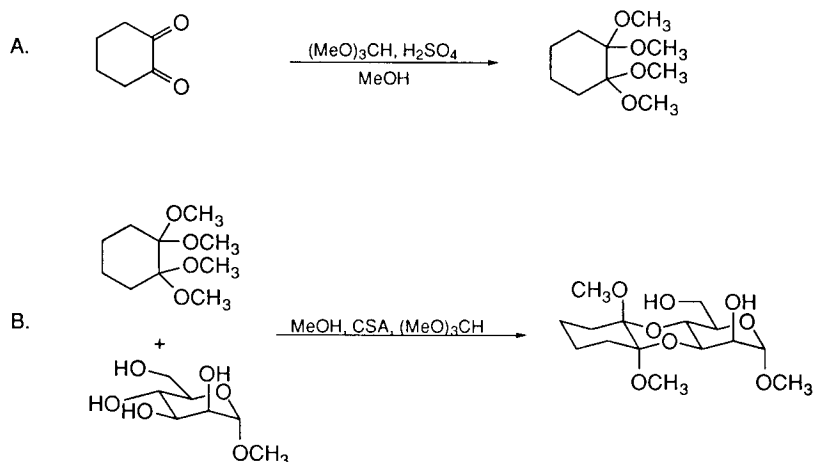
Submitted by Steven V. Ley, Helen M. I. Osborn, Henning W. M. Priepke, and Stuart L. Warriner.[1]

Checked by Karl A. Scheidt and William R. Roush.

1. Procedure

A. 1,1,2,2-Tetramethoxycyclohexane (Note 1). A 500-mL, two-necked flask equipped with a stirrer bead, condenser and heating mantle is flushed with dry argon and then charged with 44.8 g of 1,2-cyclohexanedione (0.400 mol), 100 mL of dry methanol (MeOH) and 160 mL of trimethyl orthoformate (1.46 mol) (Note 2). Stirring is

begun and approximately 32 drops of concd sulfuric acid are added to the solution. The resultant black solution is heated under argon at reflux for 5 hr. The heating mantle is removed and the solution is cooled to room temperature. Sodium hydrogen carbonate is carefully added to neutralize the solution (approx 4 g required). Methanol, methyl formate and trimethyl orthoformate are removed by distillation at ambient temperature through a straight path distillation apparatus. The residue is then distilled under reduced pressure to yield 59.5 g of 1,1,2,2-tetramethoxycyclohexane as a colorless liquid (73%) (Notes 3, 4).

B. (1'S,2'S)-Methyl-3O,4O-(1',2'-dimethoxycyclohexane-1'2'-diyl)-α-D-manno-pyranoside. A 500-mL, two-necked flask equipped with a stirrer bead, condenser and heating mantle is flushed with dry argon and charged with 30 g of methyl-α-D-mannopyranoside (0.15 mol), 300 mL of dry MeOH, 59.5 g of 1,1,2,2-tetramethoxycyclohexane (0.29 mol) and 16.1 g of trimethyl orthoformate (0.15 mol). Camphorsulfonic acid (CSA), 3.48 g, (0.015 mol) is added and the resultant black solution is heated under argon at reflux for 16 hr. The heating mantle is removed and the solution is cooled to room temperature. Sodium bicarbonate is carefully added to neutralize the solution (approx 5 g required) (Note 5). The mixture is transferred to a 1-L, round-bottomed flask, and the solvent is removed under reduced pressure on a rotary evaporator (Note 6). The crude material (Note 7) is purified by column chromatography on silica gel (1.5 Kg of silica gel using a 10-15 cm diameter column; gradient elution 0-5% ethanol in ether) followed by crystallization from ethyl acetate-hexane (Note 8) to yield 20.8-23.2 g of (1'S,2'S)-methyl-3O,4O-(1',2'-dimethoxycyclohexane-1',2'-diyl)-α-D-mannopyranoside as colorless cubes (41-46%) (Note 9).

2. Notes

1. All materials are commercially available from Aldrich Chemical Company, Inc., Acros Organics or Avocado Research Chemicals, Ltd. (Shore Road, Port of Heysham Industrial Park, Heysham, Lancashire, LA3 2XY, England). It is recommended that MeOH be distilled from calcium hydride prior to use.

2. Trimethyl orthoformate acts as a drying agent in both Step A and B. It is therefore advantageous to use an excess of this drying agent to force the reaction to completion.

3. Physical data for purified material are as follows: bp 76°C at 0.8 mm Hg. ^{1}H NMR (CDCl$_3$) δ: 1.31-1.48 (m, 4 H), 1.60-1.75 (m, 4 H), 3.32 (s, 12 H); ^{13}C NMR (CDCl$_3$) δ: 21.67, 30.61, 49.25, 102.07; IR (neat) cm^{-1}: 2950, 2880, 2840, 1520, 1500, 1480, 1350, 1340, 1200, 1150, 1100, 1050, 960, 870; HRMS calcd for C$_{10}$H$_{20}$O$_4$ m/z 204.1361, found 204.1363. Anal. Calcd for C$_{10}$H$_{20}$O$_4$: C, 58.80; H, 9.87. Found: C, 58.60; H, 9.68.

4. The checkers obtained 59.7-64.1 g (73-78%) of 1,1,2,2-tetramethoxy-cyclohexane.

5. This neutralization step should be performed for at least 20 min. During this period, the reaction turns from an indigo to a light brown color.

6. Concentration of the crude product should be stopped when solids begin to form. The checkers observed that it was difficult to dissolve the crystalline crude product in ether to load the column for chromatographic purification.

7. The crude product consists mainly of the desired product; protection of the cis-2,3-diol occurs only to a minor extent. The major side product from the reaction is the 1,3-dioxolane, which can be slowly converted to the required product under thermodynamic equilibrating conditions; i.e., further treatment of the dioxolane with boiling methanol and a trace of CSA for 4 days produced the required product in 35% yield together with recovery of the dioxolane in 16% yield.

8. The chromatographed product is dissolved in 160 mL of boiling ethyl acetate and then diluted with 150 mL of hexanes. The solution was allowed to cool to room temperature, and then placed in a -20°C freezer overnight. The crystalline product was collected by filtration and washed with cold hexanes.

9. Physical data for purified material are as follows: mp 173°C (EtOAc-hexane); $[\alpha]_D^{25}$ +170° (CHCl$_3$, c 0.95); ^{1}H NMR (CDCl$_3$) δ: 1.29-1.43 (m, 2 H), 1.45-1.55 (m, 2 H), 1.62-1.82 (m, 4 H), 2.25 (br, t, 1 H, J = 5.8), 2.89 (s, 1 H), 3.20 (s, 3 H), 3.21 (s, 3 H), 3.35 (s, 3 H), 3.72-3.86 (m, 3 H), 3.92 (br, s, 1 H), 4.14 (dd, 1 H, J = 10.6, 2.9), 4.25 (dd, 1 H, J = 2 x 10.0), 4.72 (d, 1 H, J = 0.9); ^{13}C NMR (CDCl$_3$) δ: 21.27 (2 x), 26.88, 26.91, 46.71, 46.82, 54.77, 61.18, 63.64, 68.77, 69.88, 70.73, 98.64, 99.10, 101.59; IR (KBr) cm^{-1}: 3500-3400, 3000, 3050, 2820, 1400, 1350, 1340, 1200-1000, 900, 850, 820, 800, 790, 750, 700; HRMS calcd for C$_{15}$H$_{26}$O$_8$, m/z 334.1628, found 334.1639. Anal. Calcd for C$_{15}$H$_{26}$O$_8$: C, 53.88; H, 7.84. Found: C, 53.77; H, 7.73.

The submitters reported mp 168°C (ether); $[\alpha]_D^{25}$ +191° (CHCl$_3$, c 0.94).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Until recently, the protection of the trans-hydroxyl groups of sugars has been an inefficient process.[2] This protection has now been simplified by the introduction of the dispiroketal protecting group,[3] and the cyclohexane diacetal (CDA) protecting group.[4]

As shown in this report, the CDA protecting group is easily introduced, and the present procedure allows facile protection of the trans-hydroxyl groups of a range of sugars.

SUGAR	3,4-protected	2,3-protected
	45%	11%
	53%	10%
	74%	8%
	45%	11%
	30%	50%

The ease of selective protection can be explained in terms of maximum anomeric stabilization such that both anomeric methoxy groups of the product are oriented in the axial position with respect to the central dioxane ring. All four sterically demanding alkyl substituents are then placed in the favored equatorial positions. The poor selectivity for the protection of glucose results from the existence of *two* pairs of trans-hydroxyl groups in this sugar.

The CDA protecting group has been shown to withstand common sugar derivatization reactions,[4] and is easily removed under acidic conditions.[4] Further, it has proved possible to tune the reactivity of sugars via the introduction of the CDA protecting group, and this in turn has allowed concise syntheses of complex oligosaccharides.[5]

Further research within in our laboratory has illustrated that certain substrates bearing trans-hydroxyl groups can be directly protected using cyclic and acyclic diones, thus alleviating the requirement for prior formation of the tetramethoxydiacetals.[6] For example, butane-2,3-dione has proved particularly useful for the preparation of butane diacetal (BDA) derivatives, which serve as useful alternatives to cyclohexane diacetal (CDA) derivatives.

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Appendix

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

(1'S,2'S)-Methyl-3O,4O-(1',2'-dimethoxycyclohexane-1',2'-diyl)-α-D-mannopyranoside: α-D-Mannopyranoside, methyl 3,4-O-(1,2-dimethoxy-1,2-cyclohexanediyl)-, [3[S(S)]]- (13); (163125-35-7)

1,1,2,2-Tetramethoxycyclohexane: Cyclohexane, 1,1,2,2-tetramethoxy- (13); (163125-34-6)

1,2-Cyclohexanedione (8,9); (765-87-7)

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

Methyl formate: Formic acid, methyl ester (8,9); (107-31-3)

Camphorsulfonic acid monohydrate (CSA): Bicyclo[2.2.1]heptane-1-methanesulfonic acid, 7,7-dimethyl-2-oxo-, (±)- (9); (5872-08-2)

SELECTIVE PROTECTION OF 1,3-DIOLS AT THE MORE HINDERED HYDROXY GROUP: 3-(METHOXYMETHOXY)-1-BUTANOL

(1-Butanol, 3-(methoxymethoxy)-)
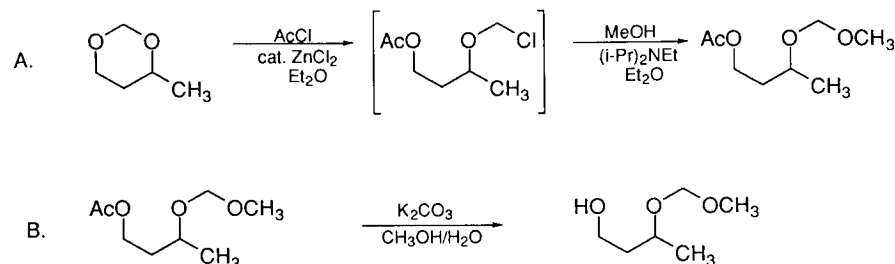
Submitted by William F. Bailey, Matthew W. Carson, and Lyn M. J. Zarcone.[1]

Checked by Thierry Happaerts and Leon Ghosez.

1. Procedure

Caution! All operations should be conducted in an efficient fume hood. The chloromethyl ether acetate intermediate is potentially toxic.

A. 1-Acetoxy-3-(methoxymethoxy)butane. A 500-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, condenser fitted with a nitrogen inlet, 50-mL pressure equalizing addition funnel, and a rubber septum is flame-dried and allowed to cool to room temperature under nitrogen. The flask is charged with 30.0 g (0.294 mol) of 4-methyl-1,3-dioxane (Note 1), 200 mL of anhydrous diethyl ether (Note 2), and 0.5 mL of a 1.0 M solution of zinc chloride in anhydrous diethyl ether (Note 3). The solution is stirred under a positive pressure of nitrogen and 25.0 mL (0.352 mol) of acetyl chloride (Note 4) is added dropwise over a 10-min period, resulting in a slightly exothermic reaction; the resulting solution is stirred for 3 hr at

room temperature. A separate 500-mL, three-necked, round-bottomed flask, equipped with a mechanical stirrer, 500-mL addition funnel fitted with a rubber septum, and a condenser fitted with a nitrogen inlet, is charged with 61.0 mL (0.350 mol) of N,N-diisopropylethylamine (Note 5), 45.0 mL (1.11 mol) of anhydrous methanol (Note 6), and 60 mL of anhydrous diethyl ether (Note 2), and the flask is cooled in an ice-bath. The chloromethyl ether acetate solution is rapidly transferred to the addition funnel via a double-tipped needle under a positive pressure of nitrogen and the solution is added dropwise over a 15-min period to the mechanically stirred, ice-cold solution of alcohol and amine. Copious quantities of ammonium salt form during the addition. After the addition is completed, the cooling bath is removed and the reaction mixture is stirred for 1 hr at room temperature. The entire two-phase reaction mixture is then transferred to a 500-mL, round-bottomed flask and volatile components are removed by rotary evaporation at water aspirator pressure. Pentane (ca. 20 mL) is added to the residue and the flask is cooled in an ice-bath for 1 hr to induce crystallization of the ammonium salt. The entire two-phase mixture is then filtered with suction through 50 g of neutral alumina (Note 7) contained in a 4.3-cm x 15-cm medium porosity, sintered-glass funnel and the salt is washed well with pentane (ca. 500 mL). Concentration of the combined filtrate and washings by rotary evaporation at water aspirator pressure affords 40.0-47.2 g (77-91%) of essentially pure 1-acetoxy-3-(methoxymethoxy)butane (Note 8). This material is used in the next step without further purification.

B. 3-(Methoxymethoxy)-1-butanol. A solution of 17.6 g (0.10 mol) of 1-acetoxy-3-(methoxymethoxy)butane in 100 mL of methanol is added to a solution of 35.0 g (0.253 mol) of potassium carbonate (Note 9) in 50 mL of water contained in an open 250-mL, round-bottomed flask equipped with a magnetic stirring bar. The resulting two-phase mixture is stirred vigorously at room temperature for 2 hr. The flask is then connected to a rotary evaporator and methanol is removed at 20-30°C (18 mm). The two-phase residue is extracted with four 20-mL portions of diethyl ether and the combined ethereal extracts are dried over anhydrous potassium carbonate. Solvent is removed by rotary evaporation at water aspirator pressure and the resulting oil is distilled at reduced pressure, bp 94-96°C at 18 mm (Note 10), to give 11.9-12.4 g (89-92%) of pure product (Note 11) as a colorless oil.

2. Notes

1. 4-Methyl-1,3-dioxane, available from the Aldrich Chemical Company, Inc., is used as received. Alternatively, the formal may be prepared from 1,3-butanediol and aqueous formaldehyde as previously described.[2]

2. Anhydrous diethyl ether was purchased from J. T. Baker Inc. and used as received.

3. A 1.0 M solution of zinc chloride in diethyl ether is available from the Aldrich Chemical Company, Inc. Alternatively, a few crystals of anhydrous zinc chloride may be added to the reaction solution to catalyze the acylation reaction.

4. Reagent grade acetyl chloride is freshly distilled immediately prior to use.

5. N,N-Diisopropylethylamine was purchased from the Aldrich Chemical Company, Inc., and distilled from potassium hydroxide immediately prior to use.

6. Anhydrous methanol was purchased from J. T. Baker Inc. and used as received.

7. Neutral, activity 1 alumina (50-200 μm particle size) purchased from ICN, Inc. was used to fill the sintered-glass funnel.

8. This material is sufficiently pure for most purposes. Distillation of the methoxymethyl ether acetate through a 5-in Vigreux column affords 42.4-43.7 g (82-84%) of pure product: bp 120-122°C (50 mm) [lit.[3] bp 95-98°C (20 mm)]. The product has the following spectroscopic properties: ^{1}H NMR (CDCl$_3$) δ: 1.18 (d, 3 H, J = 6.20), 1.75-1.79 (m, 2 H), 2.02 (s, 3 H), 3.33 (s, 3 H), 3.79 (apparent sextet, 1 H, J = 6.20),

4.14 (t, 2 H, J = 6.56), 4.57 and 4.67 (AB-pattern, 2 H, J_{AB} = 6.92); ^{13}C NMR (CDCl$_3$) δ: 19.9, 20.2, 35.5, 54.6, 60.7, 69.4, 94.4, 170.7.

9. Reagent grade, anhydrous potassium carbonate purchased from J. T. Baker Inc. was used.

10. The literature bp is 67-69°C at 5 mm.[4]

11. 3-(Methoxymethoxy)-1-butanol has the following spectroscopic properties: ^{1}H NMR (CDCl$_3$) δ: 1.18 (d, 3 H, J = 6.21), 1.68-1.79 (m, 2 H), 2.45 (br s, 1 H), 3.36 (s, 3 H), 3.66-3.79 (m, 2 H), 3.90 (apparent sextet, 1 H, J = 6.23), 4.59 and 4.69 (AB-pattern, 2 H, J_{AB} = 6.80); ^{13}C NMR (CDCl$_3$) δ: 20.2, 39.2, 55.3, 59.8, 71.8, 95.2.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion
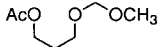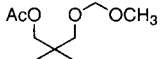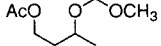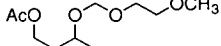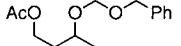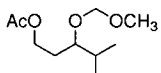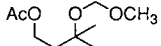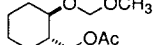
The procedure described above provides a simple, general method for the selective, differential protection of both symmetrical and unsymmetrically substituted 1,3-diols using readily available, inexpensive reagents.[3] Additional examples are summarized in the Table.[3]

While a variety of techniques are available for the monoprotection of symmetrical diols, there are few methods that allow for the chemoselective functionalization of the more hindered hydroxyl in an unsymmetrical 1,3-diol.[5] The acid-catalyzed reaction of an unsymmetrically substituted cyclic formal with acetyl chloride described here invariably proceeds via preferential rupture of the less congested C(2)-O bond to give a product having an acetate at the less congested site

and a chloromethyl ether moiety at the more hindered hydroxyl (Table). This highly selective acylative cleavage is a consequence of rate-limiting attack by the electrophilic acylating agent that is acutely sensitive to steric effects.[2] Using the procedure outlined above, the reactive OCH$_2$Cl moiety may be converted to any of a variety of traditional alkoxymethyl ether protecting groups by treatment of the intermediate chloromethyl ether acetate with an appropriate alcohol in the presence of N,N-diisopropylethylamine (Table, entries 3-5). Removal of the acetate from the alkoxymethyl ether acetate affords a diol that is selectively protected as an alkoxymethyl ether at the more sterically encumbered center. This ability to site-selectively protect the more hindered hydroxyl in an unsymmetrical 1,3-diol is a particularly attractive feature of the methodology since it complements the normal chemoselectivity that favors functionalization of the primary site in the reaction of an unsymmetrical 1,3-diol with a derivatizing reagent.[5]

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TABLE

SELECTIVE PROTECTION OF 1,3-DIOLS

entry	acetal	R'OH	product	yield, %
1		MeOH		97
2		MeOH		85
3		MeOH		90
4		MeO(CH$_2$)$_2$OH		88
5		PhCH$_2$OH		75
6		MeOH		95
7		MeOH		89
8		MeOH		90

4-DIMETHYLAMINO-N-TRIPHENYLMETHYLPYRIDINIUM CHLORIDE

(Pyridinium, 4-(dimethylamino)-1-(triphenylmethyl)-, chloride)

1

Submitted by Ashok V. Bhatia,[1a] Sunil K. Chaudhary,[1b] and Oscar Hernandez.[1c]

Checked by Joseph P. Bullock and Louis S. Hegedus.

1. Procedure

A mixture of 30.6 g (0.1 mol) of pure chlorotriphenylmethane (Note 1) and 12.2 g (0.1 mol) of 4-dimethylaminopyridine (Note 2) is placed in a 2-L, three-necked, round-bottomed flask equipped with a dropping funnel and a Y-tube holding a thermometer and a nitrogen (N_2) inlet adapter. To the mixture is added, with continuous stirring, 200 mL of dry dichloromethane (CH_2Cl_2, Note 3) through the dropping funnel. After the addition, stirring is continued for an additional 3 hr at 20-25°C under N_2.

To the clear solution is gradually added 1 L of ethyl acetate (Note 4) over 1 hr with continual stirring. The product slowly crystallizes during the addition of ethyl acetate. At the end of the addition, the product slurry is cooled to 5°C by immersing the reaction flask in an ice bath. The product is filtered and washed twice with 100 mL of cold ethyl acetate. Upon drying under vacuum at 50°C for 24 hr, 38.6 g of the product is recovered as a white solid (96% yield, mp 128-131°C) (Note 5).

2. Notes

1. Chlorotriphenylmethane was purchased from Aldrich Chemical Company, Inc., and crystallized from toluene/petroleum ether.

2. 4-Dimethylaminopyridine was purchased from Aldrich Chemical Company, Inc., and recrystallized from ethyl acetate/cyclohexane.

3. Dichloromethane was placed over 3 Å molecular sieves for 24 hr prior to use. The checkers used dichloromethane freshly distilled over calcium hydride (CaH_2).

4. HPLC grade ethyl acetate was washed with aqueous 5% sodium carbonate solution, followed by brine. After drying the organic phase over anhydrous potassium carbonate, ethyl acetate was recovered after distillation over CaH_2.

5. Because of the hygroscopic nature of the product, the melting point is somewhat broad and varies with the amount of moisture present in the product. Anal. Calcd for $C_{26}H_{25}N_2Cl \cdot 0.9H_2O$: C, 74.85; H, 6.48; N, 6.72; Cl, 8.50; O, 3.45. Found: C, 75.16; H, 6.61; N, 6.66; Cl, 8.82; O, 3.64. The sample has the following spectral characteristics: ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 3.2 (s, 6 H), 6.7 (d, 2 H, J = 7), 7.2-7.3 (m, 15 H), 8.0-8.1 (m, 2 H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 40.3, 106.9, 127.4, 128.0, 128.1, 128.3, 139.1, 147.5. The checkers dried the product under vacuum at 50°C for 72 hr; shorter drying times resulted in a different, more complex ^{1}H NMR spectrum. In addition, significant shifts were observed in the ^{13}C NMR spectrum depending upon the state of dryness.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Selective protection of a primary alcohol functionality in a molecule has considerable utility in contemporary organic synthesis. Protection of alcohol groups as triphenylmethyl ethers has found applications in the syntheses of a variety of molecules, particularly in the carbohydrate and nucleoside chemistry areas.[2,3] The authors have shown that tritylation may be accomplished in a facile manner by treating an alcohol with chlorotriphenylmethane and 4-dimethylaminopyridine in a suitable solvent.[4] A postulated intermediate in such a tritylation reaction is 4-dimethylamino-N-triphenylmethylpyridinium chloride.[5] The proposal was based on our knowledge of the mechanism of the tritylation reaction and on the enhanced nucleophilic properties of 4-dimethylaminopyridine, which would favor formation of a salt such as **1**. The use of **1** for tritylation of alcohols and amines offers distinct advantages over traditional tritylation methods using pyridine as solvent. For example, **1** may be used in combination with solvents such as dimethylformamide and dichloromethane to accommodate a variety of starting materials. Moreover, with the use of **1**, stoichiometry is better controlled, which in turn enhances selectivity.

A practical, large scale preparation of **1** further enhances the usefulness of the authors tritylation procedure.[3] The preparation involves N-tritylation of 4-dimethyl-aminopyridine under mild conditions. Isolation of the product is straightforward and the product may be stored at ambient temperature for extended periods, without degradation.

1. (a) Chemical Development Department, D-54Z, Abbott Laboratories, North Chicago, IL 60064; (b) Department of Biology, University of Victoria, Victoria, BC V8W 2Y2, Canada; (c) U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (7402), 401 M Street, S.W., Washington, DC 20460.

2. (a) Hanessian, S.; Staub, A. P. A. *Tetrahedron Lett.* **1973**, 3555; (b) Fréchet, J. M. J.; Haque, K. E. *Tetrahedron Lett.* **1975**, 3055; (c) Reddy, M. P.; Rampal, J. B.; Beaucage, S. L. *Tetrahedron Lett.* **1987**, *28*, 23; (d) Murata, S.; Noyori, R *Tetrahedron Lett.* **1981**, *22*, 2107

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4. Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 95.

5. Hernandez, O.; Chaudhary, S. K.; Cox, R. H.; Porter, J. *Tetrahedron Lett.* **1981**, *22*, 1491.

4-Dimethylamino-N-triphenylmethylpyridinium chloride: Pyridinium,

4-(dimethylamino)-1-(triphenylmethyl)-, chloride (10); (78646-25-0)

4-Dimethylaminopyridine: HIGHLY TOXIC: 4-Pyridinamine, N,N-dimethyl- (9);

(1122-58-3)

Chlorotriphenylmethane: Methane, chlorotriphenyl- (8); Benzene, 1,1',1"-

(chloromethylidyne)tris- (9); (76-83-5)

6,7-DIHYDROCYCLOPENTA-1,3-DIOXIN-5(4H)-ONE

(Cyclopenta-1,3-dioxin-5(4H)-one, 6,7-dihydro-)
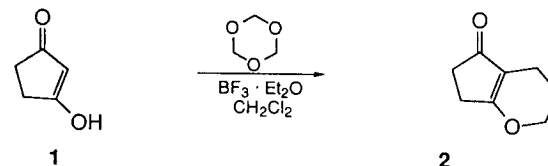
Submitted by Kwunmin Chen, Christopher S. Brook, and Amos B. Smith, III.[1]
Checked by Aimee Reed and Louis S. Hegedus.

1. Procedure

A 1-L, three-necked, round-bottomed flask equipped with a 2-cm magnetic stirring bar, rubber septum, 50-mL graduated addition funnel, and an argon inlet tube is charged with 10.0 g (0.1019 mol) of 1,3-cyclopentanedione (Note 1), 55.0 g (0.6106 mol) of 1,3,5-trioxane (Note 2), 5 g of activated, powered, 4 Å molecular sieves, and 500 mL of freshly distilled dichloromethane (Note 3). The resultant suspension is stirred at room temperature and 37.6 mL (0.3057 mol) of boron trifluoride etherate (Note 4) is added dropwise over 2 hr via the addition funnel (Note 5). After 48 hr, the reaction mixture is filtered through a pad of Celite and the yellow solid is washed twice with 100 mL of dichloromethane. The filtrate is poured into a 3-L separatory funnel containing 500 g of ice and 1 L of saturated sodium bicarbonate (Note 6). The aqueous phase is extracted with two 100-mL portions of dichloromethane, and the combined organic solutions are washed with 500 mL of brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography on 500 g of silica gel (Note 7) with hexane-acetone (3 : 1) as eluant (Note 8) gives 10.3 g (72% yield) of 2 as a white crystalline solid (Notes 9 and 10).

2. Notes

1. 1,3-Cyclopentanedione (ca. 97%) is purchased from Aldrich Chemical Company, Inc., and used without purification.

2. 1,3,5-Trioxane (99+%) is purchased from Aldrich Chemical Company, Inc., and used without purification.

3. Reagent-grade dichloromethane is distilled under argon from calcium hydride.

4. The submitters use the purified, redistilled grade of boron trifluoride etherate available from Aldrich Chemical Company, Inc.

5. Upon initial addition of boron trifluoride etherate, a slightly endothermic reaction takes place.

6. **CAUTION**: A large amount of carbon dioxide is generated in this extraction and appropriate care should be taken.

7. The crude residue is applied to the column head using a minimum of dichloromethane. The submitters use flash-grade (230-400 mesh) silica gel purchased from E. Merck and a column 10 cm in diameter. TLC values for **2** are R_f = 0.18 (hexane : acetone = 3 : 1) and for **3** (see Note 10) are R_f = 0.08 (hexane : acetone = 3 : 1), employing Whatman K6F silica gel TLC plates 60 Å. In a typical purification, collecting 200-mL fractions, **2** would elute in fractions 9-18 and **3** in fractions 20-30. The checkers found that immediate purification of the crude residue was necessary. Yields decreased dramatically with time between isolation and purification. Furthermore, the activity (related to the degree of dehydration) of the silica gel greatly affected yields. Only half the amount of silica mentioned above was used by the checkers to get the reported yields. When the full amount was used, the yield decreased to 40-50%.

8. Reagent-grade hexanes (Fisher Scientific Company) and HPLC-grade acetone (Baxter Diagnostics Inc.) were used without further purification.

9. The product can be recrystallized from hexane-ethyl acetate (5:1): mp 73-75°C; IR (CHCl$_3$) cm^{-1}: 3000 (m), 1690 (m), 1640 (s), 1430 (m), 1310 (m), 1180 (m), 1090 (br m), 910 (s), 890 (s); ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 2.36-2.38 (m, 2 H), 2.59-2.62 (m, 2 H), 4.44 (t, 2 H, J = 2.2), 5.20 (s, 2 H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 26.4, 32.6, 63.1, 92.7, 114.7, 181.9, 201.0; high resolution mass spectrum (CI, NH$_3$) m/z 140.0482 (M$^+$; calcd for C$_7$H$_8$O$_3$: 140.0473). Anal. Calcd for C$_7$H$_8$O$_3$: C, 60.00; H, 5.75. Found: C, 60.19; H, 5.82.

10. Further elution furnishes a small amount (0.57 g, 2% yield) of crystalline propellane **3**: mp 178-180°C; IR (CHCl$_3$) cm^{-1}: 3000 (m), 1760 (s), 1700 (m), 1650 (s), 1450 (s), 1400 (s), 1195 (m), 1165 (m), 970 (m); ^{1}H NMR (500 MHz, CDCl$_3$) δ: 1.95-2.06 (m, 3 H), 2.33-2.38 (m, 1 H), 2.42-2.74 (m, 6 H), 3.28 (d, 1 H, J = 11.7), 4.21 (d, 1 H, J = 11.7), 4.80 (d, 1 H, J = 6.4), 4.82 (d, 1 H, J = 6.6); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 20.4, 25.9, 30.7, 33.3, 44.7, 64.7, 87.7, 106.8, 111.0, 180.7, 202.1, 210.2; high resolution mass spectrum (CI, NH$_3$) m/z 250.0841 (M$^+$; calcd for C$_{13}$H$_{14}$O$_5$: 250.0836). Structure **3** is confirmed by single-crystal X-ray analysis.
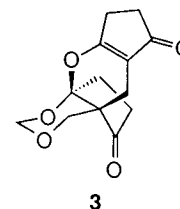
3

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

1,3-Dioxin vinylogous esters derived from cyclic 1,3-diketones (e.g., **4**) are valuable building blocks for the construction of natural and unnatural carbocyclic products.[2] In connection with a synthesis of plant-growth regulators, Crow and
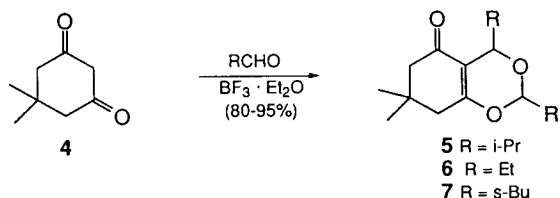
co-workers reported the preparation of substituted 1,3-dioxins **5-7** in 1982.[3] To account for their formation, Crow proposed a Prins mechanism whereby the enol of the 1,3-diketone adds to the BF₃-aldehyde complex (Scheme 1).[4] Incorporation of a second equivalent of aldehyde and cyclization then yields the dioxin. Use of a slight excess of aldehyde (ca. 2.5-3.0 equiv) was recommended.[3]

Scheme 1
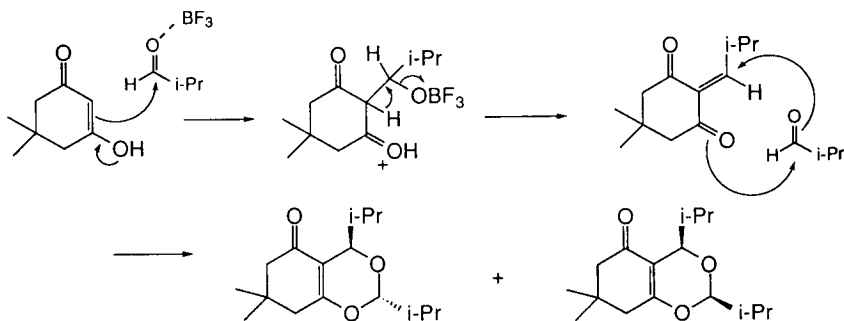
A systematic investigation[5] demonstrated that this reaction could be successfully generalized by employing a larger excess of 1,3,5-trioxane (or paraformaldehyde) and increasing the $BF_3 \cdot Et_2O$ to 1,3,5-trioxane ratio. Presumably the latter results in more rapid breakdown of 1,3,5-trioxane to formaldehyde and/or its BF_3 complex, analogous to the sulfuric acid-induced depolymerization of paraformaldehyde.[6] Best results were obtained by using 6 equiv of 1,3,5-trioxane and 3 equiv of $BF_3 \cdot Et_2O$.[5]

The synthetic usefulness of dioxin vinylogous esters as β-keto vinyl cation equivalents was demonstrated by a variety of reductive and alkylative 1,3-carbonyl transpositions.[5,7] Regioselective alkylation and hydroxylation at the α'-position (and, in some cases, at the γ-position)[8,9] further extend the usefulness of 1,3-dioxin vinylogous ester templates in organic synthesis.

1. Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

6,7-Dihydrocyclopenta-1,3-dioxin-5(4H)-one: Cyclopenta-1,3-dioxin-5(4H)-one, 6,7-dihydro- (11); (102306-78-5)

1,3-Cyclopentanedione (8,9); (3859-41-4)

1,3,5-Trioxane (8,9); (110-88-3)

4 Å Molecular sieves: Zeolites, 4 Å (10); (70955-01-0*)

Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (BF$_3$) (1:1) (8); Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1) (9); (109-63-7)

3-CYCLOPENTENE-1-CARBOXYLIC ACID
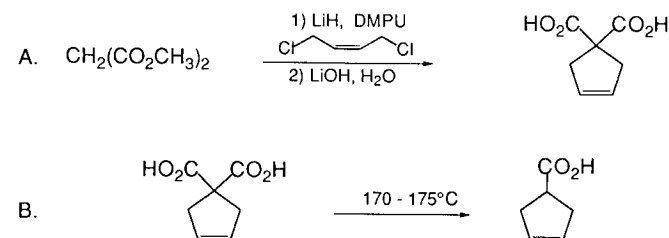
Submitted by Jean-Pierre Després and Andrew E. Greene.[1]

Checked by Tammy J. Clark and Robert K. Boeckman, Jr.

1. Procedure

Caution! These transformations should be carried out in an efficient hood.

A. 3-Cyclopentene-1,1-dicarboxylic acid. A dry, 1-L, two-necked, round-bottomed flask (Note 1), equipped with a Teflon-covered magnetic stirring bar, is charged under a current of nitrogen with 33.0 g (0.250 mol) of dimethyl malonate, 50 mL of dry N,N'-dimethylpropyleneurea, DMPU, and 450 mL of dry tetrahydrofuran, THF (Note 2). The resulting solution is cooled by means of an ice bath and treated with 5.00 g (0.629 mol) of lithium hydride powder in one portion (Note 3). The nitrogen flow is discontinued, and the flask is capped with rubber septa and connected to a Nujol-filled bubbler by means of a syringe needle. After 15 min, the cooling bath is removed and stirring is continued until hydrogen evolution is complete (ca. 2 hr), whereupon 28.4 mL (0.269 mol) of cis-1,4-dichloro-2-butene (Note 4) is rapidly added by syringe. The mixture is heated by means of an oil bath at 40-45°C for 24 hr (Note 5). After the mixture is cooled to 20°C, 50 mL of water is added dropwise followed by 31.5 g (0.750

mol) of solid lithium hydroxide monohydrate. After the reaction mixture is stirred at 20°C for an additional 24 hr, it is treated with 350 mL of water, stirred for 10 min, and then transferred to a 2-L separatory funnel. Neutral material is removed by extraction with five 500-mL portions of ethyl acetate, each of which is back-washed with 30 mL of aqueous saturated sodium chloride solution. The combined aqueous phases are then acidified with 160 mL of 6 N hydrochloric acid, and extracted three times with 500-mL portions of ethyl acetate. The ethyl acetate extracts are combined, washed three times with 100 mL of 3 N hydrochloric acid and twice with 50 mL of aqueous saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. After removal of traces of solvent under high vacuum (1 hr at 0.1 mm), 35.8 g (92%) of 3-cyclopentene-1,1-dicarboxylic acid is obtained as an off-white solid, mp 163-165°C (Note 6).

B. *3-Cyclopentene-1-carboxylic acid.* A 250-mL, one-necked, round-bottomed flask is charged with 35.8 g of 3-cyclopentene-1,1-dicarboxylic acid and then fitted with a reflux condenser capped with a rubber septum and connected to a Nujol-filled bubbler by means of a syringe needle. The contents of the flask are heated in an oil bath at 170-175°C until carbon dioxide evolution is complete (ca. 2 hr) and then allowed to cool to room temperature. The resulting oil is transferred to a 50-mL flask and vacuum distilled without fractionation to provide 23.0 g (89% or 82% overall from dimethyl malonate) of 3-cyclopentene-1-carboxylic acid as a clear, colorless oil, bp 88°C (2 mm) (Note 7).

2. Notes

1. All glassware was oven-dried and allowed to cool in a desiccator before use.

2. Dimethyl malonate (98%) was obtained from Fluka Chemical Corp., and DMPU was purchased from Aldrich Chemical Company, Inc. DMPU was distilled from calcium hydride under reduced pressure and tetrahydrofuran was distilled from the sodium ketyl of benzophenone prior to use. The checkers employed dimethyl malonate obtained from Aldrich Chemical Company, Inc.

3. Lithium hydride powder was obtained from Acros Organics. The checkers obtained lithium hydride from Aldrich Chemical Company, Inc.

4. cis-1,4-Dichloro-2-butene was either purchased from Aldrich Chemical Company, Inc. or prepared[2] from cis-2-butene-1,4-diol (Fluka Chemical Corp.). The checkers used cis-1,4-dichloro-2-butene obtained from Aldrich Chemical Company, Inc.

5. The submitters report that dimethyl 3-cyclopentene-1,1-dicarboxylate (with <1% of the vinyl isomer)[2,3] can be isolated at this stage in 92% yield and then transformed to methyl 3-cyclopentene-1-carboxylate[4] with lithium chloride in wet dimethyl sulfoxide (DMSO)[5] in 85% yield.

6. The checkers obtained a yield of 99% for the diacid, mp 160-163°C. Melting points of 164-169°C,[2] 170-172°C,[2] and 162-165°C[3] have been reported for this compound. The diacid has the following spectral properties: IR (Nujol) cm^{-1}: 3067, 1698, 1623; ^{1}H NMR [CDCl$_3$-CD$_3$COCD$_3$ (8:2), 300 MHz] δ: 3.08 [s(br), 4 H], 5.63 [s(br), 2 H], 10.90 [s(br), 2 H]; ^{13}C NMR [CDCl$_3$-CD$_3$COCD$_3$ (8:2), 75 MHz] δ: 46.5, 64.3, 133.1, 178.5.

7. The checkers obtained yields of 91-93% for the acid, bp 81-83°C (1.7 mm). Distillation temperatures of 83-84°C (2 mm)[2] and 70°C (1 mm)[3] have been reported

for this compound. The acid has the following spectral properties: IR cm^{-1}: 3060, 1707, 1623; ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 2.70 (m, 4 H), 3.12-3.25 (m, 1 H), 5.68 [s(br), 2 H], 11.96 [s(br), 1 H]; ^{13}C NMR (CDCl$_3$, 75 MHz) δ: 36.2, 41.5, 129.2, 182.5.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The preparation described here of 3-cyclopentene-1-carboxylic acid from dimethyl malonate and cis-1,4-dichloro-2-butene is an optimized version of a method reported earlier[3] for obtaining this often used and versatile building block.[6] The procedure is simple and efficient and requires only standard laboratory equipment. 3-Cyclopentene-1-carboxylic acid has previously been prepared through reaction of diethyl malonate with cis-1,4-dichloro(or dibromo)-2-butene in the presence of ethanolic sodium ethoxide, followed by hydrolysis of the isolated diethyl 3-cyclopentene-1,1-dicarboxylate intermediate, fractional recrystallization of the resultant diacid to remove the unwanted vinylcyclopropyl isomer, and finally decarboxylation.[2,7] Alternatively, this compound can be obtained from the vinylcyclopropyl isomer (prepared from diethyl malonate and trans-1,4-dichloro-2-butene)[8] or from cyclopentadiene[9] or cyclopentene.[10] In comparison with the present procedure, however, all these methods suffer from poor selectivity, low yields, length, or need of special equipment or reagents, if not a combination of these drawbacks.

1. LEDSS, Chimie Recherche, Université Joseph Fourier, BP 53, 38041 Grenoble Cédex 9, France.

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6. For selected recent examples, see: Hodgson, D. M.; Witherington, J.; Moloney, B. A. *J. Chem. Soc., Perkin Trans. I* **1994**, 3373-3378; Norman, M. H.; Almond, M. R.; Reiter, B. E.; Rahim, S. G. *Synth. Commun.* **1992**, *22*, 3197-3204; Herndon, J. W.; Wu, C.; Harp, J. J. *Organometallics* **1990**, *9*, 3157-3171; McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942-6949; Pauls, H. W.; Krantz, A. *Synthesis* **1989**, 50-51; Hutchison, A.; Grim, M.; Chen, J. *J. Heterocycl. Chem.* **1989**, *26*, 451-452; Jacobson, K. A.; De La Cruz, R.; Schulick, R.; Kiriasis, L.; Padgett, W.; Pfleiderer, W.; Kirk, K. L.; Neumeyer, J. L.; Daly, J. W. *Biochem. Pharmacol.* **1988**, *37*, 3653-3661; Paquette, L. A.; Lin, H-S.; Gunn, B. P.; Coghlan, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 5818-5826; Deshpande, M. N.; Wehrli, S.; Jawdosiuk, M.; Guy, Jr., J. T.; Bennett, D. W.; Cook, J. M.; Depp, M. R.; Weiss, U. *J. Org. Chem.* **1986**, *51*, 2436-2444. For several earlier references, see ref. 3.

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10. Hoberg, H.; Ballesteros, A.; Sigan, A.; Jegat, C.; Milchereit, A. *Synthesis* **1991**, 395-398.

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

3-Cyclopentene-1-carboxylic acid (8,9); (7686-77-3)

3-Cyclopentene-1,1-dicarboxylic acid (11); (88326-51-6)

Dimethyl malonate: Malonic acid, dimethyl ester (8); Propanedioic acid, dimethyl ester (9); (108-59-8)

N,N'-Dimethylpropyleneurea [DMPU]: 2(1H)-Pyrimidinone, tetrahydro-1,3-dimethyl- (8,9); (7226-23-5)

Lithium hydride (8,9); (7580-67-8)

cis-1,4-Dichlorobut-2-ene: 2-Butene, 1,4-dichloro-, (Z)- (8,9); (1476-11-5)

Lithium hydroxide monohydrate (8); Lithium hydroxide, monohydrate (9); (1310-66-3)

USE OF 1,2,4,5-TETRABROMOBENZENE AS A 1,4-BENZADIYNE EQUIVALENT: anti- AND syn-1,4,5,8-TETRAHYDROANTHRACENE 1,4:5,8-DIEPOXIDES

(1,4:5,8-Diepoxyanthracene, 1,4,5,8-tetrahydro-, (1α,4α,5β,8β)- and (1α,4α,5α,8α)- from benzene, 1,2,4,5-tetrabromo-)
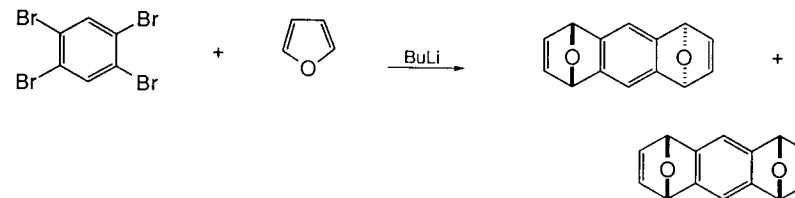
Submitted by Khalil Shahlai, Samuel Osafo Acquaah, and Harold Hart.[1]
Checked by John Leazer and Amos B. Smith, III.

1. Procedure

An oven-dried, 3-L, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a 250-mL pressure-equalizing dropping funnel and an argon inlet is charged with 1500 mL of dry toluene (Note 1), 145 mL (2.0 mol) of freshly distilled furan (Note 2) and 39.4 g (0.1 mol) of 1,2,4,5-tetrabromobenzene (Notes 3, 4). In an argon atmosphere, the solution is cooled to -23°C (dry ice, CCl_4) and 131 mL (2.1 equiv) of 1.6 M butyllithium in hexanes (Note 5) is added dropwise over 1 hr. After addition is complete, the mixture is allowed to warm to room temperature (1-2 hr) and is stirred at this temperature for 3 hr. The reaction is quenched by dropwise addition of 10 mL of methanol.

The flask contents are transferred to a separatory funnel, washed with 100 mL of water, 100 mL of saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent is removed by rotary evaporator and the solid residue is triturated with three portions of cold (0-5°C) methanol (50 mL, then 20 mL twice). The insoluble product is filtered, air dried, and recrystallized from acetone to give as the first crop 3.0-3.4 g of the pure anti isomer (Notes 6, 7) mp (dec) > 250°C (Note 8). Additional crystallizations bring the yield to 4.6 g (22%).

The methanol extracts and mother liquor from the final recrystallization of the anti isomer are combined and evaporated to dryness (rotavap). The residue is dissolved in 50 mL of boiling ethyl acetate in a 250-mL Erlenmeyer flask, to which is then added 150 mL of boiling hexanes. The solution is allowed to cool to room temperature and to stand at that temperature for 2-3 hr. Filtration yields the first crop of syn isomer (approximately 3.6 g). Second and third crops of product are obtained by evaporating the mother liquor to dryness and crystallizing the residue from the same solvent mixture (1:3 ethyl acetate/hexanes) (Note 9), to give a total of 5.3 g (25%) of syn isomer, mp 192-194°C (Notes 10, 11).

2. Notes

1. Toluene was distilled from sodium metal. The checkers used HPLC grade toluene as received.

2. Furan was distilled over anhydrous potassium carbonate. Excess furan is necessary to trap the aryne intermediates.

3. 1,2,4,5-Tetrabromobenzene used from sources other than Lancaster Synthesis contained trace amounts of an impurity that carried through the entire reaction scheme. This impurity gave a proton resonance at 1.58 ppm in the starting bromide and in both the syn and anti isomeric products. This impurity could not be removed by column chromatography.

4. All the tetrabromobenzene should be in solution before cooling the mixture. The checkers noted that all the tetrabromide did not dissolve even upon prolonged stirring.

5. Butyllithium was purchased from Aldrich Chemical Company, Inc. If fresh, it may be used directly without titration; otherwise it should be titrated.[2] More dilute and/or more concentrated (i.e., 2.5 M) butyllithium in hexanes can be used without altering the yield.

6. Two additional crystallizations, each preceded by reducing the volume of the mother liquor, give an additional 0.8-1.2 and 0.2-0.4 g of anti isomer. The principal constituent of the final mother liquor is the syn isomer.

7. The purity of the isomers is tested by thin layer chromatography (precoated plastic sheets, 0.2 mm silica gel N-HR/UV_{254}) with 3:2:1 hexanes/dichloromethane/ether as the eluant, developed in an iodine chamber; R_f (anti) = 0.45, (syn) = 0.38. The first crop of anti isomer is nearly free of syn contaminant, but the next crops contain 2-3% of the syn isomer. The ^{1}H NMR spectra of the two isomers are virtually identical: [1]H δ: 5.62 (s, 4 H), 7.01 (s, 4 H), 7.18 (s, 2 H). The syn and anti isomers display slight chemical shift differences in the 125 MHz ^{13}C NMR: anti isomer: 147.84, 143.88, 114.05 and 82.35 ppm; syn isomer: 147.85; 143.56; 113.82 and 82.37 ppm.

8. The anti isomer does not melt, but begins to decompose (gas evolution) just above 250°C.

9. One cannot simply reduce the volume of the mother liquor for the second and third crystallizations because of the changing ratio of the solvents.

10. This product contains small amounts (2-3%) of the anti isomer, which cannot be removed by further recrystallization from these or several other solvent systems.

Pure syn product, free of anti isomer, can be obtained by column chromatography over silica gel (230-400 mesh) using the same 3-component eluant as for analysis (Note 7).

11. If, instead of purification by crystallization, the crude anti/syn product mixture is chromatographed directly using the 3-component eluant, it is possible to increase the yield of each pure isomer to approximately 30%.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Wittig and Härle were the first to use tetrahaloarenes as diaryne equivalents.[3] From 1,4-dibromo-2,5-difluorobenzene, butyllithium and furan (in THF) they isolated the mono- and bis-adducts shown.

(45%)   (5%)
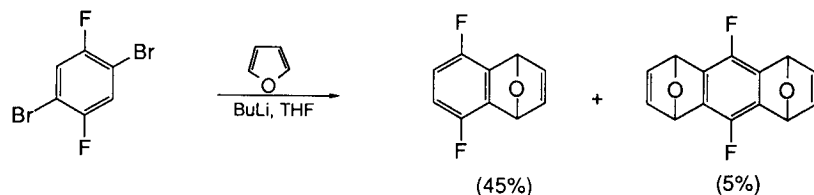
These products obviously arose from metallation at unsubstituted ring positions in the starting tetrahalobenzene. To force metallation at the carbon-bromine bonds, they used 2,6-dibromo-3,5-difluoro-p-xylene which, with magnesium in THF gave mainly mono-adduct. With butyllithium, only the bis-adduct was obtained (15%). No mention was made of syn/anti isomers of the bis-adducts.
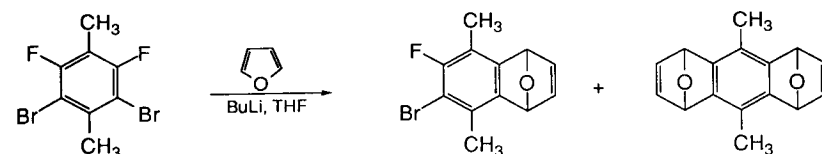
Replacement of the fluorines by bromines,[4,5] as in the procedure described here, resulted in several major improvements that made the reaction synthetically useful: (a) ring metallation is completely suppressed, (b) the starting material is either commercially available, as in the present example, or much more easily synthesized than corresponding fluorobromo analogues.

The methodology is useful for a variety of synthetic purposes. The cycloadditions are not subject to steric hindrance. Thus 'diyne' cycloadditions to 2,5-disubstituted furans or pyrroles, followed by elimination of the oxygen or nitrogen bridges, provides an excellent, short route to peri-substituted arenes, as in the following examples:[4,6-8]

X=O,-NCH₃,-NNH₂

Ti° (X=O)
m-CPBA (X=NCH₃)
Δ(X=NNH₂)

R=CH₃, OCH₃
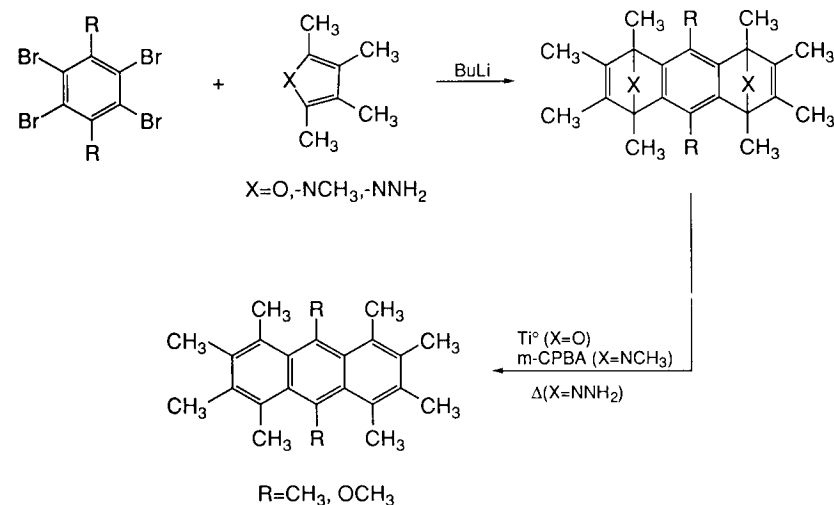
Similar sequences starting with appropriate 1,2,3,4-tetrahaloarenes (1,3-diaryne equivalents) yield hindered phenanthrenes.[9] Cyclopentadienes,[7] fulvenes,[7] isoindoles,[7] anthracenes[10] and other dienes[11] have also been used as 'diaryne' traps.

The procedure given here is a modification of the first synthesis of the tetrahydroanthracene diepoxides.[5,7] These compounds have also been prepared from another 1,4-benzadiyne equivalent, namely 1,5-diamino-1,5-dihydrobenzo[1,2-d:4,5-d']bistriazole which, although it has certain advantages,[12] is not as available as 1,2,4,5-tetrabromobenzene.
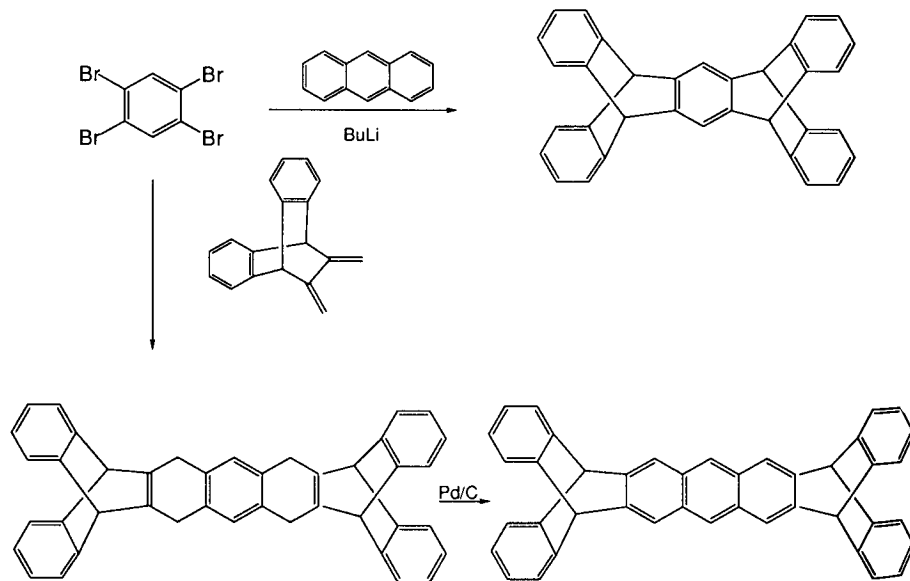
The diepoxide products obtained as described here are excellent bis-dienophiles; hence, they are useful starting materials for further synthesis. They have been used to generate linear acenes,[13,14] iptycenes,[5] and related tetraenes,[15] as exemplified by the following sequence:
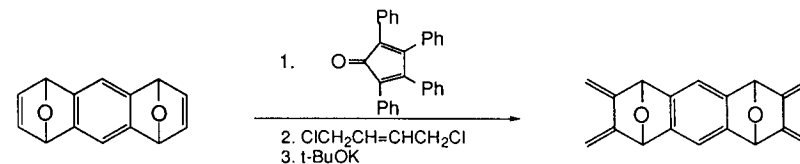
They have served as starting points for the synthesis of molecular belts, collars, and strips.[16]

Finally, it should be pointed out that the diaryne reactions of 1,2,4,5-tetrabromobenzene are stepwise. Thus the procedure described here, but using half the amounts of furan and butyllithium, can be used to prepare 6,7-dibromonaphthalene 1,4-endoxide (mp 115-117°C) in 70% yield.[17] This versatile intermediate can then be used as a benzyne precursor, to make unsymmetric adducts;[7,13,17] it also can be used as a dienophile.[15,18]
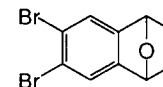
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2. See "Vogel's Textbook of Practical Organic Chemistry", 5th ed.; 1989; p. 443.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

1,2,4,5-Tetrabromobenzene: Benzene, 1,2,4,5-tetrabromo- (8,9); (636-28-2)

anti-1,4,5,8-Tetrahydroanthracene 1,4:5,8-diepoxide: 1,4:5,8-Diepoxyanthracene, 1,4,5,8-tetrahydro-, (1α,4α,5β,8β)- (11); (87207-46-3)

syn-1,4,5,8-Tetrahydroanthracene 1,4:5,8-diepoxide: 1,4:5,8-Diepoxyanthracene, 1,4,5,8-tetrahydro-, (1α,4α,5α,8α)- (11); (87248-22-4)

Furan (8,9); (110-00-9)

Butyllithium: Lithium, butyl- (11); (109-72-8)

SYNTHESIS OF 8,8-DICYANOHEPTAFULVENE FROM CYCLOHEPTATRIENYLIUM TETRAFLUOROBORATE AND BROMOMALONONITRILE

(Propanedinitrile, 2,4,6-cycloheptatrien-1-ylidene-)
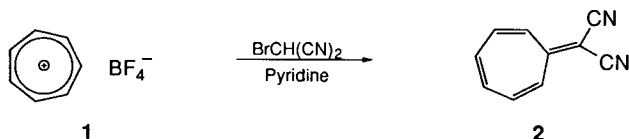
Submitted by Hitoshi Takeshita, Akira Mori, and Kanji Kubo.[1]
Checked by Yuping Qiu and Amos B. Smith, III.

1. Procedure

Caution! All operations should be conducted in a well-ventilated hood with breathing protection.

An oven-dried, 1-L, three-necked, round-bottomed flask, equipped with a nitrogen gas inlet, magnetic stirring bar, dropping funnel, thermometer, and condenser, under an inert nitrogen atmosphere, is placed in an ice bath and charged, while stirring, with 500 mL of pyridine and 17.79 g of cycloheptatrienylium tetrafluoroborate 1[2] (0.1 mol) at 0°C (Note 1). Bromomalononitrile (14.49 g, 0.1 mol) (Note 2) is added drop by drop within a 10-min period, and the mixture is vigorously stirred at that temperature for 1 hr. The ice bath is replaced by a water bath, the temperature is gradually raised to 40°C, and the stirring mixture is kept at that temperature for 5 hr. The solvent is distilled off under reduced pressure below 40°C. To the resultant residue, 1 L of chloroform (CHCl₃) is added and the solution is filtered

to remove insoluble pyridinium tetrafluoroborate. The chloroform solution is evaporated to remove a trace amount of pyridine (Note 3), and the residue is chromatographed with Wakogel C-300 (400 g) and chloroform (Note 4). The red solution that is eluted is evaporated and the mass obtained recrystallized from ethanol to yield 12.34 g (80.0% of 8,8-dicyanoheptafulvene, 2, red needles, mp 199-200°C (lit.[3a] 198-199°C, lit.[3b] 201-202°C) (Note 5).

2. Notes

1. Pyridine, purified by distillation immediately before use must be anhydrous. Cycloheptatrienylium (tropylium) tetrafluoroborate, 1, was prepared by the method of Conrow[2] and its purity was at least 99%. Aldrich Chemical Company, Inc., also provides 1.

2. Bromomalononitrile was prepared by bromination of malononitrile by the method of Ferris, et al.[4] To this end, bromine (48.5 g, 0.30 mol) was added over a period of 5 hr to malononitrile (20 g, 0.30 mol) dissolved in water (300 mL) in an ice bath, and kept overnight under those conditions. A slight brown-white precipitate separated from the solution. It was washed with water and taken up in CHCl₃ (100 mL). After drying (Na₂SO₄) and concentrating under reduced pressure to about one half the original volume, the solution was cooled in a refrigerator to deposit colorless crystals, which were then purified by recrystallization from CHCl₃ to give 21 g (48%) of the desired bromomalononitrile, mp 63-64°C (Ferris, et al.,[4] reported 20% yield).

3. Prior to chromatography, pyridine must be thoroughly eliminated by distillation. Use of dilute acid fractionation gave an inferior result.

4. From the less polar yellowish fractions, β,β-dicyanostyrene (0.23 g, 1.5%) was obtained before elution of the desired compound.

5. 8,8-Dicyanoheptafulvene **2** had the following spectroscopic properties: ^{1}H NMR (500 MHz, CDCl$_3$) δ: 6.88-7.00 (m, 4 H) and 7.34 (dm, 2 H, J = 12.1); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 70.1, 114.6 (2C), 135.4 (2C), 137.4 (2C), 138.9 (2C), and 163.7; IR (KBr) cm^{-1}: 2196, 1634, 1584, 1520, 1488, 1404, 1372, 1267, 886, 829, 763, 603, and 538.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Previously, 8,8-dicyanoheptafulvene, **2**, was prepared by (a) thermolysis of 2,2-bis(cycloheptatrienyl)malononitrile[3a] and (b) acetic anhydride-mediated condensation of tropone with malononitrile.[3b] Since 8,8-dicyanoheptafulvene, **2**, is a representative stable heptafulvene, its synthetic utility and potential for functional materials warrant an efficient synthesis. As method (a) involves disproportionation of two cycloheptatriene units, and method (b) uses tropone derivatives as the starting material, it was desirable to develop a practical method of synthesizing 8,8-dicyanoheptafulvene, **2**, from the cycloheptatrienylium salt. The late Kitahara and co-workers attempted the preparation of 8,8-dicyanoheptafulvene, **2**, based on this concept. Although they were partially successful, no experimental information is available; the literature[5] simply states that (an unspecified) base-treatment of cycloheptatrienylium salt with bromomalononitrile, according to Kitahara, formed β,β-dicyanostyrene.

The present procedure emphasizes pyridine as the solvent with mild heating. When pyridine is partially replaced with acetonitrile, the yield of 8,8-dicyanoheptafulvene, **2**, drops to less than 40%.

The present procedure is applicable only to bromomalononitrile; various α-halogen active methylene derivatives, (e.g., diethyl chloromalonate, methyl bromoacetoacetate) led predominantly to the formation of ring-contracted styrene derivatives. On the other hand, substituted cycloheptatrienylium salts with bromomalononitrile gave the desired dicyanoheptafulvene derivatives in excellent yields. One notable example is the synthesis of 5- and 7-(dicyanomethylene)-2,3-dihydrocyclohepta-1,4-dithiins.[6]

1. Institute of Advanced Material Study, 86, Kyushu University, Kasuga-koen, Kasuga, Fukuoka, 816, Japan. Professor Takeshita's present address: Tohwa Institute for Science, Tohwa University, Chikushi-ga-oka, Minami-ku, Fukuoka, 815 Japan.

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Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

8,8-Dicyanoheptafulvene: 2,4,6-Cycloheptatriene-$\Delta^{1,\alpha}$-malononitrile (8);

Propanedinitrile, 2,4,6-cycloheptatrien-1-ylidene- (9); (2860-54-0)

Cycloheptatrienylium tetrafluoroborate: Aldrich: Tropylium tetrafluoroborate:

Cycloheptatrienylium, tetrafluoroborate (1-) (8,9); (27081-10-3)

Bromomalononitrile, Malononitrile, bromo- (8); Propanedinitrile, bromo- (8);

(1885-22-9)

Pyridinium tetrafluoroborate: Pyridine, tetrafluoroborate (1-) (8,9); (505-07-7)

Malononitrile: HIGHLY TOXIC (8); Propanedinitrile (9); (109-77-3)

Bromine (8,9); (7726-95-6)

N-VINYLPYRROLIDIN-2-ONE AS A 3-AMINOPROPYL CARBANION EQUIVALENT IN THE SYNTHESIS OF SUBSTITUTED 1-PYRROLINES: 2-PHENYL-1-PYRROLINE

(2H-Pyrrole, 3,4-dihydro-5-phenyl-)
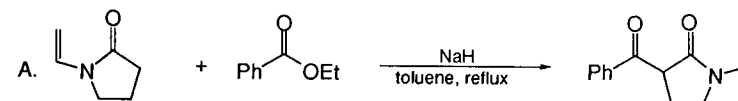
Submitted by Kirk L. Sorgi, Cynthia A. Maryanoff, David F. McComsey, and Bruce E. Maryanoff.[1]

Checked by Christopher Deur and Louis S. Hegedus.

1. Procedure

A. 3-Benzoyl-N-vinylpyrrolidin-2-one. A dry, 2-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, addition funnel, heating mantle, and reflux condenser, is charged with 26.7 g (0.665 mol) of 60% sodium hydride (NaH, Note 1) and 250 mL of dry toluene (Note 2). The stirred suspension is heated at reflux while a mixture of 55.0 g (0.50 mol) of freshly distilled N-vinylpyrrolidin-2-one (Note 3) and 75.0 g (0.50 mol) of ethyl benzoate (Note 4) is slowly added (Note 5). Heating is continued for 10 hr (Note 6). The reaction mixture is cooled to room temperature and the resultant thick slurry is carefully diluted with 250 mL of saturated, aqueous

ammonium chloride. The layers are separated and the aqueous layer is extracted again with 250 mL of toluene. The combined organic layers are dried (MgSO₄) and concentrated under reduced pressure to afford 108 g (>100%) of crude keto lactam product as an amber oil that may solidify on standing (Note 7).

B. *2-Phenyl-1-pyrroline.* A 2-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, addition funnel, heating mantle, reflux condenser, and a short-path distilling head, is charged with 0.5 L of 6 N hydrochloric acid and heated at reflux; 100 g (0.46 mol) of crude keto lactam is dissolved in 62.5 mL of tetrahydrofuran (THF) and the solution is slowly added, over 1.5-2 hr. Tetrahydrofuran is collected during the addition by use of the short-path distilling head (Note 8). Following the addition, the distilling head is removed and the solution is heated at reflux for 4 hr, cooled to room temperature, filtered through a plug of glass wool, cooled to 0°C, made basic to pH 12 by using aqueous 50% sodium hydroxide, and extracted with methylene chloride (3 x 100 mL). The combined organic layers are dried (MgSO₄) and concentrated under reduced pressure to afford 69.2 g of crude product as an amber oil. The residue is distilled at reduced pressure (1-3 mm) and the fraction boiling at 75-85°C is collected to afford 41.0 g (61% yield) of purified product as a clear, colorless oil that solidifies on standing (Note 9).

2. Notes

1. Sodium hydride was a 60% dispersion in mineral oil; 80% or 95% NaH can also be used.

2. Reagent grade toluene should be dried over 4 Å molecular sieves. Anhydrous tetrahydrofuran in SureSeal bottles from the Aldrich Chemical Company, Inc., can also be used.

3. Higher yields are obtained when freshly distilled N-vinylpyrrolidin-2-one is used.

4. Ethyl benzoate was used as received from the Aldrich Chemical Company, Inc.

5. The addition rate is determined by the rate of hydrogen evolution. Hydrogen evolution ceases before addition of the mixture is complete.

6. A thick precipitate forms at this time.

7. The crude keto lactam is used without further purification. However, the crude solid can be crystallized from warm 2-propanol to yield 68 g of material (63%): mp 66.5-69.5°C; ^{1}H NMR (400 MHz, CDCl₃) δ: 2.13-2.37 (m, 1 H), 2.65-2.75 (m, 1 H), 3.42-3.58 (m, 1 H), 3.58-3.74 (m, 1 H), 4.31-4.51 (m, 2 H), 4.57 (dd, 1 H, J = 9.4, 5.2), 7.01 (dd, 1 H, J = 15.9, 9.0, CH vinyl), 7.30-7.63 (m, 3 H), 7.64-7.47 (m, 2 H); IR (KBr) cm⁻¹: 1697, 1673, 1635, 1394, 1278, 816; MS (FAB) m/z 238 (M⁺ + Na), 216 (MH⁺), 105.

8. This high-dilution technique minimizes polymerization. To avoid formation of the brown polymer, the addition must be slow. The submitters recommend adding the keto lactam/THF solution over 1.5-2.0 hr to a vigorously boiling solution of 6 N hydrochloric acid. This addition time leads to high yields of product with minor amounts of dark polymer. It is also important to prevent hydrochloric acid vapors from coming in contact with the keto lactam/THF solution while it is in the addition funnel. This can be accomplished by passing a slow stream of an inert gas over the solution from the top of the addition funnel or by using an addition funnel without a pressure equalizing arm.

9. This material, which yellows on standing, was >95% pure by GLC analysis (DB-5 capillary column, 110°C for 2 min, increase at 30°/min to 290°C). Overall yields should range from 70-75%. The physical properties of 2-phenyl-1-pyrroline are as follows: mp 41.5-44.0°C; ^{1}H NMR (CDCl₃, 90 MHz) δ: 1.70-2.10 (m, 2 H), 2.60-2.97

(m, 2 H), 3.80-4.13 (m, 2 H), 7.13-7.47 (m, 3 H), 7.56-7.93 (m, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 22.41 (CH$_2$), 34.56 (CH$_2$), 61.34 (CH$_2$), 127.36 (CH), 128.12 (CH), 129.96 (CH), 134.40 (C), 172.69 (C=N); IR (CHCl$_3$) cm^{-1}: 3061, 2948, 2864, 1616, 1575, 1496, 1447, 1340, 1310, 1049, 991, 961; (EI, 70 ev) m/z 145 (M$^+$), 117, 104, 89, 77, 63, 51.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This method for preparing 2-phenyl-1-pyrroline, and assorted 2-substituted 1-pyrrolines, is one of the best currently available, particularly because it reproducibly affords clean materials. Generally, the procedure is amenable to various aromatic esters;[2] it has also been applied successfully to aliphatic esters (Table I).[3] An advantage of this method is the use of readily available, inexpensive N-vinyl-pyrrolidin-2-one as a key starting material. This compound serves effectively as a 3-aminopropyl carbanion equivalent. The method illustrated in this procedure has been extended to include the synthesis of 2,3-disubstituted pyrrolines. Thus, alkylation of the enolate of the intermediate keto lactam, followed by hydrolysis, leads to various disubstituted pyrrolines in good yields (see Table II).[3]

Other methods are available for the synthesis of 2-substituted 1-pyrrolines. A comparison study of their preparation from organolithium reagents and N-vinyl-pyrrolidin-2-one has been reported.[4] Additions of phenyllithium to N-acylpyrrolidin-2-one[5] and phenyl Grignard reagents to a methyl imidate derived from 2-pyrrolidinone[6] are also useful (although the latter process requires a strong methylating agent). Two

Friedel-Crafts methods[7] and the reaction of aroyl chlorides with 2-pyrrolidinone[8] have been described. There is also a useful procedure, similar to the one presented here, that employs N-trimethylsilylpyrrolidin-2-one.[9]

2-Phenyl-1-pyrroline is useful for various purposes.[10,11] In particular, its reduction product, 2-phenylpyrrolidine, is important in the synthesis of pyrroloisoquinoline antidepressants,[2c,12] and can be a starting point in alkaloid synthesis.[13] The overall reaction sequence described here has been used to prepare nicotine derivatives such as myosmine.[2a,b]

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

N-Vinyl-2-pyrrolin-2-one: 2-Pyrrolidinone, 1-vinyl-; 2-Pyrrolidinone, 1-ethenyl- (9); (88-12-0)

2-Phenyl-1-pyrroline: 1-Pyrroline, 2-phenyl- (8); 2H-Pyrrole, 3,4-dihydro-5-phenyl- (9); (700-91-4)

3-Benzoyl-N-vinylpyrrolidin-2-one: 2-Pyrrolidinone, 3-benzoyl-1-ethenyl-, (±)- (12); (125330-80-5)

Sodium hydride (8,9); (7646-69-7)
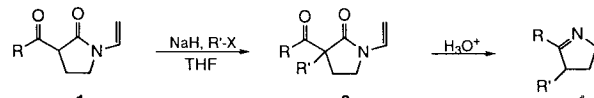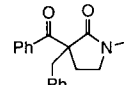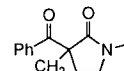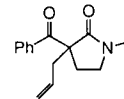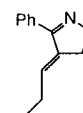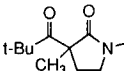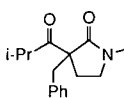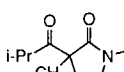
Ethyl benzoate: Benzoic acid, ethyl ester (8,9); (93-89-0)

TABLE I

PREPARATION OF 2-ALKYL-1-PYRROLINES

Entry	Ester	1	Yield 1 (%)[a]	2	Yield 2 (%)[b]
1	PhCH$_2$CO$_2$Et		96[c]		66
2	c-C$_6$H$_{11}$CO$_2$CH$_3$		99		73
3	CH$_3$(CH$_2$)$_8$CO$_2$CH$_3$		99		81
4	BnO(CH$_2$)$_3$CO$_2$CH$_3$		96		95[d]
5	i-PrCO$_2$CH$_3$		99		98
6	t-BuCO$_2$CH$_3$		99		98

a) Crude yield. b) Isolated purified yield from N-vinylpyrrolidin-2-one. c) Two equiv of NaH were used. d) Benzyl group was removed during the hydrolysis.

TABLE II

PREPARATION OF 2,3-DISUBSTITUTED-1-PYRROLINES

Entry	R	R'-X	3	Yield 3 (%)[a]	4	Yield 4 (%)[b]
1	Ph	PhCH$_2$Br		99 (70)		94[c]
2	Ph	CH$_3$I		99		87
3	Ph	H$_2$C=CHCH$_2$Br		92		86
4	t-Bu	CH$_3$I		97		82
5	i-Pr	PhCH$_2$Br		99		77
5	i-Pr	CH$_3$I		77		51

a) Crude yield. Bracketed yield is after purification by crystallization. b) Isolated purified yield from 1.
c) Yield from purified 3.

SYNTHESIS OF cis-4a(S),8a(R)-PERHYDRO-6(2H)-ISOQUINOLINONES FROM QUININE: 4a(S), 8a(R)-2-BENZOYLOCTAHYDRO-6(2H)-ISOQUINOLINONE

(6(2H)-Isoquinolinone, 2-benzoyloctahydro-, (4aS-cis)-)

A. Ph$_2$CO, Toluene / KO-t-Bu → 1

B. t-BuOK / O$_2$ / t-BuOH / THF

Cl-COPh / Pyridine CH$_2$Cl$_2$ → 2

C. H$_2$SO$_4$ / 0 °C → 30 °C → 3

D. H$_2$ / Pd-C / EtOH → 4
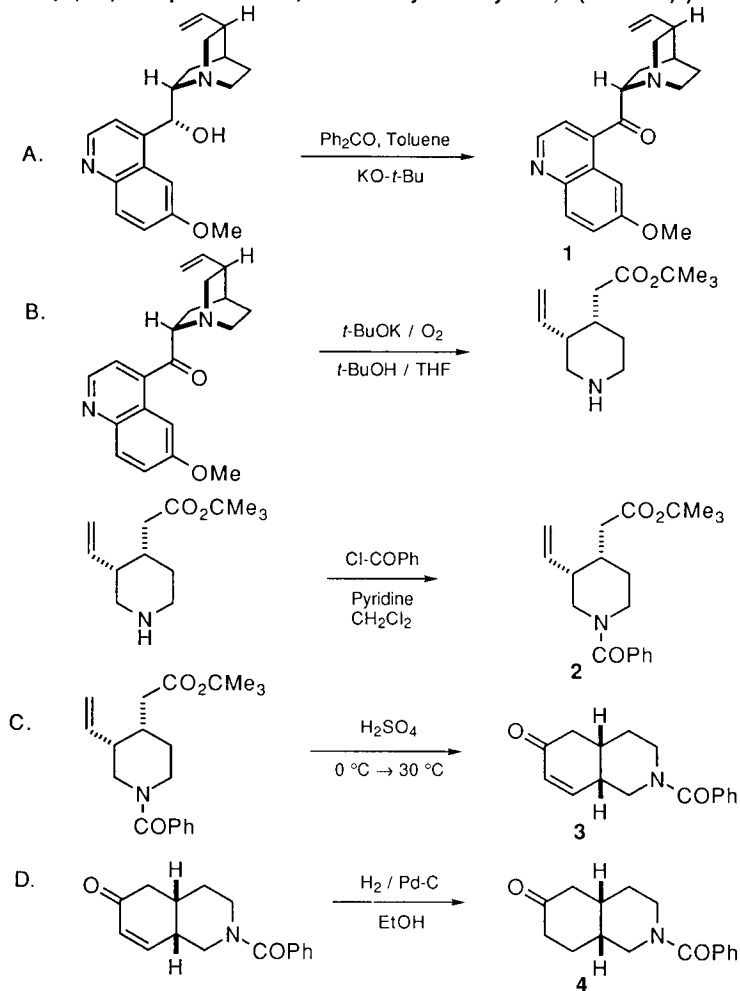
Submitted by Darrell R. Hutchison, Vien V. Khau, Michael J. Martinelli, Naresh K. Nayyar, Barry C. Peterson, and Kevin A. Sullivan.[1]

Checked by Zehong Wan and Amos B. Smith, III.

1.   Procedure

A. Quininone (**1**). A 2-L, three-necked, round-bottomed flask (Note 1) equipped with a mechanical stirrer, reflux condenser and a thermocouple is charged with 112.2 g (0.61 mol) of benzophenone (Note 2) and 600 mL of toluene (Note 3) under a positive pressure of nitrogen (N_2). Quinine, 111.11 g (0.31 mol) (Note 4), is then added in one portion (Note 5), followed by 87.1 g (0.78 mol) of potassium tert-butoxide (Note 6) added in one portion. The slurry is heated to reflux with an electric mantle for 8 hr (Note 7). The reaction mixture is allowed to cool overnight to room temperature and then to 5-10°C with an ice-water mixture. 2 N Hydrochloric acid (HCl), 400 mL, is added slowly keeping the temperature below 20°C. The contents of the flask are transferred to a 2-L separatory funnel with 300 mL of 2 N HCl. After two layers separate, the lower aqueous layer is collected in a 3-L Erlenmeyer flask, and the organic layer is washed with 2 N HCl (2 x 250 mL). The combined aqueous layers are cooled to 0-5°C and treated dropwise with 260 mL of 5 N sodium hydroxide (NaOH) with stirring to pH 9.5. An oil initially separates that becomes a yellow solid after vigorous stirring at 0-5°C. The solid is filtered using a Büchner funnel, rinsed with water (2 x 200 mL), and dried in an oven at 60°C for 48 hr to afford the ketone **1** as a light yellow solid weighing 97.9 g (98%, Note 8).

B. N-Benzoylmeroquinene tert-butyl ester (**2**). A 2-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, subsurface glass-fritted gas tube for oxygen (O_2) addition (the gas tube is also connected to a bubbler containing silicone oil to monitor the flow of oxygen gas), and a thermocouple. The flask is charged with 800 mL of tetrahydrofuran (THF) and 200 mL of tert-butyl alcohol (tert-BuOH). The solution is purged with O_2 under stirring for 15 min and then treated with 78.4 g of potassium tert-butoxide (0.70 mol) in one portion (Note 9). The yellow reaction mixture is cooled (ice bath) while the O_2 addition is continued for another 15 min. Crude quininone **1**, 90.0 g, (0.28 mol) is then added portionwise over 10 min with continued O_2 addition, resulting in a blood red mixture, concomitant with an exotherm to 35°C (Note 10). After the solution is stirred for 1.5 hr at ambient temperature, the gas purge is stopped and 80 mL of glacial acetic acid (HOAc) is added carefully with vigorous stirring. Volatile material is removed under reduced pressure at ≤ 50°C from the resulting thick slurry that is then suspended in 400 mL of water. The pH is adjusted to 10 by the addition of 60 mL of concd ammonium hydroxide (NH_4OH) and the aqueous solution is extracted with ether (4 x 200 mL), washed with a saturated solution of brine (3 x 250 mL, Note 11), dried over sodium sulfate (Na_2SO_4), filtered and concentrated (Note 12) to furnish meroquinene tert-butyl ester as a viscous oil (40.5 g, 64% crude recovery, Note 13). A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, thermocouple, addition funnel, condenser, and N_2 inlet is charged with 40.5 g (0.18 mol) of crude meroquinene tert-butyl ester and 235 mL of dichloromethane (CH_2Cl_2) (Note 14). Pyridine, 16.0 mL, (0.19 mol), (Note 15) is added, followed by dropwise addition of 25.0 mL (0.21 mol) of benzoyl chloride (Note 15) at a rate to maintain a gentle reflux over 15 min. Upon complete addition, the reaction mixture is stirred at ambient temperature for 2 hr (Note 16) and washed successively with H_2O (200 mL), 1 N HCl (2 x 150 mL), 2 N NaOH (2 x 150 mL), and brine (300 mL). The organic phase is dried over Na_2SO_4, filtered and concentrated to give the thick brown oily benzamide **2** (61.2 g, 100%, Note 17).

C. 4a(S),8a(R)-2-Benzoyl-1,3,4,4a,5,8a-hexahydro-6(2H)-isoquinolinone (**3**). A 1-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, Teflon-coated thermocouple, 500-mL addition funnel and a N_2 inlet. Concentrated sulfuric

acid (H_2SO_4), 275 mL is added to the flask and the flask is cooled to 0°C under N_2. The addition funnel is charged with a solution of 56.0 g (0.17 mol) of crude benzamide **2** in 60 mL of CH_2Cl_2, that is added dropwise over 15 min, maintaining the internal temperature between 0-10°C. Upon complete addition, the cooling bath is removed and the reaction mixture is stirred vigorously for another 2 hr (Note 18) as the temperature rises to 30°C. The reaction mixture is poured onto 1 kg of crushed ice with stirring and when the ice has melted the two layers are separated. The aqueous phase is extracted further with CH_2Cl_2 (4 x 200 mL). The combined organic phases are washed with water (2 x 500 mL), brine (500 mL), dried over Na_2SO_4, filtered, and concentrated to a light brown semisolid (Note 19) that is dissolved in 100 mL of CH_2Cl_2 and precipitated with 250 mL of hexanes to furnish 34.7 g (80%) of enone **3** as light yellow crystals (Note 20).

D. 4a(S),8a(R)-2-Benzoyloctahydro-6(2H)-isoquinolinone (**4**). Palladium (Pd), 10% on carbon, 4.0 g, (Note 21) is placed in a 500-mL Parr bottle under N_2 and carefully wetted with 50 mL of cold denatured ethanol (EtOH). A slurry of 34.7 g of enone **3** (0.14 mol) in denatured EtOH (250 mL) is added and the Parr shaker apparatus assembled. After the system is purged with nitrogen-hydrogen (N_2/H_2), the reaction is shaken at 50 psi H_2 and 50°C until H_2 uptake is complete (1 hr, Note 22). The catalyst is filtered over a Celite pad (Note 23) and rinsed with warm chloroform ($CHCl_3$) (4 x 75 mL). The filtrate is concentrated under reduced pressure, dissolved in 90 mL of CH_2Cl_2 and crystallized with 200 mL of hexanes. The crystalline solid is filtered, rinsed with hexanes and dried to afford 34.3 g (98%, Note 24) of the ketone **4**, representing a 51% yield over four steps.

2. Notes

1. All glass apparatus was dried thoroughly under a flow of dry N_2. All ground glass joints were tightly sealed with Teflon tape and then wrapped with Parafilm. All the preparations were performed in an efficient fume hood while wearing gloves and adequate eye protection.

2. Benzophenone purchased from Aldrich Chemical Company, Inc. was used as received.

3. Toluene, dichloromethane, acetic acid, ammonium hydroxide, concentrated H_2SO_4, 5 N NaOH and 37% HCl were purchased from Mallinckrodt Inc.; tetrahydrofuran, tert-butyl alcohol, anhydrous Na_2SO_4, and NaCl were purchased from EM Science; potassium tert-butoxide was purchased from Aldrich Chemical Company, Inc.; hexanes was purchased from Baxter, and dry O_2 was purchased from Air Products. All these reagents were used as received.

4. Quinine (purity 90%) purchased from Aldrich Chemical Company, Inc., was used as received.

5. A mild endotherm was noted: the temperature fell from 22°C to 19°C.

6. The color changed to yellowish brown immediately upon addition of potassium tert-butoxide and a mild exotherm was noted, as the temperature rose to 29°C.

7. The slurry became very thick as the temperature approached reflux, requiring vigorous stirring. The color of the mixture gradually changed to dark orange and at the end of the reaction the color was fluorescent orange.

8. The material was sufficiently pure as determined by HPLC (Zorbax C-8 column RX 25 cm; flow rate 2.5 mL/min; mobile phase acetonitrile / water (1:1); UV detection at 254 nm showed four peaks t_R(min.) at 0.9 (quinine), 1.3 (quininone), 4.4 (toluene), 5.4 (benzophenone). A part of this material (8.0 g) was dissolved in 250 mL

of diethyl ether at room temperature, left in a freezer for 48 hr, and 6.9 g of light yellow solid was obtained upon filtration; mp 102-104°C.

9. The reaction mixture displayed an exotherm from ambient temperature to 35°C.

10. Quininone was added at a rate to keep the temperature below 25°C; otherwise the yield of this step was much lower. Oxygen uptake increased upon the addition of quininone, but slowed as the reaction proceeded (15 min).

11. If three phases result, add the minimum amount of water (100 mL) that affords two phases (some color in the aqueous phase was noted). Additional quantities of water should be avoided because of the high water solubility of the product.

12. The product was concentrated under reduced pressure at room temperature, but concentration at higher temperature resulted in a lower yield (35-40%).

13. Any attempts to purify the product by distillation resulted in lower yields because of pyrolysis. The undistilled product was sufficiently pure for most purposes. The yield range was 60-75%; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 1.32-1.63 (m, 11 H), 2.02-2.30 (m, 4 H), 2.63-3.06 (m, 4 H), 4.90-5.18 (m, 2 H), 6.01-6.10 (m, 1 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 28.1, 28.9, 35.7, 39.4, 43.0, 46.1, 51.4, 80.1, 116.6, 137.2, 172.3.

14. Six volumes of CH$_2$Cl$_2$ are used to ensure efficient stirring, since a solid separates after the addition of benzoyl chloride.

15. Reagent grade pyridine and benzoyl chloride were purchased from Aldrich Chemical Company, Inc., and used as received.

16. The reaction appeared complete by HPLC. R$_f$ for the product=0.54 (by TLC analysis on silica gel 60 F-254 precoated plates, hexanes:EtOAc, 1:1, freshly prepared).

17. The crude product was sufficiently pure and used as such for the next step (purification by column chromatography using hexanes:EtOAc, 4:6 as an eluant affords a 92-95% yield of the purified product). A part of the crude product (5.0 g) was crystallized from 50 mL of diethyl ether to furnish light yellow needles; mp 62-64°C (lit.[5] mp 65-67°C); ^{1}H NMR (500 MHz, CDCl$_3$) δ: 1.39-1.52 (m, 11 H), 2.08-2.31 (m, 3 H), 2.33-2.65 (m, 1 H), 2.97-3.25 (m, 2 H), 3.65-3.75 (m, 1 H), 4.50-4.74 (m, 1 H), 5.08-5.12 (m, 2 H), 5.79-5.92 (m, 1 H), 7.31-7.41 (m, 5 H); ^{1}H NMR (CD$_3$SOCD$_3$, 25°C) δ: 1.39 (m, 11 H), 2.02-2.55 (m, 4 H), 2.90-3.50 (m, 3 H), 4.21-4.42 (m, 1 H), 4.90-5.12 (m, 2 H), 5.76-5.94 (m, 1 H), 7.31-7.41 (m, 5 H); ^{1}H NMR (CD$_3$SOCD$_3$, 90°C) δ: 1.39-1.51 (m, 11 H), 2.04-2.21 (m, 3 H), 2.41-2.49 (m, 1 H), 3.06 (ddd, 1 H, J = 2.7, 3.7 and 10.7), 3.24 (dd, 1 H, J = 3.2 and 13.2), 3.91-4.00 (m, 2 H), 5.02-5.13 (m, 2 H), 5.78-5.87 (m, 1 H), 7.31-7.41 (m, 5 H).; ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 28.1, 35.8, 38.7, 42.2, 46.0, 47.5, 52.4, 80.4, 118.1, 127.0, 128.3, 129.4, 134.7, 136.2, 170.8, 171.8.

18. The color of the reaction mixture changed from light yellow to dark brown at the end of the reaction with the formation of solid particles. The reaction appeared complete by TLC analysis (silica gel 60 F-254 precoated plates, hexanes:ethyl acetate, 2:8, freshly prepared); R$_f$ for benzoyl derivative = 0.74, R$_f$ for enone = 0.25.

19. HPLC of the crude product indicated the presence of only cis isomer; no trans isomer was detected in the crude product; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 1.52-1.82 (m, 2 H), 2.47-2.56 (m, 3 H), 2.82-2.96 (m, 1 H), 3.21-3.41 (m, 1 H), 3.50 (dd, 1 H, J = 13.5 and 4.1), 3.52-3.72 (m, 1 H), 4.35-4.45 (m, 1 H), 6.09 (d, 1 H, J = 9.7), 6.85-7.05 (m, 1 H), 7.27-7.42 (m, 5 H); ^{1}H NMR (CD$_3$SOCD$_3$, 25°C) δ: 1.35-1.70 (m, 2 H), 2.46-2.50 (m, 3 H), 2.82 (m, 1 H), 3.22-4.08 (m, 4 H), 5.98 (m, 1 H), 6.92 (m, 1 H), 7.34-7.44 (m, 5 H); ^{1}H NMR (CD$_3$SOCD$_3$, 90°C) δ: 1.46-1.59 (m, 2 H), 2.48-2.50 (m, 2 H), 2.80 (m, 1 H), 3.01 (m, 1 H), 3.22-3.31 (m, 1 H), 3.51 (dd, 1 H, J = 4.2 and 13.4), 3.60-3.64 (m, 1 H), 3.84-3.87 (m, 1 H), 5.9 (dd, 1 H, J = 2.2 and 10.1), 6.77 (dd, 1 H, J = 3.0 and 9.8), 7.33-7.45 (m, 5 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 27.2, 33.8, 37.0, 41.8, 44.9, 46.2, 126.8, 128.6, 129.8, 131.0, 135.8, 150.6, 170.8, 198.1.

20. If there was no crystallization, a few crystals of crude product were added to the flask to initiate crystallization. The mp was 148-150°C (lit.[5] mp 150-152°C).

21. Palladium on activated carbon (10%) was purchased from Aldrich Chemical Company, Inc., and used as received.

22. After 75 min an aliquot was drawn and analyzed by ^{1}H NMR which indicated the presence of enone (< 5%); another 1.0 g of Pd was added and the mixture heated at 50°C/50 psi of H_2 for another 45 min.

23. The palladium on activated carbon (10%) was not allowed to become completely dry because of its flammable nature.

24. The data for the pure product is: mp 179-181°C (lit.[5] mp 182-183°C); ^{1}H NMR (500 MHz, CDCl$_3$) δ: 1.49-1.60 (m, 2 H), 2.01-2.13 (m, 2 H), 2.25-2.60 (m, 6 H), 3.03-3.22 (m, 2 H), 3.61-3.81 (m, 1 H), 4.45-4.59 (m, 1 H), 7.28-7.41 (m, 5 H); ^{1}H NMR (CD$_3$SOCD$_3$, 25°C) δ: 1.30-1.62 (m, 2 H), 1.82 (m, 2 H), 2.18-2.65 (m, 6 H), 3.04 (m, 1 H), 3.20 (m, 1 H), 3.48 (m, 1 H), 4.22 (m, 1 H), 7.32-7.48 (m, 5 H); ^{1}H NMR (CD$_3$SOCD$_3$, 90°C) δ: 1.34-1.52 (m, 2 H), 1.66-1.78 (m, 1 H), 1.80-2.02 (m, 1 H), 2.20-2.31 (m, 2 H), 2.31-2.37 (m, 2 H), 2.48-2.57 (m, 2 H), 3.00-3.12 (m, 1 H), 3.27 (dd, 1 H, J = 3.6 and 13.2), 3.88 (m, 2 H), 7.30-7.50 (m, 5 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 25.5, 26.6, 27.6, 35.0, 37.4, 39.8, 45.9, 47.2, 126.8, 128.5, 129.6, 136.1, 171.0, 210.5

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion[2]

In this procedure, quinine is oxidatively degraded to meroquinene esters that are subsequently cyclized to N-acylated cis-decahydroisoquinolones in excellent overall yield, while maintaining the cis stereochemistry at the ring juncture. Furthermore, with the commercial availability of quinine, high overall yields, and ease of isolations, meroquinene and subsequent products are attractive members of a practical "chiral pool".

Oxidation of the quinine C-9 hydroxy substituent to the ketone is best accomplished using the Woodward[3] benzophenone/potassium t-butoxide method, now using toluene. The other oxidation methods investigated (Swern, Jones, ROCl variations) were less effective or limited because of the poor solubility of the substrate. Thermodynamic equilibration of these ketones has also been reported.[3]

Quininone, the most readily available member of the series, was used for the autoxidation studies. The Doering autoxidation procedure,[4] that employs only tert-BuOH, was modified to include a THF:tert-BuOH (4:1) mixture as the solvent. Likewise, the pressurized Parr bottle setup as described[4] was replaced with a simple subsurface gas addition; the solvent was presaturated with O_2 gas, (compressed air could also be used as the O_2 source) followed by t-BuOK addition and continued O_2 gas purge. The autoxidations could likewise be conducted in the presence of ethanol or methanol, thereby producing the corresponding ethyl or methyl esters. Formation of these esters could occur via the reactive intermediate bicyclic lactam.[4]

Cyclization of N-acyl meroquinenes with neat polyphosphoric acid (PPA, thick reaction mixture) required 5 days at ambient temperature and resulted in a 2.4:1 mixture of trans:cis-enones, respectively (55% yield, eq 1).[5] The diastereomeric mixture could easily be separated by column chromatography to provide pure samples of either substance. It was also shown that the pure trans- and cis-enones equilibrated

under the PPA cyclization conditions to afford the same 2.4:1 (trans:cis) mixture of enones. Thermodynamic equilibration of either enone also occurred with p-toluenesulfonic acid (p-TsOH) in THF. Cyclization of N-acyl meroquinenes could be conducted in a mixture of PPA:H_2SO_4 (0°C → 20°C) with complete cis-stereocontrol in essentially quantitative yield (30 min) affording only the cis-product. Equilibration of the γ-position occurred at elevated temperatures (> 25°C). It was then determined that concentrated H_2SO_4 could replace the PPA:H_2SO_4 mixture, with identical (cis) product profile. Trifluoroacetic anhydride (TFAA) also effected the present cyclization albeit with poor efficiency, but alternative acids (H_3PO_4, $AlCl_3$/CH_2Cl_2, TFAA, HCl, CH_3SO_3H, HOAc, HNO_3) did not.[6] Either TFAA or mixtures of Ac_2O with catalytic H_2SO_4 have been employed for the cyclization of ω-olefinic acids, although the substrates did not contain stereogenic centers. Polyphosphoric acid has also been used extensively for the acylation of alkenes at high temperatures, usually at 100°C.[7]

Furthermore, attempted cyclization of N-carboxymethyl meroquinene ethyl ester failed to afford any of the enone, suggesting that the carboxylic acid was an intermediate. The N-protecting groups, in addition to benzoyl, that are tolerated include CO_2Me, pivaloyl, acetyl, toluenesulfonyl, CBz, and alkyl.

Enones were readily reduced in EtOH solution with catalytic palladium (10% on carbon) under an atmosphere of H_2 and the perhydroisoquinolones were isolated by chromatography or crystallization.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

Quininone (8); Cinchon-9-one, 6'-methoxy-, (8a)- (9); (84-31-1)

Benzophenone (8); Methanone, diphenyl- (9); (119-61-9)

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

Quinine (8); Cinchonan-9-ol, 6'-methoxy-, (8a, 9R)- (9); (130-95-0)

Potassium tert-butoxide: tert-Butyl alcohol, potassium salt (8); 2-Propanol, 2-methyl-,

potassium salt (9); (865-47-4)

N-Benzoyl meroquinene tert-butyl ester: 4-Piperidineacetic acid, 1-benzoyl-3-ethenyl-,

1,1-dimethylethyl ester, (3R-cis)- (9); (52346-13-1)

tert-Butyl alcohol (8); 2-Propanol, 2-methyl- (9); (75-65-0)

Acetic acid (8,9); (64-19-7)

Meroquinene tert-butyl ester: 4-Piperidineacetic acid, 3-ethenyl-, 1,1-dimethylethyl

ester, (3R-cis)- (9); (52346-11-9)

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

Benzoyl chloride (8, 9); (98-88-4)

4a(S), 8a(R)-2-Benzoyl-1,3,4,4a,5,8a-hexahydro-6(2H)-isoquinolinone:

6(2H)-Isoquinolone, 2-benzoyl-1,3,4,4a,5,8a-hexahydro-, (4aS-cis)- (9); 52346-14-2)

4a(S), 8a(R)-2-Benzoyloctahydro-6(2H)-isoquinolinone: 6(2H)-Isoquinolinone,

2-benzoyloctahydro-, (4aS-cis)- (9); (52390-26-8)

Accepted for checking during the period April 1, 1966

through August 1, 1997. 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.

2620R*   Generation and Use of Lithium Pentafluoropropen-2-olate:
          4-Hydroxy-1,1,1,3,3-pentafluoro-2-hexanone Hydrate.
          C.-P Qian, Y.-Z. Liu, K. Tomooka, and T. Nakai, Department of
          Chemical Technology, Tokyo Institute of Technology, Meguro-ku,
          Tokyo 152, Japan.

2773   Photochemical Synthesis of Bicyclo[1.1.1]pentane-1,3-dicarboxylic
          Acid.
          M. D. Levin, P. Kaszynski, and J. Michl, Department of Chemistry and
          Biochemistry, University of Colorado at Boulder, Boulder, CO 80309-
          0215.

2775R*   Bromofluorination of Alkenes.
          G. Haufe, G. Alvernhe, A. Laurent, T. Emet, O. Goj, S. Kröger, and A.
          Sattler, Organisch-Chemisches Institut, Universität Münster,
          Corrensstrasse 40, D-48149, Münster, Germany.

2780   Polycycle Construction from Squarate Esters with Concomitant
          Elimination: 5,6,7,7a,8,8a-Hexahydro-3a-hydroxy-2,3-diisopropoxy-
          8a-methylcyclopent[a]inden-1(3aH)-one.
          J. Doyon and L. A. Paquette, Department of Chemistry, The Ohio
          State University, Columbus, OH 43210.

2782   (R)-2-Diphenylphosphino-2'-methoxy-1,1'-binaphthyl.
          Y. Uozumi and T. Hayashi, Department of Chemistry, Faculty of
          Science, Kyoto University, Sakyo, Kyoto 606-01, Japan.

2783   (1S,2S,4R)-Bicyclo[2.2.1]heptan-2-ol.
          Y. Uozumi and T. Hayashi, Department of Chemistry, Faculty of
          Science, Kyoto University, Sakyo, Kyoto 606-01, Japan.

2784   Catalytic Asymmetric Synthesis of Nitroaldols Using a Lanthanum-
          Lithium-BINOL Complex.
          H. Sasai, S. Watanabe, T. Suzuki, and M. Shibasaki,
          Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo,
          Bunkyo-ku, Tokyo 113, Japan.

2786   6-Chloro-1-hexene and 8-Chloro-1-octene.
          P. Mazerolles, P. Boussaguet, and V. Huc,
          Laboratoire d'Hétérochimie Fondamentale et Appliquée, Université
          Paul Sabatier, 31062 Toulouse Cedex, France.

2789   Preparation of 1,2:5,6-Dianhydro-3,4-O-isopropylidene-D-mannitol.
          B. B. Lohray, Y. Jayamma, M. Chatterjee, G. Prasuna, and V.
          Bhushan, Dr. Reddy's Research Foundation, Bollaram Road, Miyapur
          Hyderabad 500138, India.

2790   Dimethyltitanocene.
          J. F. Payack, D. L. Hughes, D. Cai, I. F. Cottrell, and T. R. Verhoeven,
          Department of Process Research, Merck Research Laboratories,
          Division of Merck & Co., Inc., P. O. Box 2000, Rahway, NJ 07065.

2791   Synthesis of (2S,3R)-N-Benzyloxycarbonyl-3-amino-1,2-epoxy-4-
          phenylbutane.
          D. A. Nugiel, K. Jacobs, C. G. Clark, and P. Y. Lam,
          DuPont Merck Pharmaceutical Company, P.O. Box 80500,
          Wilmington, DE 19880-0500.

2793   Asymmetric Synthesis of α-Amino Acids by the Alkylation of
          Pseudoephedrine Glycinamide. Preparation of L-Allylglycine and N-
          Boc L-Allylglycine.
          A. G. Myers and J. L. Gleason, Division of Chemistry and Chemical
          Engineering, California Institute of Technology, Pasadena, CA 91125.

2794*   1S-(-)-1,3-Dithiane 1-Oxide.
          P. C. B. Page, J. P. Heer, D. Bethell, E. W. Collington, and D. M.
          Andrews, Department of Chemistry, Loughborough University,
          Loughborough Leicestershire LE11 3TU, UK.

2796R   Preparation of (Z)-4-Iodo-4-decen-2-one from 1-Octyne.
          F.-T. Luo, Y.-S. Liu, and R.-T. Wang, Institute of Chemistry, Academia
          Sinica, Nankang, Taipei, Taiwan, 115, Republic of China.

2797*   Dimethyl Squarate.
          H. Liu, C. S. Tomooka, and H. W. Moore, Department of Chemistry,
          University of California, Irvine, Irvine, CA 92717.

2798   Synthesis and Diastereoselective Alkylation of Pseudoephedrine
          Amides.
          A. G. Myers and B. H. Yang, and H. Chen, Division of Chemistry and
          Chemical Engineering, California Institute of Technology, Pasadena,
          CA 91125.

2799   Transformation of Pseudoephedrine Amides into Highly
          Enantiomerically Enriched Carboxylic Acids, Aldehydes, Alcohols,
          and Ketones.
          A. G. Myers, B. H. Yang, Division of Chemistry and Chemical
          Engineering, California Institute of Technology, Pasadena, CA 91125.

2800   Synthesis of N-BOC Serinal Acetonide via Oxidation of the Alcohol.
          A. Dondoni and D. Perrone, Dipartimento di Chimica, Laboratorio di
          Chimica Organica, Universitá di Ferrara, 1-44100 Ferrara, Italy.

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FOR VOLUME 75

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The index lists the names of compounds in two forms. The first is the name used commonly in procedures. The second is the systematic name according to **Chemical Abstracts** nomenclature. Both are usually accompanied by registry numbers in parentheses. Also included are general terms for classes of compounds, types of reactions, special apparatus, and unfamiliar methods.

Most chemicals used in the procedure will appear in the index as written in the text. There generally will be entries for all starting materials, reagents, intermediates, important by-products, and final products. Entries in capital letters indicate compounds appearing in the title of the preparation.

ORGANIC
SYNTHESES

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METHODS FOR THE PREPARATION
OF ORGANIC CHEMICALS
VOLUME 75
1998

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ORGANIC SYNTHESES

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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NOTICE

With Volume 62, the Editors of *Organic Synthesis* 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.

NOMENCLATURE

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 Synthesis 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. Submissions which are longer than three steps from commercial sources or from existing *Organic Syntheses* procedures will be accepted only in unusual circumstances.

Organic Synthesis Proposal Format

1) Authors
2) Title
3) Literature reference or enclose preprint if available
4) Proposed sequence
5) Best current alternative(s)
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

Submit to: Dr. Jeremiah P. Freeman, Secretary
　　　　　　Department of Chemistry
　　　　　　University of Notre Dame
　　　　　　Notre Dame, IN 46556

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 Synthesis wishes to acknowledge the contributions of ArQule, 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 in the Laboratory*; National Academy Press; Washington, DC, 1995.

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 con-

tact, 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 in the Laboratory*, National Academy Press, Washington, D.C. 1995

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 set-

*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.

ting, provision should be made for dealing with the more environmentally offensive categories.

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 suckback 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

Since 1921 *Organic Synthesis* has provided the synthetic community with carefully checked and edited experimental procedures describing leading edge synthetic methods, important reagents and useful building blocks. This, the 75th annual volume, continues in this tradition by providing 29 procedures. Although there is no central theme to this volume, the preparations are grouped into six categories: (a) asymmetric synthesis and chiral auxiliaries; (b) palladium- and platinum-catalyzed reactions; (c) strained ring systems; (d) important synthetic transformations; (e) protecting group reagents and protocols; and (f) synthetically useful intermediates.

The collection begins with the preparation of **(R,R)-N,N'-BIS(3,5-DI-tert-BUTYLSALICYLIDENE)-1,2-CYCLOHEXANEDIAMINO MANGANESE(III) CHLORIDE,** the most enantioselective catalyst developed to date for the asymmetric epoxidation of a broad range of unfunctionalized olefins. The preparation includes a highly efficient resolution of trans-1,2-diaminocyclohexane and a general method for the determination of the enantiomeric purity of chiral 1,2-diamines. Also of interest is the Duff formylation of 2,4-di-tert-butyl phenol to produce 3,5-di-tert-butylsalicylaldehyde. The series then continues with five examples for the preparation of enantiomerically pure substances beginning with **(S)-1-(PHENYLMETHOXY)-4-PENTEN-2-OL,** which exploits a titanium tetraisopropoxide/BINOL catalytic system to effect the asymmetric allylation of aldehydes with allyl tributylstannane. The asymmetric synthesis of α-amino phosphonates, important surrogates for α-amino carboxylic acids, is documented in the preparation of **DIETHYL (R)-(-)-(1-AMINO-3-METHYLBUTYL)PHOSPHONATE.** This synthetic method takes advantage of the chelating ability of homochiral imines to achieve high levels of asymmetric induction during the addition of lithium diethyl phosphite to the C-N double bond of the imine. Introduction of the azide group at the α-position of a carbonyl with inversion of configuration is illustrated next with the preparation of **ETHYL (R)-2-AZIDOPROPIONATE** from ethyl S-(-)-lactate. This method is attractive since both alcohol activation and displacement occur in one operation upon treatment with diphenylphosphoryl azide. Mechanistically, the conversion entails activation of the α-hydroxyl group via phosphate formation followed by azide displacement. **ETHYL (R)-(+)-2,3-EPOXYPROPANOATE (ethyl**

glycidate), readily prepared from (S)-serine, is an important three-carbon chiron for the synthesis of α-hydroxy esters via addition of organometallic reagents to the β-position. Interestingly, the preparation entails three S_N2 inversions at the α-carbon. With the increasing utility of chiral auxiliaries, the preparation of **(4R,5S)-4,5-DIPHENYL-3-VINYL-2-OXAZOLIDINONE** represents a simple and safe route to this important chiral oxazolidinone.

Palladium- and platinum-catalyzed transformations continue to augment the synthetic chemist's arsenal. The first three preparations in this series of four describe significant improvements to the now classic Suzuki cross-coupling between boronic acids and aryl halides. The preparation of **4-BIPHENYLCARBOXALDEHYDE** exploits the use of palladium acetate and triphenylphosphine to generate the palladium(0) catalyst, thereby eliminating the need for expensive air and light sensitive tetrakis(triphenylphosphine)palladium(0). The preparation of **4-METHOXY-2'-METHYLBIPHENYL** illustrates the advantage of "ligandless" methodology, wherein phosphine-related side reactions, aryl-aryl exchange, and phosphonium salt formation that often plague traditional phosphine-based catalytic systems are eliminated. The third preparation describes an efficient two-step construction of α-aryl cycloalkenones. The first step entails preparation of 2-iodo-2-cyclohexenone via a process thought to involve nucleophilic addition of pyridine to the β-carbon of the enone followed by capture of the resultant enolate with iodine and then a pyridine-promoted elimination of pyridine to regenerate the α,β-unsaturated system. A silver(I) oxide-promoted Suzuki coupling of the resultant 2-iodo-2-cyclohexen-1-one with 4-methoxyphenyl boronic acid then leads to **2-(4-METHOXYPHENYL)-2-CYCLOHEXEN-1-ONE.** Importantly, only 1.6 equivalents of Ag_2O are required for efficient coupling. The final preparation in this series illustrates the hydrosilation of racemic 3-butyn-2-ol catalyzed by a phosphine based platinum(0) catalyst. The resultant racemic (E)-vinylsilane is then resolved with a commercially available lipase and subjected to a Johnson ortho ester Claisen rearrangement to afford **[3R- AND 3S-]-(4E)-METHYL 3-(DIMETHYLPHENYLSILYL)-4-HEXENOATES,** both in near enantiomerically pure form.

The next four procedures describe the preparation of strained ring systems. Preparation of **3-CHLORO-2-(CHLOROMETHYL)-1-PROPENE** provides a facile approach to the olefin required for the synthesis of **[1.1.1]PROPELLANE,** one of the most strained hydrocarbons prepared to date. The ready availability of this hydrocarbon should prove particularly useful to those interested in the development of the chemistry of this fascinating compound. Preparation of **N-BENZYL-2,3-AZETIDINEDIONE** provides an efficient approach to the unadorned α-keto-β-lactam, a potential

precursor for a variety of penicillin and cephalosporin antibiotics. Particularly attractive in this preparation is the cyclization induced by t-butylmagnesium chloride which proceeds readily without prior protection of the hydroxyl group. The preparation of **3,3-DIMETHYL-1-OXASPIRO[3.5]NONAN-2-ONE** demonstrates the recently developed spontaneous intramolecular acylation of metalated β-hydroxy alkanoates to afford β-lactones. The requisite β-hydroxy alkanoates are available by reaction of ketones with ester enolates prepared from phenyl alkanoates.

The next series of five preparations describe synthetically useful transformations. The preparation of **DEC-9-ENYL BROMIDE** illustrates a convenient and efficient alternative to the Hunsdiecker reaction by exploiting the O-acyl thiohydroxamate derivative of 10-undecenoic acid in a photoinduced free radical decarboxylation-bromination process employing bromotrichloromethane as the bromine source. The regioselective haloboration of allene followed by reaction of the derived (2-bromoallyl)diisopropoxyborane with ethyl levulinate to arrive at the corresponding γ-butyrolactone after treatment with acid is illustrated with the preparation of **4-(2-BROMO-2-PROPENYL)-4-METHYL-γ-BUTYROLACTONE.** Although the photocatalyzed-addition of alcohols to cycloalkenones is well known, similar photoinduced additions to γ-butrolactones are less precedented. The preparation of **(4R,5S)-4-HYDROXYMETHYL-(5-O-tert-BUTYLDIMETHYLSILOXYMETHYL)FURAN-2(5H)-ONE** illustrates the viability of this process. An effective method for the cyanation of terminal acetylenes with cuprous cyanide in the presence of chlorotrimethylsilane, water and a catalytic amount of sodium iodide in $DMSO/CH_3CN$ is demonstrated with the preparation of **3-PHENYL-2-PROPYNENITRILE.** The last procedure in this series illustrates the use of a Wittig olefination reaction to produce an enol ether from ethyl trifluoroacetate, which in turn is subjected to m-chloroperbenzoic acid epoxidation to provide **1,1,1-TRIFLUORO-2-ETHOXY-2,3-EPOXY-5-PHENYLPENTANE,** a potentially useful synthon for the preparation of perfluoroalkylated organic compounds.

The next series of four preparations describe the synthesis and/or use of recently introduced reagents for functional group protection. The first in this series describes the preparation of **2-TRIMETHYLSILYLETHANE-SULFONYL CHLORIDE (SEC-Cl),** an effective reagent for protection of primary and secondary amines as the corresponding sulfonamide. The SES-protected amines are stable intermediates which can be readily purified; treatment with CsF in DMF or TBAF in acetonitrile liberates the parent amine. The preparation of **(1'S,2'S)-METHYL-3O,4O-(1',2'-DIMETHOXYCYCLOHEXANE-1',2'-DIYL)-α-D-MANNOPYRANO-**

SIDE illustrates a novel tactic for the protection of trans vicinal hydroxyl groups found in sugars and related compounds. Importantly, the cyclohexane diacetal (CDA) protecting group will withstand common sugar derivatization reactions and is easily removed with acid. Site-selective protection of the more hindered hydroxyl in unsymmetrical 1,3-diols is often required in complex molecule synthesis. The preparation of **3-(METHOXYMETHOXY)-1-BUTANOL** illustrates one such tactic, which complements the more normally observed chemoselectivity that favors functionalization of the less hindered (primary) site of an unsymmetrical 1,3-diol. The protection protocol entails rupture of the less congested C—O bond in the initially prepared unsymmetrical cyclic formal with acetyl chloride to furnish the product having an acetate at the less congested site and a chloromethyl ether moiety attached to the more hindered hydroxyl. Reaction of the chloromethyl ether with an appropriate alcohol in the presence of N,N-diisopropylethylamine, followed by removal of the acetate completes the protection process. Preparation of **4-DIMETHYLAMINO-N-TRIPHENYLMETHYLPYRIDINIUM CHLORIDE** provides ready access to a highly reactive tritylation reagent for the protection of alcohols.

Volume 75 concludes with six procedures for the preparation of valuable building blocks. The first, **6,7-DIHYDROCYCLOPENTA-1,3-DIOXIN-5(4H)-ONE,** serves as an effective β-keto vinyl cation equivalent when subjected to reductive and alkylative 1,3-carbonyl transpositions. **3-CYCLOPENTENE-1-CARBOXYLIC ACID,** the second procedure in this series, is prepared via the reaction of dimethyl malonate and cis-1,4-dichloro-2-butene, followed by hydrolysis and decarboxylation. The use of tetrahaloarenes as diaryne equivalents for the potential construction of molecular belts, collars, and strips is demonstrated with the preparation of **anti-** and **syn-1,4,5,8-TETRAHYDROANTHRACENE 1,4 : 5,8-DIEPOXIDES.** Also of potential interest to the organic materials community is **8,8-DICYANOHEPTAFULVENE,** prepared by the condensation of cycloheptatrienylium tetrafluoroborate with bromomalononitrile. The preparation of **2-PHENYL-1-PYRROLINE,** an important heterocycle for the synthesis of a variety of alkaloids and pyrroloisoquinoline antidepressants, illustrates the utility of the inexpensive N-vinylpyrrolidin-2-one as an effective 3-aminopropyl carbanion equivalent. The final preparation in Volume 75, **cis-4a(S), 8a(R)-PERHYDRO-6(2H)-ISOQUINOLINONES,** illustrates the conversion of quinine via oxidative degradation to meroquinene esters that are subsequently cyclized to N-acylated cis-perhydroisoquinolones and as such represent attractive building blocks now readily available in the pool of chiral substrates.

The continued success of *Organic Syntheses* derives from the dedicated

RICHARD E. BENSON
May 8, 1920–February 24, 1997

Richard E. Benson, Editor-in-Chief of Volume 51 of *Organic Synthesis*, died of emphysema on February 24, 1997.

Dick was born in Racine, Wisconsin in 1920. His parents later moved to Tempe, Arizona, which led to Dick's attending Arizona State University. He had originally planned to major in education and become a teacher, but he got hooked by an interesting chemistry course and set out to become a chemist instead.

Dick did so well in chemistry that he received a local award, and a young woman who was majoring in English and honing her literary skills on the college newspaper came around to interview the bright young awardee. It must have been a good interview, for soon he was dating his interviewer, Katherine MacPhail.

Dick received his B.S. at Arizona State in 1942 and then moved to the University of Nebraska to do doctoral research under Clifford S. Hamilton.

He soon learned a lot about *Organic Syntheses*, for Hamilton was an editor of that then young publication.

Another important event occurred in 1942: Dick married Katherine MacPhail. His meager income as a teaching assistant was supplemented by Kay's income as a secretary.

Dick received his Ph.D. in organic chemistry from the University of Nebraska in 1946 and headed east to join the Central Research Department of the DuPont Company. His first project was to study the chemistry of a polyamide monomer, caprolactam.

Dick turned up some interesting chemistry of caprolactam and its O-alkyl imino ethers. He and collaborators went on to explore the chemistry of allene, for example, its reactions with acetylene, carbon monoxide, and tetrafluoroethylene. He did extensive work on the chemistry of cyclooctatetraene and of ferrocene. In the cyanocarbon area he collaborated on studies of the anion radical of tetracyanoethylene, that is, tetracyanoethylene bearing an extra electron. He was author or coauthor of 45 papers and 16 U.S. Patents that came out of the Central Research Department.

Since Dick bore responsibility well, DuPont's Central Research Department gave him more and more of it. He became a research supervisor in 1956, and an associate research director in 1967. He served as the Department's Director of Analytical Science in 1980 until his retirement in 1985.

Dick was very active in professional activities outside the laboratory. He was a founder of the Wilmington Organic Chemists Club in 1949 and was its first president. This was an organization that was very active for about 15 years before falling victim to TV and other evils. He was a leader of ChemVets, an organization of retired Delaware chemists who meet for lunch six or eight times a year to hear a technical lecture and swap tales of the good old days. He was on the ACS National Committee and helped the Technicians Division of the ACS come into being. Finally, he was founder of a group of a dozen DuPont chemists who have been meeting monthly for nearly 50 years to discuss scientific topics.

Dick was an exceptionally conscientious editor of *Organic Syntheses*. For example, when William Sheppard died before his term on the Board of Editor had expired, Dick, although retired from that Board, picked up Sheppard's unchecked assigned preps and saw to it that they all got checked.

Dick is survived by his wife, two daughters, and two grandchildren.

BLAINE C. McKUSICK

August 5, 1997

WILLIAM GARFIELD DAUBEN
November 6, 1919–January 2, 1997

William G. Dauben, Editor-in-Chief of Volume 45 of *Organic Syntheses* and long-standing member of its Board of Directors, died in his home in Kensington, California, on January 2, 1997 at the age of 77.

Bill Dauben was born in Columbus, Ohio, and received his B.A. degree from the Ohio State University in 1941. He followed his brother Hyp J. Dauben Jr. to Harvard University where Bill obtained his M.A. in 1942 and Ph.D. in 1944 with R. P. Linstead. Following post-doctoral research with Louis Fieser at Harvard in the wartime antimalarial program, he joined the faculty at the University of California-Berkeley as instructor in 1945 and rose to the rank of full Professor in 1957. In 1947 he married Carol Hyatt, then a graduate student studying x-ray crystallography with D. H. Templeton in the Chemistry Department. His career at Berkeley was contemporary with those of two other distinguished chemistry faculty members, Professor James Cason and Henry Rapoport. These three young scientists launched what would soon become a world class program in organic chemistry at the University of California. On the occasion of his retirement from the teaching faculty in 1990, Bill was awarded the Berkeley Citation in special recognition of his outstanding career in teaching, research, and professional service.

He maintained an active research program throughout his academic career up to the time of his death. During his 52 years in the Chemistry Department at Berkeley he provided research training for more than 200 graduate stu-

dents, undergraduates, and post-doctoral associates. His career-long interests in the chemistry of steroids and polycyclic compounds no doubt originated at Harvard University from his associations with the Linstead and Fieser research groups. Dauben's early work on the use of carbon 14 labeling to track steroid biosynthesis not only revived the squalene hypothesis, but it also led to the development of an efficient procedure for sidechain degradation that became widely adopted in the pharmaceutical industry. Bill's research interests were very broad-ranging and his 300+ publications had a profound impact on the development of synthetic organic chemistry, steroid and terpene chemistry, mechanisms of carbonium ion and metal-induced rearrangements, polycyclic compounds, and photochemistry.

His elucidation of the structure of suprasterol, an over-irradiation product of vitamin D, eventually led him into extensive research on the diverse photochemical reactions of conjugated dienes. He was early to recognize the power of NMR spectroscopy, using this new analytical tool in 1954 to deduce the structure of ψ-santonin. The structure determination of cembrene in 1962 and later its total synthesis by the Dauben group laid the foundation for the growth of this now huge family of macrocyclic diterpenes. In characteristic Dauben style the total synthesis of thujopsene was followed by fascinating studies on the stereochemistry and mechanism of the cyclopropylcarbinyl rearrangements of this sesquiterpene and its hydration product, widdrol. Intramolecular [2+2] photocycloadditions of polycyclic dienes provided access to highly strained cage molecules for investigations in the Dauben group on carbonium ion and metal-catalyzed skeletal rearrangements. More recent accomplishments were challenging total syntheses of the natural products kempene, crassin methyl ester, spatol, and the ceroplastol nucleus. He was also a pioneer in the use of high-pressure reactors to facilitate otherwise unfavorable transformations such as Diels-Alder cycloadditions.

Bill was elected to the National Academy of Sciences in 1970, he was chairman of its Chemistry Section during 1977–1981, and he was member of the American Academy of Arts and Sciences. He was awarded Guggenheim fellowships in 1951 and 1966, a National Science Foundation Senior Fellowship in 1958, and a Miller Research Professorship at Berkeley in 1963. His numerous honors from the American Chemical Society include the California Section Award in 1959, the Ernest Guenther Award in 1973, and an Arthur C. Cope Scholar Award in 1990. Among the international recognitions Bill received are a U.S. Senior Scientist Award from the Alexander von Humboldt Foundation, an honorary doctorate from the University of Bordeaux, two Japan Society for the Promotion of Science Awards, and an honorary membership in Pharmaceutical Society of Japan.

Bill Dauben's service to the organic chemistry community was extraordinary. He served on the Medicinal Chemistry Study Section of the National Institutes of Health, the Chemistry Panel of the National Science Foundation, and the editorial boards of the *Journal of Organic Chemistry and Steroids,* and he chaired the American Chemical Society's committee on publications. As a member of the Board of Directors of Organic Syntheses, Inc. for thirty years to the time of his death, he was influential in the management of its investments and financial affairs. Bill's leadership is widely credited for the resuscitation of *Organic Reactions* in 1969 when he became Editor-in-Chief and President, and he was instrumental in its publication and operation for 19 years.

Letters collected in 1976 to celebrate his 30 years at Berkeley show the profound admiration and high esteem of his former students and research collaborators, their fond memories of the time spent in the Dauben laboratories, and the impact he had on their lives and careers. Always fastidiously dressed in stylish Ivy League attire, invariably in the earlier years sporting a bow tie, "The Man (in some periods "The Boss") was the consummate gentleman-scholar. He was an inspiring classroom teacher, a patient and encouraging research advisor, and an understanding, forthright counselor to his students. In frequent travels and sabbaticals abroad he made numerous friends throughout the US. and worldwide who advised their own students to join the Dauben group. He was keenly interested in each student as an individual, and he and Carol took great pride in keeping close track of Dauben group members after their departure. He was an excellent golfer, more frequently than not winning the annual Dauben Group Open.

Bill Dauben is survived by his wife Carol, his two daughters, Barbara Baumer of Portland, Oregon and Ann Klaus of College Station, Texas, and two grandchildren. His comradeship, his wise counsel, and his savoir faire will be sorely missed by friends, colleagues, and family.

ROBERT M. COATES

August 25, 1997

WATARU NAGATA
February 17, 1922–May 9, 1995

Wataru Nagata, the second Foreign Editor elected to the Board of Editors of Organic Synthesis (1971–1976), was born in Takeno-cho, Hyogo Prefecture, Japan in 1922 and received his B.Sc. (Pharmaceutical Sciences) from Tokyo Imperial University (currently the University of Tokyo) in 1945, with the late Professor Eiji Ochiai. He then joined the Research Laboratories of the Shionogi Company as a senior organic chemist and in 1954 he was given the opportunity to continue his chemical studies by working with Professor T. Reichstein as a research fellow at the University of Basel for two years. He received a Ph.D. in Pharmaceutical Science from the University of Tokyo in 1961.

Soon after returning to the Shionogi Research Laboratories from the University of Basel, he became Section Manager to pursue the total synthesis of steroids. This work led to total or partial synthesis of the racemic form of many steroids and steroidal alkaloids, such as estrone 3-methyl ether, 3α-acetoxy-5β-pregna-9(11), 16-dien-20-one, aldosterone, latifoline, and conessine (1961–1963). With extensive support and encouragement from the late

Dr. Ken'ichi Takeda, then Director of Shionogi Research Laboratories, Nagata extended his research efforts to include the first total synthesis of the diterpene alkaloid group including atisine, garryine, and veatchine as well as the gibberellins all in their racemic form.

The key reaction in these syntheses was the stereoselective introduction of angular cyano groups as latent methyl groups into perhydropolycyclic α, β-unsaturated compounds. The new hydrocyanation method developed gave excellent chemoselectivity and stereochemical control.

The Nagata group also developed a new approach to the construction of bridged aziridines via nitrene intermediates that led to the total synthesis of the indole alkaloids, ibogamine, velbanamine, and coronaridine (1968–1971).

Later in his career, Nagata's group made notable and useful synthetic contributions to the beta lactam field. This included developing an economically feasible synthetic method for the industrial manufacture of 1-oxacephems from penicillin G. These efforts led to the worldwide introduction in the 1980s of several clinically prominent and effective beta lactam antibiotics of the 1-oxacephem class including moxalactam.

Wataru Nagata was an active and highly prominent participant in the post World War II period leading to the renaissance and development of synthetic organic chemistry in Japan. His many significant contributions during his distinguished career at Shionogi enhanced and strengthened the vital Japanese industrial-academic interface. He will be remembered by colleagues for his warm and courtly manners, scholarliness, and his inspirational leadership.

At Shionogi his talent was well recognized and he was promoted to Deputy General Manager in 1961, to General Manager in 1965, and Executive General Manager of the Manufacturing Division in 1986. He was a member of the Board of Directors from 1974–1988 and Director of the Cell Science Research Foundation from 1988 to his retirement in 1991.

WILLIAM G. DAUBEN

October 1, 1996

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