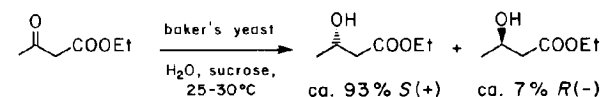


YEAST REDUCTION OF ETHYL ACETOACETATE:

(S)-(+)-ETHYL 3-HYDROXYBUTANOATE

(Butanoic acid, 3-hydroxy-, ethyl ester, (S))



Submitted by Dieter Seebach, Marius A. Sutter, Roland H. Weber,
and Max F. Züger.¹

Checked by Terry Rosen and Clayton H. Heathcock.

1. Procedure

A 4-L, three-necked, round-bottomed flask equipped with mechanical stirrer, bubble counter, and a stopper is charged with 1.6 L tap water, 300 g of sucrose (Note 1), and 200 g baker's yeast (Note 2), which are added with stirring in this order. The mixture is stirred for 1 hr at about 30°C, 20.0 g (0.154 mol) of ethyl acetoacetate (Note 3) are added, and the fermenting suspension (Note 4) is stirred for another 24 hr at room temperature. A warm (ca. 40°C) solution of 200 g sucrose (Note 1) in 1 L of tap water is then added, followed 1 hr later by an additional 20.0 g (0.154 mol) of ethyl acetoacetate (Note 3). Stirring is continued for 50-60 hr at room temperature. When the reaction is complete by gas chromatographic analysis

(Note 5), the mixture is worked up by first adding 80 g of Celite and filtering through a sintered glass funnel (porosity 4, 17 cm diameter). After the filtrate is washed with 200 mL of water, it is saturated with sodium chloride and extracted with five 500-mL portions of ethyl ether (Note 6). The combined ether extracts are dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator at 35°C bath temperature to a volume of 50-80 mL. This residue is fractionally distilled at a pressure of 12 mm through a 10-cm Vigreux column, and the fraction boiling at 71-73°C (12 mm) is collected to give 24-31 g (59-76%) of (S)-(+)-ethyl 3-hydroxybutanoate (Note 7, 8); the specific rotation $[\alpha]_D^{25} + 37.2^\circ$ (chloroform, c 1.3) corresponds to an enantiomeric excess of 85% (Note 9).

The enantiomeric excess may be enhanced by several crystallizations of the 3,5-dinitrobenzoate derivative (Note 10).

2. Notes

1. Commercially available sugar (sucrose) from a grocery store is used.
2. Commercially available baker's yeast can be used. The submitters used baker's yeast from E. Klipfel & Co. AG, CH-4310 Rheinfelden (Switzerland). The checkers used Fleischmann's yeast (cubes), obtained from a supermarket, or Red Star Baker's yeast (Universal Food Corporation), obtained from a bakery. The optical rotation of the final product was essentially the same for runs in which the two brands were employed.
3. Ethyl acetoacetate is freshly distilled before use (bp 65°C/12 mm).
4. One to two bubbles per second of CO₂ are developed.

5. A small sample (ca. 1 mL) is removed from the mixture and extracted with ethyl ether. The ether solution is analyzed for remaining ethyl acetoacetate by capillary gas chromatography: 0.3 mm by 20 m glass capillary column Carbowax 20 M, oven temperature 100°C, carrier gas: hydrogen (0.4 atm); retention time of ethyl acetoacetate: 450 sec, of (S)-(+)-ethyl 3-hydroxybutanoate: 610 sec. It is important that all the starting material be consumed. If small amounts of ethyl acetoacetate are detected, 100 g of sucrose is added and the mixture is stirred for a further period of 2 days. The checkers detected the presence of residual ethyl acetoacetate by TLC on 250 micron silica gel plates with 1:1 ether/hexane as eluant. Plates are developed by dipping the dried plate into a solution of 10% vanillin and 5% sulfuric acid in 95% ethanol and then gently warming over a hot plate; ethyl acetoacetate appears as an intense blue spot with R_f 0.45.

6. In the case of emulsions, addition of methanol may be helpful. The very fine and stable emulsion which still remains is included with the aqueous phase.

7. The spectral properties of (S)-(+)-ethyl 3-hydroxybutanoate are as follows: IR^{2a} (film) cm⁻¹: 3440, 2980, 1730, 1375, 1300, 1180, 1030; ¹H NMR^{2b} (CCl₄) δ : 1.15 (d, 3 H, J = 6.5, CH₃), 1.28 (t, 3 H, J = 7 Hz, CH₃), 2.35 (d, 2 H, J = 6.5, CH₂CO), 3.15 (s, 1 H, OH), 4.05 (q, 2 H, J = 7, CH₂O), 4.15 (m, 1 H, CHOH).

8. This ester should be stored in a refrigerator as there has been some indication that it may undergo a transesterification/oligomerization upon standing at room temperature.

9. The specific rotation $[\alpha]_D^{25}$ varies from +35.5° to +38° (82-87% enantiomeric excess). The enantiomeric purity can also be checked by formation of the ester with (R)-(+)-1-methoxy-1-trifluoromethylphenylacetyl

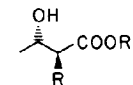
(MTPA) chloride.³ The ¹⁹F NMR chemical shifts of the diastereomeric esters are 6.13 (R,R) and 6.01 (R,S) ppm downfield of external trifluoroacetic acid.

10. The procedure of enriching the (S)-(+)-enantiomer to 100% enantiomeric excess by the previously described crystallization method is tedious.⁴ It provides optically pure ethyl (S)-(+)-3-(3',5'-dinitrobenzoyloxy)butanoate of $[\alpha]_D^{25} +26.3^\circ$ (chloroform, *c* 2), which after cleavage gives enantiomerically pure (S)-(+)-ethyl 3-hydroxybutanoate of $[\alpha]_D^{25} + 43.5^\circ$ (chloroform, *c* 1.0). This optically pure compound has recently become commercially available from Fluka AG, CH-9470 Buchs (Switzerland), but it is very expensive. After submission and checking of this procedure, it was shown⁵ that the ee of the product can be increased to >95% by working under aerobic conditions and by adding the ketoester more slowly.

3. Discussion

3-Hydroxybutanoic acid in both enantiomeric forms has been obtained by resolution of the racemic mixture.⁶ Hydrogenation of methyl acetoacetate using a Raney nickel catalyst which had been treated with tartaric acid resulted in methyl 3-hydroxybutanoate with an enantiomeric excess of 83-88%.⁷ Furthermore, optically active 3-hydroxybutanoic acid has been obtained in good chemical and optical yield by condensation of chiral α -sulphonyl ester enolates with aldehydes followed by desulfurization.⁸ (R)-(-)-Ethyl 3-hydroxybutanoate in 100% enantiomeric excess resulted from depolymerization of poly-(R)-3-hydroxybutanoate, an intracellular storage product of *Alcaligenes eutrophus* H 16.⁹ The method presented in this paper is easy to perform. The (S)-(+)-ethyl 3-hydroxybutanoate obtained may be enriched to 100% enantiomeric excess by crystallization of its 3,5-dinitrobenzoate derivative, followed by alcoholysis.⁴

Optically active ethyl 3-hydroxybutanoate is a very useful chiral building block for natural product synthesis. Some applications are shown in Table I. Alkylation of doubly deprotonated ethyl 3-hydroxybutanoate gives branched structures of the following type:¹⁰



The yeast reduction is not limited to ethyl acetoacetate. It has been applied to other β -keto esters, α -keto esters, α -keto alcohols, α -keto phosphates and some ketones (Table II). The reductions show a high degree of stereoselectivity. The absolute configuration of the product obtained by reduction of a carbonyl group containing a large group L and a small group S to the alcohol may be determined by application of Prelog's rule.^{11,12}

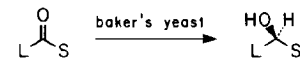


TABLE I

NATURAL PRODUCTS FROM (S)- OR (R)-ETHYL 3-HYDROXYBUTANOATE
 The Skeleton of Ethyl 3-Hydroxybutanoate is Indicated by Heavy Lines

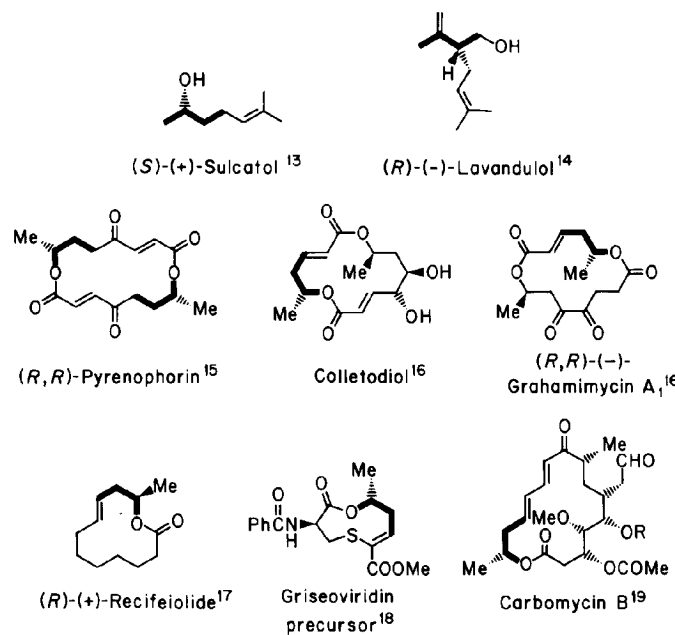


TABLE II

Enantioselective preparation of alcohols
 from the corresponding ketone by yeast reduction

Substrate	Product	Yield (%)	Enantiomeric excess (%)	Ref.
		57-67	84-87	20
		58	90	9
		61	85	9
		67	40	10a
			>90	10a
		65	86	20b, 21
		57	74	22
		59	>97	20b
		56	100	23
		45	85-87	12
		34	>97	24

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Appendix

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

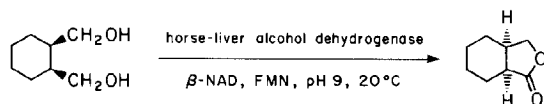
Ethyl acetoacetate: Acetoacetic acid, ethyl ester (8); Butanoic acid, 3-oxo-ethyl ester (9); (141-97-9)
(S)-(+)-Ethyl 3-hydroxybutanoate: Butanoic acid, 3-hydroxy-, ethyl ester, (S)- (9); (56816-01-4)

PREPARATION OF CHIRAL, NON-RACEMIC γ -LACTONES BY ENZYME-

CATALYZED OXIDATION OF MESO-DIOLS:

(+)-(1R, 6S)-8-oxabicyclo[4.3.0]nonan-7-one

(1(3H)-Isobenzofuranone, hexahydro-, (3aS-cis)-)



Submitted by J. Bryan Jones and Ignac J. Jakovac.¹

Checked by Roland H. Weber, Max F. Ziger, and Dieter Seebach.

1. Procedure

In a 1-L Erlenmeyer flask are placed 475 mL of distilled water (Note 1) and 3.75 g (0.05 mol) of reagent grade glycine, and the pH is adjusted to 9 by the careful addition of aqueous 10% sodium hydroxide. In the buffer solution thus obtained are dissolved 2.00 g (13.87 mmol) of cis-1,2-bis(hydroxymethyl)-cyclohexane (Note 2), 0.58 g (0.852 mmol) of β -NAD (Note 3), and 7.8 g (16.2 mmol) of FMN (Note 4). To the clear orange solution obtained is added 80 units of horse liver alcohol dehydrogenase (Note 5). After the solution is gently swirled for 1 min, the pH is readjusted to 9 and the mixture is kept at room temperature (Note 6) with the mouth of the flask loosely covered by a watchglass. After a few minutes the color of the solution begins to darken and after several hours becomes an opaque green-brown. The pH is readjusted

to 9 after 6, 12, 24, 48 and 72 hr by the careful addition of aqueous 10% sodium hydroxide since the pH of the mixture drops progressively as the reaction proceeds. After 4 days (Note 7), the mixture is brought to a pH of ca. 13.3 by the addition of 20 mL of aqueous 50% sodium hydroxide solution. After 1 hr, the mixture is continuously extracted with chloroform for 10 hr (Note 8). The chloroform extract is discarded. The aqueous layer is acidified to pH 3 with concentrated hydrochloric acid and again extracted continuously for 15 hr with chloroform. To the green-orange solution are added charcoal (0.5 g), and magnesium sulfate. The dried and partially decolorized mixture is filtered through a bed of Celite, and the chloroform is removed under reduced pressure using a rotatory evaporator. The residual orange-green oil is distilled in a Kugelrohr to give 1.4-1.5 g (72-77% yield, Note 9) of (+)-(1R, 6S)-8-oxabicyclo[4.3.0]nonan-7-one (> 97% e.e., (Note 10)) as a colorless oil, bp 85-100°C (0.1-0.05 mm), mp 26-29°C, $[\alpha]_D^{22} +51.3^\circ$ (CHCl₃, c 1.1) (Note 11).

2. Notes

1. It is not necessary to use doubly distilled or deionized water in this buffer preparation.

2. cis-1,2-Bis(hydroxymethyl)cyclohexane was purchased from Aldrich Chemical Company, Inc. (or EGA, D-Steinheim).

3. β -NAD is the standard biochemical abbreviation for the coenzyme β -nicotinamide adenine dinucleotide. The β -NAD used was of 95% purity and was purchased from Kyowa Hakko (U.S.A.), New York. It is also available from Sigma Chemical Company.

4. FMN is the standard biochemical abbreviation for flavin mononucleotide (or riboflavin phosphate). The sodium salt (95-97% pure) of FMN is used. This grade is inexpensive and is available from Sigma Chemical Company. Its purpose is to effect recycling² of the catalytic amount used of the much more costly NAD. A larger than stoichiometric amount of FMN is employed in order to ensure rapid recycling of the NAD.

5. Horse liver alcohol dehydrogenase (HLADH or LADH, also called equine liver alcohol dehydrogenase) is the crystalline preparation (> 98% protein) sold by Sigma Chemical Company. It is also available from Worthington and Boehringer. The amount added is quoted in units of activity since the activity of the enzyme from different sources can vary. For example, the Sigma enzyme is sold as having an activity of 1-2 units per mg of protein. The enzyme used in this preparation had 1.5 units of activity per mg. We have used Worthington and Boehringer enzyme with equal success. The activity of the enzyme diminishes slowly on prolonged storage, even at -20°C. For controlled results, the enzyme activity may be determined prior to use and the requisite number of units used.

The assay method of Dalziel³ is convenient. In a recording ultraviolet spectrophotometer set at 340 nm is placed a 3-mL quartz cuvette containing 2.4 mL of 0.10 M glycine-sodium hydroxide buffer solution, pH 9, 500 µL of a 54 mM solution of ethanol in the same buffer, and 100 µL of a 15 mM solution of NAD, also in the same pH 9 buffer. The volume is made up to 3.0 mL, and the assay initiated by the addition of 10 µL of a 1 mg per mL solution of HLADH in 0.10 M "Tris-hydrochloric acid buffer", pH 7.4. The change in optical density at 340 nm is monitored at 25°C and the activity calculated from the following equation:

$$\text{Units of activity/mg protein} = \frac{\Delta OD_{340}/\text{min}}{6.23 \times \text{mg HLADH/mL of assay volume}}$$

If the above assay concentrations are followed exactly, this becomes:

$$\text{Units/mg protein} = \frac{\Delta OD_{340}/\text{min}}{20.75}$$

6. Ambient temperatures of up to 30°C can be employed but the reaction temperature should not be allowed to fall below 20°C.

7. The end of the reaction is checked by gas chromatography using 3% QF-1 or OV-101 on Chromosorb columns. The checkers used an OV-101, at 190°C oven temperature. A sample is extracted with ether. The organic layer is analyzed. At 20°C the reaction usually goes to completion within 4 days.

8. This removes residual starting material and other non-acidic impurities.

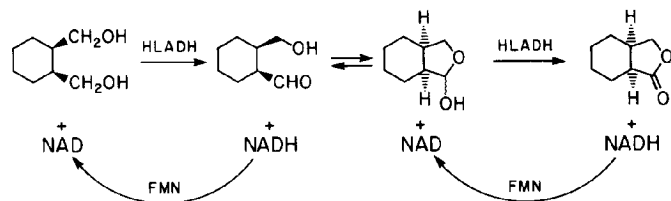
9. Scaling up the preparation is easily accomplished. It is best done by increasing the number of reaction vessels rather than by increasing the reaction volume. For example, 10 g of the cis-diol substrate can be oxidized simultaneously using 2.5 g in each of four 1-L Erlenmeyer flasks as described in the procedure. After 4 days, the reaction mixtures are combined prior to the chloroform extraction and the lactone is isolated.

10. The absolute configuration and optical purity of the lactone was established by its hydrolysis and epimerization to (1R, 2R)-trans-2-hydroxymethylcyclohexanecarboxylic acid followed by lithium aluminum hydride reduction to (1R, 2R)-trans-1,2-bis(hydroxymethyl)cyclohexane.⁴ By ¹H NMR,⁵ the e.e. was > 97%.

11. The spectral properties of the product obtained were as follows: IR (thin film): C = O at 1770 cm^{-1} ; ^1H NMR (CDCl_3) δ : 0.9-2.8 (m, 10 H, all cyclohexane H), 3.87-4.34 (m, 2 H, $\text{CH}_2\text{-O}$).

3. Discussion

Horse liver alcohol dehydrogenase is a well-documented enzyme capable of operating with high stereoselectivity on a broad structural range of alcohol and carbonyl substrates.⁶ The present reaction proceeds via the pathway shown below, where NAD and NADH represent the oxidized and reduced forms, respectively, of the nicotinamide adenine dinucleotide coenzyme.



Chemical oxidations of diols to racemic lactones can be achieved by a broad spectrum of oxidizing agents.⁷ However, at the present time, only the enzymic route described can provide a versatile, one-step, access to such a wide range of highly enantiomerically enriched γ -lactones, useful as chiral building blocks for syntheses.

The lactones which have thus far been obtained by this route have been assembled in the Table. Each oxidation proceeds in high chemical yield (65-90%) to give products of > 97% enantiomeric excess.⁵

TABLE I

PREPARATION OF γ -LACTONES BY HLADH-CATALYZED OXIDATIONS OF MESO-DIOLS (YIELD^{ref.}).

The optical purities and/or enantiomeric excesses were determined by ^1H NMR to be > 97%;⁵ 2 was obtained with 85% e.e.

	1 (90% ¹⁶)		2 (80% ⁴)
	(72% ¹⁶)		(81% ⁹)
	(68% ¹⁶)		3 (71% ¹⁶)
	4 (87% ⁹)		5 (64% ⁹)
	(73% ⁹)		(74% ⁹)
	(86% ⁹)		6 (64% ⁹)
	(65% ¹⁶)		7 (65% ¹⁶)

The maximum reaction time required for any one of the substrates shown in the Table is 7 days. In reaction mixtures which contain lactones 4 and 5, minor amounts of the hemiacetal intermediates are present; they are removed during the extraction at pH 13. After chromatographic separation from any unreacted diols, they can be readily converted to the corresponding lactones by chemical oxidation with silver carbonate on Celite.⁸

The lactones shown in the Table include several representatives of recognized or potential value as starting materials in natural product synthesis. Lactone 1 is a precursor of grandisol,^{9,10} lactone 3 of some pyrethroids,^{9,11} lactone 6 of some prostaglandins,^{9,12} and lactone 7 of multistriatin,¹³ methynolide¹⁴ and monensin.¹⁵

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Appendix

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

(+)-(1R, 6S)-8-Oxabicyclo[4.3.0]nonan-7-one: 1(3H)-Isobenzofuranone, hexahydro-, (3aS-cis)- (9); (65376-02-5)

cis-1,2-Bis(hydroxymethyl)cyclohexane: 1,2-Cyclohexanedimethanol, cis- (8,9); (15753-50-1)

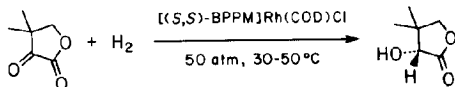
β-NAD; β-Nicotinamide adenine dinucleotide: Pyridinium, 3-carbamoyl-1-β-D-ribofuranosyl hydroxide, 5' → 5' - ester with adenosine 5'-(trihydrogen pyrophosphate), inner salt (8); Adenosine 5'-(trihydrogen diphosphate), 5' → 5' ester with 3-(aminocarbonyl)-1-β-D-ribofuranosylpyridinium hydroxide, inner salt (9); (53-84-9)

FMN; Flavin mononucleotide as sodium salt: Riboflavine 5'-(dihydrogen phosphate), monosodium salt (8,9); (130-40-5)

ASYMMETRIC HYDROGENATION OF KETOPANTOYL LACTONE:

D-(-)-PANTOYL LACTONE

(2(3H)-Furanone, dihydro-3-hydroxy-4,4-dimethyl-)



Submitted by I. Ojima, T. Kogure, and Y. Yoda.¹

Checked by Larry K. Truesdale, Stanley D. Hutchings, and Gabriel Saucy.

1. Procedure

A. Preparation of catalyst solution. A 250-mL round-bottomed flask fitted with a septum and magnetic stirring bar is charged with 486.9-488.2 mg (Note 1) ($0.985\text{--}0.990 \times 10^{-3}$ mol) of chloro(1,5-cyclooctadiene)rhodium (I) dimer (Note 2) and, under argon (Note 3), with 1.20 g (2.15×10^{-3} ml) of (2*S*,4*S*)-*N*-tert-butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine, (*S,S*)-BPPM (Note 4). The sealed flask is charged by cannula, under argon, with 150 mL of degassed benzene (Note 5) and stirred under argon for 15 min at room temperature. The catalyst is transferred by cannula, under argon, into the autoclave (see below).

B. Asymmetric hydrogenation. A stainless steel stirred autoclave with a total volume of 500 mL is charged with 25.6 g (0.2 mol) of ketopantoyl lactone (Notes 6-9). The autoclave is flushed with argon and the catalyst solution (see above) is added by cannula, under argon. The autoclave is sealed and hydrogenation is carried out at 40°C, 750 psig hydrogen and 950-1050 rpm for 48 hr (Note 10). Care should be taken to flush all the lines before connecting to the autoclave. After the autoclave is cooled to room temperature, it is vented and opened. The reaction mixture is then transferred to a 500-mL, round-bottomed flask and most of the solvent is removed by rotary evaporator. Distillation (Note 11) of this reddish solid affords 24-25.6 g (92-98%) (Note 11) of D-(-)-pantoyl lactone: bp 90-110°C (4 cm); $[\alpha]_D^{25} -39.3^\circ$ to -42.4° (c 2, H₂O) (Note 12) (78 to 84% ee) (Notes 1, 10).

The pantoyl lactone thus obtained (25.41 g), $[\alpha]_D^{25} -40.8^\circ$ (80.5% ee) (Note 13) is refluxed with 75 mL benzene and 290 mL of UV-grade hexanes. The cloudy solution is stirred briskly overnight as solids form. Filtration of the solids and drying for 3 hr at 0.25 mm, 30°C in a vacuum oven affords 21.51 g of product; $[\alpha]_D^{25} -47.7^\circ$ (94.27% ee). This material is again refluxed and crystallized (Note 14) from 30 mL of benzene and 116 mL of UV-grade hexanes to afford 19.97 g (77%) of product; $[\alpha]_D^{25} -49.87^\circ$ (98.5% ee); Anal. Calcd for C₆H₁₀O₃: C, 55.37; H, 7.75. Found: C, 55.34; H, 7.57 (Note 15).

2. Notes

1. The reaction was done four times at this scale. The range represents the high and low amounts of catalyst precursor used over the four reactions.

2. Chloro(1,5-cyclooctadiene)rhodium (I) dimer is commercially available from Strem Chemicals, Inc., Newburyport, MA.

3. The addition and measurement of (S,S)-BPPM is most conveniently done in a dry box or glove bag under argon. A Schlenk tube apparatus can be used if these are not available.

4. (2S,4S)-N-tert-Butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine, (S,S)-BPPM,^{2,3} is commercially available from Chemical Dynamics Corp., South Plainfield, NJ.

5. The submitter claims that tetrahydrofuran can also be used giving D-(-)-pantoyl lactone with 83.3-84.8% ee. This was not checked.

6a. Ketopantoyl lactone is readily prepared by the oxidation of *d*,*L*-pantoyl lactone (Note 8) with bromine as follows.⁴ Into a 500-mL round-bottomed flask fitted with a mechanical stirrer, dropping funnel, condenser and thermometer is charged 13.0 g (0.1 mol) of *d*,*L*-pantoyl lactone (Note 7) and 150 mL of carbon tetrachloride. The mixture is stirred and heated to reflux. Bromine (16.5 g, 0.103 mol) in 100 mL of carbon tetrachloride is slowly added from the dropping funnel over 3 hr. After 8 hr, generation of hydrogen bromide subsides and the red color of bromine almost disappears, indicating completion of the reaction. Dry air is bubbled through the solution to remove the remaining hydrogen bromide and the small quantity of bromine. The solvent is removed with a rotary evaporator and further evacuated with a vacuum pump to afford 12.8 g (100%) (Note 9) of almost pure ketopantoyl lactone. One recrystallization from 150 mL of carbon tetrachloride (heat to reflux and then cool to -10°C) affords 11.6-12.2 g (90-95%) of pure ketopantoyl lactone, mp 66-67.5°C.

6b. An alternative procedure preferred by the checkers to prepare highly pure ketopantoyl lactone follows: A 5-L, round-bottomed flask equipped with a mechanical stirrer, condenser, thermometer, and dropping funnel is charged with 700 g of $\text{Ca}(\text{OCl})_2$ (analyzed as 20% active chlorine) and 1.5 L of acetonitrile dried overnight over 4Å sieves. *d*,*L*-Pantoyl lactone (165 g) (Note 7) is dissolved in 500 mL of dried acetonitrile. The $\text{Ca}(\text{OCl})_2$ slurry is stirred while ~ 1/7 of the pantoyl lactone solution is added. The temperature of the exothermic reaction is controlled with an ice bath to below 35°C. The remainder of the pantoyl lactone solution is added in ~ 75-mL aliquots over 25-30 min taking care to control the temperature. The ice bath is removed and stirring is continued. After 3.5 hr, GLC analysis indicates 94% product. The reaction mixture is filtered and the solids are rinsed with acetonitrile. The crude product is dried on a rotary evaporator and further evacuated overnight to yield 105.6 g. The material is dissolved in methylene chloride, dried over Na_2SO_4 , filtered through Celite and concentrated under reduced pressure. The crude product (94.1 g) is then purified by refluxing and stirring overnight with 500 mL of ethyl ether. The slurry is allowed to stand at 5°C. The solids are filtered, washed with cold ether, and dried in a vacuum oven at room temperature for 6 hr to afford 80.8 g (86% recovery) of pure ketopantoyl lactone.

Ketopantoyl lactone has also been reported to be easily prepared by the oxidation of *d*,*L*-pantoyl lactone with alkaline metal hypochlorite⁵ or by reaction of sodium dimethylpyruvate with formaldehyde in the presence of potassium carbonate.⁶

7. *d*,*L*-Pantoyl lactone is very hygroscopic. Care must be taken during this oxidation that dry starting material is used and that water does not contaminate the reaction; the yield will fall drastically probably because of hydrolysis.

8. *d,L*-Pantoyl lactone is commercially available from Sigma Chemical Company, St. Louis, MO 63178.

9. GLC analysis indicates 97-98% yield. A simple GLC system to determine the relative completion of the reaction is a 3 ft x 1/8 in column packed with 10% carbowax 20 M on Anakrom Q 90/100. With this column a program of 150° to 210°C at 8°/min and a 7-min hold, gives baseline separation of ketopantoyl lactone at 2.75-3.2 min and pantoyl lactone at 3.7-3.95 min. The flow rate of the carrier gas is 20 mL/min.

10. When ketopantoyl lactone prepared by method 6b was used, the reaction was complete in 2 hr.

11. A bulb-to-bulb distillation using a Kugelrohr apparatus is most convenient.

12. The reported maximum rotation, $[\alpha]_D^{25}_{\text{max}}$, for pure D-(-)-pantoyl lactone is -50.7° (*c* 2.05, H₂O).⁷

13. The enantiomeric excess and the speed of reduction are both greatly influenced by impurities that are not detectable by GLC. Digestion in ether seems to remove these impurities better than recrystallization from CCl₄.

14. This recrystallization is very temperature sensitive, e.g., this purification was done at ambient temperature (28-30°C). The first recrystallization removes 3.7 g of *d,L*-pantoyl lactone and 0.2 g of D-(-)-pantoyl lactone. When the recrystallization was done at 5°C, twice as much solvent served to remove only 4.2 g of *d,L*-pantoyl lactone and none of the D-isomer.

15. The procedure described is a scaled-up version (20 x) of the original submission worked out by the checkers.

3. Discussion

D-(-)-Pantoyl lactone is a key intermediate for the synthesis of pantothenic acid which is a member of the vitamin B-complex and is an important constituent of Coenzyme A. Although D-(-)-pantoyl lactone has been obtained by classical optical resolution using quinine, ephedrine, and other chiral amines, catalytic asymmetric synthesis appears to be more effective from a practical point of view.⁸ One problem of the present approach was the availability of ketopantoyl lactone, but the recent method developed by Hoffmann-La Roche⁶ comprising the condensation of sodium dimethylpyruvate with formaldehyde may open a commercial route to ketopantoyl lactone. Thus, asymmetric reduction of ketopantoyl lactone now becomes an important route to D-(-)-pantoyl lactone. Asymmetric reduction of ketopantoyl lactone can also be achieved with microorganisms. For example, microbial reduction of ketopantoyl lactone using baker's yeast was reported to give ca. 72% ee,⁹ and the specific strain of an ascomycete, *Byssoschlamys fulva*, was reported to give D-(-)-pantoyl lactone with 95-100% ee.⁹ However, the isolation procedure from aqueous media in these microbial reductions, i.e., extraction, recovery of raw materials, and purification, is very troublesome because of the high solubility of the product in water. Consequently, the present method has considerable advantages from a synthetic point of view, e.g., (i) the yield of the reaction is virtually 100%, and (ii) isolation of the product is simple and convenient since the reaction is carried out in small amounts of nonaqueous media.

The present method has been successfully applied¹⁰ to the asymmetric reduction of various α -keto carboxylates and α -keto lactones.

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Appendix

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

Ketopantoyl lactone: 2,3-Furandione, dihydro-4,4-dimethyl (8,9); (13031-04-4)

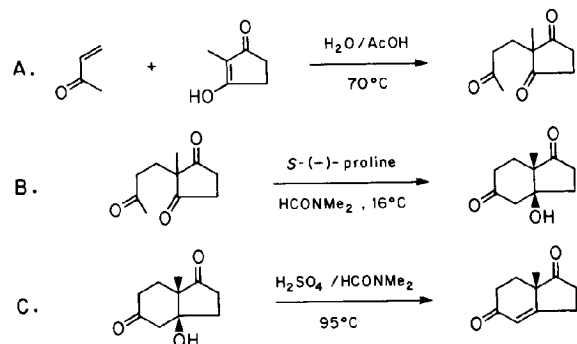
D-(-)-Pantoyl lactone: 2(3H)-Furanone, dihydro-3-hydroxy-4,4-dimethyl-, D- (8); 2(3H)-Furanone, dihydro-3-hydroxy-4,4-dimethyl- (9); (599-04-2)

Chloro(1,5-cyclooctadiene)rhodium (I) dimer: Rhodium, di- μ -chlorobis(1,5-cyclooctadiene) di- (8); Rhodium, di- μ -chlorobis[(1,2,5,6-)-1,5-cyclooctadiene] di- (9); (12092-47-6)

(2S,4S)-N-tert-Butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphino-methylpyrrolidine: 1-Pyrrolidinecarboxylic acid, 4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]-, 1,1-dimethylethyl ester, (2S-cis)- (9); (61478-28-2)

d,L-Pantoyl lactone: 2(3H)-Furanone, dihydro-3-hydroxy-4,4-dimethyl-, (\pm)- (8,9); (79-50-5)

(+)-(7a*S*)-2,3,7,7a-Tetrahydro-7a-methyl-1*H*-indene-1,5-(6*H*)-dione
(1*H*-Indene-1,5(6*H*)-dione, 2,3,7,7a-tetrahydro-7a-methyl-, (S)-)



Submitted by Zoltan G. Hajos¹ and David R. Parrish.²

Checked by Stuart Remington, David Lust, and Gabriel Saucy.

1. Procedure

A. *2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione*. A 1.0-L, three-necked, round-bottomed flask equipped with a condenser, magnetic stirring bar and thermometer is charged with 112.1 g (1.0 mol) of 2-methyl-1,3-cyclopentanedione (Note 1), 230 mL of deionized water, 3.0 mL of glacial acetic acid, and 140 mL (120.96 g, 1.72 mol) of methyl vinyl ketone (Note 2). The system is shielded from light with aluminum foil and placed under a slight positive pressure of nitrogen. The flask is placed in an oil bath and

the temperature is raised to 70°C. The reaction is monitored by gas chromatography (GLC, Note 3) until complete (1-2 hr). The mixture is cooled, transferred to a separatory funnel and extracted with 500 mL and then two 100-mL portions of dichloromethane. The combined extracts are washed with 500 mL and 100 mL of saturated brine. The combined brine wash is extracted with a further two 100-mL portions of dichloromethane. The total dichloromethane extract is dried over sodium sulfate and filtered. The solvent is removed on a rotary evaporator at 45°C (70 mm). Drying on the rotary evaporator at 40-45°C (0.03 mm) for 16 hr gives 181.8 g (100%) of the desired triketone as an orange oil (Notes 4,5).

B. *(+)-(3a*S*,7a*S*)-2,3,3a,4,7,7a-Hexahydro-3a-hydroxy-7a-methyl-1*H*-indene-1,5(6*H*)-dione*. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar and a nitrogen inlet is charged with 188 mL of *N,N*-dimethylformamide (Note 6) and 863 mg (7.5 mmol) of *S*-(-)-proline (Notes 7,8). The mixture is degassed four times by alternate evacuation and refilling with nitrogen. The system is shielded from light with aluminum foil and the contents of the flask are stirred in a 15-16°C bath (Note 9) for 1.0 hr. To the resultant suspension is added 45.5 g (0.25 mol) of the 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione prepared in step A. A total of 62.5 mL of *N,N*-dimethylformamide is used to insure complete transfer. The degassing procedure is repeated four times and stirring at 15-16°C (Note 10) is continued for 40-120 hr (Note 11) as the mixture becomes yellow and then brown. The reaction is monitored for completeness by thin layer chromatography (TLC, Note 12). The solution of the desired ketol (Note 13) is used directly in step C.

C. (+)-(7aS)-2,3,7,7a-Tetrahydro-7a-methyl-1H-indene-1,5(6H)-dione. A 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, pressure-equalizing dropping funnel and a nitrogen inlet is charged with 50 mL of N,N-dimethylformamide (Note 6). The contents of the flask are cooled to -20°C with a dry ice-acetone bath and 2.70 mL (4.97 g, 48.6 mmol) of concd sulfuric acid is added over 5-10 min at a rate to maintain a temperature of -15 to -20°C (Note 14).

The flask containing the solution of the (+)-(3aS,7aS)-2,3,3a,4,7,7a-hexahydro-3a-hydroxy-7a-methyl-1H-indene-1,5(6H)-dione in N,N-dimethylformamide is placed in an oil bath and heated to 95°C. When the temperature reaches 70-75°C, an 18.8-mL aliquot of the concd sulfuric acid in N,N-dimethylformamide solution is added in one portion. The reaction mixture is heated to 95°C for 3.0 hr. After 1.0 hr, an additional 7.5-mL aliquot of the concd sulfuric acid in N,N-dimethylformamide solution is added in one portion. The reaction is monitored for completeness by GLC (Note 15) and cooled. The solvent is removed on a rotary evaporator at 45°C (0.3-0.5 mm) to give a brown oil. The material is taken up in 375 mL of dichloromethane. The solution is washed with two 190-mL portions of 2.0 N sulfuric acid solution which have been saturated with sodium chloride, two 190-mL portions of saturated sodium bicarbonate solution which have been saturated with sodium chloride and 190 mL of saturated brine. Each aqueous wash is extracted, in turn, with the same two 190-mL portions of dichloromethane. The combined dichloromethane solutions are dried over sodium sulfate, filtered, and the solvent is removed on a rotary evaporator at 40°C (70 mm) to give 38.8-39.6 g of oily, brown semisolid. This material is taken up in 78 mL of ethyl acetate and the solution is applied to a dry column of 78 g of silica gel (Note 16). The column is eluted with 600 mL of ethyl acetate and the total eluate is

stripped of solvent on a rotary evaporator at 40°C (70 mm) to give 37.2-38.8 g of tan crystalline solid. The solid is subjected to bulb-to-bulb distillation³ (Note 17) at 120-135°C (0.1 mm) to give 35.9-36.9 g of a slightly yellowish (cream white) solid, mp 56-61°, $[\alpha]_D^{25} +324-329^\circ$ (toluene, c 1.0) (Notes 18,19,20). This material is taken up in 74 mL of ether at reflux: The solution is brought at reflux to the point of turbidity with 19 mL of hexanes. The mixture is seeded, allowed to stand at ambient temperature for 2 hr and then chilled in a 17°C water bath for 30 min (Note 21). The solid is collected by filtration on medium porosity sintered glass, washed with two 12-mL portions of cold (3°C) 1:1 v/v ether:hexanes and dried at 20°C (70 mm) to give 28.7-31.3 g (70-76%) of white crystalline solid (Note 22), mp 64-66°C, $[\alpha]_D^{25} +347.5-349^\circ$ (toluene, c 1.0) (Note 23), purity by GLC 99.4-99.5% (Notes 24,25,26).

2. Notes

1. 2-Methyl-1,3-cyclopentanedione, 98%, purchased from the Aldrich Chemical Company, Inc., was used. Material prepared according to Hengartner, U.; Chu, V. *Org. Synth.* **1979**, *58*, 83-85 was determined by the checkers to be equally satisfactory.

2. Methyl vinyl ketone, technical grade, purchased from the Aldrich Chemical Company, Inc., was fractionally distilled into ca. 1% w/v hydroquinone shortly before use. The fraction boiling at 33-36°C (120 mm) was used.

3. Analyses were carried out on a Hewlett Packard HP 5840 A gas chromatograph operated isothermally at 150°C. A 25-m capillary column packed with crosslinked phenylmethylsilicone was employed. 2-Methyl-1,3-cyclopentanedione and 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione had retention times of ca. 7 min and 12.5 min, respectively.

4. If desired, pure triketone can be isolated by distillation of the crude triketone through a Vigreux column. The yield of light yellow oil, bp 115-120°C (0.2-0.3 mm), is 80-89%.

5. The triketone has the following spectral properties: IR (neat) cm^{-1} : 1770, 1725; ^1H NMR (CDCl_3) δ : 1.12 (s, 3 H, CH_3), 2.22 (s, 3 H, CH_3CO), 2.8 (m, 4 H), $\text{COCH}_2\text{CH}_2\text{CO}$.

6. N,N-Dimethylformamide, purchased from the Fisher Scientific Co., was mixed with 10% v/v toluene and distilled at atmospheric pressure. After all of the toluene had been distilled (head temperature to 148°C), vacuum was cautiously applied. The fraction of N,N-dimethylformamide which distilled at 78-82°C (56-64 mm) was collected and stored under nitrogen prior to use.

7. L-(-)-Proline [(S)-configuration], 99⁺%, purchased from the Aldrich Chemical Company, Inc., was employed. The material was finely ground in a mortar and pestle immediately before use.

8. The L-(-)-proline was established by the checkers to be of >99.8% (estimated level of detection) enantiomeric purity by conversion to N-pentafluoropropionyl-L-(-)-proline isopropyl ester and GLC analysis on a 50-m glass capillary column containing the chiral phase, Chirasil-Val (Quadrex Inc.). Analyses were performed on a Hewlett-Packard HP 5710 A instrument operated isothermally at 140°C. Racemic proline was used as a control.

9. The checkers used a flask with a built-in jacket. Water at 15-16°C was continuously circulated through the jacket.

10. Temperature control in this reaction is critical. At higher temperatures, the enantioselectivity of the reaction drops off significantly, while at lower temperatures, the reaction time becomes unacceptably long.

11. The reaction time varied substantially from run to run, but generally complete conversion was observed in 48-72 hr.

12. E. Merck silica gel F-254 plates were used, with 20:1 v/v dichloromethane : methanol as eluent. The plates were developed by drying, spraying with 9:1 v/v deionized water:concentrated sulfuric acid, light drying with a hot air gun, spraying with 3% w/v vanillin solution in ethanol and strong heating with the hot air gun. The approximate R_f values observed were 0.67 (starting triketone) and 0.37 (product ketol). In addition, a minor spot at R_f 0.59 (enone arising from dehydration of the ketol) was seen.

13. If desired, the ketol can be isolated as follows. The reaction mixture from 18.0 g of distilled 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione is evaporated on a rotary evaporator at 45°C (0.3 mm) to give 22.0 g of brown oil. A solution of this material in 200 mL of ethyl acetate is filtered through 80 g of J. T. Baker silica gel. Elution with ca. 1.3 L of ethyl acetate in 200-mL fraction is monitored by TLC (Note 12). The fractions containing the desired product are combined and stripped of solvent on a rotary evaporator at 45°C (70 mm). Final drying on the rotary evaporator at 45°C (0.3 mm) gives 18.0 g (100%) of crude ketol as a slightly oily, brown solid having the following spectral properties: IR (CHCl_3) cm^{-1} : 3600, 3500-3300, 1742, 1722; ^1H NMR (CDCl_3) δ : 1.26 (s, 3 H, CH_3), 2.63 (s, 2 H, COCH_2COH). Further purification of the compound by crystallization from ether (ca. 50% recovery) gives material of mp 118-119°C, $[\alpha]_D^{25} +59.8^\circ$ (lit⁴ mp 119-119.5°C, $[\alpha]_D^{25} +60.4^\circ$).

14. The solution is prepared immediately before use and kept at -20°C.

15. The GLC system described in Note 3 was employed. The intermediate ketol and product enone had retention times of ca. 23 min and 16.5 min, respectively. A trace of ketol (<1%) is observed at the end of the reaction.

16. E. Merck silica gel 60 (70-230 mesh) was used. The column dimensions were 3.2 x 60 cm.

17. A Kugelrohr apparatus, purchased from the Aldrich Chemical Company, Inc., was used. The receiving bulb was cooled with an ice-water bath. The temperature indicated is that of the oven air bath.

18. The ratio of rotations obtained in toluene and benzene has been determined to be 1.00:1.03. The rotation of enantiomerically pure material in toluene, based on the accepted⁴ value of +362° in benzene, is 351°. The enantiomeric purity at this stage is thus 92-94% (Note 19).

19. Attempts by both the submitters and checkers to find a method other than optical rotation to determine the enantiomeric purity have been unsuccessful.

20. Material of this purity is satisfactory for many synthetic purposes, cf. reference 3.

21. Further cooling results in a higher recovery of material. However, the melting point and rotation of the samples thus obtained are lower.

22. The compound is somewhat unstable. It is best stored in an amber bottle under nitrogen at 3°C.

23. The enantiomeric purity of the purified material is thus 99.0-99.4% (cf. Note 18).

24. GLC analysis was carried out on a Hewlett Packard HP 5710 A gas chromatograph operated isothermally at 155°C. A 50-m capillary column of OV-17 on fused silica was employed. The enone had a retention time of ca. 14.5 min.

25. The material has the following spectral properties: UV (CH₃OH) λ 235 nm (ϵ = 11,200); IR (CHCl₃) cm⁻¹: 1746, 1665; ¹NMR (CDCl₃) δ : 1.31 (s, 3 H), 7a-CH₃, 5.97 (broad, s, 1 H, vinylic-H).

26. Steps B and C have been scaled up to the 2.0-mol level with no loss in yield or enantiomeric purity.

3. Discussion

The (S)-(-)-proline catalyzed asymmetric aldol cyclization of the triketone to the optically active bicyclic aldol product, followed by dehydration to the optically active enedione, (+)-(7aS)-2,3,7a-tetrahydro-7a-methyl-1H-indene-1,5(6H)-dione, has been described, and two alternative reaction mechanisms have been suggested by the submitters.⁵ The exact mechanism of the extremely high asymmetric induction in the crucial conversion of the prochiral triketone to the optically active ketol still needs to be clarified.^{6a,b,c}

The synthesis of the triketone has been included (Part A of the Procedure), since identification of the crystalline compound originally claimed⁷ to be the triketone has been shown to be in error.⁸ After completion of our work, the triketone was correctly characterized by another research group.⁹

Asymmetric aldol cyclization of the triketone with (S)-(-)-proline can also be effected in solvents other than N,N-dimethylformamide; acetonitrile is outstanding.⁵

Of the asymmetric amino acid reagents investigated, (S)-(-)-proline gave the highest optical yield (93.4%); (-)-trans-4-hydroxyproline gave 73.1%, and (S)-(-)-azetidinecarboxylic acid gave 63.9% optical yields in the asymmetric synthesis of the optically active bicyclic ketol.

The use of (R)-(+)-proline in acetonitrile induced the asymmetric aldol cyclization of the triketone to the enantiomeric ketol, (-)-(3aR,7aR)-2,3,3a,4,7,7a-hexahydro-3a-hydroxy-7a-methyl-1H-indene-1,5(6H)-dione.¹⁰

The ethyl homolog of the triketone, 2-ethyl-2-(3-oxobutyl)-1,3-cyclopentanedione, has been converted with (S)-(-)-proline in N,N-dimethylformamide to (+)-(3aS,7aS)-7a-ethyl-2,3,3a,4,7,7a-hexahydro-3a-hydroxy-1H-indene-1,5(6H)-dione in good yield.⁵ This in turn could be dehydrated to the homologous bicyclic enedione, (+)-(7aS)-7a-ethyl-2,3,7,7a-tetrahydro-1H-indene-1,5(6H)-dione.⁵

Circular dichroism studies of the 7a-methyl bicyclic ketol suggested, and a single-crystal X-ray diffraction study of the racemic compound confirmed, the cis conformation with an axial 7a-methyl and an equatorial 3a-hydroxy group in the six-membered ring of the bicyclic system. On the other hand, similar measurements of the 7a-ethyl bicyclic keto established the alternate possible cis conformation to avoid the 1,3-diaxial interactions between the angular ethyl group and the C-4 and C-6 axial hydrogens.

Dehydration of the optically active bicyclic ketols in refluxing benzene with a little p-toluenesulfonic acid could readily be effected without loss of optical purity.⁵ It has been shown by a research group at Schering A. G., Berlin, Germany that the triketone can be converted directly to the optically active enedione with 0.5 eq. of (S)-(-)-proline and 0.25 eq. of 1 N aqueous HClO₄ in refluxing acetonitrile.¹¹

The optically active bicyclic enedione, (+)-(7aS)-2,3,7,7a-tetrahydro-7a-methyl-1H-indene-1,5(6H)-dione, was prepared first by microbiological means,⁴ and its absolute stereochemistry has been established.¹² The compound was later prepared by optical resolution.¹³

The products of this highly efficient asymmetric synthesis are important intermediates in natural product chemistry, e.g., the total synthesis of steroids and prostaglandins.

1. Formerly with Hoffmann-La Roche Inc., Nutley, NJ 07110; present address: 65 Shady Brook Lane, Princeton, NJ 08540.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

(+)-(7a*S*)-2,3,7,7a-Tetrahydro-7a-methyl-1*H*-indene-1,5(6*H*)-dione: 1,5(6*H*)-Indanedione, 7,7a-dihydro-7a*β*-methyl-, (+)-(8); 1*H*-Indene-1,5(6*H*)-dione, 2,3,7,7a-tetrahydro-7a-methyl-, (*S*)-(9); (17553-86-5)

2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione: 1,3-Cyclopentanedione, 2-methyl-2-(3-oxobutyl)- (8,9); (25112-78-1)

2-Methyl-1,3-cyclopentanedione: 1,3-Cyclopentanedione, 2-methyl- (8,9); (765-69-5)

Methyl vinyl ketone: 3-Buten-2-one (8,9); (78-94-4)

(+)-(3a*S*,7a*S*)-2,3,3a,4,7,7a-Hexahydro-3a-hydroxy-7a-methyl-1*H*-indene-1,5(6*H*)-dione: 1*H*-Indene-1,5(4*H*)-dione, hexahydro-3a-hydroxy-7a-methyl-, (3a*S*-cis)- (9); (33879-04-8)

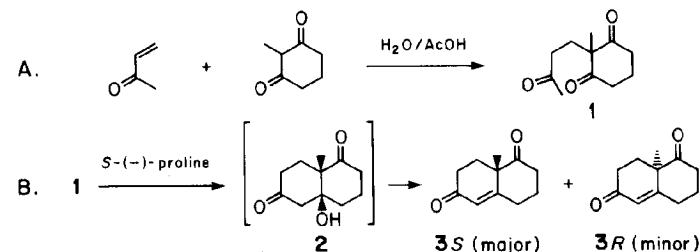
N,N-Dimethylformamide: Formamide, N,N-dimethyl- (8,9); (68-12-2)

S-(-)-Proline: Proline, L- (8); L-Proline (9); (147-85-3)

ASYMMETRIC SYNTHESIS OF (*S*)-8a-METHYL-3,4,8,8a-

TETRAHYDRO-1,6(2*H*,7*H*)-NAPHTHALENEDIONE

(1,6(2*H*,7*H*)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-methyl-, (*S*)-)



Submitted by Paul Buchschacher[†] and A. Fürst.¹

Checked by P. S. Belica, P. S. Manchand, and Gabriel Saucy.

1. Procedure

Caution! Part A should be performed in a well-ventilated hood because methyl vinyl ketone is a lachrymator.

A. *2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione.* A 1-L, round-bottomed flask equipped with a thermometer, and a reflux condenser capped with an argon-inlet tube, is charged with 126.1 g (1 mol) of 2-methyl-1,3-cyclohexanedione (Note 1) and 300 mL of distilled water. To the well-stirred suspension are added 3 mL of acetic acid, 1.1 g of hydroquinone, and 142 g (167 mL, 2 mol) of freshly distilled methyl vinyl ketone (Note 2). The reaction mixture is stirred under argon at 72-75°C for 1 hr, treated with

sodium chloride (103 g), and poured into a separatory funnel containing ethyl acetate (400 mL). The organic phase is collected and the aqueous phase is re-extracted twice with ethyl acetate (150 mL each time). The combined extracts are washed with two 200-mL portions of saturated brine, dried over anhydrous magnesium sulfate, filtered, and the filtrate is evaporated at 40°C under reduced pressure (water aspirator) on a rotary evaporator. The residue is kept under high vacuum (1.0 mm) at 40°C for 30 min to give 210.8 g of crude 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (1, "trione") as a pale yellow oil, homogeneous by thin layer chromatography (Note 3). This crude material is used in Part B.

B. *(S)*-8 α -Methyl-3,4,8,8 α -tetrahydro-1,8(2H,7H)-naphthalenedione (*δ* -S). A 3-L, one-necked, round-bottomed flask, equipped with an argon-inlet tube and containing a magnetic stirrer, is charged with 5.75 g (0.05 mol) of finely ground L-proline (Note 4), and a solution of 210.8 g of crude trione 1 (from Part A) in anhydrous dimethyl sulfoxide (Note 5). The mixture is stirred at room temperature (ca. 25°C) under argon for 120 hr, the magnetic bar is removed, and the solvent is removed under high vacuum (1.0 mm) at 65°C (Note 6) on a rotary evaporator to give 206.9 g of a dark reddish-violet oil. The oil is dissolved in toluene (100 mL) and is adsorbed on a column (9 cm x 60 cm) of silica gel (1.5 kg, 70-230 mesh) (Note 7), which was previously packed in hexane. Elution is carried out under a slight positive pressure of argon (ca. 1 atm) (Note 8) initially with 1 L of hexane:ethyl acetate (5:1) and then with a 3:2 mixture of hexane:ethyl acetate taking 300-mL fractions. The progress of the purification is monitored by thin layer chromatography (Note 9): no product is observed until ca. 5 L of eluant is collected. Fractions containing the product are combined, and the solvents are removed under reduced pressure (water aspirator) at 45-50°C. The residue is then kept

under high vacuum (0.1 mm) at 40°C for 30 min to give 154.2 g of an orange-colored oil, $[\alpha]_D^{25} +68^\circ$ (toluene, c 1.463). This material is dissolved in 535 mL of ether and is filtered through a fluted filter paper to remove small particles. The flask is rinsed with 500 mL of ether and this is passed through the filter paper. The combined filtrates are seeded with a few crystals of pure 3-S (Note 10), and the mixture is left at -20°C for 18 hr. Most of the supernatant liquid is carefully decanted without agitation, and the crystals are collected by filtration. The flask is rinsed with cold (0°C) 50% ether in hexane and the rinse is used to wash the crystals. The crystals are melted at 55°C under reduced pressure (12 mm) on a rotary evaporator and allowed to crystallize at 25°C to yield 85.9 g of (*S*)-enedione (first crop), mp 49-50°C, $[\alpha]_D^{25} +96.91^\circ$ (toluene, c 1.1743) (Note 11). The combined filtrate and washings are evaporated to give 67.1 g of an orange-colored oil, which is dissolved in 604 mL of ether, cooled to 3°C, and seeded with (*R,S*)-enedione (Note 12). The mixture is left at -20°C for 18 hr, and the supernatant liquid is carefully decanted (no agitation). The wet crystals are then collected by filtration, washed with cold (0°C) 50% ether in hexane, and dried under reduced pressure at room temperature to give 36.3 g of racemic material (3R + 3S). The filtrate and washing are evaporated to give 30.6 g of an oil, which is dissolved in 100 mL of ether and filtered through a fluted filter paper. The flask is rinsed with 114 mL of ether, filtered through the fluted filter paper, and the combined filtrates are cooled to 3°C and seeded with crystals of the pure 3-S. The mixture is left at -20°C overnight, the supernatant liquid is carefully decanted without much agitation and the wet crystals are collected by filtration and washed with cold (0°C) 50% hexane in ether. The product is melted under reduced pressure (12.0 mm) at 55°C and allowed to crystallize at room temperature to give 15.3 g of light amber-

colored crystals (second crop), mp 49-50°C, $[\alpha]_D^{25} +97.3^\circ$ (toluene, d 1.05). The total yield of (S)-enedione is 101.2 g (56.8%) (Note 13).

2. Notes

1. 2-Methyl-1,3-cyclohexanedione² was obtained from Aldrich Chemical Company, Inc. and had mp 208-210°C.

2. Methyl vinyl ketone, bp 34°C/120 mm, was obtained from Aldrich Chemical Company, Inc.

3. Thin layer chromatography was performed on silica gel with ethyl acetate:hexane (3:2). Visualization of the spots was achieved by spraying the plates with 10% ceric sulfate in 10% sulfuric acid, heating the plates to ca. 120°C, and spraying again with 10% phosphomolybdic acid in isopropyl alcohol. The product has R_f 0.50; 2-methyl-1,3-cyclohexanedione has R_f 0.30.

4. S-(-) Proline was obtained from Aldrich Chemical Company, Inc.

5. Dimethyl sulfoxide was dried over molecular sieves type 4 Å. Anhydrous N,N-dimethylformamide was used by the submitter; cf. ref. 3.

6. The temperature should be kept below 70°C.

7. Silica gel was purchased from EM Reagents, E. Merck, Darmstadt, Germany.

8. The procedure of W. C. Still⁴ is used.

9. Silica gel and 60% ethyl acetate in hexane were used. The product, R_f 0.40, is visible under short wavelength ultraviolet light whereas the starting trione, also R_f 0.40, is not. Visualization is achieved as described in Note 3.

10. Compound 3-S was obtained from material having $[\alpha]_D^{25} +68^\circ$ (toluene, d 1.60) that was prepared in another experiment. Thus, 28.2 g of this (S)-

enedione is dissolved in 90 mL of ether and the solution is left at -20°C for 18 hr. The crystals are collected by filtration without much agitation, washed with 30 mL of cold (0°C) 50% ether in hexane, and redissolved in 117 mL of ether. The solution is left at -20°C for 18 hr, and the crystals are collected by filtration, washed with 30 mL of cold (0°C) 50% ether in hexane, and dried under reduced pressure (1.0 mm) at room temperature to give 12.0 g of (S)-enedione, mp 50°C, $[\alpha]_D^{25} +100^\circ$ (benzene, d 1.461). It should be possible to prepare seed crystals from a small aliquot, but this was not attempted by the checkers.

11. This assures consistency of material.

12. Racemic Wieland-Miescher ketone was obtained from Aldrich Chemical Company, Inc. or prepared according to the procedure of Ramachandran and Newman.⁵

13. ¹H NMR studies (100 MHz, CDCl₃) using the shift reagent tris[3-(heptafluoropropyl)hydroxymethylene]-d-camphorato]europium(III) (purchased from Aldrich Chemical Company, Inc.) indicated that the two crops were enantiomerically pure. Under identical conditions (10 mg of reagent per 9.6 mg of substrate), absorption due to the vinyl proton at δ 5.86 in the racemate appeared as two peaks (1 Hz separation) of equal intensity.

3. Discussion

Racemic 8a-methyl-3,4,8,8a-tetrahydro-1,6(2H,7H)-naphthalenedione (the Wieland-Miescher ketone)^{5,6} is a versatile building block for the synthesis of steroids⁷ and terpenoids.⁸ The (S) enantiomer, 3-S, was first obtained by microbiological means⁹ and by classical resolution via a derived hemiphthalate.¹⁰ The present synthesis³ of 3-S is based¹¹ on the asymmetric

intramolecular aldolization of the prochiral triketone 1 using S-(-)-proline catalytically. The product is obtained in 56% yield (from 2) and is enantiomerically pure based on optical rotation and on NMR spectroscopy determined in the presence of a chiral shift reagent. Despite numerous synthetic investigations and modifications of this asymmetric Robinson annulation,¹² the mechanism of enantiodifferentiation is still not fully understood;¹³ cf. discussion in the preceding procedure relating to the asymmetric synthesis of the corresponding S-(+)-tetrahydro-7-methylindenedione.

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Appendix

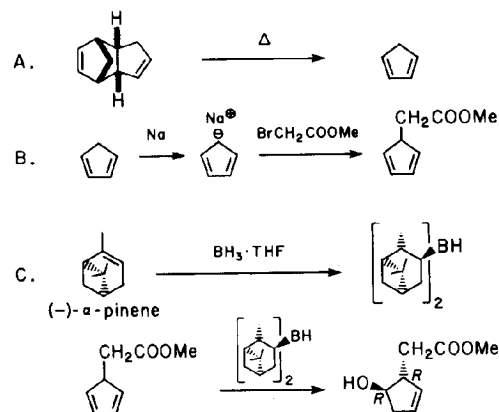
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S)-8a-Methyl-3,4,8,8a-tetrahydro-1,6(2H,7H)-naphthalenedione: 1,6(2H,7H)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-methyl-(S)-(+)- (8); 1,6(2H,7H)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-methyl-, (S)- (9); (33878-99-8)
 2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione: 1,3-Cyclohexanedione, 2-methyl-2-(3-oxobutyl)- (9); (5073-65-4)
 2-Methyl-1,3-cyclohexanedione: 1,3-Cyclohexanedione, 2-methyl- (8,9); (1193-55-1)
 L-Proline: Proline, L- (8); L-Proline (9); (147-85-3)
 Methyl vinyl ketone: 3-Buten-2-one (8,9); (78-94-4)
 8a-Methyl-3,4,8,8a-tetrahydro-1,6(2H,7H)-naphthalenedione: 1,6(2H,7H)-Naphthalenedione, 3,4,8,8a-tetrahydro-8a-methyl- (8,9); (20007-72-1)

ASYMMETRIC HYDROBORATION OF 5-SUBSTITUTED CYCLOPENTADIENES:

SYNTHESIS OF METHYL (1R,5R)-5-HYDROXY-2-CYCLOPENTENE-1-ACETATE

(2-Cyclopentene-1-acetic acid, 5-hydroxy-, methyl ester, (1R-trans)-)



Submitted by John J. Partridge, Naresh K. Chadha, and Milan R. Uskoković.¹

Checked by Bai Dong-lu and Clayton H. Heathcock.

1. Procedure

A. *Pyrolysis of dicyclopentadiene to form cyclopentadiene.* Cyclopentadiene is prepared from its dimeric form by distillation according to the method of Moffett.² The apparatus for the distillation is assembled as shown in Diagram 1. The equipment consists of a 250-mL flask, a Friedrichs condenser fitted with a Haake Model FE hot water circulator, a Claisen head, a thermometer, a gas inlet tube, and a collection receiver which is cooled to -78°C in a dry ice-acetone bath.

In the 250-mL flask is placed 100 mL of dicyclopentadiene (Note 1). The material is heated at reflux (bath temperature 200-210°C) under a nitrogen atmosphere (Note 2). After a 5-mL forerun is collected and discarded, the collection receiver is cooled to -78°C and 25 mL (0.30 mol) of cyclopentadiene is rapidly distilled at bp 36-42°C. A slight positive pressure of nitrogen is maintained throughout the distillation to prevent moisture from entering the system.

The distilled cyclopentadiene is stored at -78°C until it is used (Note 3). Residual dicyclopentadiene can be reused until it solidifies on cooling.

B. *Preparation in situ of methyl 2,4-cyclopentadiene-1-acetate* (Note 4). Cyclopentadienylsodium is prepared by modification of the methods of King³ and Hafner⁴ (Note 5).

In a 500-mL, three-necked Morton flask fitted with a condenser, mechanical stirrer, and gas inlet tube is placed 8.6 g (0.375 g atom) of sodium and 75 mL of dry xylene (Note 6); the unstirred mixture is heated at reflux under a nitrogen atmosphere. After the xylene has reached its boiling point and the sodium has melted, the solution is rapidly stirred to produce a very fine-grained sodium sand. Quickly the heating mantle is removed and stirring stopped (Note 7). After cooling, the xylene is pipetted or siphoned away from the sodium sand and stored for future use.

The sand is washed with 3 x 25 mL of dry tetrahydrofuran (Note 8), then is layered with 100 mL of dry tetrahydrofuran, and the mixture is cooled to -10°C (Note 9) under a nitrogen atmosphere. A solution of 25 mL (0.30 mol) of cyclopentadiene in 25 mL of tetrahydrofuran is added dropwise using a dropping funnel. After the addition is complete, the mixture is stirred overnight at room temperature, by which time hydrogen evolution has ceased. In the absence of air, the solution ranges from near colorless to bright pink (Note 10).

In a 1-L, three-necked flask fitted with a 200-mL pressure-equalizing dropping funnel, mechanical stirrer, and a gas inlet tube, is placed 45.9 g (0.30 mol) of methyl bromoacetate (Note 11) and 75 mL of tetrahydrofuran and the mixture is cooled to -78°C in an inert atmosphere.

The solution of ca. 0.30 mol of cyclopentadienylsodium is decanted from residual sodium sand with a U-tube into the dropping funnel (Note 12) and is added dropwise over a 2-hr period (Note 13). A white precipitate of sodium bromide forms during the addition. The heterogeneous solution is stirred overnight at -78°C to insure complete formation of methyl 2,4-cyclopentadiene-1-acetate.

C. *Asymmetric hydroboration with (+)-di-3-pinanylboration to form methyl (1R,5R)-5-hydroxy-2-cyclopentene-1-acetate* (Note 4). The (+)-di-3-pinanylboration is prepared from (-)- α -pinene by a modification^{5,6} of the method of Brown⁷ (Note 14).

In a 2-L, three-necked flask fitted with a condenser, mechanical stirrer, and a gas inlet tube is placed 90.0 g (0.66 mol) of (-)- α -pinene (Note 15). The flask is cooled to 0°C and under an inert atmosphere a total of 300 mL (0.30 mol) of 1 M borane in tetrahydrofuran (Note 16) is added dropwise over a 1-hr period. The solution is stirred for 18 hr at 0°C during which time a white precipitate of (+)-di-3-pinanylboration forms. This solution is then cooled to -78°C . The ca. 0.30 mol solution of methyl 2,4-cyclopentadiene-1-acetate (Part B) is transferred at -78°C to a 500-mL pressure-equalizing dropping funnel through a U-tube in an inert atmosphere, and is added rapidly, in one portion, to the stirring solution of di-3-pinanylboration at -78°C . After this mixture is stirred for 6 hr at -78°C , the bath temperature is allowed to rise to 0°C and the mixture is stirred for 16 hr at 0°C to complete the hydroboration reaction.

To the reaction mixture is added dropwise 90 mL of 3 N aqueous sodium hydroxide, followed by 90 mL of 30% hydrogen peroxide (Note 17). The mixture is stirred for 30 min to complete the oxidation process. A total of 3 g of sodium bisulfite, 5 g of sodium chloride, and 125 mL of ether are added and the mixture is stirred for 10 min (Note 18). On standing, the reaction mixture separates into two layers, which are separated with a 1-L separatory funnel. The organic layer is washed with brine (2 x 50 mL). The water layer and the brine washes are combined and extracted with ether (3 x 125 mL). All the organic layers are then combined and dried over anhydrous magnesium sulfate. Filtration and removal of solvent under reduced pressure yield 110 g of a pale yellow oil containing the desired product as well as (+)-isopinocampheol, and (-)- α -pinene (Note 19). The product mixture is dissolved in 250 mL of ether and is extracted with 1 M aqueous silver nitrate solution (3 x 100 mL). The aqueous layers are combined and back-extracted once with 50 mL of ether. The ether layers containing (+)-isopinocampheol are discarded.

The aqueous layers containing the silver(I) complex of methyl (1R,5R)-5-hydroxy-2-cyclopentene-1-acetate are then treated with an excess of saturated brine to precipitate silver chloride and free the desired product. After precipitation is complete, the water layer is decanted from the solid silver chloride. The solids are washed with ether (4 x 100 mL) and each ether layer is used to extract the water layer (Note 20). The combined ether layers are washed with 50 mL of brine and dried over anhydrous magnesium sulfate. Filtration and removal of solvent under reduced pressure yield 16-19 g of crude product. The product is distilled through a 4"-Vigreux column at 0.1 mm pressure to yield 12.8-14.7 g (27-31%) of methyl (1R,5R)-5-hydroxy-2-cyclopentene-1-acetate, bp $74-78^{\circ}\text{C}$ at 0.1 mm, $[\alpha]_D^{25} -132^{\circ}$ (CH_3OH , c 1.06) (Notes 21, 22).

2. Notes

1. Dicyclopentadiene was obtained from Ace Scientific, (TX 315) practical grade, 95%.
2. The Haake water circulator was employed with the circulating water temperature at 50°C. This allows only cyclopentadiene to distill.
3. Cyclopentadiene is stable at -78°C but dimerizes readily at room temperature.
4. Steps B and C must be run concurrently.
5. The efficient formation of cyclopentadienylsodium is of paramount importance for the entire reaction sequence. Variations in the yield of methyl 2,4-cyclopentadiene-1-acetate have been traced to the degree of efficiency in producing a fine sodium sand which is used to produce cyclopentadienylsodium. In the alkylation reaction of cyclopentadienylsodium with methyl bromoacetate, the entire process must be carried out in an inert dry atmosphere at -78°C. At higher temperatures, the desired product can undergo undesired dimerization and double bond migration side reactions. Methyl 2,4-cyclopentadiene-1-acetate, once formed, is used immediately.
6. Xylene was obtained from Fisher Scientific Company. The xylene is initially dried over sodium and is saved and reused in making additional batches of sodium sand.
7. If stirring continues while the xylene cools, the sodium sand coagulates into a large lump.
8. Tetrahydrofuran was obtained from Fisher Scientific Company. The tetrahydrofuran employed was freshly distilled from lithium aluminum hydride. Care should be exercised in drying tetrahydrofuran; cf. *Org. Synth., Collect. Vol. V* 1973, 976. The checkers also examined the use of

tetrahydrofuran that had been dried by distillation from sodium/benzophenone ketyl. When material that has been purified in this manner is used, the fine sodium sand coagulates, giving small porous lumps. No such coagulation occurs when tetrahydrofuran that has been dried by distillation from lithium aluminum hydride is used. However, the method of drying had no effect on overall yield of final product.

9. A bath of carbon tetrachloride containing a little dry ice is used for cooling.

10. The efficient formation of cyclopentadienylsodium was found to be the product-limiting step for the reaction sequence. *If air is present or if the sodium sand is not fine-grained, quantitative formation of cyclopentadienylsodium cannot be assumed.* Residual sodium sand may be washed with tetrahydrofuran, dried in a nitrogen atmosphere and weighed to determine approximately the extent of cyclopentadienylsodium formation.

11. Methyl bromoacetate was obtained from Ace Scientific (MX 755).

12. Care must be taken during this transfer to minimize exposure of the cyclopentadienylsodium to air. Trace amounts of oxygen cause the formation of a dark brown color and brown solid in the solution.

13. The drip rate should be adjusted so that the dropping funnel is not plugged by crystalline cyclopentadienylsodium.

14. After the asymmetric hydroboration-oxidation sequence is completed, the desired product is separated via its silver(I) complex from (+)-isopinocampheol. The desired product can also be isolated by column chromatography.

15. (-)- α -Pinene was obtained from Chemical Samples Company. The (-)- α -pinene was distilled from sodium metal: bp 155-156°C; $[\alpha]_D^{25}$ -47° (neat).

16. Borane-tetrahydrofuran was obtained from Alfa Products, Morton/Thiokol Inc.

17. The hydrogen peroxide oxidation is a very exothermic process and efficient cooling and stirring are necessary.

18. After the addition of ether, some inorganic salts precipitate. The checkers found it advantageous to remove this solid by suction filtration. The solid was washed with ether, which was combined with the organic solution.

19. Vacuum distillation does not effectively purify the desired product from the other impurities.

20. Methyl (1R,5R)-5-hydroxy-2-cyclopentene-1-acetate is found in both the aqueous layer and occluded with the solid silver chloride.

21. In like manner and employing (+)- α -pinene [bp 155-156°C; $[\alpha]_D^{25} +47^\circ$ (neat)], the sequence affords the methyl (1S,5S)-5-hydroxy-2-cyclopentene-1-acetate, bp 74-77°C (0.1 mm); $[\alpha]_D^{25} +131^\circ$ (CH₃OH, c 1.03).

22. The checkers used (-)- α -pinene (bp 155°C, $[\alpha]_D^{22} -42^\circ$ (neat)) from Aldrich Chemical Company, Inc., and obtained a product having bp 75-80°C (0.15 mm) and $[\alpha]_D^{21} -126^\circ$ (CH₃OH, c 0.039).

3. Discussion

Several highly enantioselective asymmetric hydroboration reactions with prochiral olefins have been reported⁸ with the di-3-pinanylborane reagents (diisopinocampheylboranes) discovered by Brown and Zweifel.⁹ Recently, alternative reagents such as the mono-3-pinanylboranes (monoisopinocampheylboranes),^{10,11} and (+)-dilongifolylborane¹² have been used in effecting asymmetric hydroborations on prochiral olefins. With the di-3-pinanylborane reagents, cis-disubstituted olefins^{8,9} and 5-substituted cyclopentadienes^{5,6}

yield alcohols of high optical purity (80-95% ee). Lower asymmetric inductions (20-40% ee) occur when 1,1-disubstituted, trans-disubstituted, or trisubstituted olefins are employed as substrates. However, significantly higher enantioselective hydroborations occur when these olefins are treated with the mono-3-pinanylboranes^{10,11} and (+)-longifolylborane.¹² Tetrasubstituted olefins have not successfully been asymmetrically hydroborated with any of these reagents.

Several racemic cis- or trans-2-alkyl-3-cyclopenten-1-ols have been prepared by multistep sequences from cyclopentadiene¹³⁻¹⁶ or from substituted 1,3-dienes.¹⁷ However, optically active cis- and trans-2-alkyl-3-cyclopenten-1-ols have been prepared directly by asymmetric hydroboration reactions using prochiral 5-substituted cyclopentadienes as substrates.^{5,6} This asymmetric hydroboration method, described above, gives moderate yields of highly optically active trans-2-alkyl-3-cyclopenten-1-ols (94-96% ee) which are readily converted into the corresponding cis isomers.^{5,6} Several of these substances are intermediates in the synthesis of such natural products as the monoterpene glycoside loganin,⁵ the carbohydrate daunosamine,¹⁸ and the prostaglandins such as PGF_{2 α} .⁶

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Diagram 1. Apparatus for Producing Cyclopentadiene

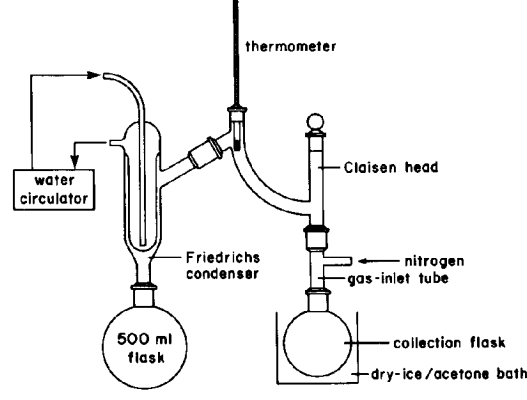
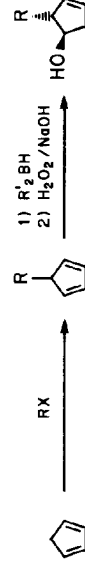


TABLE I

ASYMMETRIC HYDROBORATION OF 5-SUBSTITUTED CYCLOPENTADIENES



Substituent	Alkylating		Hydroborating		Yield	Absolute Stereochemistry		%* Enantio- meric Excess	Reference
	Agent		Agent						
R = CH ₃	CH ₃ I		(+)-di-3-pinanylborane		40-50%	R,R		94-96%	(5), (19)
	CH ₃ I		(-)-di-3-pinanylborane		40-50%	S,S		94-96% ee	(5), (19)
	(CH ₃) ₂ SO ₄		(+)-di-3-pinanylborane		2%	R,R		----	(19)
R = CH ₂ CO ₂ CH ₃	BrCH ₂ CO ₂ CH ₃		(+)-di-3-pinanylborane		40-50%	R,R		94-96% ee	(6), (19)
	BrCH ₂ CO ₂ CH ₃		(-)-di-3-pinanylborane		40-50%	S,S		94-96% ee	(6), (19)
	ClCH ₂ CO ₂ CH ₃		(+)-di-3-pinanylborane		trace	R,R		----	(19)
R = CH ₂ CO ₂ -t-Bu	BrCH ₂ CO ₂ -t-Bu		(+)-di-3-pinanylborane		trace	R,R		----	(19)

*The percent enantiomeric excess was determined by HPLC analysis of products esterified with pure (S)-α-methoxy-α-trifluoromethylphenylacetyl chloride (Mosher Reagent).^{20,21}

Appendix

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

Methyl (1R,5R)-5-hydroxy-2-cyclopentene-1-acetate: 2-Cyclopentene-1-acetic acid, 5-hydroxy-, methyl ester, (1R-trans)- (9); (49825-99-2)

Dicyclopentadiene: 4,7-Methanoindene, 3a,4,7,7a-tetrahydro- (8); 4,7-Methano-1H-indene, 3a,4,7,7a-tetrahydro- (9); (77-73-6)

Methyl 2,4-cyclopentadiene-1-acetate: 2,4-Cyclopentadiene-1-acetic acid, methyl ester (9); (37455-98-4)

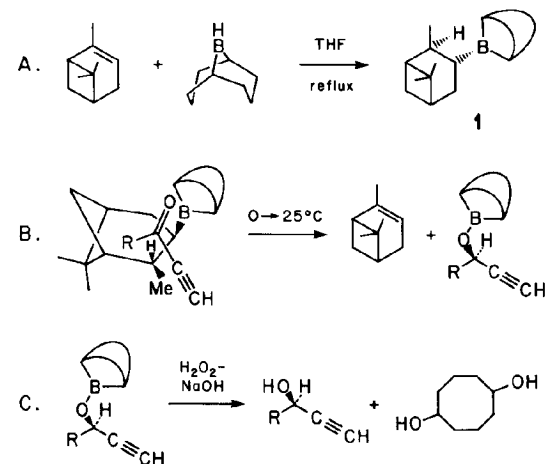
Methyl bromoacetate: Acetic acid, bromo-, methyl ester (8,9); (96-32-2)

(+)-Di-3-pinanylborene: Borene, di-3-pinanyl-, (+)- (8); Borene, bis (2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)-, [1 α ,2 α ,3 β (1R*,2R*,3S*,5S*), 5 α]-(+)- (9); (21947-87-5)

(-)- α -Pinene: 2-Pinene, (1S,5S)-(-)- (8); Bicyclo[3.1.1]hept-2-ene, 2,6,6-trimethyl-, (1S)- (9); (7785-26-4)

Borene-tetrahydrofuran: Furan, tetrahydro-, compd. with borene (1:1) (8,9); (14044-65-6)

ASYMMETRIC REDUCTION OF α,β -ACETYLENIC KETONES WITH B-3-PINANYL-9-BORABICYCLO[3.3.1]NONANE: (R)-(+)-1-OCTYN-3-OL (1-Octyn-3-ol, (R)-)



Submitted by M. Mark Midland and Richard S. Graham.¹

Checked by Joel M. Hawkins and K. Barry Sharpless.

1. Procedure

4. A 2-L, round-bottomed flask equipped with a septum-capped side arm, magnetic stirring bar, reflux condenser and stopcock adaptor connected to a mercury bubbler, is flame dried while being flushed with nitrogen. A nitrogen atmosphere is maintained during the procedure through the oxidation step. After the apparatus is cooled, it is charged, via a double-ended needle,² with

800 mL of a 0.5 M tetrahydrofuran (THF) solution of 9-borabicyclo[3.3.1]nonane (9-BBN, 0.4 mol, Note 1). Then 61.3 g (71.5 mL, 0.45 mol) of (+)- α -pinene (Note 2) is added. After the solution is refluxed for 4 hr, the excess α -pinene and THF are removed by vacuum (Note 3) to provide a thick clear oil of neat B-3-pinanyl-9-borabicyclo[3.3.1]nonane, 1 (Note 4).

B. The flask is cooled to 0°C (ice bath) and 35.3 g (0.285 mol) of 1-octyn-3-one (Note 5) is added. After an initially exothermic reaction, the reaction is allowed to warm to room temperature. The reduction can be monitored by gas chromatography (Note 6), but generally 8 hr is required for completion. The color of the reaction mixture is initially light yellow and darkens to red at the end of the reduction.

C. Excess 1 is destroyed by adding 22 mL (0.3 mol) of freshly distilled propionaldehyde and stirring for 1 hr at room temperature. Liberated α -pinene is then removed by vacuum (Note 7). Tetrahydrofuran, 200 mL, is added, followed by 150 mL of 3 M aqueous NaOH. Hydrogen peroxide (150 mL, 30%) is added dropwise (CAUTION! Note 8). Oxidation is complete in 3 hr at 40°C. The reaction mixture is transferred to a separatory funnel and extracted with three 50-mL portions of ethyl ether. The ether layers are combined and dried with copious amounts of anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to give an oil. Distillation at 60–65°C (3.0 mm) yields 31 g (0.245 mol) of 1-octyn-3-ol, 86% yield (Note 9). The distillation pot residue is a thick oil consisting for the most part of cis-1,5-cyclo-octanediol. An NMR lanthanide shift study showed the alcohol to be 93% (R) and 7% (S), 86% ee, (Note 10 and 11).

2. Notes

1. A 0.5 M THF solution of 9-BBN is available from Aldrich Chemical Company in 800 mL bottles.

2. (+)- α -Pinene (90–92% ee) is available from Aldrich Chemical Company. The pinene was distilled from lithium aluminum hydride before use.

3. Most of the THF is removed by water aspirator vacuum. Excess pinene (0.05 mol, ~8 mL) is removed by applying a 0.05-mm vacuum for 2 hr while warming to 40°C with a water bath. The vacuum should be bled with nitrogen to maintain an inert atmosphere in the reaction flask. Recently Brown's group³ has shown that reduction occurs at an enhanced rate with neat organoborane 1. Excess 1, 1.4 equiv per equiv of 1-octyn-3-one, is used to provide a slight excess of reducing agent to increase the rate for this bimolecular process.

4. B-3-Pinanyl-9-borabicyclo[3.3.1]nonane, 1, is also available from Aldrich Chemical Company under the trade-name, R-Alpine-Borane.

5. 1-Octyn-3-one was obtained by standard Jones oxidation⁴ of racemic 1-octyn-3-ol (in ~80% yield). Racemic 1-octyn-3-ol is available from Aldrich Chemical Company. It is essential to check the ketone for unreacted starting alcohol since racemic alcohol will contaminate the final, optically-active product.

6. GLC can be used to monitor the disappearance of the acetylenic ketone. 1-Octyn-3-one is eluted just after α -pinene from a SE-30 6 ft column at 80°C. The checkers followed the disappearance of ketone by TLC (15% ethyl acetate in hexane).

7. This is the most convenient stage to remove α -pinene since α -pinene and 1-octyn-3-ol have similar boiling points, making separation by distillation difficult. Application of a 0.05-mm vacuum while the flask is warmed to 40°C for several hours will remove most of the α -pinene (0.4 mol, ~ 63.5 mL). Because of the volume of α -pinene, cold traps in the vacuum system may become plugged; therefore the traps will have to be emptied several times. This provides a convenient method to recover liberated (+)- α -pinene.

8. Hydrogen peroxide oxidation of organoboranes is exothermic. Careful, dropwise addition of 30% hydrogen peroxide to the organoborane will provide sufficient heating to maintain a reaction temperature in the 40-50°C range.

9. 1-Octyn-3-ol has the following properties: bp 60-65°C (3.0 mm); IR (neat) cm^{-1} : 3315, 2950, 2860, 2120, 1475, 1380, 1120, 1060, 1025, 650; ^1H NMR (CDCl_3) δ : 0.86 (t, 3 H, $J = 6.6$, CH_3), 1.3-1.4 (m, 6 H), 1.65 (m, 2 H), 2.42 (d, 1 H, $J = 2$, $\text{C}\equiv\text{C}-\text{H}$), 3.0 variable (broad, 1 H, OH), 4.33 (m, 1 H); ^{13}C NMR (CDCl_3) δ : 72.6 (C-1), 85.1 (C-2), 62 (C-3), 37.4 (C-4), 31.3 (C-5), 24.6 (C-6), 22.4 (C-7), 13.9 (C-8); $[\alpha]_D^{25} +7.50^\circ$ (neat, density 0.864 g/mL). It has been shown that optical rotation is an unreliable criterion of enantiomer purity of 1-octyn-3-ol.⁵

10. Commercially available $\text{Eu}(\text{hfc})_3$, tris [3-(heptafluoropropyl)hydroxy-methylene]-d-camphorato]europium III, NMR shift reagent, was used as received from Aldrich Chemical Company. The proton on the chiral carbinol carbon was shifted downfield to ~ 11 ppm in CDCl_3 . The R isomer was shifted ~ 0.5 ppm further downfield than the S isomer.

11. Optically pure (+)-1-octyn-3-ol may be obtained by recrystallization of the half acid phthalate with (+)- α -methylbenzylamine (Aldrich Chemical Company). The half acid phthalate salt is made by heating equal molar amounts of 1-octyn-3-ol and phthalic anhydride. This half acid phthalate derivative

is a waxy solid which does not lend itself to recrystallization. Attempts to form crystalline salts of the phthalate derivative with achiral alkyl amines only lead to waxy solids or thick oils. The phthalic amine salt made with racemic 1-octyn-3-ol requires 3-4 recrystallizations from methylene chloride to resolve enantiomers.⁶ The first recrystallization may take several days, with successive recrystallizations becoming easier. If the 86% ee 1-octyn-3-ol is used to make the phthalic amine salt only one facile recrystallization is needed to provide optically-pure alcohol. The pure amine salt melts at 132-134°C. The enantiomeric purity of the salt may be determined by NMR by observing the ethynyl hydrogen doublets at δ 2.48 (minor) and 2.52 (major) (CDCl_3 solvent).

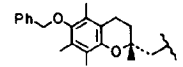
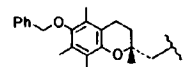
3. Discussion

In this procedure, we describe a general method for the synthesis of alkynyl alcohols of high enantiomeric purity. The one-pot asymmetric reduction of 1-octyn-3-one with B-3-pinanyl-9-borabicyclo[3.3.1]nonane provides a mild and efficient method for the preparation of optically active 1-octyn-3-ol. The reduction occurs in good chemical yield and is virtually (>95%) stereospecific (correcting for the use of 90% ee α -pinene). The availability of optically pure α -pinene is a limiting factor in this method, but recently Brown's group has developed a process that provides enantiomerically pure α -pinene.⁷ The reduction can be applied to prepare both enantiomers of 1-octyn-3-ol, since both enantiomers of α -pinene are commercially available; although commercial (-)- α -pinene is only 81.3% ee,⁷ (-)- α -pinene of 92% ee is easily obtained by isomerizing commercial (-)- β -pinene (92% ee).⁸ (Reducing agent 1, made with (-)- α -pinene, will provide (-)-S-1-octyn-3-ol). The α -pinene

liberated (by β -hydride elimination) in the reduction may be recycled without loss of optical purity. Another attractive feature of this reduction is that organoborane **1** is a mild reagent and generally does not affect other functional groups present within the acetylenic ketone. For base sensitive systems that cannot tolerate the standard sodium hydroxide-hydrogen peroxide oxidation an alternative work-up using ethanolamine is available.⁹ Table I illustrates the application of this reduction to other propargyl ketones.⁹ In these cases, tetrahydrofuran was not removed prior to reduction. Removal of tetrahydrofuran provides a faster reaction and slightly higher optical purity.³

The most popular methods of preparing optically active 1-octyn-3-ol involve asymmetric reduction of 1-octyn-3-one with optically-active alcohol complexes of lithium aluminum hydride or aluminum hydride.¹⁰ These methods give optical purities and chemical yields similar to the method reported above. A disadvantage of these metal-hydride methods is that some require exotic chiral alcohols that are not readily available in both enantiomeric forms. Other methods include optical resolution of the racemic propargyl alcohol (100% ee)⁶ (and Note 11) and microbial asymmetric hydrolysis of the propargyl acetates (~15% ee for 1-heptyn-3-ol).¹¹

TABLE I

Ketone R	RCOC \equiv CR' R'	Yield (%) ^a	Enantiomeric excess (%) ^b
Ph	Bu	72	89 ^c
Me	Ph	98	72(78)
Pr	C ₆ H ₁₃	68	77 ^c
2-Pr	H	78	91(99)
	Me	77	85:15 ^d
	H	75	91:9 ^d
Me	COOEt	59	71(77)
C ₅ H ₁₁	COOEt	72	85(92)
Ph	COOEt	64	92(100)
t-Bu	Me	0	
Me	t-Bu	62	73 ^c

^aIsolated yield based on starting ketone. ^bDetermined by analysis of the Eu(dcm)₃ shifted NMR spectrum. The numbers in parentheses are corrected for 92% ee α -pinene. ^c100% optically pure (+)- α -pinene was used. ^dDiastereomeric ratio (R,R to R,S) determined by LC or NMR analysis of the mixture.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number):

(Registry Number)

B-3-Pinanyl-9-borabicyclo[3.3.1]nonane: 9-Borabicyclo[3.3.1]nonane, 9-(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)- (10); (73624-47-2)

(R)-(+)-1-Octyn-3-ol: 1-Octyn-3-ol, (R)-(+)- (8); 1-Octyn-3-ol, (R)- (9); (32556-70-0)

9-Borabicyclo[3.3.1]nonane (8,9); (280-64-8)

(+)- α -Pinene: 2-Pinene, (1R,5R)-(+)- (8); Bicyclo[3.1.1]hept-2-ene, 2,6,6-trimethyl-, (R)- (9); (7785-70-8)

1-Octyn-3-one (8,9); (27593-19-7)

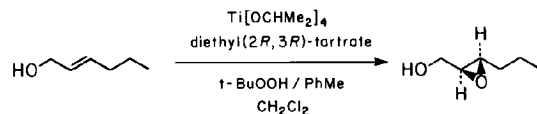
Propionaldehyde (8); Propanal (9); (123-38-6)

Tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium III:
Europium, tris[3-(2,2,3,3,4,4,4-heptafluoro-1-oxobutyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-onato-0,0']- (9); (34788-82-4)

ENANTIOSELECTIVE EPOXIDATION OF ALLYLIC ALCOHOLS:

(2S,3S)-3-PROPYLOXIRANEMETHANOL

(Oxiranemethanol, 3-Propyl-, (2S,3S)-)



Submitted by J. Gordon Hill,¹ K. Barry Sharpless,¹

Christopher M. Exon,² and Ronald Regenye,²

Checked by Mark H. Norman and Clayton H. Heathcock.

1. Procedure

A 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer with Teflon blades, thermometer, and nitrogen inlet is charged with 1.00 L of methylene chloride (Note 1) and 39.9 mL (38.1 g, 0.134 mol) of titanium(IV) isopropoxide (Note 2). The flask content is stirred and cooled under nitrogen in a dry ice-ethanol bath to -70°C. To the flask is then added 33.1 g (27.5 mL, 0.161 mol) of diethyl (2R,3R)-tartrate (Note 3) and 25.0 g (0.25 mol) of E-2-hexen-1-ol (Note 4). A small volume of methylene chloride is used to ensure complete transfer of each material to the reaction flask. To the flask is then added 184.5 mL (0.50 mol) of 2.71 M anhydrous tert-butyl hydroperoxide in toluene (Note 5) which has been precooled to -20°C (Note 6). The addition causes a temperature increase to -60°C; the temperature of the reaction mixture is allowed to come to 0°C over a 2.0-hr period (Note 7).

A 4-L beaker equipped with a magnetic stirring bar and thermometer is charged with a solution of 125 g of ferrous sulfate and 50 g of tartaric acid in a total volume of 500 mL of deionized water. The solution is stirred and cooled by means of an ice-water bath to 10°C. When the epoxidation reaction mixture reaches 0°C, it is immediately (Note 8) poured into the stirred contents of the beaker. The resulting reaction is mildly exothermic, causing a temperature rise to ca. 20°C (Note 9). After the exothermic reaction has subsided and the temperature has begun to drop (ca. 5 min), the cooling bath is removed and the mixture is stirred at ambient temperature for 30 min. The contents of the beaker are transferred to a 2-L separatory funnel and the aqueous phase is separated and extracted with two 250-mL portions of ether. The combined organic layers are dried over sodium sulfate and filtered. The solvent is removed with a rotary evaporator at 35°C (70 mm) to give 85.9-89.9 g (Note 10) of pale amber oil.

A 2-L, three-necked, round-bottomed flask equipped with a thermometer and a mechanical stirrer with Teflon blades is charged with a solution of the reaction product in 750 mL of ether. The contents of the flask are cooled in an ice-water bath to 3°C. To the flask is added a precooled (3°C) solution of 20 g (0.50 mol) of sodium hydroxide in 500 mL of brine (Note 11). The two-phase mixture is stirred vigorously for 1 hr with continued cooling (Note 12) and then is transferred to a separatory funnel. The aqueous phase is separated and extracted with two 150-mL portions of ether (Notes 13, 14). The combined organic solution (Note 15) is dried over sodium sulfate and filtered. Solvent removal with a rotary evaporator at 35°C (70 mm) followed by concentration with the rotary evaporator at 35°C (12 mm) for 1.0 hr gives 24.7-25.0 g of crude (2S,3S)-3-propyloxiranemethanol as a pale amber oil (Note 16).

The crude product is distilled through a 10-cm Vigreux column (the receiving flask is cooled in an ice-water bath) to yield 22.45-22.84 g (80-81%) of (2S,3S)-3-propyloxiranemethanol as a colorless liquid, bp 31-33°C (0.30-0.40 mm). Analysis by GC indicates a chemical purity of 89-93% (Note 17). The material is fractionally distilled through a 20-cm vacuum-jacketed Vigreux column to obtain 17.69-19.44 g (63-69%), $[\alpha]_D^{22}$ -38.1 to -38.6° (neat), $[\alpha]_D^{23}$ -46.2 to -48.6° (CHCl₃, *c* 1.0) of a colorless liquid. Analysis by GC indicates a chemical purity of 96-98% (Note 17). An enantiomeric purity of 96.4-97.5% is determined by ¹H NMR analysis of the derived acetate using Eu(hfc)₃, tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium-[III], (Note 18) as the chiral shift reagent (Note 19). The enantiomeric purity may also be determined by GC analysis (Note 20) of the derived α-methoxy-α-(trifluoromethyl)phenylacetic acid esters³ (Notes 21, 22). An alternative to the distillation method is purification by preparative HPLC (Notes 23, 24), and bulb-to-bulb distillation (Note 25) to give 21.85 g (78%) of (2S,3S)-3-propyloxiranemethanol as a white solid, mp 19°C, $[\alpha]_D^{25}$ -46.6° (CHCl₃, *c* 1.0). Analysis by GC of material purified in this manner indicates a chemical purity of >99% (Note 14) and an enantiomeric purity of 96.8% (Notes 20, 21, 22).

2. Notes

1. Fisher Scientific Company methylene chloride, certified ACS grade containing 0.02% water was used; a fresh bottle was used for each run.

2. Titanium(IV) isopropoxide is available from the Aldrich Chemical Company, Inc.

3. (+)-Diethyl L-tartrate was obtained from the Aldrich Chemical Company, Inc.

4. trans-2-Hexen-1-ol was obtained from Alfa Products, Morton/Thiokol, Inc. Analysis by GC (Hewlett-Packard HP 5710A; 50 m x 0.25 mm capillary column of bonded CPS-2 on fused silica; 120°C isothermal) with appropriate standards indicated an E-2-hexen-1-ol content of 96.1% with 0.9% Z-2-hexen-1-ol and 2.9% hexanol as impurities. trans-2-Hexen-1-ol from the Aldrich Chemical Company, Inc. could also be used. This material was of similar composition: 95.4% E-2-hexen-1-ol, 0.8% Z-2-hexen-1-ol and 3.2% hexanol.

5. Anhydrous tert-butyl hydroperoxide in toluene⁴ was prepared starting with Aldrich Chemical Company, Inc. 70% aqueous tert-butyl hydroperoxide. A 500-g lot of this material was swirled in a separatory funnel with 1.0 L of toluene. The aqueous phase was removed and discarded. The organic solution was heated at reflux under nitrogen for 4 hr in a flask equipped with a Dean-Stark trap for water separation (for greater detail see reference 4). The solution was cooled and stored under nitrogen at -20°C (Note 6). The content of tert-butyl hydroperoxide was determined by ¹H NMR according to the equation:

$$\text{Molarity} = \frac{X}{0.1X + 0.32Y}$$

X = integration of tert-butyl resonance
Y = integration of methyl resonance

6. Storage of the solution at -20°C is not necessary.⁴ It does, however, provide a convenient method of precooling the material.

7. Addition of dry ice to the cooling bath was stopped. If the rate of temperature increase was too slow, the ethanol bath was lowered.

8. If the mixture is allowed to stand at 0°C or to warm above this temperature, undesired by-products (TLC) are formed.

9. The temperature should be kept ≤20°C. In some cases, the addition of small amounts of ice to the reaction is necessary.

10. This weight can vary substantially, depending upon the extent to which the solvents, especially toluene, have been stripped from the solution. Concentration need only be carried out until the weight is <100 g.

11. This mixture is prepared by dissolving the sodium hydroxide in the brine at ambient temperature and then cooling the total to 3°C. The resultant cloudy, supersaturated suspension is used in toto. The use of this reagent ensures complete extraction (vide infra) of the somewhat water-soluble product. In addition, it minimizes contact of this material with the aqueous base, conditions which can lead to the Payne rearrangement.⁵

12. Saponification serves to remove the diethyl tartrate as well as to liberate any product which has been transesterified to form a tartrate ester.

13. GC analysis (Note 14) of a third extract showed no product.

14. GC analysis was performed on a column with the following properties: Hewlett-Packard HP 5702A, 2 m x 1/4" OV-101 column, programmed 70-200°C at 8°C/min.

15. GC analysis (Note 14) shows no diethyl (2R,3R)-tartrate, indicating that the saponification was complete.

16. Material of this quality is suitable for many synthetic purposes.

17. The properties of the column are as follows: Hewlett-Packard HP 5790A, 12 m x 0.2 mm cross-linked methyl silicone (fast analysis) column, programmed from 35 to 140°C at 3°C/min.

18. The shift reagent was obtained from the Aldrich Chemical Company, Inc. Drying the Eu(hfc)₃ overnight with a drying pistol at 56°C (refluxing acetone) under vacuum afforded optimum results.

19. The analytical sample of the acetate derivative is prepared as follows. Into a 5-mL, round-bottomed flask equipped with a magnetic stirring bar are placed 2 drops of the reaction product, 16 drops of acetic anhydride,

and 32 drops of pyridine. The solution is stirred at ambient temperature for 2 hr, and the mixture is then transferred to a separatory funnel with the aid of 10 mL of methylene chloride. The methylene chloride solution is washed with two 10-mL portions of 1 M phosphoric acid, the organic layer is dried over MgSO₄, and the filtered solution is concentrated with a rotary evaporator to give approximately 20 mg of acetate as a colorless oil.

A 5-μL sample of this crude acetate is dissolved in 0.5 mL of benzene-d₆ and transferred to an NMR tube. A solution of 75 mg of Eu(hfc)₃ in 0.5 mL of benzene-d₆ is prepared. A 50-μL portion of the shift reagent solution is added to the acetate sample, the mixture is shaken well, and the ¹H NMR spectrum is recorded. Additional portions of shift reagent are added in 10-μL portions until the acetate methyl resonance (originally at δ = 1.65 ppm) shifts downfield to the region 2.3-3.1 ppm and shows baseline resolution of the resonances from the two enantiomers. A total of 50-90 μL of the shift reagent solution should be required to achieve the desired shift, at which point a chemical shift difference of about 0.2 ppm should be obtained. The %ee is obtained by integration of the two acetate peaks.

20. The column had the following properties: Hewlett-Packard HP 5710A, 50 m x 0.25 mm capillary column of OV-17 (bonded) on fused silica; 175°C isothermal.

21. The analytical sample of α-methoxy-α-(trifluoromethyl)phenylacetic acid ester is prepared as follows. Into a 5-mL, capped, amber vial equipped with a magnetic stirring bar are placed 20 mg of the reaction product, 1.0 mL of methylene chloride, 87 mg of (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Note 22), 4 drops of triethylamine and 1 crystal of 4-dimethylaminopyridine. The mixture is stirred at ambient temperature for 1.5 hr, at which point TLC (Note 26) indicates complete conversion to the ester.

Addition of 4 drops of N,N-dimethyl-1,3-propanediamine and concentration on a rotary evaporator at 35°C (70 mm) affords a yellow oil. This material is filtered through 10 g of E. Merck silica gel 60 (70-230 mesh) with 9:1 hexanes-ethyl acetate until TLC analysis indicates no further product elution. The total eluate is concentrated on a rotary evaporator at 35°C (70 mm). The resultant colorless oil is subjected to GC analysis.

A sample of E-2-hexen-1-ol in methylene chloride was epoxidized at 20°C with m-chloroperoxybenzoic acid. The resultant racemic epoxy alcohol, upon conversion to the diastereomeric (+)- α -methoxy- α -(trifluoromethyl)phenylacetic acid esters in the manner described above, provided a GC standard for determination of the enantiomeric excess obtained in the asymmetric epoxidation.

22. The acid chloride was prepared³ from (+)- α -methoxy- α -(trifluoromethyl)phenylacetic acid which was used as obtained from Aldrich Chemical Company, Inc.

23. Purification by preparative HPLC is accomplished as follows. The crude product is taken up in 60 mL of 4:1 hexanes-ethyl acetate. The solution is subjected to preparative HPLC (Note 24) using the same solvent system. Chromatography is monitored by TLC (Note 26) and the appropriate fractions are combined. Solvent removal with a rotary evaporator at 35°C (12 mm) gives a colorless oil. This material is subjected to bulb-to-bulb distillation at 75-90°C (8 mm).

24. A Waters Associates Prep LC/System 500 with two cartridges (1.0 kg) of PrepPak-500/Silica was used. The course of the chromatography was followed with a refractive index detector. Approximately 3.6 L of solvent was eluted prior to the product band.

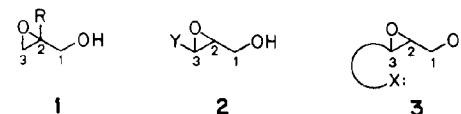
25. A Kugelrohr apparatus purchased from the Aldrich Chemical Company, Inc., was used. The receiving bulb was cooled with an ice-water bath. The temperature indicated is the oven temperature.

26. E. Merck silica gel F-254 plates were used, with 2:1 hexanes-ethyl acetate as eluent. Visualization was effected by spraying with a 10% phosphomolybdic acid in ethanol solution followed by heating with a hot air gun. (2S,3S)-3-Propyloxiranemethanol had an R_f of ca. 0.3.

3. Discussion

Both the synthetic^{6a} and mechanistic^{6b} aspects of this asymmetric epoxidation process have been reviewed recently. While the process has great scope regarding the allylic alcohol substrate, there are two classes of substrates which present difficulties. These limitations will be best appreciated by reference to the recent reviews;⁶ however, the main problems are worth mentioning here. When difficulties arise, they are almost never due to the failure of the asymmetric epoxidation process itself, but can be traced instead to the nature of the epoxy alcohol product.

Water-soluble products (e.g., 3- and 4-carbon epoxy alcohols) present obvious isolation problems which have been only partly solved. The other troublesome class of products includes those epoxy alcohols which are unstable under the epoxidation and/or isolation conditions. This latter class consists of the three main types shown below:



Type 1 is sensitive to nucleophilic opening at the primary epoxide carbon (C-3). Type 2 represents cases where the substituent Y facilitates opening at carbon-3 through resonance stabilization of the incipient carbonium ion. Finally, type 3 includes those cases in which the product bears a heteroatom substituent (X) placed so that a five- or six-membered ring results from anchimerically-assisted opening of the epoxide at carbon-3. Not even these structural features (i.e., as in 1, 2, and 3) are always fatal, for some representatives of types 1, 2 and 3 afford good yields of the desired epoxy alcohols.⁶ Furthermore, when the structure of a given case is marginal, we have found that modification of the epoxidation and/or isolation procedures can lead to substantially improved yields. With such sensitive epoxy alcohols, milder isolation procedures are always employed (see ref. 6a and 9 for a discussion of these modified work-up methods). However, certain substrates of types 1, 2 and 3 still fail completely with all current procedures. The best we have been able to do in these difficult cases is to use a strategy which actually takes advantage of the facile epoxide opening process.^{6,7}

Questions are often asked concerning the catalytic nature of the asymmetric epoxidation. One notes that the present procedure calls for 50% catalyst. With very favorable substrates, one can realize complete conversion and >95% ee using as little as 2% catalyst.⁶ In the present case, the reaction stops at about 80% conversion using 2% catalyst, and almost reaches completion with 10% catalysis.⁸ The selection of 50% catalyst is a compromise aimed at making the procedure applicable to a wider range of substrates. In the literature, most applications of asymmetric epoxidation use 100% catalyst. This is rarely necessary, but ensures rapid and complete epoxidation in small scale reactions where cost of the reagents is not an

issue. The cases yielding epoxy alcohols which are sensitive to opening require the most catalyst, because the open-diol products are potent inhibitors of the epoxidation catalysis.^{6a} If one wished to produce molar amounts of a given epoxy alcohol, it would be worthwhile to determine the optimum catalyst loading for the case at hand. In addition to the cost incentive, the isolation procedure becomes simpler as the amount of catalyst is decreased.

The aqueous tartaric acid work-up procedure described here is the simplest method for removing the titanium species, but it should only be used with relatively stable epoxy alcohols which are not water-soluble. In this regard, the six carbon epoxy alcohol made here probably represents the lower limit, as it is on the verge of water solubility. Of course, one cannot assume this work-up will succeed with all six carbon or larger epoxy alcohols, for in addition to limited water solubility, the product must be fairly resistant to acid-catalyzed epoxide opening processes. For water-soluble and/or acid-sensitive epoxy alcohols, the "sodium sulfate work-up" is generally preferred.^{6a,9} When making a particularly sensitive epoxy alcohol, one should not only use this sodium sulfate work-up but one should also modify the initial stage of the epoxidation process so that the reaction mixture only warms to -20°C rather than to 0°C.

Finally, two other practical points are worth mentioning. The early procedures for asymmetric epoxidation called for dilute solutions of sodium hydroxide to effect tartrate ester hydrolysis. For the reasons given in Note 11, one should always (unless one is certain that the epoxy alcohol is completely insoluble in water) use instead NaOH in brine. In this procedure, the excess tert-butyl hydroperoxide (TBHP) was destroyed early in the work-up (FeSO₄), although this is not essential because dilute solutions of TBHP are

not dangerous. Other methods for removing excess TBHP in these epoxidations have been reviewed.^{6a} One of the simplest is to remove it as the azeotrope with toluene. We have removed up to 0.5 mol of TBHP by this means.¹⁰

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8. Note, however, that in some cases, lower catalyst levels cause the enantiomeric excess to fall off. For example, the title compound is produced with 90% ee using 10% catalyst and with 97% ee using 50% catalyst.

9. The "sodium sulfate work-up" should be used in place of the "tartaric acid work-up", employed in the present procedure, whenever one is dealing with a water-soluble and/or acid-sensitive epoxy alcohol. The early stages of this alternate work-up are as follows: the reaction mixture is removed from the freezer (ca. -20°C), and, while it is stirred (magnetic or mechanical depending on the scale), ether is added to the cold reaction mixture, followed immediately by a saturated sodium sulfate solution (no cooling bath is used at this stage and the ether is not precooled). We use 1 mL of saturated Na₂SO₄ solution per mmol of Ti(O-*i*-Pr)₄ (note this is about 3.3 times more than was recommended in an earlier¹¹ procedure). The volume of ether added should be at least 1 mL per mL of saturated Na₂SO₄ solution used, and more ether is beneficial.

The heterogeneous mixture that results is stirred vigorously for about 2 hr at room temperature. It is then filtered through a Celite pad and the resulting orange-yellow paste is washed with several portions of anhydrous ether until the paste becomes somewhat granular. The orange-yellow layer is scraped off the Celite pad into an Erlenmeyer flask. Ethyl acetate is added along with a magnetic stirring bar and the resulting suspension is stirred vigorously for 5 min in boiling ethyl acetate. The slurry is then filtered through the same Celite pad, and the orange-yellow solid is washed once with hot ethyl acetate. Treatment of the filtrand in this manner is a key improvement which usually increases the total isolated yield by 10 to 15%. The combined filtrates are concentrated to afford crude product along with the tartrate diester and any excess TBHP. This material is ready for the next stage of the work-up which involves removal of the tartrate ester. The present preparation describes (vide supra) hydrolysis of the ester with

NaOH/brine. For alternate ways of separating the epoxy alcohols from the tartrate ester see reference 6a (this reference also describes several ways for removing the TBHP).

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Appendix

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

Titanium(IV) isopropoxide: Isopropyl alcohol, titanium(4+) salt (8);

2-Propanol, titanium(4+) salt (9); (546-68-9)

Diethyl (2R,3R)-tartrate: Tartaric acid, diethyl ester, L-(+)- (8);

Butanedioic acid, 2,3-dihydroxy-[R-(R*,R*)]-, diethyl ester (87-91-2)

E-2-Hexen-1-ol: 2-Hexen-1-ol, (E)- (8,9); (928-95-0)

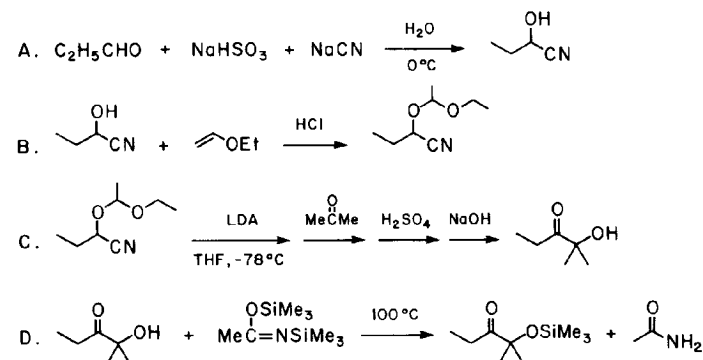
tert-Butyl hydroperoxide (8); Hydroperoxide, 1,1-dimethylethyl (9); (75-91-2)

Tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III):

Europium, tris[3-(2,2,3,3,4,4,4-heptafluoro-1-oxobutyl)-1,7,7-

trimethylbicyclo[2.2.1]heptan-2-onato-0,0']- (9); (34788-82-4)

2-METHYL-2-TRIMETHYLSILOXYPENTAN-3-ONE (3-Pentanone, 2-methyl-2-[(trimethylsilyl)oxy]-)



Submitted by Steven D. Young, Charles T. Buse, and Clayton H. Heathcock.¹

Checked by Joseph R. Flisak, Sami Farahat, Stan S. Hall, Hugh W. Thompson, and Gabriel Saucy.

1. Procedure

A. *2-Hydroxybutyronitrile*. A 3-L, three-necked, round-bottomed flask is fitted with a mechanical stirrer and thermometer and charged with 312 g (3.0 mol) of sodium bisulfite and 1050 mL of water. The stirrer is started and after the sodium bisulfite has dissolved, the flask is placed in an ice-salt bath. A solution of 147 g (3.0 mol) of sodium cyanide (Note 1) in 450 mL of water and 174 g (3.0 mol) of propionaldehyde (Note 2) are separately cooled to 0°C in ice-salt baths. When the temperature of the vigorously-stirring sodium

bisulfite solution has stabilized at 0°C the cold propionaldehyde is added in one portion. The temperature of the reaction solution immediately increases to ca. 35°C, then returns to ca. 0°C. After 30 min the cold sodium cyanide solution is added in one portion. The reaction mixture again warms to ca. 15°C and then returns to ca. 0°C. This mixture is stirred for 2 hr at 0°C, during which time a thick white precipitate of sodium sulfite forms. The supernatant liquid is decanted into a 4-L separatory funnel and the precipitate is washed with 1 L of ice-water. The combined aqueous solution is extracted with three 1-L portions of ethyl ether. The combined ether extracts are washed with 1 L of saturated brine and dried by stirring (magnetic stirring bar) over magnesium sulfate for 2 hr. The solution is filtered through a coarse, sintered-glass funnel and the ether is removed with a rotary evaporator at water aspirator pressure. After the pH of the residue is adjusted to 5 with a few drops of concentrated hydrochloric acid (Note 3), the residue is distilled to give 154-192 g (60-75%) of 2-hydroxybutyronitrile, bp 108-114°C (30 mm), as a colorless liquid (Note 4).

B. 2-[(1'-Ethoxy)-1-ethoxy]butyronitrile. A 1-L three-necked, round-bottomed flask is equipped with a condenser topped with a calcium chloride drying tube, a magnetic stirring bar, a 500-mL pressure-equalizing addition funnel, and a thermometer. The flask is charged with 174 g (2.05 mol) of 2-hydroxybutyronitrile to which 0.5 mL of concentrated hydrochloric acid has been added. The addition funnel is charged with 221 g (3.07 mol) of ethyl vinyl ether (Note 5), which is then added dropwise to the stirred cyanohydrin at such a rate that the temperature is maintained at ca. 50°C. When the addition is complete, the mixture is heated to 90°C for 4 hr. The condenser is replaced with a distillation head and the dropping funnel and thermometer are replaced with stoppers. Direct distillation of the gold-yellow solution

from the reaction flask yields 226-277 g (70-86%) of nearly pure 2-[(1'-ethoxy)-1-ethoxy]butyronitrile, bp 85-87°C (30 mm), as a colorless liquid (Note 6).

C. 2-Hydroxy-2-methylpentan-3-one. A dry, 5-L three-necked (including a thermometer well), round-bottomed flask is equipped with a mechanical stirrer, low temperature thermometer, nitrogen inlet, rubber septum, and a 1-L, graduated, pressure-equalizing addition funnel that is sealed with a rubber septum. The flask is charged with 775 mL of dry tetrahydrofuran (Note 7) and 166 g (1.64 mol) of dry diisopropylamine (Note 8). The contents of the flask are cooled to -10°C (dry ice-acetone bath) and 1095 mL (1.6 mol) of 1.5 M butyllithium in hexane (Note 9), which has been transferred to the addition funnel by means of a 16-gauge cannula and argon pressure, is slowly added to the stirred solution at such a rate as to maintain a temperature of -10°C. After the addition is complete 50 mL of dry THF is added to the addition funnel with a syringe to rinse the walls of the funnel; the rinse is added, and then the mixture is cooled to -75°C. The addition funnel is charged by syringe with 246 g (1.6 mol) of 2-[(1'-ethoxy)-1-ethoxy]butyronitrile, which is then added at such a rate that the temperature does not exceed -70°C. The mixture is stirred for 10 min and 104 g (1.8 mol) of dry acetone (Note 10) is added by syringe over a 30-min period at such a rate that the temperature of the reaction mixture does not exceed -70°C. When the addition is complete the cooling bath is removed and the reaction mixture is allowed to warm to 0°C. The solution is poured into 1 L of water and the resulting mixture is concentrated at aspirator pressure with a rotary evaporator (30°C water bath) to remove the volatile organic compounds. The aqueous residue is extracted with three 1-L portions of methylene chloride. The organic extracts are combined and washed with two 500-mL portions of water, then concentrated with

a rotary evaporator (25°C water bath) at aspirator pressure to obtain a yellow syrupy residue. This material is stirred with 680 mL of methanol and 340 mL of aqueous 5% sulfuric acid overnight at room temperature. The methanol is evaporated with a rotary evaporator (30°C water bath) at aspirator pressure and the yellow residue is extracted with three 1-L portions of ethyl ether. The combined ether extracts are shaken in a 4-L separatory funnel with 210 mL of 10 N aqueous sodium hydroxide for 15 min (Note 11). The layers are separated, and the ether layer is washed with 500 mL of brine and dried by stirring (magnetic stirring bar) over magnesium sulfate for 2 hr. The drying agent is removed by filtration through a coarse sintered-glass funnel and the ether is removed with a rotary evaporator (water bath below 40°C) at aspirator pressure. The yellow-orange liquid residue is distilled to obtain 82-115 g (45-63%) of 2-hydroxy-2-methylpentan-3-one, bp 57-65°C (15 mm), as a pale yellow liquid (Notes 12, 13).

D. *2-Methyl-2-trimethylsilyloxypentan-3-one*. A dry, 500 mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser with a nitrogen inlet, and a thermometer is charged with 84 g (0.72 mol) of 2-hydroxy-2-methylpentan-3-one and 74 g (0.36 mol) of N,O-bis(trimethylsilyl)acetamide (Note 14). The mixture is heated at 100°C for 12 hr with stirring and then cooled to room temperature, at which point the mixture becomes a semisolid as the acetamide crystallizes. The semisolid mixture is diluted with 50 mL of water and stirred at room temperature for 1 hr (Note 15). After the stirring is stopped, 200 mL of hexane is added and the layers are separated. The aqueous layer is extracted with 100 mL of hexane. The combined hexane extracts are washed with four 100 mL portions of water and then dried over magnesium sulfate for 2 hr. After removal of the drying agent by filtration through a coarse sintered-glass funnel, the hexane

is evaporated with a rotary evaporator (25°C water bath) at aspirator pressure. The crude, pale yellow oil is distilled to afford 105-112 g (75-80%) of 2-methyl-2-trimethylsilyloxypentan-3-one, bp 71-75°C (15 mm), as a colorless liquid (Note 16).

2. Notes

1. *CAUTION! Sodium cyanide and the propionaldehyde cyanohydrin are extremely toxic. Great care should be taken when using these materials. Reactions should be carried out in a well-ventilated hood and suitable protective clothing should be worn at all times.*

2. Propionaldehyde was obtained from Aldrich Chemical Company, and was used without further purification.

3. If HCl is omitted, the cyanohydrin reverts to HCN and propionaldehyde upon attempted distillation. The checkers found it necessary to ensure that the residue was acidic by adjusting the pH to 5 by testing the residue with wet pH paper.

4. The infrared spectrum (neat) shows absorption at 3420, 2960, 2310, and 1460 cm^{-1} .

5. Ethyl vinyl ether was obtained from Aldrich Chemical Company, and was used without further purification.

6. The infrared spectrum (neat) shows absorption at 2970, 1425, and 1385 cm^{-1} . The $\text{C}\equiv\text{N}$ absorption is not observed.

7. Tetrahydrofuran is distilled under a nitrogen atmosphere from sodium/benzophenone immediately prior to use.

8. Diisopropylamine is distilled under a nitrogen atmosphere from calcium hydride prior to use. It may be stored under nitrogen for one week without redistillation.

9. *Caution! Concentrated butyllithium may ignite spontaneously on exposure to air or moisture. Manipulations with this reagent should be performed with care.* The submitters used butyllithium, 1.5 M in hexane from Foote Mineral Company, and measured it by transferring the solution to a 2-L, graduated cylinder stoppered with a rubber septum with a 15-gauge cannula and argon. The solution was then transferred directly to the reaction vessel by the same procedure. The checkers used fresh butyllithium, 1.55 M in hexane under argon, from Aldrich Chemical Company. A reagent bottle was connected in series with the addition funnel by using the cannula, and then about half of the required amount of reagent was transferred using positive argon pressure. After this quantity has been added to the reaction vessel, the rest of the reagent is transferred to the funnel and the addition continued. Stainless steel cannulas with deflected points (double-tip syringe needles) are available from Ace Glass, Inc. and Aldrich Chemical Co.

10. ACS Certified acetone was obtained from Fisher Chemical Company, and distilled from 3 Å molecular sieves immediately prior to use.

11. Periodic shaking (once every 3 min) is sufficient to effect cyanohydrin hydrolysis.

12. The ^1H NMR (200 MHz, CDCl_3) spectrum is as follows δ : 1.12 (t, 3 H, $J = 7.2$), 1.39 (s, 6 H), 2.59 (q, 2 H, $J = 7.2$), 3.85 (s, 1 H). The infrared spectrum (neat) shows absorption at 3450, 2960, and 1705 cm^{-1} .

13. In one run, the checkers, at this point obtained 241 g, bp 116–120°C (12 mm) of the protected cyanohydrin (NMR), which had not been deprotected and hydrolyzed, rather than the expected product. In this case, the entire distillate was resubjected to the acid and base sequence, which afforded the desired product in a 61% overall isolated yield.

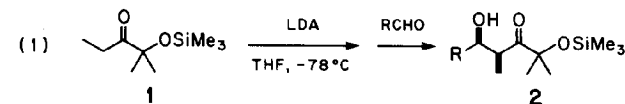
14. N,O-Bis(trimethylsilyl)acetamide was obtained from Aldrich Chemical Company and used without further purification.

15. This process is necessary to insure hydrolysis of any unreacted N,O-bis(trimethylsilyl)acetamide which inevitably contaminates the product if the step is omitted.

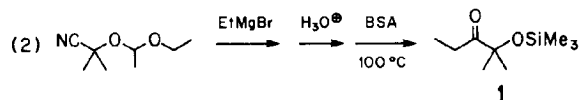
16. The ^1H NMR spectrum (200 MHz, CDCl_3) is as follows δ : 0.15 (s, 9 H), 1.02 (t, 3 H, $J = 7.2$), 1.33 (s, 6 H), 2.67 (q, 2 H, $J = 7.2$). The infrared spectrum (neat) shows absorptions at 2980 and 1720 cm^{-1} .

3. Discussion

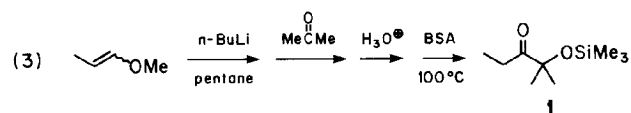
2-Methyl-2-trimethylsilyloxypentan-3-one (**1**) is the prototype member of a series of α -trimethylsilyloxy ketones that are useful for stereoselective aldol addition reactions (eq 1).² β -Hydroxy ketones **2** may be converted into β -hydroxy acids,² β -hydroxy aldehydes,³ and other β -hydroxy ketones.⁴



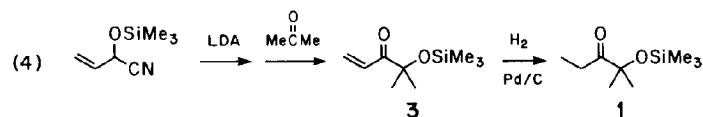
Compound **1** has also been prepared by the following methods. Addition of ethylmagnesium bromide to the protected cyanohydrin of acetone, followed by hydrolysis and silylation provides **1** in 40% yield (eq 2).² Metallation of 1-methoxypropene by butyllithium in pentane⁵ gives 1-lithio-1-methoxypropene, which reacts with acetone to give, after hydrolysis and silylation, ketone **1**.



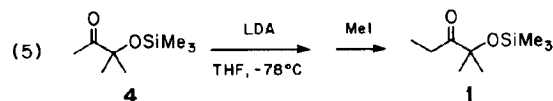
in 25-30% overall yield (eq 3).⁶ The trimethylsilyl ether of acrolein



cyanohydrin, prepared by the method of Hünig,⁷ may be metallated and added to acetone to provide an enone which is hydrogenated to 1 (eq 4).⁸ Although the



overall yield in this sequence can be quite high, the intermediate enone 3 polymerizes very readily, and the procedure is not reliable on a large scale. Compound 1 has also been prepared by methylation of the lithium enolate of the lower homolog, 4, (eq 5).⁹ Although this alkylation provides



1 in 60% yield on a 2-mmol scale, the desired product is accompanied by a significant quantity of the dimethylated product, from which it is not easily separated.⁸

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Appendix

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

2-Methyl-2-trimethylsilyloxypentan-3-one: 3-Pentanone,
2-methyl-2-[(trimethylsilyl)oxy]- (9); (72507-50-7)
2-Hydroxybutyronitrile: Butyronitrile, 2-hydroxy- (8); Butanenitrile,
2-hydroxy- (9); (4476-02-2)
Propionaldehyde (8); Propanal (9); (123-38-6)

2-[(1'-Ethoxy)-1-ethoxy]butyronitrile: Butanenitrile, 2-(1-ethoxyethoxy)-, (R*,R*)- or (R*,S*)- (9); (72658-42-5) or (72658-43-6), respectively

Ethyl vinyl ether: Ether, ethyl vinyl (8); Ethene, ethoxy- (9); (109-92-2)

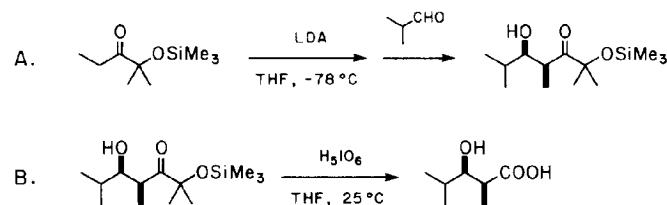
2-Hydroxy-2-methylpentan-3-one: 3-Pentanone, 2-hydroxy-2-methyl- (8,9); (2834-17-5)

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

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

N,O-Bis(trimethylsilyl)acetamide: Acetamidic acid, N-(trimethylsilyl)-, trimethylsilyl ester (8); Ethanimidic acid, N-(trimethylsilyl)-, trimethylsilyl ester (9); (10416-59-8)

(2SR,3RS)-2,4-DIMETHYL-3-HYDROXYPENTANOIC ACID
(Pentanoic acid, 3-hydroxy-2,4-dimethyl-, (R*,S*)-(±)-)



Submitted by B. Bal, C. T. Buse, K. Smith, and Clayton H. Heathcock.¹

Checked by Joseph R. Flisak, Stan S. Hall, Hugh W. Thompson,
and Gabriel Saucy.

1. Procedure

A. *5-Hydroxy-2,4,6-trimethyl-2-trimethylsilyloxyheptan-3-one*. A dry, 1-L, four-necked (including a thermometer well), round-bottomed flask equipped with an efficient mechanical stirrer, thermometer, graduated 250-mL pressure-equalizing addition funnel sealed with a rubber septum, and a nitrogen inlet is charged with 125 mL of dry tetrahydrofuran (Note 1) and 31 mL (0.22 mol) of diisopropylamine (Note 2). The stirrer is started and 137 mL (0.20 mol) of 1.5 M butyllithium in hexane is transferred to the addition funnel by means of a 16-gauge cannula and argon pressure (Note 3). The reaction flask and its contents are cooled to below -5°C by immersion in a dry ice-acetone bath that is maintained at -10 to -15°C by the occasional addition of dry ice. The butyllithium is added dropwise over a period of 20 min. After the addition is

complete 10 mL of dry tetrahydrofuran is added to the addition funnel with a syringe to rinse the walls of the funnel and the rinse is then added to the pale yellow solution. After the addition is complete the solution is stirred for an additional 15 min, and is then cooled to below -70°C (dry ice-acetone bath). While the reaction solution is cooling, a solution of 37.7 g (0.20 mol) of 2-methyl-2-trimethylsilyloxypentan-3-one (Note 4) in 10 mL of dry tetrahydrofuran is introduced through the septum into the addition funnel. When the lithium diisopropylamide (LDA) solution has cooled to below -70°C the ketone is slowly added to the solution over a period of 20-25 min to ensure that the reaction temperature is maintained below -70°C. After the addition is complete 10 mL of dry tetrahydrofuran is added to rinse the walls of the addition funnel, the rinse is added, and the stirred reaction solution is maintained below -70°C for an additional 30-40 min. During this time the addition funnel is charged through the septum with a solution of 14.4 g (0.20 mol) of isobutyraldehyde (Note 5) in 10 mL of dry tetrahydrofuran. The aldehyde solution is added dropwise to the vigorously stirring yellow enolate solution at -70°C over a 15-min period and then the addition funnel is again rinsed with 10 mL of dry tetrahydrofuran, and the rinse added to the reaction mixture. After 10-15 min 200 mL of a saturated aqueous ammonium chloride solution is added to the vigorously stirred, -70°C reaction mixture. At this point stirring is discontinued, the cooling bath is removed and the partially frozen mixture is allowed to warm to room temperature. The contents of the reaction flask are introduced into a 2-L separatory funnel, 200 mL of ether is added to the flask and the ether rinse is then transferred to the separatory funnel. The layers are shaken, then separated, and the aqueous phase is extracted again with 200 mL of ether. The combined organic phase is washed with 200 mL of water and 200 mL of saturated brine and then dried over

magnesium sulfate. After removal of the drying agent by filtration the solvents are removed with a rotary evaporator at aspirator pressure to give 52.1-52.4 g of a pale yellow oil that is a 63:37 mixture of the expected product and the starting material. Most of the starting material is then selectively removed by stirring (magnetic stirring bar) at 25°C at reduced pressure (vacuum pump, 0.1-0.08 mm) for 19 hr to yield 35.2 g of a 90:10 mixture (31.7 g, 61%), which is used without further purification for Part B (Notes 6 and 7).

B. *(2SR,3RS)-2,4-Dimethyl-3-hydroxypentanoic Acid.* A dry, 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, and a nitrogen inlet is flushed with nitrogen, charged with 12.5 g (55 mmol) of periodic acid (Note 8) and 150 mL of dry tetrahydrofuran (Note 1), and then sealed with a stoppered, 25-mL, pressure-equalizing addition funnel. The solution is stirred vigorously and cooled to 0-5°C with an ice-salt bath. During this time the addition funnel is charged with a solution of 12.0 g of 5-hydroxy-2,4,6-trimethyl-2-trimethylsilyloxyheptan-3-one (10.8 g, 41 mmol of ketone from a 90:10 mixture from Part A) in 10 mL of dry tetrahydrofuran, which is then rapidly introduced (1 min) to the cold, stirred solution. After the addition is complete 5 mL of dry tetrahydrofuran is added to the addition funnel to rinse the walls of the funnel and this rinse is then added to the reaction solution. The cooling bath is removed after 15 min and stirring is continued for 1.5 hr, during which time a white precipitate forms. In the meantime, 52 g (0.5 mol) of sodium bisulfite is mixed with 100 mL of distilled water in a 500-mL filtering flask with a side hose connection and cooled to 0-5°C with an ice-salt bath. The reaction mixture is filtered directly through filter paper with suction into the cold slurry of sodium bisulfite. The residue is rinsed with 50 mL of dry ether (Note 9), which is

added to the filter funnel and drawn by suction into the yellow solution. After magnetic stirring of the cold mixture for 20 min the contents of the flask are introduced into a 500-mL separatory funnel and the layers are separated. The aqueous layer (pH 4.3) is extracted twice with 100 mL of ether and the combined yellow organic layer is washed with 125 mL of distilled water and separated (the pH of the wash is 2.6-3.5). The organic layer is dried over magnesium sulfate for 1 hr, filtered to remove the drying agent, and the solvents are removed with a rotary evaporator at aspirator pressure. Distillation of the dark yellow oil affords 4.9-5.4 g (82-89%) of (2SR,3RS)-2,4-dimethyl-3-hydroxypentanoic acid, bp 85-89°C (0.01 mm), as a viscous, yellow-green liquid (Note 10). Crystallization from hexane using decolorizing carbon provides 4.6-5.0 g (77-83%) of pure hydroxy acid, mp 75-76°C, as white crystals (Note 11).

2. Notes

1. Tetrahydrofuran was distilled under a nitrogen atmosphere from sodium/benzophenone immediately prior to use.
2. Diisopropylamine was distilled, bp 85°C, under a nitrogen atmosphere from calcium hydride immediately prior to use.
3. *Caution! Concentrated butyllithium may ignite spontaneously on exposure to air or moisture. Manipulations with this reagent should be performed with care.* The submitters used fresh butyllithium from Foote Mineral Company, Johnsonville, Tennessee. The checkers used fresh butyllithium, 1.6 M in hexane under argon, from Aldrich Chemical Company, Inc. The butyllithium solutions may be standardized;² however, both the submitters and the checkers chose to use fresh reagents and forego the titration. Stainless

steel cannulas with deflected points (double-tip syringe needles) are available from Ace Glass Inc. and Aldrich Chemical Company, Inc.

4. 2-Methyl-2-trimethylsilyloxypentan-3-one was prepared by the method of Young, Buse and Heathcock, *Org. Synth.*, preceding article, this volume.

5. Isobutyraldehyde was freshly distilled, bp 64-65°C.

6. The submitters report that the starting material can be removed within 4 hr to give 38-42 g of the 90:10 mixture if the concentration is continued with the rotary evaporator rather than a stationary flask at 0.5-0.1 mm.

7. The ¹H NMR (200 MHz, CDCl₃) spectrum of the product (taken from a spectrum of a 90:10 mixture) is as follows δ: 0.18 (s, 9 H), 0.89 (d, 3 H, J = 6.7), 1.02 (d, 3 H, J = 6.5), 1.08 (d, 3 H, J = 7.1), 1.36 (s, 3 H), 1.37 (s, 3 H), 1.68 (d of septets, 1 H, J = 8.4 and 6.6), 2.95 (d, 1 H, J = 2.6, OH), 3.42 (dt, 1 H, J = 8.5, 2.6, and 2.6), 3.59 (dq, 1 H, J = 7.0 and 2.6). The infrared spectrum (film) of a 93:7 mixture shows absorptions at 1700 and 3600-3300 cm⁻¹.

8. Fresh periodic acid was obtained from Aldrich Chemical Company, Inc. and stored in a desiccator.

9. Reagent grade diethyl ether from a freshly opened container was used without further drying.

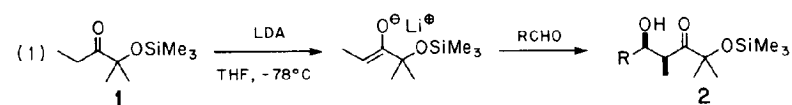
10. The checkers discovered that the desired hydroxy acid is sensitive to strong acid and heat. Early runs of Part B by the checkers using the original conditions recommended by the submitters involved stirring the bisulfite slurry at room temperature for 3-4 hr, simple partitioning without an aqueous backwash and drying of the bisulfite oxidation mixture, and distillation of the product at 0.8 mm reduced pressure. These runs consistently resulted in acid-catalyzed transformation, either in the workup

or in distillation, and led to mixtures contaminated with isobutyraldehyde produced by a retroaldol reaction, as well as with other unsaturated materials. Distillation of one of these runs, which had used a crude 58:42 mixture from Part A as starting material, afforded 13.4 g (53%) of α,γ,γ -trimethylbutyrolactone, bp 85-105°C (0.8 mm), as a yellow-green liquid by dehydration-lactonization. Crystallization from hexane provided 10.1 g (40%) of pure lactone, mp 50-51°C, as white crystals. The lactone had the following spectral properties: ^1H NMR (200 MHz, CDCl_3) δ : 1.28 (d, 3 H, $J = 7.1$), 1.38 (s, 3 H), 1.46 (s, 3 H), 1.71 (superficial t, 1 H, $J = \text{ca. } 12$), 2.30 (dd, 1 H, $J = 12.6$ and 8.9), 2.83 (16-line m; 1 H, $J = 11.2, 8.9, \text{ and } 7.1$); ^{13}C NMR (50 MHz, CDCl_3) δ : 15.6, 27.0, 29.0, 35.6, 43.5, 81.8, 179.1; IR (CCl_4) cm^{-1} : 1780; Mass spectrum, m/z (rel intensity): 129 ($\text{M}^+ + 1$, 1), 113 (33), 84 (16), 69 (30), 59 (34), 43 (100).

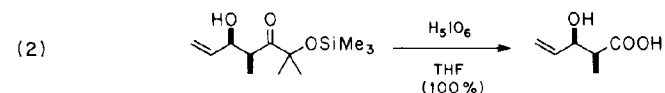
11. The hydroxy acid showed the following spectral properties: ^1H NMR (200 MHz, CDCl_3) δ : 0.89 (d, 3 H, $J = 6.6$), 1.02 (d, 3 H, $J = 6.6$), 1.21 (d, 3 H, $J = 7.1$), 1.71 (octet, 1 H, $J = 6.7$), 2.71 (dq, 1 H, $J = 7.3$ and 3.4), 3.64 (dd, 1 H, $J = 8.1$ and 3.4), 6.7 (br s, 2 H, OH and CO_2H); IR (CCl_4) cm^{-1} : 1700, 3600-2500.

3. Discussion

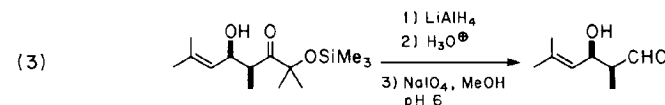
The stereochemistry of the aldol addition reaction has been actively investigated in recent years and several methods for achieving high stereoselectivity have been developed.³ One of these utilizes the preformed lithium enolates of compounds such as 1.⁴ Compound 1 gives a single enolate, which has the *Z* configuration. This enolate reacts with aldehydes to give β -hydroxy ketones (2) with high stereoselectivity (eq 1).



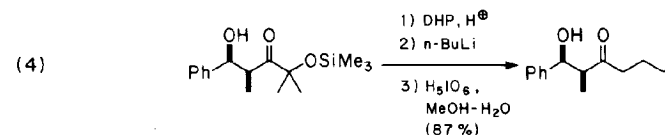
Compounds 2 may be directly cleaved with periodic acid to obtain β -hydroxy acids (e.g., eq 2).^{4,5}



Alternatively, the carbonyl group may be reduced, the silyl group hydrolyzed, and the resulting vicinal diol cleaved with buffered sodium periodate to obtain the β -hydroxy aldehyde (e.g., eq 3).^{6,7}


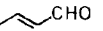


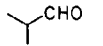
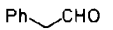

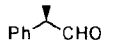
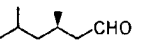
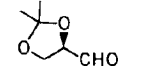


Finally, the hydroxy group may be protected as the tetrahydropyranyl ether, an aryl or alkyl lithium reagent added to the carbonyl, and the resulting vicinal diol cleaved to obtain the corresponding β -hydroxy ketone (e.g., eq 4).⁸



Selected examples of the addition of ketone 1 to a variety of aldehydes are collected in Table I.

TABLE I
CONDENSATION OF KETONE 1 WITH ALDEHYDES (eq 1)

Aldehyde	β -Hydroxy Ketone Yield (%)	Ketone mp	β -Hydroxy Acid Yield (%)	Acid mp	Ref.
	80	oil	100	oil	5
	98	oil	62	oil	9
	96	oil	97	oil	10
	43	oil	—	—	7
	93	oil	61	73-75°C	4
	51	oil	76	119-120°C	4
	78	oil	87	oil	4
	100 ^a	oil	65	134-135°C ^d	4
	61 ^b	oil	—	—	7
	75 ^c	oil	—	—	6

a. This is a 4:1 mixture of Cram: anti-Cram isomers.

b. Major isomer.

c. This is a 15:1 mixture of Cram: anti-Cram isomers.

d. This is a 1.3:1 mixture of Cram: anti-Cram isomers.

1. Department of Chemistry, University of California, Berkeley, CA 94720.
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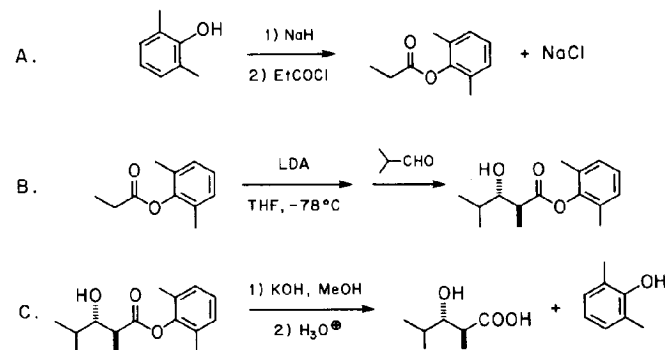
Appendix

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

(2SR,3RS)-2,4-Dimethyl-3-hydroxypentanoic acid: Pentanoic acid, 3-hydroxy-2,4-dimethyl-(R*,S*)-(±)- (9); (64869-26-7)
5-Hydroxy-2,4,6-trimethyl-2-trimethylsilyloxyheptan-3-one: 3-Heptanone, 5-hydroxy-2,4,6-trimethyl-2-[(trimethylsilyloxy)]-, (R*,S*)-(±)- (9); (64869-24-5)
Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)
Butyllithium: Lithium, butyl- (8,9); (109-72-8)
2-Methyl-2-trimethylsilyloxypentan-3-one: 3-Pentanone, 2-methyl-2-[(trimethylsilyl)oxy]- (9); (72507-50-7)
Isobutyraldehyde (8); Propanal, 2-methyl- (9); (78-84-2)
Periodic acid (8,9); (10450-60-9)

(2SR,3SR)-2,4-DIMETHYL-3-HYDROXYPENTANOIC ACID

(Pentanoic acid, 3-hydroxy-2,4-dimethyl-, (R*,R*)-)



Submitted by Stephen H. Montgomery, Michael C. Pirrung, and
Clayton H. Heathcock.¹

Checked by Pauline J. Sanfilippo and Andrew S. Kende.

1. Procedure

A. *2,6-Dimethylphenyl propanoate.* To a 2-L, three-necked, round-bottomed flask is added 26.4 g (0.55 mol) of a 50% dispersion of sodium hydride in mineral oil (Note 1). The sodium hydride is washed several times by decantation with dry hexane and is then covered with 1 L of dry ether (Note 2). The flask is immersed in an ice bath and equipped with a dropping funnel, a mechanical stirrer, and a reflux condenser. A solution of 61.1 g (0.50 mol) of 2,6-dimethylphenol (Note 3) in 150 mL of dry ether is added dropwise over a

10-min period and the mixture is stirred for 5 min, during which time hydrogen evolution ceases. The cold solution is stirred continuously while a solution of 48 mL (50.9 g, 0.55 mol) of propanoyl chloride (Note 1) in 100 mL of dry ether is added dropwise over a 30-min period. After stirring for a further 1-hr the reaction mixture is poured into a 2-L separatory funnel containing 200 mL of water. The mixture is shaken vigorously and the ether layer is separated and washed successively with 200 mL of aqueous 10% sodium hydroxide, 200 mL of water, and 200 mL of 4% hydrochloric acid, then dried over magnesium sulfate. The ether is removed with a rotary evaporator and the residue distilled through a short, indented Claisen apparatus to obtain 85-86 g (96-97%) of 2,6-dimethylphenyl propanoate, bp 60-65°C (0.05 mm) (Note 4).

B. *2',6'-Dimethylphenyl (2SR,3SR)-2,4-dimethyl-3-hydroxypentanoate*. The reaction is carried out in a 2-L, three-necked, round-bottomed flask equipped with an efficient mechanical stirrer, a thermometer, and a 500-mL, pressure-equalizing dropping funnel. The dropping funnel is marked to hold 325 mL and is topped with a rubber septum pierced with a syringe needle attached to a source of dry nitrogen. The flask is charged with 300 mL of dry tetrahydrofuran (Note 2) and 69 mL (0.49 mol) of diisopropylamine (Note 1). Butyllithium (325 mL, 0.49 mol, 1.5 M in hexane) (Note 5) is transferred into the addition funnel with a cannula. The reaction flask and its contents are cooled to below -5°C by immersion in a bath of dry ice and isopropyl alcohol which is maintained at -10 to -15°C by periodic additions of dry ice. The butyllithium is added dropwise at such a rate as to maintain the temperature of the reaction mixture in the range 0 to -5°C. After the addition is complete the mixture is stirred for an additional 15 min and is then cooled to -70°C. While the reaction mixture is cooling, the septum is briefly removed and a solution of 85 g (0.48 mol) of 2,6-dimethylphenyl propanoate in 100 mL

of dry tetrahydrofuran is added to the addition funnel, the septum is replaced, and nitrogen is passed through the apparatus in a slow stream for 5 min. The ester is then added to the lithium diisopropylamide solution at such a rate that the temperature of the reaction mixture does not exceed -65°C. The total addition time is 30-40 min. After the addition is complete the reaction mixture is kept at -70°C for an additional hour during which time the dropping funnel is charged with a solution of 35.3 g (0.49 mol) of 2-methylpropanal (Note 1) in 100 mL of dry tetrahydrofuran. The aldehyde solution is added dropwise to the vigorously stirred enolate solution at such a rate as to maintain a reaction temperature of less than -65°C. After the addition is complete the reaction mixture is kept at -70°C for an additional 30 min. To the vigorously stirred solution is added 500 mL of saturated aqueous ammonium chloride. At this point stirring is discontinued, the cooling bath is removed, and the partially frozen mixture is allowed to warm to room temperature. The contents of the reaction flask are introduced into a large separatory funnel and diluted with 500 mL of ether. The layers are separated and the organic phase is washed with 300 mL of water and 300 mL of saturated brine and then dried over magnesium sulfate. After removal of the drying agent the solvents are removed with a rotary evaporator to give 112-120 g of an oily semisolid, which is a 7:2 mixture of the β -hydroxy ester and 2,6-dimethylphenyl propanoate. This material may be crystallized from ether-hexane to provide 70 g (60%) of pure β -hydroxy ester, mp 75.5-76°C (Note 6). However, it is not necessary to purify the crude product before hydrolysis to the β -hydroxy acid (Note 7).

C. (2SR,3SR)-2,4-Dimethyl-3-hydroxypentanoic acid. The crude product from the foregoing preparation (112-120 g) is dissolved in 500 mL of methanol and placed in a 2-L Erlenmeyer flask. A solution of 112 g (2 mol) of potassium hydroxide in a mixture of 500 mL of water and 500 mL of methanol is added with stirring, whereupon the reaction mixture warms to about 40°C. After stirring for 15 min crushed dry ice is added in portions to the vigorously stirred mixture until the pH is 7-8. The resulting solution is concentrated to a volume of about 500 mL with a rotary evaporator and extracted with two 300-mL portions of methylene chloride, which are discarded. The aqueous phase is then acidified to pH 1-2 by addition of 75 mL of concentrated hydrochloric acid (vigorous evolution of CO₂) and extracted with two 500-mL portions of methylene chloride. The combined organic extracts are washed with 200 mL of saturated brine and dried over magnesium sulfate. After removal of the drying agent the solvent is removed with a rotary evaporator to obtain 36-53 g of (2SR,3SR)-2,4-dimethyl-3-hydroxypentanoic acid as a semisolid. Crystallization from hexane provides 30-43 g (41-60% overall yield) of pure hydroxy acid, mp 76-79°C (Note 8).

2. Notes

1. Sodium hydride was obtained from Ventron Corporation, Beverly, Massachusetts. 2,6-Dimethylphenol and propanoyl chloride were obtained from Aldrich Chemical Company and used without further purification. Diisopropylamine was distilled from calcium hydride prior to use. 2-Methylpropanal was distilled prior to use.

2. Reagent grade diethyl ether from a freshly opened container was used without further purification. Reagent grade tetrahydrofuran was dried over sodium before use.

3. 2,6-Dimethylphenol is a corrosive, poisonous substance which is readily absorbed through the skin. All reactions should be carried out in an efficient hood and appropriate protective apparel should be used.

4. The infrared spectrum (neat) shows an absorption at 1755 cm⁻¹. The ¹H NMR spectrum (CDCl₃) is as follows δ: 1.27 (t, 3 H, J = 7), 2.13 (s, 6 H), 2.55 (q, 2 H, J = 7), 6.90 (s, 3 H).

5. Butyllithium was obtained from Foote Mineral Company, Johnsonville, Tennessee. It may be standardized by a double titration procedure.²

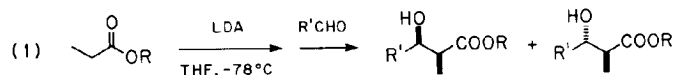
6. The infrared spectrum (neat) has absorptions at 3500 and 1750 cm⁻¹. The ¹H NMR spectrum is as follows δ: 1.00 (d, 3 H, J = 7), 1.07 (d, 3 H, J = 7), 1.40 (d, 3 H, J = 7), 2.20 (s, 6 H), 2.93 (quintet 1 H, J = 7), 3.50 (m, 2 H), 7.03 (s, 3 H).

7. The checkers found that hydrolysis of once-crystallized aldol (mp 74-75°C) gives a hydroxy acid that crystallizes readily from hexane, for an overall-two step yield of 32%. Hydrolysis of the crude aldol product gives the hydroxy acid as an oil that crystallizes with difficulty, for an overall two-step yield of 45%.

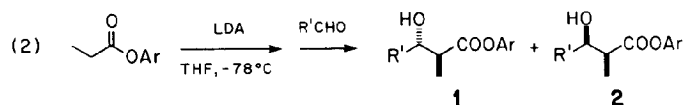
8. The infrared spectrum (neat) has absorptions at 3500, 3300-2500, and 1695 cm⁻¹. The ¹H NMR spectrum is as follows δ: 0.93 (d, 3 H J = 7) 0.99 (d, 3 H, J = 7), 1.24 (d, 3 H, J = 7), 1.81 (octet, 1 H, J = 6), 2.69 (quintet, 1 H, J = 7), 3.44 (t, 1 H, J = 5.6), 7.4 (br s, 2 H, OH).

3. Discussion

A number of methods have been developed for accomplishing aldol addition reactions in a stereoselective manner.³ The preformed lithium enolates of alkyl esters normally react with aldehydes to give mixtures of the two diastereomeric β -hydroxy esters (eq 1).⁴ However, the enolates derived from

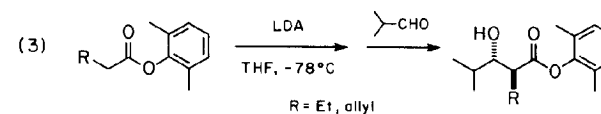


certain aryl esters add to aldehydes to give largely one stereoisomeric product (eq 2).⁵ The aryl groups that have been investigated are 2,6-



dimethylphenyl (DMP), 2,6-di-*tert*-butyl-4-methylphenyl (BHT), and 2,6-di-*tert*-butyl-4-methoxyphenyl (DBHA). Selected examples are shown in Table I. The most convenient reagents, because of the ease of their further manipulations, are the DMP esters. With aliphatic aldehydes branched at the α -carbon, the DMP esters give essentially one diastereomeric product, β -hydroxy ester **1**. With aromatic and α -unbranched aliphatic aldehydes, the DMP esters give predominantly, but not entirely, one isomer. In these cases the BHT or DBHA esters may be used. Acrolein gives a mixture of **1** and **2** even with the BHT and DBHA esters.

Aryl esters of other acids show similar stereoselectivity; examples are shown in eq 3. In addition, the BHT esters of *O*-benzylsuccinic acid condense



with aldehydes to give diastereomerically homogeneous adducts (eq 4).⁶

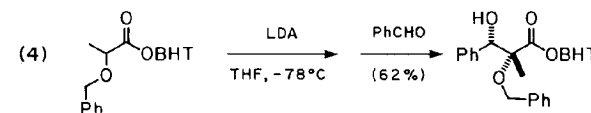


TABLE I
CONDENSATION OF ARYL ESTERS WITH ALDEHYDES

Ar	R Yield, % ^a	1:2	mp, °C
DMP	C ₆ H ₅ -	72	88/12 62-63 ^c
DMP	n-C ₅ H ₁₁	70	86/14 oil
DMP	i-C ₃ H ₇ -	78	>98/2 76
DMP	t-C ₄ H ₉ -	82	>98/2 70-71
DMP	C ₆ H ₅ (CH ₃)CH-	81	>98/2 oil ^d
BHT	CH ₂ =CH-	88	85/15 64-67 ^e
BHT	CH ₂ =C(CH ₃)-	88	>98/2 70-71
BHT	C ₆ H ₅ -	96	>98/2 oil
BHT	i-C ₃ H ₇ -	100 ^b	>98/2 105-106
BHT	C ₆ H ₅ (CH ₃)CH-	100 ^b	>98/2 oil ^d
DBHA	CH ₂ =CH-	90	87/13 65-72 ^f
DBHA	C ₆ H ₅ -	75	>98/2 59-61
DBHA	n-C ₅ H ₁₁ -	70	>98/2 oil
DBHA	i-C ₃ H ₇ -	79	>98/2 91-93
DBHA	t-C ₄ H ₉ -	77	>98/2 88-89

a. All reactions were carried out on a 1-mmol scale. Unless otherwise noted, yields are for hplc-purified product. On a larger scale, such as is given in this procedure, yields are somewhat lower.

b. This is the yield of crude product; these products were not purified by chromatography.

c. Melting point given is that of the major diastereomer (1).

d. Mixture of Cram's rule and anti-Cram's rule diastereomers: ratio = 4:1.

e. Melting point given is for a 95:5 mixture of 1:2.

f. Melting point given is for a 90:10 mixture of 1:2.

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Appendix

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

(2SR,3SR)-2,4-Dimethyl-3-hydroxypentanoic acid: Pentanoic acid, 3-hydroxy-2,4-dimethyl-, (R*,R*)- (10); (73198-99-9)

2,6-Dimethylphenyl propanoate: Phenol, 2,6-dimethyl-, propanoate (9); (51233-80-8)

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

2,6-Dimethylphenol: Phenol, 2,6-dimethyl- (9); (576-26-1)

Propanoyl chloride: Propionyl chloride (8); Propanoyl chloride (9); (79-03-8)

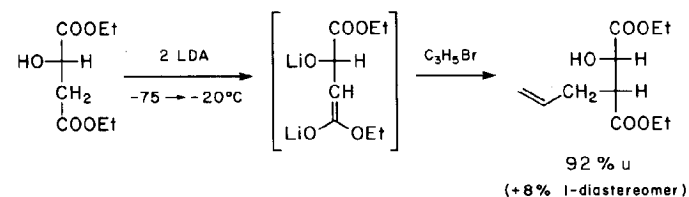
2',6'-Dimethylphenyl (2SR,3SR)-2,4-dimethyl-3-hydroxypentanoate: Pentanoic acid, 3-hydroxy-2,4-dimethyl-, 2,6-dimethylphenyl ester, (R*,R*)- (10); (73198-92-2)

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

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

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

DIASTERESELECTIVE α -ALKYLATION OF β -HYDROXYCARBOXYLIC ESTERS THROUGH ALKOXIDE ENOLATES: (+)-DIETHYL (2S,3R)-3-ALLYL-2-HYDROXYSUCCINATE FROM (-)-DIETHYL S-MALATE (Butanedioic acid, 2-hydroxy-3-(2-propenyl)-, diethyl ester, [S-(R,S)])



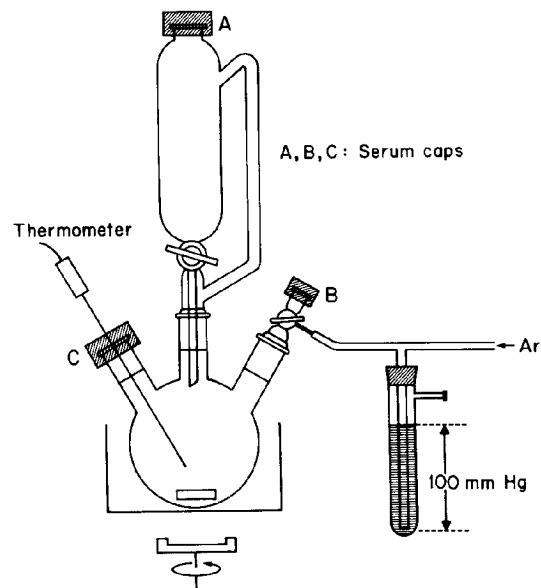
Submitted by Dieter Seebach, Johannes Aebi, and Daniel Wasmuth.¹

Checked by Brian Maxwell and Clayton H. Heathcock.

1. Procedure

A 500-mL, three-necked flask containing a magnetic stirring bar is equipped with a 100-mL pressure-equalizing and serum-capped dropping funnel, a three-way stop cock, and a low-temperature thermometer (Note 1). The dry apparatus is filled with argon and kept under an inert gas pressure of ca. 100 mm against the atmosphere until the aqueous workup (Note 2); see the accompanying figure.

The flask is charged through serum cap B with 17 mL (120 mmol) of diisopropylamine (Note 3) and 200 mL of tetrahydrofuran (THF) (Note 4), using syringe techniques. It is cooled to -75°C in a dry-ice bath. With stirring, exactly 100 mmol of butyllithium (hexane solution) (Note 5) is introduced from the dropping funnel (Note 6) within 10 min, followed after 0.5 hr, by a



mixture of 9.51 g (50 mmol) of (-)-diethyl (S)-malate (Note 7) and 5 mL of THF, which is added dropwise through cap B at such a rate that the temperature does not rise above -60°C . The addition takes approximately 10 min (Note 8). The dry-ice cooling bath is replaced by an ice-salt bath (ca. -15°C) in which the contents of the flask warm to -20°C within 0.5 hr. The solution is stirred at $-20^{\circ} \pm 2^{\circ}\text{C}$ for 0.5 hr and then is cooled to -75°C .

To the solution of the alkoxide enolate thus prepared is added by syringe within 5 min 10.7 mL (124 mmol) of neat 3-bromo-1-propene (Note 9) at such a rate that the temperature of the reaction mixture does not rise above -70°C . Stirring is continued, first for 2 hr at -75°C , then overnight while the temperature rises to -5°C (Note 10).

The reaction mixture is quenched by adding a solution of 12 g (200 mmol) of glacial acetic acid in 20 mL of diethyl ether at -50°C and is then poured into a 1-L separatory funnel containing 500 mL of ether and 70 mL of water. The organic layer is washed successively with 40 mL each of saturated sodium bicarbonate and sodium chloride solution, and the aqueous phases are extracted with two 200-mL portions of ether. The combined ethereal solutions are dried by vigorous stirring with dry MgSO_4 for 15 min. Removal of the solvent first with a rotatory evaporator at a bath temperature no higher than 35°C and then at room temperature under oil pump vacuum (0.1 mm) furnishes 10.4 g of a yellow oil consisting, according to capillary GC (Note 11), of 81.3% of the desired allylated (2S,3R) product (73.5% yield), 8.5% of the (2S,3S) diastereomer (90.5% ds^2), and 6.3% of the starting diethyl malate (Note 12).

The product is purified by flash chromatography (Notes 13-15): A flash column of 7-cm diameter is charged with 450 g of silica gel (Kieselgel 60, Merck, Korngrösse 0.040-0.063 mm, 230-400 mesh ASTM) and 10.4 g of the crude product. A 1:1 mixture of ether and pentane is used for elution, with a running rate of 5 cm column-length per min (pressure 1.25 atm). After a 200-mL forerun, 33-mL fractions are collected. No attempt is made to separate the two diastereomers; fractions 22-40 are combined to give 8.0 g (70%) of pure allylated product [ratio of diastereomers 92:8 (Note 11)], after removal of the solvent; $[\alpha]_{\text{D}}^{20} + 11.2^{\circ}$ (chloroform, c 2.23) (Note 16).

2. Notes

1. A Pt-100 thermometer (Testoterm KG, Lenzkirch, Germany) was used by the submitters. This is preferred to a conventional thermometer, because it is more accurate and more convenient to read. Careful temperature control is essential for the present procedure. Unless stated otherwise, all temperatures given are those of the reaction mixture. The checkers found that a +30 to -100°C alcohol thermometer is satisfactory.

2. The glass components of the apparatus are dried overnight in a 170°C oven and allowed to cool in a desiccator over a drying agent before assembly. The apparatus is filled with argon by evacuating and pressurizing several times through the three-way stop cock, as previously described.³

3. Diisopropylamine was freshly distilled from calcium hydride.

4. Tetrahydrofuran (THF) was first distilled under an inert atmosphere from KOH and then from the blue solution obtained with potassium and benzophenone, as described previously.³ [However, see warning notice, *Org. Synth., Collect. Vol. 5* 1973, 976-977.]

5. Before use, the commercial 1.6 M solution of butyllithium in hexane was titrated acidimetrically using diphenylacetic acid as an indicator.⁴

6. The dropping funnel was calibrated before use in this procedure. With standard graduated dropping funnels and syringes, the submitters noticed up to 10% deviation from true volumes! Syringe techniques were applied; the dropping funnel was rinsed with ca. 5 mL of dry THF.

7. Commercial (S)-(-)-malic acid was esterified under standard conditions, following a procedure by Fischer and Speier.⁵ The freshly distilled ester employed by the submitters had an $[\alpha]_D^{20} = 10.5^\circ$ (neat) ($d_{20}^4 = 1.128 \text{ g/cm}^3$), which corresponds to an optical purity of 100%.⁶

8. The flask, in which the ester/THF mixture was prepared, and the syringe are rinsed with a total of ca. 5 mL of dry THF.

9. Commercial allyl bromide was distilled before use.

10. The submitters used a 2-L Dewar cylinder holding, besides the flask, ca. 1 L of ethanol as a cooling liquid. If no excess dry ice was present at the beginning of the warm-up period, it took ca. 12 hr to reach -5°C.

11. GLC-analysis were performed using the following column and conditions: 0.3 mm x 20 m glass capillary column Pluronic L 64, program 120°C, (3 min), 10°C/min up to 200°C, temperature of injector and detector 200°C, carrier gas: hydrogen (1.3 atm).

12. A total of ca. 4% of four minor side products with longer retention times is also present.

13. This is the fastest method, although it consumes large amounts of solvent and of silica gel. The procedure is that of Still, et al.⁷ Conventional chromatography is also possible, but is more time consuming.

14. Kugelrohr distillation does not separate the starting material, diethyl malate. Distillation through a 30-cm Vigreux column (silvered vacuum jacket) leads to loss of material (only 40% yield, diastereomer ratio 90:10, free of starting material).

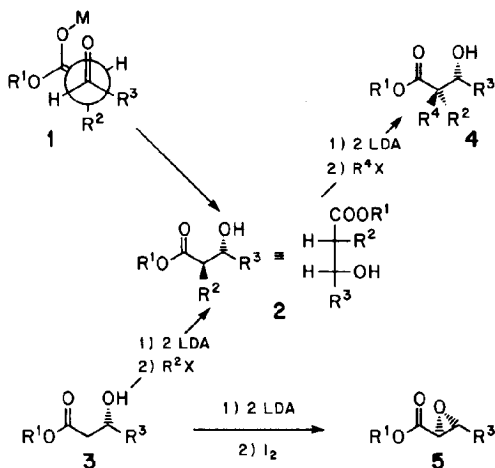
15. Hydrolysis of the crude product yields pure (2S,3R)-3-allyl-2-hydroxysuccinic acid, mp 96.0-97.5°C, $[\alpha]_D^{20} + 14.7^\circ$ (acetone, c 1.69).

16. The boiling point is 77-78°C (0.07 mm). Previously, a specific rotation of $[\alpha]_D^{25} + 11.9^\circ$ (chloroform, c 1.77) was reported.^{8a} The ¹³C NMR spectrum (CDCl₃) of the (2S,3R) isomer shows the following signals δ (off-resonance multiplicity, assignment): 14.12 (q, CO₂CH₂CH₃), 32.21 (t, C(3)CH₂), 48.25 (d, C(3)), 60.86 and 61.81 (2 t, CO₂CH₂CH₃), 70.36 (d, C(2)), 117.78 (t, C(3)CH₂CH=CH₂), 134.94 (d, C(3)CH₂CH=CH₂), 171.92 and 173.48 (2 s, CO₂CH₂CH₃).

3. Discussion

The compound described here had not been known prior to our first synthesis of it.⁸ Generally, aldol derivatives of this configuration are prepared by the addition of E enolates of esters to aldehydes,^{9,10} 1 → 2 in Scheme 1. The method of preparing α-branched β-hydroxy esters by

Scheme 1

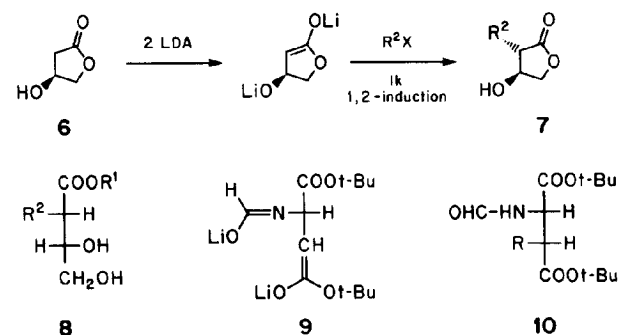


alkylation of dianion derivatives of the parent compounds was first discovered by Herrmann and Schlessinger.¹¹ It is highly diastereoselective¹² and

applicable without racemization to optically active derivatives, as first demonstrated independently by Fráter with β-hydroxybutanoate¹³ and by us with malate^{8,14} (see 3 → 2 and 3 → 5 in Scheme 1). In the meantime, many applications have been published.^{15,16} A related method of preparing derivatives belonging to the same diastereomeric series is the alkylation of β-lactone enolates.¹⁷

Examples of alkylation of malic esters are listed in Table I, together with those of double alkylation, which can also be achieved, see 2 → 4 in Scheme 1. Since the (S) and the (R) forms of malic acid are both readily available,¹⁸ the enantiomers of all structures shown in Table I can be

Scheme 2



prepared as well. The method is also applicable to β-hydroxy γ-lactones of type 6, the alkylations of which lead¹⁹ to derivatives of opposite configuration 8, see 6 → 7 in Scheme 2. Finally, the dilithio derivative 9 of di-*t*-butyl *N*-formylaspartate is alkylated (→ 10, see Scheme 2)²⁰ with the same relative topology,²¹ as the malate dianion derivative (Table I).

In Table II, a series of useful chiral building blocks is shown, which are accessible through alkylations of malic acid derivatives; the table also contains some natural products which were synthesized from such building blocks.

The alkylation of doubly deprotonated β -hydroxy esters, an example of which is described in the procedure above, is not just a useful alternative to the diastereoselective aldol-type addition, but can supply enantiomerically pure products from appropriate precursors, and it can be used for the preparation of α,α -disubstituted derivatives (see 4 in Scheme 1). These were hitherto not available stereoselectively from enolates of α -branched esters and aldehydes.

TABLE I
PRODUCTS OF MONO- AND DIAALKYLATION WITH RELATIVE TOPICITY u^a OF (S)-MALIC ESTERS THROUGH ALKOXIDE ENOLATES. THE RATIOS OF DIASTEREOMERS (SEE % ds) WAS DETERMINED BY ^1H or ^{13}C NMR SPECTROSCOPY OR BY GC ANALYSIS.

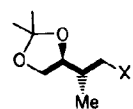
$ \begin{array}{c} \text{COOR}^1 \\ \\ \text{HO}-\text{C}-\text{H} \\ \\ \text{H}-\text{C}-\text{H} \\ \\ \text{COOR}^1 \end{array} \xrightarrow{\quad} \begin{array}{c} \text{COOR}^1 \\ \\ \text{LiO}-\text{C}-\text{H} \\ \\ \text{CH} \\ \\ \text{LiO}-\text{C}=\text{OR}^1 \end{array} \xrightarrow{\text{R}^2\text{X}} \begin{array}{c} \text{COOR}^1 \\ \\ \text{HO}-\text{C}-\text{H} \\ \\ \text{R}^2-\text{C}-\text{H} \\ \\ \text{COOR}^1 \end{array} \xrightarrow{\quad} \begin{array}{c} \text{COOR}^1 \\ \\ \text{LiO}-\text{C}-\text{H} \\ \\ \text{CR}^2 \\ \\ \text{LiO}-\text{C}=\text{OR}^1 \end{array} \xrightarrow{\text{R}^3\text{X}} \begin{array}{c} \text{COOR}^1 \\ \\ \text{HO}-\text{C}-\text{H} \\ \\ \text{R}^3-\text{C}-\text{R}^2 \\ \\ \text{COOR}^1 \end{array} $						
						a
						b
Product	R ¹	R ²	R ³	% Yield	% ds ^b	ref
(malate → a)						
a	CH ₃	CH ₃	-	65	91	8a, 14b
	CH ₃	C(OH)(CH ₃) ₂	-	55	75	8a
	C ₂ H ₅	CH ₃	-	88	91	8a
	C ₂ H ₅	CH ₂ C ₆ H ₅	-	48	91	8a
	C ₂ H ₅	I	-	80	67	8a
	CH ₃	CH ₂ CH ₂ NO ₂	-	31	85	14a
	CH ₃	C ₂ H ₅	-	64	90	14b
	CH ₃	CH ₂ CH=CH ₂	-	63	93	8b, 14c
(a → b)						
b	CH ₃	CH ₃	CH ₃	94	-	14b
	CH ₃	CH ₃	C ₂ H ₅	36	95	14b
	CH ₃	C ₂ H ₅	CH ₃		72	14b
	CH ₃	CH ₃	CD ₃	92	89	14b
	CH ₃	CH ₃	¹³ CH ₃	81	88	14b
	CH ₃	CH ₃	CH ₂ CH=CH ₂	74	95	14c
	CH ₃	CH ₃	H	100	67	14c

^aSee reference 21. ^bSee reference 2.

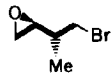
TABLE II

CHIRAL, NON-RACEMIC BUILDING BLOCKS AND NATURAL PRODUCTS SYNTHESIZED THROUGH ALKYLATION OF MALIC ACID DERIVATIVES. THE FOUR-CARBON UNIT OF THE STRUCTURE WHICH IS DERIVED FROM MALIC ACID IS INDICATED BY HEAVY LINES.

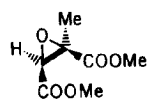
PRODUCTS AND INTERMEDIATES FROM (S)-MALIC ACID



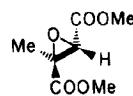
ref. 15b, 22



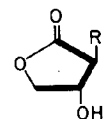
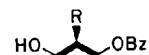
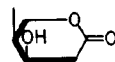
ref. 8b



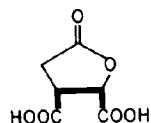
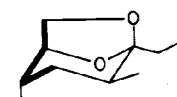
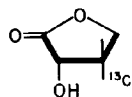
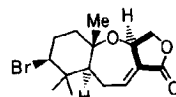
ref. 14c



ref. 14c

R = Me, Et, higher alkyl,
allyl, benzyl; ref. 19R = Me, allyl, benzyl
(by oxidative degradation
after alkylation); ref. 8c

ref. 23

(+)-isocitric acid
ref. 8b(-)-8-multistriatin
ref. 15b, 22(+)-pantolactone
ref. 14b(-)-aplysistatin
ref. 19c

1. Laboratorium für Organische Chemie, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich, Switzerland.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number):

(Registry Number)

(+)-Diethyl (2S,3R)-3-allyl-2-hydroxysuccinate: Butanedioic acid, 2-hydroxy-3-(2-propenyl)-, diethyl ester, [S-(R*,S*)]- (9); (73837-97-5)

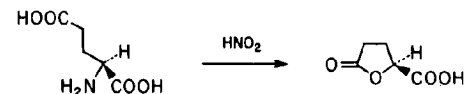
(-)-Diethyl S-malate: Malic acid, diethyl ester, (S)- (8); Butanedioic acid, hydroxy-, diethyl ester, (S)- (9); (691-84-9)

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

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

3-Bromo-1-propene: 1-Propene, 3-bromo- (8,9); (106-95-6)

(S)-(+)-γ-BUTYROLACTONE-γ-CARBOXYLIC ACID (2-Furancarboxylic acid, tetrahydro-5-oxo-, (S)-)



Submitted by Olivier H. Gringore and Francis P. Rouessac.¹

Checked by Matthew F. Schlecht, Howard Drossman, and Clayton H. Heathcock.

1. Procedure

Caution! This procedure should be conducted in a well-ventilated hood to avoid inhalation of poisonous NO₂ vapors. To protect the operator the distillation must be carried out with the usual precautions associated with vacuum distillation.

A 6-L Erlenmeyer flask which contains a large magnetic stirring bar is charged with 294 g (2 mol) of L-glutamic acid (Note 1) and 2 L of distilled water. The suspension is stirred vigorously while solutions of 168 g (2.4 mol) of sodium nitrite in 1.2 L of water and 1.2 L of aqueous 2 N sulfuric acid are added simultaneously from separatory funnels (Note 2). After the addition is complete (Note 3), the solution is stirred at room temperature for an additional 15 hr. The water is then removed by heating below 50°C under reduced pressure with a rotary evaporator (Note 4). The resulting pasty solid is triturated with 500 mL of boiling acetone and the hot solution is filtered

and set aside to cool. This operation is repeated four times (Notes 5 and 6). Removal of solvent with a rotary evaporator affords 312 g of crude (+)- γ -butyrolactone- γ -carboxylic acid as a slightly yellow oil (Notes 7 and 8).

A 250-mL, round-bottomed flask is equipped with a magnetic stirring bar and charged with 100 g of the foregoing crude lactone acid (Note 9). The flask is fitted with a Claisen distillation apparatus and connected to a vacuum pump (Notes 10 and 11). The flask is gradually heated with an oil bath (160°C) until gas evolution ceases (Note 12). At this point the oil bath is removed and the black, viscous oil is distilled with the use of a flame (Note 13). The product, 58 g (70%), is collected as a colorless oil at 146-154°C (0.03 mm). The distillate crystallizes in the receiver, mp 66-68°C (Notes 14 and 15).

2. Notes

1. This material was purchased from the Aldrich Chemical Company Inc., $[\alpha]_D^{23} + 29^\circ$ (6 N HCl, *c* 1).

2. The addition requires about 30 min. During addition the reaction mixture should warm to 30-35°C and smooth evolution of NO₂ and N₂ should occur. If the solutions of NaNO₂ and H₂SO₄ are added too rapidly, more gas appears to be generated and a reduction in yield occurs.

3. At this point the reaction mixture is clear and colorless. Residual brown gas usually remains in the flask.

4. If a conventional aspirator pump is employed, concentration can require several days. The checkers employed a rotary evaporator that was evacuated to approximately 3 mm by a vacuum pump. Two traps, one cooled in an ice-salt bath and the other in an acetone/dry-ice bath, were inserted between

the rotary evaporator and the vacuum pump. In this way, the reaction mixture can be concentrated to a paste in about 16-20 hr.

5. Repetitive extraction may also be performed in a flask heated with a water bath to 65°C; acetone is removed by decantation. Ethyl acetate has also been used for the extraction.²

6. The checkers found that a higher recovery is obtained if the pasty solid is vigorously agitated during trituration with five 750-mL portions of boiling acetone.

7. The crude yield reported is in excess of the theoretical yield (260 g). The checkers obtained crude yields of 243-259 g, probably because water was more efficiently removed in the concentration step.

8. Although this material is sufficiently pure for some applications, it is advisable to purify it further before use. Distillation² and crystallization³ have been described. The submitters recommend purification by the distillation procedure given. By direct crystallization of 101 g of crude lactone acid from ether/petroleum ether, the checkers obtained 36.5 g (35%) of material, mp 72-74°C.

9. If the distillation is carried out on a larger scale, the yield is lower.

10. The submitters recommend a short path distillation apparatus with large sections (i.e., wide bore) since the distillate partially crystallizes in the condenser during the distillation. It is important that the distillation apparatus have a Claisen head because the viscous material tends to bump.

11. The vacuum pump should be protected by a soda-lime trap.

12. During this heating period the system pressure should rise from 0.03 mm to 0.5 mm and the crude lactone acid should become black. When gas evolution ceases, the pressure decreases to its initial value.

13. Distillation should be carried out briskly. If a simple bunsen burner with a low flame is used, distillation requires several hours. The checkers used a hot flame, about 13 cm in length, from a gas-air torch. In this way, the distillation requires only about 15 min. Distillation is discontinued when colored vapors appear.

14. The checkers distilled crude lactone acid obtained in approximately quantitative yield (259 g). When this material was used, distillation of 100-g portions gave 64.3-66.4 g (65-66% yield).

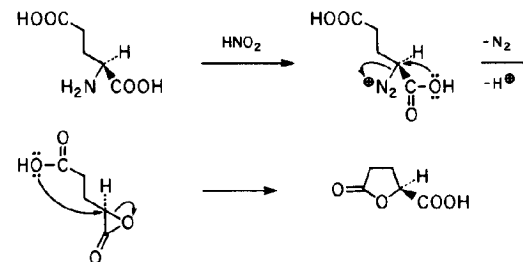
15. The submitters report that recrystallization from ethyl acetate-petroleum ether raises the melting point to 73°C. The product obtained is analytically pure, $[\alpha]_D^{21} + 16^\circ$ (EtOH, c 2). When the checkers used ethyl acetate-petroleum ether they often obtained an oily product.

The spectrum of the lactone acid is as follows: ^1H NMR (CD_3COCD_3) δ : 2.1-2.9 (m, 4 H), 4.85-5.15 (m, 1 H), 5.1 (s, 1 H, COOH).

3. Discussion

The (S)-(+)- γ -butyrolactone- γ -carboxylic acid is a useful intermediate for the synthesis of pheromones,⁴ natural lignans,⁵ and other derivatives.⁶ In the same manner, but starting with D-glutamic acid, the (R)-(-)-lactone acid may be prepared.⁷ Lactonization occurs with full retention of configuration at the chiral center.^{8,9} Recently, authors have described an efficient method which allows the formation of derivatives of the (R)-(-)-lactone from the more available (S)-(+) counterpart.¹⁰

The procedure is a detailed description of the Austin and Howard preparation.² The mechanism presumably involves anchimeric assistance of the carboxy group in decomposition of an intermediate diazonium ion, leading to a labile α -lactone:⁴



The title compound has also been prepared¹¹ using hydrochloric acid instead of sulfuric acid, and ethyl acetate instead of acetone. In the hands of the submitters, this procedure gave a lower yield.

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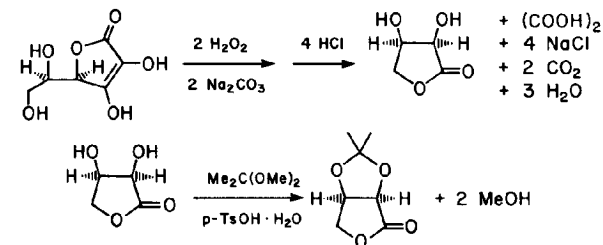
Appendix

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

(S)-(+)- γ -Butyrolactone- γ -carboxylic acid: 2-Furoic acid, tetrahydro-5-oxo-,
(S)-(-)- (8); 2-Furancarboxylic acid, tetrahydro-5-oxo-, (S)- (9);
(21461-84-7)
L-Glutamic acid (8,9); (56-86-0)

2,3-O-ISOPROPYLIDENE-D-ERYTHRONOLACTONE

(Furo[3,4-d]-1,3-dioxol-4(3aH)-one, dihydro-2,2-dimethyl-(3aR-cis)-)



Submitted by Noal Cohen, Bruce L. Banner, Anthony J. Laurenzano,
and Louis Carozza.¹

Checked by Lee A. Flippin and Clayton H. Heathcock.

1. Procedure

A 1-L, three-necked, round-bottomed flask fitted with a thermometer, addition funnel, and an air motor-driven paddle stirrer is charged with 35.2 g (0.20 mol) of erythorbic acid (Note 1) and 500 mL of deionized water. The solution is stirred with ice bath cooling (Note 2) and 42.4 g (0.40 mol) of anhydrous, powdered sodium carbonate (Note 3) is added in small portions (Note 4). The resulting yellow solution (Note 5) is stirred with ice bath cooling while 44 mL (0.45 mmol) of 31.3% by weight aqueous hydrogen peroxide (Note 6) is added dropwise over a 10-min period. The internal temperature rises from 6°C to 19°C (Note 7). The solution, containing a few solid particles, is stirred for 5 min with ice bath cooling, during which time the internal

temperature continues to rise to 27°C. The flask is now immersed in a water bath which is heated to 42°C. The solution is stirred for 30 min, during which time the internal temperature reaches a maximum of 42°C (Note 8). Norit A (8 g) is added in portions over 10 min to decompose the excess peroxide and the mixture is heated on a steam bath with continued stirring for 30 min, at which point gas evolution has essentially ceased and a negative starch-iodide test is observed. The internal temperature reaches and is kept at 75-78°C. The hot mixture is filtered with suction on a Celite pad into a 2-L, three-necked, round-bottomed flask and the filter cake is washed, in several small portions, with a total of 100 mL of deionized water. The combined filtrate and washes are acidified to pH 1 by the *cautious* (Note 9) addition of 150 mL (0.90 mol) of 6 N aqueous hydrochloric acid, in portions, with swirling. The acidic solution is concentrated with a rotary evaporator at 50°C/water aspirator pressure. The residue is dried at 50°C/0.2 mm, to give 84.6 g of a pale-yellow solid residue containing D-erythrionolactone, oxalic acid, and sodium chloride (Notes 10, 11). To this material is added 175 mL of acetone (Note 13) and the mixture is swirled to loosen the solids caked on the sides of the flask. A 50-g portion of anhydrous, powdered magnesium sulfate (Note 14) is now added and the mixture is stirred by means of an air motor-driven paddle stirrer as 350 mL (2.85 mol) of 2,2-dimethoxypropane (Note 15) is added in one portion. To the stirred mixture is added 0.42 g (0.0022 mol) of p-toluenesulfonic acid monohydrate, at room temperature. The slurry is blanketed with nitrogen and stirred at room temperature for 18 hr. In a 2-L, three-necked, round-bottomed flask fitted with a thermometer and an air motor-driven paddle stirrer, a mixture of 500 mL of anhydrous ether and 61.3 mL (0.44 mol) of triethylamine (Note 16) is cooled in an ice bath to 5°C. The reaction mixture is decanted into this solution. The residual solids are

rinsed with 60 mL of ether which is also decanted into the triethylamine solution. After being stirred for a few minutes (Note 17), the mixture is filtered with suction on a 600-mL, coarse, sintered glass funnel. The solids are washed thoroughly with a total of 300 mL of anhydrous ether by slurrying three times on the funnel with the vacuum turned off; the vacuum is then applied to draw the wash ether through the funnel. The filtrate and washes are combined and concentrated with a rotary evaporator at water aspirator pressure, and the residue is dried at 45°C/0.5 mm, to give 34.3 g of a pale-yellow solid (Note 18). This material is dissolved in approximately 150 mL of 1:1 hexanes-ethyl acetate and the solution (Note 19) is adsorbed on a column of 200 g of silica gel (Note 20) packed in 1:1 hexanes-ethyl acetate. The column is eluted with a total volume of 2 L of 1:1 hexanes-ethyl acetate (Note 21). The eluate is concentrated with a rotary evaporator at aspirator pressure and the solid residue is dried under high vacuum to afford 27.3 g of a colorless solid. This material, contained in a 1-L, one-necked, round-bottomed flask, is treated with 150 mL of anhydrous ether and the mixture is refluxed on a steam bath for 5 min to dissolve all the solid. The solution is removed from the steam bath and treated with 225 mL of hexanes. An immediate precipitate results. The mixture is refrigerated (0°C) for 3.5 hr and then filtered with suction. The solid is washed with a total of 100 mL of hexanes, in small portions, and then dried under high vacuum at 20°C. There is obtained 23.6 g (74.7%) of 2,3-O-isopropylidene-D-erythrionolactone as a white solid, mp 65.5-66°C, $[\alpha]_D^{25} -113.8^\circ$ (c 1.11 H₂O) (Notes 22, 23, 24, 25).

2. Notes

1. Erythorbic acid is the same compound as D-isoascorbic acid, available from the Aldrich Chemical Company, Inc. This substance is also known as araboascorbic acid.

2. The internal temperature is 6°C initially.

3. Sodium carbonate was obtained from the Fisher Scientific Company.

4. Vigorous evolution of carbon dioxide is observed. The internal temperature rises to 8°C.

5. A few particles of undissolved sodium carbonate may remain.

6. Aqueous hydrogen peroxide was obtained from the Fisher Scientific Company. The lot analysis given on the bottle is used to calculate the volume of hydrogen peroxide solution required. Approximately 10% molar excess of peroxide appears to be required to provide a clean product.

7. The oxidation is quite exothermic. Attempts to increase the concentrations of the reactants led to an exotherm which was difficult to control and which was complicated by the precipitation of solids which hampered stirring.

8. A small amount of gas evolution is noted during this period.

9. Evolution of carbon dioxide is vigorous.

10. It is essential that all the water be removed at this point and that a constant weight of approximately 84 g be obtained.

11. If desired, D-erythronolactone can be isolated at this point by treatment of the residue with boiling ethyl acetate. On this scale, the solid is triturated at reflux with 325 mL of ethyl acetate for 5 min. The solution is decanted and the trituration is repeated with 130 mL of ethyl acetate. The combined solutions are cooled to 5°C and filtered. The solid is washed i

portions with a total of 400 mL of cold ethyl acetate. After air drying, there is obtained 15.4 g (77.0%) of D-erythronolactone as a white solid, mp 97.5-99.5°C, $[\alpha]_D^{25} - 72.8^\circ$ (H_2O , c 0.498) (Note 12).

12. The physical properties of D-erythronolactone are as follows: Lit.² mp 104-105°C, $[\alpha]_D^{20} - 73.2^\circ$ (H_2O , c 0.533).

13. Acetone was obtained from Fisher Scientific Company.

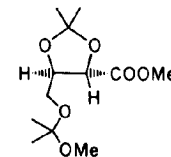
14. The drying agent is added to remove any residual moisture and to facilitate the subsequent filtration.

15. 2,2-Dimethoxypropane was obtained from the Aldrich Chemical Company, Inc.

16. Triethylamine was obtained from Eastman Chemical Products, Inc.

17. The mixture is alkaline to pH paper.

18. TLC analysis of the crude product (1:3 hexane-ethyl acetate, EM Silica Gel 60 F-254 plates) reveals the desired acetonide lactone to be the major component (R_f 0.6) with one minor, less polar impurity and several minor, more polar impurities. The 1H NMR and IR spectra of a pure sample of the less polar impurity (an oil) were compatible with the following structure:



1H NMR (100 MHz, $CDCl_3$) δ : 1.31 (2 s, 6 H, $(CH_3)_2C$), 1.39 (s, 3 H, C_2-CH_3), 1.59 (s, 3 H, C_2-CH_3), 3.20 (s, 3 H, OCH₃), 3.41 (dd, 1 H, $J = 6, 10.5$, CH_2O), 3.57 (dd, 1 H, $J = 4.5, 10.5$, CH_2O), 3.76 (s, 3 H, CO_2CH_3), 4.49 (m, 1 H, H_5), 4.67 (d, 1 H, $J_{4,5} = 7$, H_4); IR ($CHCl_3$) cm^{-1} : 1760, 1735 (ester C=O).

19. A small amount of insoluble material is present.

20. EM Silica Gel 60, 0.063-0.2 mm was used. The column dimensions are approximately 1.75 in x 14 in.

21. TLC is utilized to insure that all of the desired product is eluted from the column. This procedure removes the minor, polar impurities present in the crude product which appear at or near the origin of the TLC plate.

22. This material is homogeneous on TLC analysis; ^1H NMR (100 MHz, CDCl_3) δ : 1.37 (s, 3 H, $\text{C}_2\text{-CH}_3$), 1.46 (s, 3 H, $\text{C}_2\text{-CH}_3$), 4.42 (d, 2 H, $J_{6,6a} = 2$, H_6), 4.75 (d, 1 H, $J_{3a,6a} = 6$, H_{3a}), 4.89 (dt, 1 H, $J_{3a,6a} = 6$, $J_{6,6a} = 2$, H_{6a}); IR (CHCl_3) cm^{-1} : 1786 (γ -lactone C=O).

23. The physical properties are as follows: Lit.³ mp 68-68.5°C, $[\alpha]_D^{20} -112^\circ$ (H_2O , c 1.5).

24. The reaction sequence has been run on a 176-g (1.0 mol) scale with no loss in yield.

25. The checkers obtained 22.5 g (71.1%) of product as a white solid, mp 68.0-68.5°C, $[\alpha]_D^{25} -123.4^\circ$ (H_2O , c 0.96). It is important that crystallization from the ether-hexane mixture be carried out at 0°C. In one run in which crystallization was carried out at 8°C, the checkers obtained only 15.3 g (48.4%) of product, mp 65.5-66.0°C.

3. Discussion

2,3-0-Isopropylidene-D-erythronolactone and the corresponding lactol, 2,3-0-isopropylidene-D-erythrose are useful chiral synthons in the total synthesis of certain natural products such as the leukotrienes.⁴ The lactol is readily available from the lactone, in excellent yield, by reduction with diisobutylaluminum hydride.^{4,5} 2,3-0-Isopropylidene-L-erythrose has been employed as the starting material in an enantioselective synthesis of (+)-15S-

prostaglandin A_2 .⁶ Optically pure, selectively protected, polyfunctional C_4 -units such as these have great potential in synthesis if readily available, in substantial quantity, from inexpensive members of the "chiral pool".⁷

D-Erythronolactone and/or its isopropylidene derivative have been prepared starting from L-rhamnose,⁸ D-ribose,⁹ D-ribonolactone,³ potassium D-glucuronate,¹⁰ D-glucose,¹¹ erythorbic acid,² by optical resolution of racemic erythronolactone,¹² and by asymmetric total synthesis.¹³ 2,3-0-Isopropylidene-D-erythrose has been obtained from D-arabinose by a route which does not involve the intermediacy of the lactone.¹⁴ All of these processes suffer from either relatively low overall yields or the requirement of a large number of individual stages. The procedure described here, which is based on a similar oxidative degradation of L-ascorbic acid (vitamin C) to L-threonic acid,¹⁵ is undoubtedly the most expeditious route to the acetonide of D-erythronolactone available. In addition, the starting material, erythorbic acid, is an inexpensive and readily available substance, commonly used as a food preservative. It is pertinent to note that recently L-ascorbic acid has itself found synthetic utility as a precursor to (R)-glycerol acetonide, an important C_3 chiral synthon.¹⁶

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Appendix

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

2,3-O-Isopropylidene-D-erythrionolactone: Erythronic acid, 2,3-O-isopropylidene- γ -lactone, D- (8); Furo[3,4-d]-1,3-dioxol-4(3aH)-one, dihydro-2,2-dimethyl-, (3aR-cis)- (9); (25581-41-3)

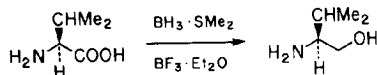
Erythorbic acid: D-*erythro*-Hex-2-enoic acid, γ -lactone (8,9); (89-65-6)

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

p-Toluenesulfonic acid monohydrate: p-Toluenesulfonic acid (8); Benzenesulfonic acid, 4-methyl- (9); (104-15-4)

L-VALINOL

(1-Butanol, 2-amino-3-methyl-, (S)-)



Submitted by G. A. Smith and Robert E. Gawley.¹

Checked by Karl M. Smith and Clayton H. Heathcock.

1. Procedure

Caution! Because of the foul odor of the methyl sulfide given off, this procedure, up to the methanol quench, should be carried out in a hood.

A 2-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, heating mantle, 250-mL graduated addition funnel, and an 8 in. air-cooled reflux condenser (West type) topped with a water-cooled distillation head and a 1-L receiving flask. It is connected to a nitrogen line through the still head. The glassware is either oven dried and cooled in a desiccator or flame dried and assembled while still hot. The assembly is flushed with nitrogen, and charged with 200 g of L-valine (1.7 mol), 400 mL of tetrahydrofuran (THF) (Note 1), and 210 mL of freshly distilled boron trifluoride etherate (242 g, 1.7 mol). The mixture is heated at a rate sufficient to cause the THF to reflux gently (Note 2) and 188 mL (1.88 mol) of borane-methyl sulfide complex, BMS, (Note 3) is added dropwise over the course of 2 hr (Note 4). The solution is then refluxed for 18 hr. The methyl sulfide which has

collected at the stillhead is discarded (Note 5), and the reaction mixture is cooled to 0°C and quenched by the slow addition of 200 mL of methanol. The addition funnel is replaced by a glass stopper, and the air-cooled condenser is removed, leaving the flask equipped for distillation of solvent through the distillation head. The reaction mixture is concentrated under reduced pressure with heating and stirring. The distillation head is replaced by a water-cooled reflux condenser, and the residue is dissolved in 1 L of 6 M sodium hydroxide and refluxed for 4 hr. The mixture is saturated with potassium carbonate (ca. 400 g), cooled, filtered through a Celite pad on a coarse, fritted funnel, and extracted with three 1-L portions of chloroform. The combined extracts are washed with three portions of saturated sodium chloride (500 mL each), stirred over anhydrous potassium carbonate for 24 hr, and concentrated under reduced pressure to give a yellow oil. The crude material is vacuum distilled to give 77.5 g (44%) of purified L-valinol; bp 62-67°C/2.5 mm; $[\alpha]_D^{20} +14.6^\circ$ (neat), n_D^{20} 1.455; IR (neat film) cm^{-1} : 3300 (OH), and 1590 (NH_2); NMR δ : 0.92 (d, 6 H), 1.54 (m, 1 H), 2.38-2.74 (m, 4 H), 3.13-3.78 (m, 2 H).

2. Notes

1. Tetrahydrofuran is dried by distillation from sodium/benzophenone ketyl.
2. The temperature is maintained at a sufficiently high point so that THF refluxes in the air-cooled condenser while ether and methyl sulfide distill through the short path distillation head.
3. The borane-methyl sulfide complex is available from Aldrich Chemical Company, Inc.

4. It is important that gentle reflux be maintained throughout the addition. If the solution is not heated during this period, an exothermic reaction occurs when the solution is refluxed.

5. Methyl sulfide should be destroyed by slowly pouring the volatile distillate into 1 gallon of household bleach (5% sodium hypochlorite). After 30 min, the bleach solution may be discarded in the drain.

3. Discussion

Reduction of amino acids to the corresponding amino alcohols via their ethyl ester hydrochlorides has been reported using lithium aluminum hydride² and sodium borohydride.³ The ability to reduce amino acids with borane - methyl sulfide (BMS) and boron trifluoride etherate was reported in a patent.⁴ The present procedure is a hybrid of two procedures: Lane's procedure for the BMS/trimethyl borate reduction of anthranilic acid,⁵ and Brown's procedure for enhanced-rate reductions of several functional groups with BMS by distilling off the methyl sulfide during the course of the reaction.⁶ The submitters have obtained a 97% crude yield (44-51% yield after distillation) of prolinol using this procedure. Lane reports that the following additional amino acids may be reduced using BMS/BF₃ etherate: leucine, phenylalanine, and 6-aminocaproic acid.⁴ Meyers has added phenylglycine to the list, and has confirmed the optical purity of the amino alcohols obtained by preparation of the Mosher amides.⁷

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Appendix

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

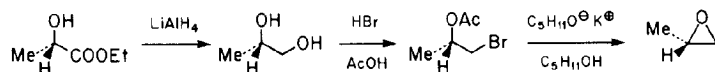
L-Valinol: 1-Butanol, 2-amino-3-methyl-, L- (8); 1-Butanol,
2-amino-3-methyl-, (S)- (9); (2026-48-4)

L-Valine (8,9); (72-18-4)

Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (BF₃)
(1:1) (8); Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1) (9);
(109-63-7)

Borane-methyl sulfide complex: Methyl sulfide, compd. with borane (1:1) (8);
Borane, compd. with thiobis[methane] (1:1) (9); (13292-87-0)

OPTICALLY ACTIVE EPOXIDES FROM VICINAL DIOLS VIA
VICINAL ACETOXY BROMIDES: THE ENANTIOMERIC METHYLOXIRANES



Submitted by Martin K. Ellis and Bernard T. Golding.¹

Checked by Stephen H. Montgomery and Clayton H. Heathcock.

1. Procedure

A. *(S)-(+)-Propane-1,2-diol*. Into a three-necked, 500-mL, round-bottomed flask fitted with a mechanical stirrer, dropping funnel and reflux condenser are placed 10.8 g (0.284 mol) of lithium aluminum hydride and 200 mL of dry ethyl ether. To this slurry is added, from the dropping funnel, 33 g (0.28 mol) of ethyl L-(-)-lactate (Note 1) in 150 mL of dry ethyl ether at a rate which maintains a steady reflux. The heterogeneous mixture is stirred for 3 hr. Then 25 mL (1.39 mol) of water is carefully added and stirring is continued for a further 1.5 hr. The mixture is filtered and the white solid (LiOH) is washed well with ether and dichloromethane. The organic phases are combined, dried over magnesium sulfate and concentrated at reduced pressure with a rotary evaporator to give a portion of the crude product (3 g). Aqueous 1 M sulfuric acid is added to the solid until the milky suspension is just acidic (pH 6-6.5). The suspension is subjected to continuous extraction with twice its volume of dichloromethane (about 500 mL) for 168 hr. The

dichloromethane layer is dried over magnesium sulfate and concentrated at reduced pressure with a rotary evaporator. The crude products are combined and distilled at reduced pressure to obtain 14.4-15.6 g (68-73%) of *(S)-(+)-propane-1,2-diol*, bp 52-56°C (0.5 mm), as a colorless liquid (Note 2).

B. *(S)-(-)-2-Acetoxy-1-bromopropane*. A three-necked, 100-mL, round-bottomed flask fitted with a magnetic stirring bar, dropping funnel and reflux condenser is charged with 7.6 g (0.1 mol) of *(S)-(+)-propane-1,2-diol*. A solution of 45% w/v hydrogen bromide-acetic acid (71 g, 0.3 mol) (Note 3) is added from the dropping funnel with cooling over ca. 5 min. The homogeneous solution is stirred at room temperature for 45 min, after which it is added to 200 mL of water and the mixture neutralized immediately with solid sodium carbonate (Note 4). The neutral solution is extracted three times with 150 mL of ethyl ether, the organic phases are combined, dried over magnesium sulfate and concentrated at reduced pressure with a rotary evaporator. Distillation of the crude product at reduced pressure affords 14.1-15.4 g (78-85%) of *(S)-(-)-2-acetoxy-1-bromopropane*, bp 54-57°C (7 mm), as a colorless liquid (Note 5).

C. *(S)-(-)-Methyloxirane*. To a three-necked, 100-mL, round-bottomed flask equipped with a magnetic stirring bar, pressure equalizing dropping funnel and 10-cm Vigreux column connected to an efficiently-cooled condenser and receiver are added 9.05 g (50 mmol) of the acetoxybromopropane and 20 mL of dry 1-pentanol. The solution is stirred at room temperature and 41.66 mL (50 mmol) of 1.2 M potassium pentoxide in 1-pentanol (Note 6) is added from the dropping funnel over ca. 20 min. A white precipitate of potassium bromide is observed. After addition is complete the flask is warmed in an oil bath at ca. 130-145°C to attain distillation (Note 7). The product, *(S)-(-)-methyloxirane*, 2.0-2.35 g (69-81%), is collected as a colorless liquid, bp 34-35°C (Note 8).

2. Notes

1. Ethyl L-(-)-lactate was purchased from Fluka AG, Buchs, Switzerland and was used directly. Checkers found that fresh ethyl lactate purchased from Fluka is only 97-98% ee, by ^{19}F NMR spectroscopy on the Mosher ester.

2. An optical rotation of $[\alpha]_D^{16} +20.3^\circ$ (H_2O , c 7.5), [lit.² $[\alpha]_D^{20} +20.7^\circ$ (H_2O , c 7.5)] was observed for this product. It had the following spectral properties: IR (liquid film, polystyrene reference) cm^{-1} : 3350 (s), 2970 (m), 2930 (m), 2870 (m), 1455 (m) 1375 (m); ^1H NMR (CDCl_3) δ : 1.15 (d, 3 H, $-\text{CH}_3$), 3.40 (q, 1 H, $\text{H}_2\text{C}(\text{OH})-$) and 3.59 (q, 1 H, $\text{H}_2\text{C}(\text{OH})-$), 3.89 (m, 1 H, $-\text{CH}(\text{OH}) \text{CH}_3$), $-\text{OH}$ resonances variable.

3. 45% Hydrogen bromide-acetic acid was purchased from BDH Chemicals Ltd., Poole, England. The checkers used hydrobromic acid (30-32% in acetic acid, 4.1 M) from Fisher Scientific, 711 Forbes Ave., Pittsburgh, PA 15219.

4. Approximately 80 g of sodium carbonate is required. On addition of solid sodium carbonate a considerable amount of frothing occurs. To prevent the loss of product, the addition of the reaction mixture to the water and subsequent neutralization with solid sodium carbonate is performed in a 2-L beaker.

5. An optical rotation of $[\alpha]_D^{20} -13.7^\circ$ (CHCl_3 , c 5.8), [lit.² $[\alpha]_D^{23} -13.55$ (CHCl_3 , c 5.8)] was observed for (S)-(-)-2-acetoxy-1-bromopropane. (R)-(+)-2-Acetoxy-1-bromopropane, obtained from (R)-(-)-propane-1,2-diol^{3,4} gave an optical rotation of $[\alpha]_D^{18} +14.1^\circ$ (CHCl_3 , c 5.8). Both enantiomers of acetoxybromopropane had the following spectral properties: IR (liquid film, polystyrene ref) cm^{-1} : 2980 (w), 2937 (w), 1735 (s), 1450 (w), 1425 (w) and 1370 (s); ^1H NMR (CCl_4) δ : 1.34 (d, 3 H, CH_3), 2.10 (s, 3 H, $-\text{OCOCH}_3$), 3.38 (d, 2 H, $-\text{CH}_2\text{Br}$), and 4.97 (m, 1 H, $-\text{CH}(\text{OCOCH}_3)\text{CH}_3$) due to 2-acetoxy-1-

bromopropane (94% by integration) and 1.70 (3 H) and 4.16 (3 H) due to 1-acetoxy-2-bromopropane (6%).

6. Potassium pentoxide in 1-pentanol is prepared by dissolving freshly cut potassium in dry, freshly-distilled 1-pentanol under nitrogen. The molarity of this solution may be determined by titration against standard aqueous acid.

7. The oil bath is pre-heated to 120-130°C. It is then transferred to a pre-warmed heater with stirrer upon a lab jack below the reaction flask. The oil bath can then be moved into position with the aid of the lab jack.

8. An optical rotation of $[\alpha]_D^{20} -18.7^\circ$ (CCl_4 , c 5.83), [lit.² $[\alpha]_D^{22} -18.55^\circ$ (CCl_4 , c 5.84)] was observed for (S)-(-)-methyloxirane. (R)-(+)-Methyloxirane, obtained from (R)-(+)-acetoxybromopropane (Note 5), gave an optical rotation of $[\alpha]_D^{18} +19.13^\circ$ (CCl_4 , c 5.66), [lit.² $[\alpha]_D^{20} +18.7^\circ$ (CCl_4 , c 5.83)], bp 34-35°C and a range of yields within the limits of those obtained for (S)-(-)-methyloxirane. Both enantiomers of methyloxirane had the following spectral properties; ^1H NMR (CCl_4) δ : 1.27 (d, 3 H, $-\text{CH}_3$), 2.27 (q, 1 H, $-\text{CH}(\text{O})\text{CH}_2$), 2.59 (t, 1 H, $-\text{CH}(\text{O})\text{CH}_2$) and 2.83 (m, 1 H, $\text{H}_3\text{C}-\text{CH}(\text{O})\text{CH}_3$) ppm.

3. Discussion

This procedure illustrates the stereospecific conversion of 1,2-diols into vicinal acetoxy bromides by hydrogen bromide in acetic acid.² The acetoxy bromides which are formed are easily transformed into epoxides by base treatment. In the examples presented, the base is used in a high boiling solvent to facilitate isolation of epoxide by direct distillation from the reaction mixture (see also refs. 5-8). For other examples, a solvent may be used which is either more volatile than the epoxide (e.g. methanol²) or easily

removed by aqueous work-up and solvent extraction of the epoxide (e.g. ethane-1,2-diol⁹). The hydrogen bromide-acetic acid method is superior to the preparation of epoxides from 1,2-diols via 1-O-sulfonate esters, because any contaminating 2-O-sulfonate ester will detract from the optical purity of the epoxide.¹⁰ The optical purities of the samples of (R)- and (S)-methyloxirane prepared as described were better than 98% according to complexation chromatography and ¹H NMR analysis with chiral shift reagent.^{11,12} Other procedures for preparing (R)-^{13,14} and (S)-methyloxirane have been described.¹⁵⁻¹⁷ These compounds are valuable starting materials for preparing a variety of optically active natural products (nonactin,¹⁸ sulcatol,¹⁹ recifeiolid, ²⁰ methyl-1,6-dioxaspiro[4.5]decanes²¹), drugs (e.g. N-2-hydroxypropyl-6,7-benzomorphans²²) and for studies of stereoregular polymerizations.²³

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Appendix

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

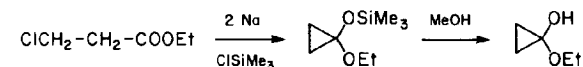
(S)-(+)-Propane-1,2-diol: 1,2-Propanediol, L- (8); 1,2-Propanediol, (S)- (9);
(4254-15-3)

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

(S)-(-)-2-Acetoxy-1-bromopropane: 2-Propanol, 1-bromo-, acetate, (S)- (9);
(39968-99-5)

(S)-(-)-Methyloxirane: Oxirane, methyl-, (S)- (9); (16088-62-3)

CYCLOPROPANONE ETHYL HEMIACETAL FROM ETHYL 3-CHLOROPROPANOATE (Cyclopropanol, 1-ethoxy-)



Submitted by J. Salaün and J. Marguerite.¹

Checked by Steven D. Young, Syun-ichi Kiyooka, and Clayton H. Heathcock.

1. Procedure

A. *1-Ethoxy-1-trimethylsiloxy-cyclopropane*. A 1-L, three-necked, round-bottomed flask is fitted with an efficient mechanical stirrer (Note 1), reflux condenser provided with a calcium chloride tube, and a 500-mL pressure equalizing dropping funnel equipped at the top with a nitrogen inlet. The flask is flushed with dry nitrogen, and 500 mL of anhydrous toluene (Note 2) and 52.9 g (2.3 g-atom) of sodium cut in small pieces (Note 3) are introduced. The mixture is brought to reflux by means of a heating mantle and the sodium is finely pulverized by vigorous stirring. Heating and stirring are stopped (Note 4), and the mixture is allowed to cool to room temperature. Toluene is removed under nitrogen pressure by means of a double-ended needle and replaced by 500 mL of anhydrous diethyl ether (Notes 5, 6). At this point, 108.5 g (1 mol) of chlorotrimethylsilane (Note 7) is added to the flask. To the mixture, 136.58 g (1 mol) of ethyl 3-chloropropoate is added dropwise with stirring at a rate sufficient to maintain a gentle reflux

over a period of 3 hr (Note 8). When about 0.3 mol of chloro ester has been added, a deep-blue precipitate appears (Note 9). When the addition is over, the reaction mixture is heated at reflux for 30 min. The contents of the flask are cooled and filtered through a sintered glass funnel under a stream of dry nitrogen (Note 10). The precipitate is washed twice with 100 mL of anhydrous diethyl ether.

The colorless filtrate is transferred to a distilling flask and the solvent is distilled through a 25-cm vacuum-jacketed Vigreux column, and the residue is distilled under reduced pressure. After a small forerun (1-2 g), 1-ethoxy-1-trimethylsiloxycyclopropane is obtained at 43-45°C (12 mm) as a colorless liquid, 106 g (61%) (Note 11).

B. Cyclopropanone ethyl hemiacetal. Into a 500-mL Erlenmeyer flask fitted with a magnetic stirring bar is placed 250 mL of reagent grade methanol. Freshly distilled 1-ethoxy-1-trimethylsiloxycyclopropane (100 g, 0.56 mol) is added all at once to the methanol and the solution is stirred overnight (12 hr) at room temperature (Note 12). An aliquot (50 mL) of the solution is concentrated by slow evaporation of methanol with a rotary evaporator at room temperature (Note 13) and formation of the methanolysis product is checked by NMR examination of the residue (Note 14). When the reaction is complete (Note 15), the solution is concentrated by removal of the methanol (Note 16). Distillation of the residue through a 20-cm helix-packed, vacuum-insulated column under reduced pressure gives 52 g (89%) of 1-ethoxycyclopropanol, bp 60°C (20 mm) (Note 14, 17), which contains trace amounts of 1-methoxycyclopropanol (Notes 18, 19).

2. Notes

1. An efficient stirrer is used at a spinning rate sufficient to disperse the molten sodium into small beads of a diameter of approximately 0.1 mm. The checkers found it necessary to use a mechanical stirrer equipped with a nichrome wire "beater", rather than a Teflon paddle. If the sodium and particles are too large, the final product will be contaminated with starting chloro ester, from which it is very difficult to separate.

2. Toluene is freshly distilled from phosphorus pentoxide into the reaction flask.

3. Sodium pieces are washed in dry pentane or toluene to remove oil.

4. It is essential that stirring be discontinued before cooling is begun to prevent the molten sodium from coalescing into one gigantic lump.

5. Diethyl ether is dried by molecular sieves and distilled from lithium aluminum hydride.

6. To remove the toluene completely, the finely divided sodium is washed under nitrogen with anhydrous diethyl ether (3 x 50 mL).

7. Chlorotrimethylsilane, obtained from Aldrich Chemical Co. or Prolabo (France), is distilled from quinoline or calcium hydride.

8. For the acyloin condensation of diesters it has been recommended that the diester and chlorotrimethylsilane be added together to the sodium dispersion;² no difference has been noted with our procedure.

9. The deep blue color seems to be indicative of a satisfactory reduction. When the color is yellow-green the yield is usually poor.

10. *Caution!* Because of the pyrophoric nature of finely divided alkali metal residues or production of free acid (HCl) from the chlorosilane, the products are sensitive to moisture. Unreacted sodium is destroyed by careful addition of ethanol to the residual solid.

11. The yield varies from 60 to 85%, bp 50–52°C (18 mm); 60–62°C (35 mm); 66–68°C (40 mm); the proton magnetic resonance spectrum (CCl_4 solution, HCCl_3 external reference) shows absorption at δ : 0.08 (s, 9 H), 0.70 (m, 4 H), 1.05 (t, 3 H, $J = 7.11$) and 3.55 (q, 2 H, $J = 7.11$); the infrared spectrum (CCl_4) exhibits absorption at 3090 and 3010 (cyclopropane), 1250, 845 and 758 cm^{-1} ($-\text{Si}[\text{CH}_3]_3$).

12. After the solution is stirred for 5–10 min, the clear solution becomes slightly turbid for a few minutes and then turns clear again. When these changes are not observed, methanolysis has not occurred.

13. If some 1-ethoxy-1-trimethylsilylcyclopropane is still present, it will be lost by too rapid evaporation of methanol.

14. The product has the following spectral properties: IR (CCl_4): 3600 and 3400 (hydroxyl), 3010 and 3090 cm^{-1} (cyclopropyl); ^1H NMR (CCl_4) δ : 0.84 (s, 4 H), 1.18 (t, 3 H, $J = 7.11$), 3.73 (q, 2 H, $J = 7.11$) and 4.75 (m, 1 H).

15. Lack of NMR absorption around δ 0.08 shows that the trimethylsiloxy group has been completely removed.

16. If the reaction is not complete, as shown by the presence of a singlet around δ 0.08, a spatula-tip full of pyridinium *p*-toluenesulfonate³ is added and the mixture is stirred for 4 hr. Methanol is then removed, and the residue is dissolved in 200 mL of diethyl ether. The solution is washed with saturated sodium chloride until neutral, dried over anhydrous sodium sulfate, and concentrated. Addition of a drop of HCl , or of chlorotrimethylsilane is also effective to complete the reaction. Then, the hydrochloric acid is removed with methanol. (Thus, it is not necessary to wash with saturated sodium chloride until neutral).

17. The yield varies from 78 to 95%, bp 51°C (12 mm), 64°C (25 mm), 75°C (46 mm).

18. On standing with methanol at 25°C for 1 week, 65% of 1-ethoxycyclopropanol is converted into 1-methoxycyclopropanol; conversion appears to be complete after 15 days.⁴ The spectral properties of the 1-methoxycyclopropanol are: IR (CCl_4): 3600 and 3400 (hydroxyl), 3010 and 3090 cm^{-1} (cyclopropyl); ^1H NMR (CCl_4) δ : 0.85 (s, 4 H) and 3.40 (s, 3 H).

19. Cyclopropanone hemiacetal can be kept unaltered for several months at 0°C in the refrigerator. On heating above 100°C or on standing in acidic solvents, it undergoes ring opening to give ethyl propionate.

3. Discussion

Cyclopropanone ethyl hemiacetal was first synthesized by the reaction of ketene and diazomethane in ether at -78°C in the presence of ethanol.⁴ The yield is low (43%) and the reaction is hazardous, especially when a large-scale reaction is required. The method described in this procedure for the preparation of cyclopropanone ethyl hemiacetal from ethyl 3-chloropropanoate is an adaptation of that described previously;⁵ the procedure described for the synthesis of 1-ethoxy-1-trimethylsilylcyclopropane is patterned after the method reported by Rühlmann.⁶

Cyclopropanone ethyl hemiacetal is a molecule of considerable interest since its reactions appear to involve the formation of the labile cyclopropanone.⁷ It readily undergoes nucleophilic addition of Grignard reagents,^{4,5} azides,⁴ and amines⁸ to provide 1-substituted cyclopropanols in high yields. It has been reported that upon treatment with an equimolar amount of methylmagnesium iodide, the cyclopropanone ethyl hemiacetal is converted into iodomagnesium 1-ethoxycyclopropylate,⁹ which can react with hydrides, organometallic reagents, cyanide carbanion, and phosphorus ylides¹⁰

to provide useful synthons. Very recently, the preparation of some challenging 2,3-disubstituted cyclopentanones including a total synthesis of the 11-deoxyprostaglandin, has been reported from the cyclopropanone hemiacetal.¹¹ The ready availability of this compound should lead to other synthetic applications. For a recent review dealing with the chemistry of the cyclopropanone hemiacetals, see reference 12.

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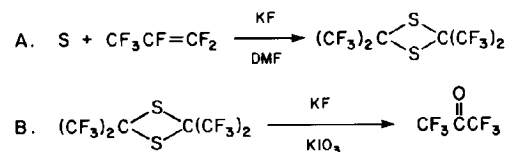
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Appendix

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

Cyclopropanone ethyl hemiacetal: Cyclopropanol, 1-ethoxy- (8,9); (13837-45-1)
 1-Ethoxy-1-trimethylsiloxy-cyclopropane: Silane, [(1-ethoxycyclopropyl)oxy]-trimethyl- (8,9); (27374-25-0)
 Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)
 Ethyl 3-chloropropanoate: Propionic acid, 3-chloro-, ethyl ester (8);
 Propanoic acid, 3-chloro-, ethyl ester (9); (623-71-2)

HEXAFLUOROACETONE
(2-Propanone, 1,1,1,3,3,3-hexafluoro-)



Submitted by Michael Van Der Puy and Louis G. Anello.¹

Checked by Evan D. Laganis and Bruce E. Smart.

Caution! Hexafluoroacetone and its precursor are toxic. Both procedures should be conducted in an efficient hood.

1. Procedure

A. *2,2,4,4-Tetrakis(trifluoromethyl)-1,3-dithietane*. A 500-mL, three-necked flask is fitted with a good magnetic stirring bar, thermometer, water-cooled condenser, and a fritted gas inlet tube (Note 1). The outlet of the condenser is attached to a tared -78°C cold trap and the inlet tube is connected via flexible tubing to a graduated -78°C cold trap into which 60 mL (96 g, 0.64 mol) of hexafluoropropene has been condensed under nitrogen. The flask is charged with 3 g of potassium fluoride and is flamed gently under vacuum. The apparatus is cooled while purging with nitrogen. Sulfur (23 g, 0.72 mol) and 200 mL of dry dimethylformamide are then added (Note 2). The reaction mixture is heated to 40-45°C with stirring. The heat source is

removed, the stopcock on the trap containing the hexafluoropropene is opened, and the trap is gently thawed. The rate of hexafluoropropene bubbling into the reaction mixture is adjusted to about 0.6 mL (1 g)/min by cooling or warming the trap containing the hexafluoropropene (Notes 3, 4 and 5). When all of the hexafluoropropene has been added, the reaction mixture is cooled to -20°C to -30°C and quickly filtered under suction (Note 6). The filtercake is transferred to an Erlenmeyer flask and is allowed to melt. Water (50 mL) is added, and the mixture is filtered. The lower liquid phase is separated, washed with 50 mL of water, and distilled through a 20-cm Vigreux column at atmospheric pressure to give 93.0-99.4 g (80-85%) of product, bp 106-108°C (Note 7).

B. *Hexafluoroacetone*. A 1-L, three-necked flask is fitted with a sealed mechanical stirrer, thermometer, and condenser. A -78°C glass trap is attached to the condenser via flexible tubing. While the system is purged with nitrogen, 3 g of potassium fluoride is added and the flask and potassium fluoride are flame dried (Note 8). After the flask has cooled, 300 mL of dry dimethylformamide, 80 g (0.374 mol) of powdered potassium iodate and 60 g (0.165 mol) of 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane are added (Note 9). The stirrer and water condenser are started and the reaction mixture is heated over a 45-min period to 149°C and is kept at 149°C for an additional 15 min. The heat source is then removed, and a slow stream of nitrogen is used to flush any remaining product gas into the cold trap (Note 8). The condensate is transferred under vacuum to a tared, evacuated gas cylinder (Note 10). The cylinder contains 37.0-39.9 g (68-73%) of material (Note 11). This material is distilled to give 35.0-37.6 g (64-69%) of pure product, bp -28°C [lit² bp -27°C] (Note 12).

2. Notes

1. The checkers dried the glassware overnight at 150°C in an oven and assembled it hot under a nitrogen purge.

2. The checkers obtained potassium fluoride, potassium iodate, dimethylformamide (reagent grades), and sulfur (sublimed) from Fisher Scientific Co. The submitters purchased hexafluoropropene from PCR Research Chemicals, Inc.; the checkers used hexafluoropropene from E. I. du Pont de Nemours & Company, Inc. The potassium fluoride was pre-dried overnight in a vacuum oven at 110°C. The sulfur was dried in a vacuum desiccator and the dimethylformamide was distilled from P₂O₅ prior to use.

3. The mixture of dimethylformamide, sulfur and potassium fluoride turns brown prior to the addition of hexafluoropropene, which quickly brings the color back to bright yellow. The submitters report that the reaction mixture will turn blue or green prior to the addition of hexafluoropropene, if the dimethylformamide is dry (less than about 0.05% water).

4. The reaction is moderately exothermic. The temperature rises to about 55°C and remains there as the reaction proceeds.

5. With good stirring, the reaction proceeds as fast as the hexafluoropropene is added. The dry-ice trap attached to the condenser should be checked periodically, however. When the required amount of hexafluoropropene is added, little or no undissolved sulfur remains.

6. 2,2,4,4-Tetrakis(trifluoromethyl)-1,3-dithietane melts at 24°C. Thus, this operation must be done quickly to minimize product loss.

7. The product is more than 99% pure by GLPC (6 ft x 1/8 in 20% FS-1265 on 60/80 Gaschrome R, 50-200°C) and by ¹⁹F NMR (CDCl₃) δ : -73.3 (s). The submitters report that they obtained 78-90 g of 98% pure product, bp 110°C.

8. The nitrogen initially should come from the cold trap, itself cooled under a nitrogen flush. At the end of the reaction, the flow of nitrogen should be reversed. This can be done by replacing the thermometer with a gas inlet tube.

9. The submitters report that a ratio of KIO₃ to 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane of 2.26 is near the optimum since a ratio of 2.5 did not increase the yield, whereas a ratio of 2.0 gave 5-10% lower yields.

10. This transfer is best done on a vacuum manifold system equipped with a manometer. The trap and a stainless steel cylinder of 100-300 mL capacity are attached via vacuum tubing to the manifold system, cooled in liquid nitrogen baths, and evacuated to 0.5-1 mm. The system is closed, the trap is removed from its cold bath and is slowly thawed. The volatile material in the trap is transferred to and condensed in the cylinder at such a rate that no positive pressure builds up in the closed system.

11. The submitters report collecting 45-50 g of product (98% pure or better by GLPC on a 10 ft x 1/8 in Porapak P column) in the cold trap attached to reaction vessel. The checkers found that the trap contained relatively non-volatile material, principally dimethylformamide, in addition to the desired product.

12. The checkers used a 30-cm jacketed, low temperature spinning band column for this distillation. The IR spectrum of the distilled product is identical to that of an authentic sample; IR (vapor) cm⁻¹: 1806 (C=O).

3. Discussion

Earlier methods of preparing 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (hexafluorothioacetone dimer, HFTA dimer) include the reaction of hexafluoropropene (HFP) and sulfur over a carbon bed at 425°C,³ and the reaction of HFP and sulfur in tetramethylene sulfone at 120°C in the presence of potassium fluoride (autoclave).⁴ Dimethylformamide appears to be a far superior solvent for this reaction, permitting the use of atmospheric pressure and modest temperatures, as well as affording a cleaner product.

The generation of hexafluoroacetone (HFA) from HFTA dimer has been accomplished by the hot-tube oxidation with nitric oxide at 650°C (high temperature converts dimer into monomer).⁵ The present method uses the more convenient interconversion of dimer to monomer effected by potassium fluoride in dimethylformamide. This permits many reactions to be conducted on the very reactive monomer without actually isolating it.

For occasional laboratory synthesis of HFA, the present method offers distinct advantages of convenience (cost, work-up, standard equipment) over other known methods. These include the epoxidation of HFP followed by isomerization of the epoxide to HFA,⁶ the high temperature halogen exchange of hexachloroacetone with Cr^{+3}/HF ,⁷ and permanganate oxidation of the extraordinarily toxic perfluoroisobutylene.⁸

Hexafluoroacetone is a reactive electrophile. It reacts with activated aromatic compounds (e.g., phenol), and can be condensed with olefins, dienes, ketenes, and acetylenes. It forms adducts with many compounds containing active hydrogen (e.g., H_2O or HCN). Reduction of HFA with NaBH_4 or LiAlH_4 affords the useful solvent hexafluoroisopropyl alcohol. The industrial importance of HFA arises largely from its use in polymers and as an intermediate in monomer synthesis.⁹

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Appendix

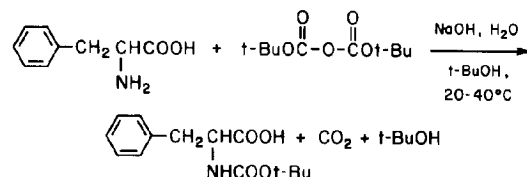
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Hexafluoroacetone: 2-Propanone, 1,1,1,3,3,3-hexafluoro- (8,9); (684-16-2)
2,2,4,4-Tetrakis(trifluoromethyl)-1,3-dithietane: 1,3-Dithietane, 2,2,4,4-tetrakis(trifluoromethyl)- (8,9); (791-50-4)
Hexafluoropropene: Propene, hexafluoro- (8); 1-Propene, 1,1,2,3,3,3-hexafluoro- (9); (116-15-4)

tert-BUTOXYCARBONYLATION OF AMINO ACIDS AND THEIR DERIVATIVES:

N-tert-BUTOXYCARBONYL-L-PHENYLALANINE

(L-Phenylalanine, N-[(1,1-dimethylethoxy)carbonyl]-)



Submitted by Oskar Keller, Walter E. Keller, Gert van Look,
and Gernot Wersin.¹

Checked by Thomas von Geldern, Mark A. Sanner,
and Clayton H. Heathcock.

1. Procedure

A 4-L, four-necked, round-bottomed flask, equipped with an efficient stirrer, a dropping funnel, reflux condenser, and thermometer is charged with a solution of 44 g (1.1 mol) of sodium hydroxide in 1.1 L of water. Stirring is initiated and 165.2 g (1 mol) of L-phenylalanine (Note 1) is added at ambient temperature, and then diluted with 750 mL of tert-butyl alcohol (Note 2). To the well-stirred, clear solution (Note 3) is added dropwise within 1 hr, 223 g (1 mol) of di-tert-butyl dicarbonate (Note 4). A white precipitate appears during addition of the di-tert-butyl dicarbonate. After a short induction period, the temperature rises to about 30-35°C. The reaction is brought to completion by further stirring overnight at room temperature. At

this time, the clear solution will have reached a pH of 7.5-8.5. The reaction mixture is extracted two times with 250 mL of pentane and the organic phase is extracted three times with 100 mL of saturated aqueous sodium bicarbonate solution. The combined aqueous layers are acidified to pH 1-1.5 by careful addition of a solution of 224 g (1.65 mol) of potassium hydrogen sulfate in 1.5 L of water (Note 5). The acidification is accompanied by copious evolution of carbon dioxide. The turbid reaction mixture is then extracted with four 400-mL portions of ethyl ether (Note 6). The combined organic layers are washed two times with 200 mL of water, dried over anhydrous sodium sulfate or magnesium sulfate, and filtered. The solvent is removed under reduced pressure using a rotary evaporator at a bath temperature not exceeding 30°C (Note 7). The yellowish oil that remains is treated with 150 mL of hexane and allowed to stand overnight (Note 8). Within 1 day the following portions of hexane are added with stirring to the partially crystallized product: 2 x 50 mL, 4 x 100 mL, and 1 x 200 mL. The solution is placed in a refrigerator overnight; the white precipitate is collected on a Buchner funnel and washed with cold pentane. The solid is dried under reduced pressure at ambient temperature to constant weight to give a first crop. The mother liquor is evaporated to dryness leaving a yellowish oil, which is treated in the same manner as described above, giving a second crop (Note 9). The total yield of pure white N-tert-butoxycarbonyl-L-phenylalanine is 207-230 g (78-87%), mp 86-88°C, $[\alpha]_D^{20} + 25.5^\circ$ (ethanol, c 1.0) (Note 10).

2. Notes

1. L-Phenylalanine puriss. from Fluka AG or Tridom Chemical Inc. was used.
2. All of the solvents and reagents used were of purum grade and obtained from Fluka AG.
3. At this stage, the reaction mixture has a pH of 12-12.5.
4. Di-tert-butyl dicarbonate can be prepared according to Pope, B. M.; Yamamoto, Y.; Tarbell, D. S. *Org. Synth.* **1977**, *57*, 45-60 or purchased from Fluka AG. Di-tert-butyl dicarbonate melts at 22-24°C; this compound can be liquified by immersing the reagent bottle in a water bath with a maximum temperature of 35°C. Commercial material is 97-98% pure; a total of 223 g must be employed.
5. It is recommended that acidification be carried out at a temperature of 0-5°C.
6. Ethyl or isopropyl acetate may also be used as extraction solvents for less lipophilic N-tert-butoxycarbonyl amino acids.
7. Evaporation should be performed first at 10-20 mm, then at a pressure less than 1 mm in order to remove the tert-butyl alcohol completely. Remaining small quantities of tert-butyl alcohol lead to difficulty in crystallization.
8. Seeding or scratching with a glass rod helps to induce crystallization.
9. Normally it is not worthwhile to isolate a third crop, which is of lower purity.
10. N-tert-Butoxycarbonyl-L-phenylalanine prepared by this method is obtained in a very pure state. Thin layer chromatography shows a single spot

and a content of less than 0.05% free amino acid. Acylation of lipophilic amino acids with excess di-tert-butyl dicarbonate may result to some extent in formation of the corresponding N-tert-butoxycarbonyl dipeptide.

3. Discussion

In recent years the tert-butoxycarbonyl (BOC) group has achieved a leading role as a protective group for the amino moiety of amino acids in peptide synthesis.² At one time the most widely used tert-butoxycarbonylating agent was the hazardous³ and toxic tert-butyl azidoformate.⁴ Di-tert-butyl dicarbonate⁵ is a highly reactive and safe reagent of the "ready-to-use" type which reacts under mild conditions with amino acids,^{5a,6a-i} peptides,^{6j-l} hydrazine and its derivatives,⁷ amines,^{8a-g} and CH-acidic compounds^{8h} in aqueous organic solvent mixtures to form pure derivatives in very good yields. Acylation with di-tert-butyl dicarbonate proceeds normally without strict pH control. The procedure given here demonstrates a suitable large-scale and safe preparation of an N-tert-butoxycarbonyl amino acid with extremely simple experimental operations. Table I shows some other BOC-amino acids and derivatives prepared by this method. N-tert-Butoxycarbonyl-L-phenylalanine has also been prepared by acylation of L-phenylalanine with other tert-butoxycarbonylating agents: tert-butyl 4-nitrophenyl carbonate,⁹ tert-butyl azidoformate,¹⁰ tert-butyl 2,4,5-trichlorophenyl carbonate,¹¹ tert-butyl pentachlorophenyl carbonate,¹² tert-butyl 8-quinolyl carbonate,¹³ tert-butyl chloroformate,¹⁴ tert-butyl fluoroformate,¹⁵ tert-butyl phenyl carbonate,¹⁶ N-tert-butoxycarbonyl-1H-1,2,4-triazole,¹⁷ tert-butyl 4,6-dimethylpyrimidyl-2-thiol carbonate,¹⁸ N-tert-butoxycarbonyloxymino-2-phenylacetone nitrile,¹⁹ tert-butyl α -methoxyvinyl carbonate,²⁰ tert-butyl minocarbonate (tert-butoxycarbonyloxamine).²¹

Table I

BOC-AMINO ACIDS PREPARED BY ACRYLATION WITH DI-tert-BUTYL DICARBONATE

BOC-Amino Acids ^a	Solvent ^b	Base	Time (hr) ^c	Yield, %	mp, °C	$[\alpha]_D^{20}$	Remarks
BOC-Ala-OH	A	NaOH	16	92-94	82-83	-25.5 (acetic acid, σ 2.0)	pH 8.0 ^e
BOC-B-Ala-OH	A	NaOH	16	85-86	76-77		
BOC-Arg-OH	B	--	15	88	159-160 (dec)	- 6.8 (acetic acid, σ 1.0)	extraction with n-butyl alcohol
BOC-Arg(NO ₂)-OH ^d	B	NaOH	15	82	107	-22.0 (pyridine, σ 2.0)	pH 8.8 ^e
BOC-Asn-OH	C	NaOH	18	80-81	176 (dec)	- 7.2 (dimethylformamide, σ 2.0)	5 hr, 45-50°C
BOC-Asp(OBzl)-OH	A	NaOH	16	81-89	101-102	-19.7 (dimethylformamide, σ 2.0)	pH 8.0 ^e
BOC-Cys(Bzl)-OH	B	NaOH	15	65	86-87	-43.4 (acetic acid, σ 1.0)	
(BOC-Cys-OH) ₂	D	NaOH	16	85	143-145 (dec)	-115.6 (acetic acid, σ 2.0)	
BOC-Gln-OH	E	NaOH	18	76	125 (dec)	- 3.4 (ethanol, σ 2.0)	pH 8.0 ^e
BOC-Glu(OBzl)-OH ^f	B	NaOH	15	86	142-143	+13.2 (methanol, σ 1.0)	pH 8.5-9 ^e
BOC-Gly-OH	A	NaOH	16	96	87-88		
BOC-His(BOC)-OH	A	KHCO ₃	18	75	170 (dec)	+19.5 (chloroform, σ 2.0)	
BOC-Ile-OH	A	NaOH	16	78	69-71	+ 2.8 (acetic acid, σ 2.0)	
BOC-Leu-OH ^g	A	NaOH	18	96	85-87	-24.7 (acetic acid, σ 2.0)	
BOC-Lys(BOC)-OH ^f	A	NaOH	16	82	138-139	+ 6.1 (dimethylformamide, σ 1.5)	
BOC-Lys(CBZ)-OH	A	NaOH	18	96	oil		
BOC-Met-OH	A	NaOH	18	60 ^h	50-51	-22.8 (methanol, σ 1.3)	
BOC-Met-OH ^f	A	NaOH	18	85	139-140	+18.2 (ethanol, σ 2.0)	
BOC-Pro-OH	A	NaOH	12	95	134-135	-60.6 (acetic acid, σ 2.0)	

Table I (cont.)

BOC-Amino Acids ^a	Solvent ^b	Base	Time (hr) ^c	Yield, %	mp, °C	$[\alpha]_D^{20}$	Remarks
BOC-Ser-OH	A	NaOH	16	66-82	86-88	- 3.6 (acetic acid, σ 2.0)	pH 8.5-9 ^e
BOC-Ser(Bzl)-OH	B	NaOH	16	90	62-63	+19.2 (80% ethanol, σ 2.0)	pH 8.5-9 ^e
BOC-Tyr-OH	A	NaOH	16	85	71-73	- 8.2 (acetic acid, σ 1.0)	
BOC-Tyr-OH ⁱ	A	NaOH	16	96	137-138 (dec)	-18.2 (dimethylformamide, σ 1.0)	
BOC-Trp-(FOR)-OH ^f	F	Et ₃ N	48	61	158-159 ^k	+36.0 (ethanol, σ 2.0)	
BOC-Tyr-OH	A	NaOH ^l	24	75	137 ^m	+ 2.6 (acetic acid, σ 1.0)	
BOC-Tyr-OH ^f	A	NaOH ^l	24	84	216	+ 2.6 (acetic acid, σ 1.0)	
BOC-Tyr(Bzl)-OH	B	NaOH	18	70	110-111	+27.6 (ethanol, σ 1.0)	pH 10.4 ^e
BOC-Tyr(2,6-Cl ₂ -Bzl)-OH	A	NaOH	24	48	104 (dec)	+20.6 (ethanol, σ 2.0)	
BOC-Val-OH	A	NaOH	16	85	76-78	- 7.5 (acetic acid, σ 1.0)	

^aThe amino acids used, with the exception of β -alanine and glycine, were of L-configuration. The abbreviations used for amino acids and their protecting substituents concur with E. Münsch.²

^bSolvent systems: A: tert-butyl alcohol/water; B: dioxane/water; C: dimethylformamide/water; D: methanol/water; E: acetonitrile/water; F: dimethylformamide.

^cThe reaction was generally carried out at room temperature after the exothermic starting period had subsided. Progress of the reaction was monitored by thin layer chromatography. Reaction times are not optimized.

^dCrystallizes with ~15% solvent (ethyl acetate).

^epH control is necessary.

^fTricyclohexylamine salt.

Table I (cont.)

^gMonohydrate.

^hThe yield of crude semi-solid product was 90%. This material was pulverized by efficient stirring in hexane over a period of 24 hr at -10°C under strictly anhydrous conditions.

ⁱCrystallizes with ~4% solvent (ethyl acetate).

^kDecomposes below 130°C if heated rapidly.

^lTwo equivalents of base were employed.

^mResolidifies at 138°C and does not melt below 300°C.

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Appendix

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

L-Phenylalanine (8,9); (63-91-2)
 tert-Butyl alcohol (8); 2-Propanol, 2-methyl- (9); (75-65-0)
 Dicarboxic acid, bis(1,1-dimethylethyl) ester (9); (24424-99-5)
 Ethyl ether (8); Ethane, 1,1'-oxybis- (9); (60-29-7)
 Alanine, N-carboxy-3-phenyl-N-tert-butyl ester, L- (8); L-Phenylalanine, N-[(1,1-dimethylethoxy)carbonyl]- (9); (13734-34-4)

Carbonic acid, tert-butyl p-nitrophenyl ester (8); Carbonic acid, 1,1-dimethylethyl 4-nitrophenyl ester (9); (13303-10-1)

Formic acid, azido-, tert-butyl ester (8); Carbonazidic acid, 1,1-dimethylethyl ester (9); (1070-19-5)

Carbonic acid, tert-butyl 2,4,5-trichlorophenyl ester (8); Carbonic acid, 1,1-dimethylethyl 2,4,5-trichlorophenyl ester (9); (16965-08-5)

Carbonic acid, tert-butyl pentachlorophenyl ester (8); Carbonic acid, 1,1-dimethylethyl pentachlorophenyl ester (9); (18942-25-1)

Carbonic acid, 1,1-dimethylethyl 8-quinoliny1 ester (9); (18595-55-6)

Formic acid, chloro-, tert-butyl ester (8); Carbonochloridic acid, 1,1-dimethylethyl ester (9); (24608-52-4)

Formic acid, fluoro-, tert-butyl ester (8); Carbonofluoridic acid, 1,1-dimethylethyl ester (9); (18595-34-1)

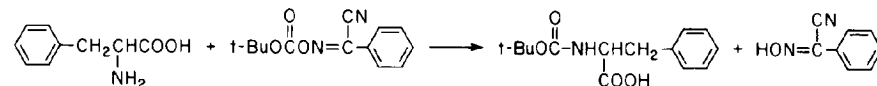
Carbonic acid, tert-butyl phenyl ester (8); Carbonic acid, 1,1-dimethylethyl phenyl ester (9); (6627-89-0)

1H-1,2,4-Triazole-1-carboxylic acid, 1,1-dimethylethyl ester (9); (41864-24-8)

Carbonothioic acid, O-(1,1-dimethylethyl) S-(4,6-dimethyl-2-pyrimidinyl) ester (9); (41840-28-2)

Benzeneacetonitrile, α-[[[(1,1-dimethylethoxy)carbonyl]oxy]imino]- (9); (58632-95-4)

tert-BUTOXYCARBONYL-L-PHENYLALANINE
(L-Phenylalanine, N[(1,1-dimethylethoxy)carbonyl])-



Submitted by William J. Paleveda, Frederick W. Holly, and Daniel F. Veber.¹
 Checked by Mark A. Sanner, Thomas von Geldern, and Clayton H. Heathcock.

1. Procedure

To a stirred mixture of 16.51 g (0.1 mol) of L-phenylalanine in 60 mL of water and 60 mL of peroxide-free dioxane (Note 1) is added 21 mL of triethylamine. To the resulting solution is added 27.1 g (0.11 mol) of 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (Note 2). Solution is obtained during the first hour of stirring. After 3 hr (Note 3) the solution is diluted with 150 mL of water. The resulting turbid solution is extracted with at least four 200-mL portions of ethyl ether (Note 4). The aqueous layer is then acidified to pH 2.5 with cold 2.5 N hydrochloric acid to yield an oily layer. The mixture is extracted with three 100-mL portions of methylene chloride. The combined organic extracts are dried with anhydrous sodium sulfate. After filtration of the sodium sulfate, the filtrate is evaporated under reduced pressure at a bath temperature of 30°C. Hexane is added to the thick oil to turbidity. Crystallization occurs after cooling and stirring the mixture for a short time. More hexane is added in portions until no further

crystallization occurs. A total of 200 mL of hexane is required. The mixture is allowed to stand for 1 hr. The white crystalline solid is collected by filtration, washed with three 100-mL portions of hexane, and dried under reduced pressure to yield 21.4-22.0 g (80-83%) of tert-butoxycarbonyl-L-phenylalanine, mp 86-88°C, $[\alpha]_D^{20}$ -3.6° (HOAc, c 1), $[\alpha]_{546}^{20}$ 29.9° [EtOH, c 1] (Note 5).

2. Notes

1. Peroxides are removed from dioxane by passage through an alumina column.²

2. 2-(tert-Butoxycarbonyloxyimino)-2-phenylacetonitrile is obtained from Aldrich Chemical Company, Inc., under the trademark "BOC-ON".

3. The reaction is allowed to continue until TLC (Whatman KIF, ethyl acetate-pyridine-acetic acid-water, 10:5:1:3) shows that the unprotected amino acid (R_f 0.4) is no longer present, as evidenced by negative ninhydrin spray.

4. It is imperative that all of the by-product is removed at this point; otherwise it will contaminate the product, making crystallization difficult. Each ether extract is spotted on a Whatman KIF plate and the plate viewed under UV light to ascertain that all of the by-product has been extracted. The checkers found that six or seven ether extractions were required to remove the by-product completely.

5. The literature gives melting points ranging from 79-80°C to 84-86°C. The optical rotation is reported as $[\alpha]_D^{25}$ -0.8° (HOAc, c 4.957), $[\alpha]_D^{20}$ -4.8 (HOAc, c 1), $[\alpha]_{546}^{20}$ 30° (EtOH, c 1).

The spectral properties of tert-butoxycarbonyl-L-phenylalanine are as follows: ^1H NMR (CD_3OD) δ : 1.36 (s, 9 H, t-butyl), 2.87 (dd, 1 H, $J = 14.9$, H_β), 3.16 (dd, 1 H, $J = 14.6$, H_β), 4.36 (dd, 1 H, $J = 9.6$, H_α), 7.26 (s, 5 H, phenyl). In CDCl_3 solution, both carbamate rotamers may be seen in the ^1H NMR spectrum.

3. Discussion

Various reagents have been used for the introduction of the tert-butoxycarbonyl group, including tert-butyl p-nitrophenyl carbonate,³ tert-butyl azidoformate⁴ (no longer commercially available because of its toxic and potentially explosive nature), tert-butyl 2,4,5-trichlorophenyl carbonate,⁵ di-tert-butyl dicarbonate,⁶ and the reagent described herein, 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile.⁷ Using the same reagent, the crystalline BOC derivatives of the following amino acids have been prepared in these laboratories in the indicated yields: 7-aminoheptanoic acid (88%), DL-tyrosine (96%), 6-fluoro-DL-tryptophan (87%), 5-methyl-DL-tryptophan (95%), 5-bromo-DL-tryptophan (94%), 5-methoxy-DL-tryptophan (67%), 1-methyl-DL-tryptophan (82%), and 5-fluoro-DL-tryptophan (62%).

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Appendix

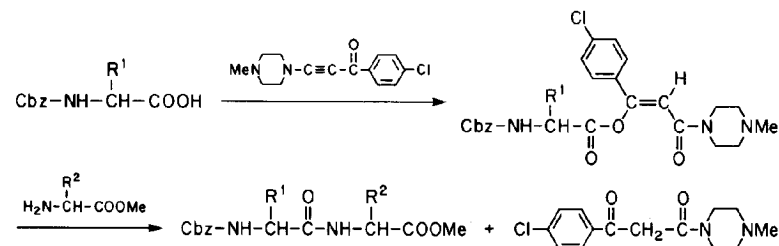
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

tert-Butoxycarbonyl-L-phenylalanine: L-Phenylalanine, N-[(1,1-dimethylethoxy)carbonyl]- (9); (13734-34-4)

L-Phenylalanine (8,9); (63-91-2)

2-(tert-Butoxycarbonyloxyimino)-2-phenylacetonitrile; Aldrich "BOC-ON": Benzeneacetonitrile, α -[[[(1,1-dimethylethoxy)carbonyl]oxy]imino]- (9); (58632-95-3)

PEPTIDE SYNTHESIS USING 1-(4-CHLOROPHENYL)-3-(4'-METHYL-1'-PIPERAZINYL)-2-PROPYN-1-ONE AS REAGENT: BENZYLOXYCARBONYL-L-ALANYL-L-CYSTEINE METHYL ESTER AND BENZYLOXYCARBONYL-L-ASPARTYL-(tert-BUTYL ESTER)-L-PHENYLALANYL-L-VALINE METHYL ESTER



Submitted by H. P. Fahrni, U. Lienhard and M. Neuenschwander.¹

Checked by David R. Bolin and Gabriel Saucy.

1. Procedure

A. *Benzylloxycarbonyl-L-alanyl-L-cysteine methyl ester.* A round-bottomed, three-necked, 100-mL flask is equipped with a magnetic stirring bar, 10-mL dropping funnel, thermometer and nitrogen bubbler (Note 1). The apparatus is flushed with dry nitrogen and then charged with 446.5 mg (0.002 mol) of benzylloxycarbonyl-L-alanine in 10 mL of dry dichloromethane. The mixture is stirred until solution is complete and then cooled to 0°C. Within 20 min a solution of 525.5 mg (0.002 mol) of 1-(4-chlorophenyl)-3-(4'-methyl-1'-piperazinyl)-2-propyn-1-one (Note 2) in 5 mL of dry dichloromethane is added. Stirring is continued for 1 hr at 0°C and for a further hour at room

temperature (t_1). The mixture is cooled again to 0°C and a suspension of 343.3 mg (0.002 mol) of L-cysteine methyl ester hydrochloride is quickly added, followed by a solution of 202.3 mg (0.002 mol) of N-methylmorpholine in 5 mL of dry dichloromethane. While the nitrogen atmosphere is maintained, the mixture is allowed to warm up and is stirred for 12 hr (t_2) at room temperature. The solvent is removed by rotary evaporation, and the residue is shaken intensively with 30 mL of ethyl acetate and 10 mL of water. The organic layer is extracted two times with 10-mL portions of aqueous 10% citric acid and once with 5 mL of 1 N sodium hydrogen carbonate. The organic phase is dried over sodium sulfate. The solvent is removed by rotary evaporation to leave 647 mg (95%) of the crude pale yellow dipeptide. Recrystallization from ethyl acetate provides 551 mg (81%) of colorless crystals of benzyloxycarbonyl-L-alanyl-L-cysteine methyl ester, mp 115-117°C; $[\alpha]_D^{20}$ -26.4° (CH₃OH, c 1.29), (Note 3).

B. *Benzyloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanyl-L-valine methyl ester*. A round-bottomed, three-necked, 100-mL flask is equipped with a 10-mL dropping funnel, thermometer, magnetic stirring bar and a nitrogen bubbler. The flask is flushed with dry nitrogen and then charged with a solution of 941.1 mg (0.002 mol) of benzyloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanine (Note 4) in 10 mL of dry dichloromethane. The flask is maintained under a dry nitrogen atmosphere and cooled to 0°C with an ice/salt bath. The mixture is stirred and a solution of 525.5 mg (0.002 mol) of 1-(4-chlorophenyl)-3-(4'-methyl-1'-piperazinyl)-2-propyn-1-one (Note 2) in 5 mL of dry dichloromethane is added during a period of 20 min. Stirring is continued for 1 hr at 0°C and for 5 hr at room temperature (t_1). The mixture is again cooled to 0°C and a suspension of 335.3 mg (0.002 mol) of L-valine methyl ester hydrochloride and 202.3 mg (0.002 mol) of N-methylmorpholine in 5

mL of dichloromethane is added. After 30 min the reaction mixture is allowed to warm up and is stirred overnight (18 hr; t_2) at room temperature. The solvent is removed by rotary evaporation and the residue is shaken intensively with 40 mL of ethyl acetate and 10 mL of water. The organic layer is extracted twice with 10-mL portions of aqueous 10% citric acid and once with 5 mL of 1 N sodium hydrogen carbonate.

The organic phase is dried over sodium sulfate, and solvent is removed by rotary evaporation to leave 1132 mg (97%) of the crude pale-yellow tripeptide. For further purification the crude product is dissolved in ethyl acetate, treated with some activated carbon and filtered through Celite. Removal of the solvent and crystallization from ethyl acetate/ether/petroleum ether (ca. 2:1:1) yields 993 mg (85%) of colorless crystals of benzyloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanyl-L-valine methyl ester; mp 119-120°C (Note 5).

2. Notes

1. Cysteine derivatives are oxidized to cystine by oxygen. The nitrogen atmosphere for preparation of Cbz-alanilcysteine methyl ester is therefore indispensable and is recommended for other cases as well.

2. This reagent is available from Fluka Chemical Corp.

3. The literature² value is $[\alpha]_D^{20}$ -26.5° (CH₃OH, c 1.27). The reported² mp is 116.5-118°C.

4. Benzyloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanine dicyclohexylamine salt was conveniently prepared by standard procedures.³ The salt was dissolved in ethyl acetate and extracted three times with aqueous 10% citric acid, and once with water. The organic phase was dried and solvent was removed to leave the dipeptide as an oil.

5. The product has the following physical properties: Specific rotation: $[\alpha]_D^{20} -36.5^\circ$ (C_2H_5OH , c 2); IR (KBr), cm^{-1} : 3285, 1732, 1691, 1640, 1531, 1367, 1229, 1158, 1050, 746, 701; 1H NMR (100 MHz, $CDCl_3$), δ : 7.57 (s, 5 H), 7.21 (s, 5 H), 7.02 (d, 1 H, $J = 8$), 6.28 (d, 1 H, $J = 8$), 5.78 (d, 1 H, $J = 8$), 5.11 (s, 2 H), 4.8-4.3 (m, in total 3 H), 3.71 (s, 3 H), 3.08 (d, 1 H, $J = 8$), 2.86 (d of d, 1 H, $J = 17$, $J' = 5$), 2.62 (d of d, 1 H, $J = 17$, $J' = 6$), 2.3-1.8 (m, 2 H), 1.41 (s, 9 H), 0.84 (d, 3 H, $J = 7$), 0.81 (d, 3 H, $J = 7$).

3. Discussion

This procedure illustrates the use of 1-(4-chlorophenyl)-3-(4'-methyl-1'-piperazinyl)-2-propyn-1-one⁴ as a reagent for peptide synthesis.⁵ The same method also gives amides in excellent yields.⁶

The preparation of Cbz-L-alanylcysteine methyl ester shows the advantage of using, as the amine component, an amino acid with an unprotected sulfhydryl moiety. No problems were encountered with the use of amino acid derivatives with unprotected hydroxyl or sulfhydryl groups as either the amine⁵ or carboxyl component.⁷ This procedure is based on the pronounced selective reactivity of the enol ester, which is generated by the addition of carboxylic acids to "push-pull acetylenes." Generally, the yields of peptides are good and a broad variety of solvents (e.g., dichloromethane, tetrahydrofuran, acetonitrile, dimethylformamide) may be used, depending on the solubility of the coupling components. It is also possible to change the solvent after the activation step or to isolate the activated components. However, normally this is neither necessary nor recommended. Purification of the reaction mixture is simple, since the piperazine by-product is conveniently extracted with an acidic water phase.

The following peptides and further examples have been prepared⁵ by this procedure:

Peptide	t_1^a	t_2^b	Yield ^c
Cbz-L-Ala-Gly-OMe	2 ^d	12	91%
Cbz-L-Ala-L-Val-OMe	2 ^d	24	84%
Cbz-L-Ala-L-Phe-OMe	2 ^d	18	88%
Cbz-Gly-L-Phe-Gly-OEt	2	12	90%
Cbz-L-Asp(O-t-Bu)-L-Phe-L-Val-OMe	6	18	85%
Cbz-L-Ile-L-Ile-OBzl	18	24	75%
Cbz-L-Ala-L-Ser-OMe	2 ^d	72	90%
Cbz-L-Ala-L-Tyr-OMe	2 ^d	72	91%
Cbz-L-Ala-L-Cys-OMe	2 ^d	12	81%
Cbz-L-Ala-L-Met-OMe	2 ^d	15	85%
Cbz-L-Ser-Gly-OEt	2	24	81%

^a t_1 : time for activation of the carboxylic component (see procedures).

^b t_2 : time for coupling (see procedures). ^cYield of pure recrystallized product. ^dStirring 1 hr at 0°C, then 1 hr at 20°C.

During our experiments no side reactions were detected. This is in contrast to peptide synthesis with isoxazolium salts,⁸ where some side reactions, one leading to a diacyl amino compound, were observed.⁹ In most cases, these side reactions are due to a secondary amino group in the reagent which is impossible in the case of push-pull-acetylenes.

Compared with ynamines, which have also been applied to peptide synthesis,¹⁰ push-pull-acetylenes are much more selective. They do not show the side reactions observed with ynamines,¹¹ and the yields are not markedly influenced by the sequence of addition of compounds in the activation step or by excess of acetylene reagent.

A crucial point in peptide synthesis is racemization of the activated amino acid. Three different tests were made to evaluate the degree of racemization. Using the Anderson test-peptide¹² Cbz-Gly-Phe-Gly-OEt, no racemization could be detected when the peptide was prepared in dichloromethane, acetonitrile or tetrahydrofuran. This means racemization is below the detection limit of 1%. Benzylleucylglycine ethyl ester is used in the very sensitive Young test.¹³ In this test, designed to exaggerate racemization, we found 5% of racemate, when the solvent was dichloromethane. In the more polar solvent, dimethylformamide, this value rose to 12%. Therefore racemization is in the same range as that observed for the racemization-resistant azide procedure. The coupling of Cbz-L-aspartyl(O-t-Bu)-L-phenylalanine with valine methyl ester is reported to be very sensitive to racemization.¹⁴ The tripeptide was prepared as described above, and the crude product was hydrolyzed. GLC showed the presence of 2-3% D-phenylalanine. Again, in contrast to the ynamine procedure,¹⁵ racemization seems to be no problem when push-pull acetylenes are used.

So far, the only observable disadvantage of the reagent is the somewhat long reaction time for the coupling of the activated amino acids (or peptides) with the amine component. The increase in reaction time t_2 could be a limiting factor, if longer peptide fragments are to be linked.

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Appendix

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

1-(4-Chlorophenyl)-3-(4'-methyl-1-piperazinyl)-2-propyn-1-one: Piperazine, 1-[3-(4-chlorophenyl)-1-oxo-2-propynyl]-4-methyl- (9); (42122-11-2)

Benzyloxycarbonyl-L-alanyl-L-cysteine methyl ester: L-Cysteine, N-[N-[(phenylmethoxy)carbonyl]-L-alanyl]-, methyl ester (9); (34804-98-3)

Benzyloxycarbonyl-L-alanine: Alanine, N-carboxybenzyl ester, L- (8); L-Alanine, N-[(phenylmethoxy)carbonyl]- (9); (1142-20-7)

L-Cysteine methyl ester hydrochloride: Cysteine, methyl ester, hydrochloride, L- (8); L-Cysteine, methyl ester, hydrochloride (9); (18598-63-5)

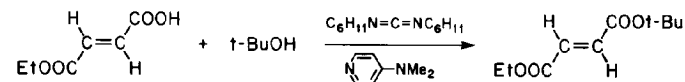
N-Methylmorpholine: Morpholine, 4-methyl- (8, 9); (109-02-4)

Benzyloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanyl-L-valine methyl ester: L-Valine, N-[N-[N-[(phenylmethoxy)carbonyl]-L- α -aspartyl]-L-phenylalanyl]-, 4-(1,1-dimethylethyl) 1-methyl ester (10); (57850-41-6)

Benzyloxycarbonyl-L-aspartyl-(tert-butyl ester)-L-phenylalanine: L-Phenylalanine, N-[N-[(phenylmethoxy)carbonyl]-L- α -aspartyl]-, 4-(1,1-dimethylethyl) ester (10); (32771-88-3)

L-Valine methyl ester hydrochloride: Valine, methyl ester, hydrochloride, L- (8); L-Valine, methyl ester, hydrochloride (9); (6306-52-1)

ESTERIFICATION OF CARBOXYLIC ACIDS WITH DICYCLOHEXYL-CARBODIIMIDE/4-DIMETHYLAMINOPYRIDINE: tert-BUTYL ETHYL FUMARATE ((E)-2-Butenedioic acid, ethyl 1,1-dimethylethyl ester)



Submitted by B. Neises and Wolfgang Steglich.¹

Checked by Cheryl Stubbs and Robert V. Stevens.

1. Procedure

Caution! Dicyclohexylcarbodiimide is a potent allergen and should be handled with gloves.

A 500-mL, one-necked flask, equipped with a calcium chloride drying tube is charged with 28.83 g (0.20 mol) of monoethyl fumarate (Note 1), 200 mL of dry dichloromethane (Note 2), 44.47 g (0.60 mol) of tert-butyl alcohol (Note 3) and 2.00 g (0.16 mol) of 4-dimethylaminopyridine (Note 4). The solution is stirred and cooled in an ice bath to 0°C while 45.59 g (0.22 mol) of dicyclohexylcarbodiimide (Note 5) is added over a 5-min period. After a further 5 min at 0°C the ice bath is removed and the dark brown reaction mixture is stirred for 3 hr at room temperature. Dicyclohexylurea which has precipitated is removed by filtration through a fritted Buchner funnel (G3), and the filtrate is washed with two 50-mL portions of 0.5 N hydrochloric acid

(Note 6) and two 50-mL portions of saturated sodium bicarbonate solution. During this procedure some additional dicyclohexylurea is precipitated, which is removed by filtration of both layers to facilitate their separation. The organic solution is dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. The concentrate is distilled under reduced pressure, affording, after a small forerun, 30.5-32.5 (76-81%) of tert-butyl ethyl fumarate, bp 105-107°C (12 mm) (Note 7).

2. Notes

1. Monoethyl fumarate was purchased from Ega-Chemie, D-7924 Steinheim, Germany.
2. Dichloromethane was freshly distilled over P_4O_{10} .
3. tert-Butyl alcohol was purchased from E. Merck, D-6100 Darmstadt, Germany, and used without further purification.
4. 4-Dimethylaminopyridine was obtained from Schering AG, D-1000 Berlin, Germany. 4-Pyrrolidinopyridine, which is equally well suited as a catalyst in this reaction may be purchased from Ega-Chemie, D-7924 Steinheim, Germany.
5. Dicyclohexylcarbodiimide was freshly distilled with a Kugelrohr apparatus (Büchi GKR-50), bp 135-140°C (0.5 mm). It may be added either in crystalline form or dissolved in 50 mL of dry dichloromethane.
6. For esters more sensitive to acids, the use of concentrated aqueous citric acid solution is advisable.
7. The proton magnetic resonance spectrum of the product in chloroform-d shows the following absorptions: δ 1.30 (t, 3 H, $J = 7.5$, CH_3CH_2), 1.50 (s, 9 H, $C(CH_3)_3$), 4.23 (q, 2 H, $J = 7.5$, CH_3CH_2), 6.77 (s, 2 H, $CH=CH$). tert-Butyl ethyl fumarate may be easily converted into ethyl fumarate by alkaline hydrolysis.

3. Discussion

This procedure offers a convenient method for the esterification of carboxylic acids with alcohols^{2,3,4} and thiols² under mild conditions. Its success depends on the high efficiency of 4-dialkylaminopyridines as nucleophilic catalysts in group transfer reactions.⁵ The esterification proceeds without the need of a preformed, activated carboxylic acid derivative, at room temperature, under nonacidic, mildly basic conditions. In addition to dichloromethane other aprotic solvents of comparable polarity such as diethyl ether, tetrahydrofuran, and acetonitrile can be used. The reaction can be applied to a wide variety of acids and alcohols, including polyols,^{2,4,6} α -hydroxycarboxylic acid esters,⁷ and even very acid labile alcohols like vitamin A.⁸ It has also been used for the esterification of urethane-protected α -amino acids with polymeric supports carrying hydroxy groups.⁹ In this case, however, some racemization of the amino acid is observed, because of 2-alkoxyoxazolin-5-one formation.¹⁰ Racemization can be decreased by shortening the coupling time¹⁰ or completely avoided by working with N-(p-nitrophenylsulfonyl)amino acids.¹¹

With increasing steric hindrance, the rate of esterification is decreased and the formation of N-acylureas may become a serious side reaction. This is indicated by the decrease in yield in the esterification of 2,5-cyclohexadiene-1-carboxylic acid with different alcohols: MeOH (95%), EtOH (84%), i-PrOH (75%), α -C₆H₁₁OH (65%), t-BuOH (65%).¹² Diminished acidity because of the influence of electron-donating substituents in aromatic carboxylic acids can also lead to low yields.

The dicyclohexylcarbodiimide/4-dialkylaminopyridine method is also well suited to the synthesis of a wide variety of thiol esters.^{2,13}

4-Dimethylaminopyridine also catalyzes the formation of esters and thiol esters in the reaction of mixed carboxylic anhydrides¹⁴ or 2,4,6-trinitrophenyl esters¹⁵ with alcohols and thiols. 1-Acyl-4-benzylidene-1,4-dihydropyridines have been introduced recently as promising reagents for the synthesis of sterically hindered esters.¹⁶ The current methods available for ester and thiol ester formation have been reviewed recently by Haslam.¹⁷

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Appendix

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

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

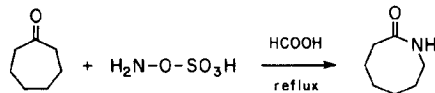
4-Dimethylaminopyridine: Pyridine, 4-(dimethylamino)- (8); 4-Pyridinamine, N,N-dimethyl- (9); (1122-58-3)

Monoethyl fumarate: Fumaric acid, monoethyl ester (8); 2-Butenedioic acid (E)-, monoethyl ester (9); (2459-05-4)

tert-Butyl alcohol (8); 2-Propanol, 2-methyl- (9); (75-65-0)

HEXAHYDRO-2-(1H)-AZOCINONE

(2(1H)-Azocinone, hexahydro-)



Submitted by George A. Olah and Alexander P. Fung.¹

Checked by David Varie and Edwin Vedejs.

1. Procedure

A 100-mL, three-necked flask is equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, and a reflux condenser connected to a nitrogen flow line. The system is dried with a heat gun while it is flushed with dry nitrogen. The reaction vessel is then cooled in a water bath while a light positive pressure of nitrogen is maintained. The flask is charged with hydroxylamine-O-sulfonic acid² (8.48 g, 0.075 mol) (Note 1) and 95-97% formic acid (45 mL) (Note 2). A solution of cycloheptanone (5.61 g, 0.05 mol) (Note 3) in 15 mL of 95-97% formic acid is added with stirring over a 3-min period. After addition is complete, the reaction mixture is heated under reflux for 3 hr and then cooled to room temperature. The reaction mixture is quenched with 75 mL of ice/water. The aqueous solution is slowly neutralized to pH ~ 7 with 6 N sodium hydroxide (Note 4) and extracted with three 100-mL portions of chloroform. The combined organic layers are dried with anhydrous

magnesium sulfate. After removal of the solvent on a rotary evaporator, the product hexahydroazocinone is purified by distillation to give 3.8-4.0 g (60-63%) bp 94-96°C/0.2 mm, (short path apparatus), lit⁴ bp 133-135°C/4 mm (Note 5).

2. Notes

1. The hydroxylamine-O-sulfonic acid used by the submitters was purchased from Ventron Corporation and used directly. However, it can be readily made in the laboratory.^{3,4}

2. Formic acid 95-97% was obtained from the Aldrich Chemical Company.

3. Commercial cycloheptanone (bp 179°C) obtained from MCB was used directly.

4. An external ice-salt bath is used.

5. The product exhibits the following spectra: ¹H NMR (CDCl₃) δ: 7.16 (br, 1 H, NH), 3.31 (m, 2 H, CH₂-N), 2.57 (m, 2 H, CH₂C=O), 2.40 (3 H, m), 1.6-1.8 (m, 6 H, CH₂); IR (cm⁻¹): 3270, 3200, 1650; GLC analysis: 20% SE 30, 60/80 on Chrom-W, 1/8" x 20' column, 180°C: one peak.

3. Discussion

The procedure described is a one-step conversion of cycloheptanone into hexahydro-2(1H)-azocinone. The method is general and is characterized by good yields, mild conditions, and easy preparation of the product in pure form from readily available starting materials. Several methods are described in the patent literature for simultaneous oximation of ketones and rearrangement to the corresponding oxime, including the use of hydroxylamine and sulfuric

acid^{6,7} or by employing primary nitroparaffins as a source of hydroxylamine.^{8,9} The present method has been shown¹⁰ to be applicable to a wide variety of lactams (C₅ ~ C₁₂). In the specific case of hexahydroazocinone, the yield from cycloheptanone (60-63%) appears lower than for the conventional two-step method,^{11,12} but the latter requires isolation of the intermediate oxime.

1. Institute of Hydrocarbon Chemistry and Department of Chemistry, University of Southern California, University Park, Los Angeles, California 90007.
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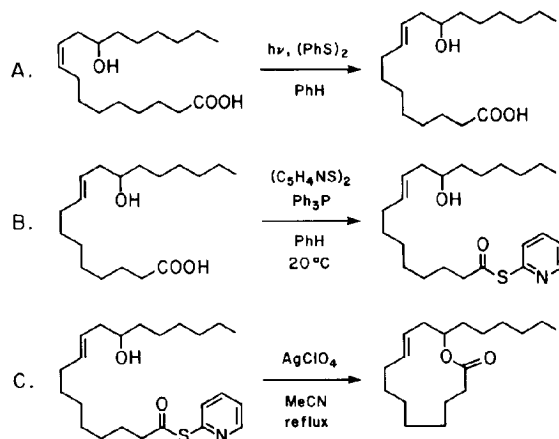
Appendix

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

Hexahydro-2(1H)-azocinone: 2(1H)-Azocinone, hexahydro- (9); (673-66-5)
 Hydroxylamine-O-sulfonic acid (8,9); (2950-43-8)
 Cycloheptanone (9); (502-42-1)
 Formic acid (8,9); (64-18-6)

RICINOLEIC ACID LACTONE

(9-Octadecenoic acid, 12-hydroxy-, [(+)-(R)-trans]-, lactone)



Submitted by Adolf Thalmann, Konrad Oertle, and Hans Gerlach.¹

Checked by James R. Pribish and Edwin Vedejs.

1. Procedure

A. *Ricinelaidic acid*. Ricinolic acid (Note 1) (39.75 g, 0.106 mol) and 586 mg (2 mol %) of diphenyl disulfide dissolved in 1000 mL of hexane are placed in a photochemical reactor (Note 2) and irradiated for 3 hr with a Philips HP(L) 250-watt medium pressure mercury lamp. After irradiation the solvent is removed under reduced pressure and the semisolid residue is recrystallized from 185 mL of hexane to yield 11.3 g of crude ricinelaidic acid, mp 39-43°C. The irradiation is repeated with the mother liquor under

the same conditions to yield, after removal of the solvent and recrystallization of the residue from 135 mL of hexane, an additional 7.2 g, mp 38-42°C; total yield of crude ricinelaidic acid is 18.5 g (58%). The product after recrystallization from 220 mL of hexane weighs 15.6 g (49%), mp 43-45°C and is suitable for the following step. Repeated recrystallization from hexane yields ricinelaidic acid with mp 51.0-51.5°C (Notes 3 and 4).

B. *Ricinelaidic acid S-(2-pyridyl)carbothioate*. In a dry, stoppered 10-mL flask containing a magnetic stirring bar are placed 360 mg (1.2 mmol) of ricinelaidic acid (see above), 308 mg (1.4 mmol) of 2,2'-dipyridyl disulfide (Note 5), 1 mL of benzene and 367 mg (1.4 mmol) of triphenylphosphine, and the mixture is stirred for 30 min. The resulting slurry is then dissolved in 55 mL of dry acetonitrile (Note 6).

C. *Ricinelaidic acid lactone*. Dry acetonitrile (100 mL), 3.5 mL of 1 M silver perchlorate in toluene (Notes 7 and 8), and a magnetic stirring bar are placed in a 500-mL flask equipped with a reflux condenser that carries a Hershberg dropping funnel. The solution is heated in an oil bath so that the boiling acetonitrile returns from the condenser at the rate of 5 to 10 drops per sec (Note 9). Then the acetonitrile solution of the ricinelaidic acid S-(2-pyridyl)carbothioate is added dropwise during 1 hr through the condenser to the magnetically stirred refluxing silver perchlorate solution (Note 9). The slightly turbid mixture is boiled for an additional 15 min and the solvent is removed under reduced pressure in a rotatory evaporator. The residue is diluted with 30 mL of 0.5 M potassium cyanide solution and the mixture containing suspended solids is extracted with three 50-mL portions of benzene. The benzene extracts are washed with 30 mL of water, dried with anhydrous magnesium sulfate, and filtered, and the solvent is removed under reduced pressure. Crude product is obtained as an oil (710 mg). It can be

purified by chromatography on 40 g of silica gel (Note 10) with benzene as eluant. Fractions of 10 mL are collected at 30-min intervals. Fractions 7 to 19 contain 283 to 296 mg (84-88%) of ricinelaidic acid lactone (Note 11).

2. Notes

1. Technical grade (80%) ricinolic acid was obtained from Fluka A.G. Buchs, Switzerland or from Tridom Chemicals, Inc. Saponification of methyl ricinoate² also gives suitable material.

2. The photochemical reactor used is quite similar to the one described in *Org. Synth., Collect. Vol. 5* 1973, 298.

3. The purity of the products has been checked by capillary gas liquid chromatography of the corresponding methyl ester obtained with ethereal diazomethane solution (Carlo Erba Fractovap 20 meter glass capillary coated with UCON HB at 160°C). Ricinelaidic acid, mp 49-50°C, contains 4%, that with mp 51.0-51.5°C, less than 1% of ricinolic acid. Submitters obtained higher yields (58%, mp 49-50°C), perhaps due to better quality starting material.

4. (+)-(R)-Ricinelaidic acid, mp 51.0-51.5°C, has an optical rotation of $[\alpha]_D +6.6^\circ$ (C₂H₅OH, c 10).

5. 2,2'-Dipyridyl disulfide obtained from Fluka A.G., Buchs, Switzerland, was recrystallized from hexane (30 mL/g) to yield a suitable product, mp 58-59°C.

6. Commercially available acetonitrile is distilled over phosphorus pentoxide.

7. Silver perchlorate monohydrate (9 g) (obtained from Fluka A.G.) is suspended in 110 mL of toluene together with a Teflon-coated magnetic stirring bar. The solution is magnetically stirred and heated in an oil bath until 70 mL of toluene has distilled.

8. The silver perchlorate solution may be substituted by 8.5 mL of 0.4 M silver trifluoromethanesulfonate (Fluka) in toluene.

9. This reflux rate is crucial for predilution of the carbothioate in the condenser. Lower reflux rates require an accordingly slower addition of the S-(2-pyridyl)carbothioate during 2 to 4 hr.

10. Silica gel 60 MERCK in a 2.5-cm diameter column was used.

11. The product distills at 110°C (0.01 mm) in a Kugelrohr distillation apparatus and has an optical rotation of $[\alpha]_D +42^\circ$ (CHCl₃, c 1).

3. Discussion

The silver-ion promoted lactonization of hydroxy-S-(2-pyridyl)-carbothioates was introduced by the submitters³ as a mild method for the synthesis of naturally occurring macrolides as, for example, nonactin⁴ and recifeolide⁵ from the corresponding hydroxy acids. If the method of Mukaiyama et al.⁶ is used for the formation of the S-(2-pyridyl)carbothioate no protection of the hydroxyl group is needed in this step. The cited examples show that silver-ion promoted lactonization can be used to effect ring closure of base-sensitive and unsaturated acid-sensitive hydroxy acids in good yield.

Similar methods to effect lactonization have been proposed by Corey et al.⁷ and Masamune et al.⁸ The first consists of prolonged heating of hydroxy-S-(2-pyridyl)carbothioates in boiling xylene; the second is the mercury trifluoroacetate-promoted cyclization of a hydroxy-S-tert-butyl carbothioate.

Ricinelaidic acid was selected for the submitted procedure because it has a moderately complex structure and can be prepared easily from commercially available technical grade ricinolic acid. This conversion represents an

example of the facile cis-trans interconversion of olefins⁹ caused by photochemically generated phenylthiyl radicals leading to the thermodynamic equilibrium.

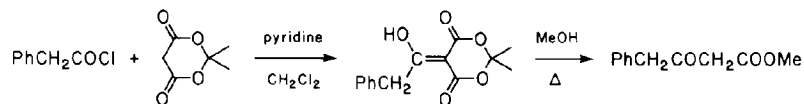
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Appendix

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

Ricinelaidic acid: 9-Octadecenoic acid, 12-hydroxy-, [R-(E)]- (9); (540-12-5)
 Ricinolic acid: 9-Octadecenoic acid, 12-hydroxy-, [R-(Z)]- (9); (141-22-0)
 Diphenyl disulfide: Phenyl disulfide (8); Disulfide, diphenyl (9); (882-33-7)
 2,2'-Dipyridyl disulfide: Pyridine, 2,2'-dithiodi- (8); Pyridine, 2,2'-dithiobis- (9); (2127-03-9)
 Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)
 Silver perchlorate: Perchloric acid, silver(1 +) salt, monohydrate (8,9); (14242-05-8)

**METHYL PHENYLACETYLACETATE FROM PHENYLACETYL
CHLORIDE AND MELDRUM'S ACID**
(Benzenebutanoic acid, β -oxo-, methyl ester)



Submitted by Y. Oikawa, T. Yoshioka, K. Sugano, and Osamu Yonemitsu.¹
Checked by Michael J. Taschner, Hans P. Märki, and Clayton H. Heathcock.

1. Procedure

Into a 300-mL, round-bottomed flask equipped with a dropping funnel and a magnetic stirrer is placed a solution of 23.75 g (0.165 mol) of recrystallized Meldrum's acid (Note 1) in 65 mL of anhydrous dichloromethane. The flask and its contents are cooled in an ice-bath, and 32.5 mL (0.40 mol) of anhydrous pyridine (Note 2) is added with stirring under an argon atmosphere over a period of 10 min. To the resulting colorless clear solution is added a solution of 25.0 g (0.16 mol) of freshly distilled phenylacetyl chloride (Note 3) in 50 mL of anhydrous dichloromethane over a period of 2 hr. After the addition is complete, the resulting orange, cloudy reaction mixture is stirred for 1 hr at 0°C, then for an additional 1 hr at room temperature. The reaction mixture is diluted with 35 mL of dichloromethane, and then poured into 100 mL of 2 N hydrochloric acid containing crushed ice. The organic phase is separated and the aqueous layer extracted twice with 25-mL portions

of dichloromethane. The organic phase and the extracts are combined, washed twice with 25-mL portions of 2 N hydrochloric acid and 30 mL of saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent is removed with a rotary evaporator to yield an acyl Meldrum's acid (Note 4) as a pale yellow solid.

The solid acyl Meldrum's acid, without purification, is refluxed in 250 mL of anhydrous methanol for 2.5 hr. The solvent is removed with a rotary evaporator, and the residual oil is distilled under reduced pressure to give 25.2 g (82%) of methyl phenylacetylacetate as a colorless liquid, bp 126-128°C/(0.6 mm).

2. Notes

1. Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione, is available from the Aldrich Chemical Company, Inc. It may also be prepared from malonic acid and acetone.² It is used in this preparation after recrystallization from acetone or from acetone-hexane. The checkers found that a final product of significantly lower purity is obtained if the Meldrum's acid is not recrystallized.

2. The checkers used pyridine that had been distilled from calcium hydride.

3. Phenylacetyl chloride is supplied by Wako Pure Industries, Ltd. (Japan) and the Aldrich Chemical Company, Inc. It is distilled before use, bp 95-96°C/(12 mm). The checkers found the distilled commercial material to be slightly pink. However, material of this quality gave a good yield of pure product.

4. The product, 2,2-dimethyl-5-phenylacetyl-1,3-dioxane-4,6-dione is isolated in its enol form in 97% yield. If desired, it may be further purified by recrystallization from ether-hexane to give pale yellow prisms, mp 96-97°C (dec). The checkers recrystallized the material from dichloromethane-hexane and obtained 65% yield of material, mp 94-96°C (dec) and 7%, mp 84-90°C. The ^1H NMR spectrum of this compound has absorptions at δ 1.65 (s, 6 H), 4.30 (s, 2 H), 7.20 (s, 5 H), and 15.0 (br s, 1 H).

3. Discussion

Because β -keto esters are among the most important intermediates in organic synthesis, many methods have been developed for their synthesis.³ However, it is still desirable to have a general and practical method for preparation of β -keto esters of the general type $\text{RCOCH}_2\text{CO}_2\text{R}'$, and thence by alkylation with alkyl halides compounds of the type $\text{RCOCHR}\text{'CO}_2\text{R}'$.⁴ The available synthetic methods can be classified broadly in three categories: those involving acetoacetic esters,⁵ those involving mixed malonic esters,⁶ and those involving malonic acid half esters.⁷ The procedure described herein⁸ may be classified as one of the malonic ester methods. The procedure consists of two simple steps and it utilizes readily-accessible starting materials. When the carboxylic acid chloride is not available, the carboxylic acid may be condensed with Meldrum's acid in the presence of a condensing agent such as ethyl phosphorocyanidate.⁹

Methanolysis or ethanolysis of an acyl Meldrum's acid is performed simply by refluxing in methanol or ethanol solution. The products are methyl or ethyl β -keto esters, and they can usually be purified by distillation. When a higher ester (such as benzyl, t-butyl, or trichloroethyl) is required, it is

easily prepared by refluxing the acyl Meldrum's acid in benzene containing about three equivalents of the appropriate alcohol.

Recently, Melillo et al., applied this Meldrum's acid method with some modifications to the synthesis of thienamycin. A carboxylic acid was treated with carbonyldiimidazole, followed by treatment with Meldrum's acid to give an acyl Meldrum's acid, which was converted to a β -keto p-nitrobenzyl ester by refluxing in acetonitrile containing p-nitrobenzyl alcohol.¹⁰

1. Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan.
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Appendix

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

Methyl phenylacetylacetate: Benzenebutanoic acid, β -oxo-methyl ester (9);
(37779-49-0)

Phenylacetyl chloride: Acetyl chloride, phenyl- (8); Benzeneacetyl chloride
(9); (103-80-0)

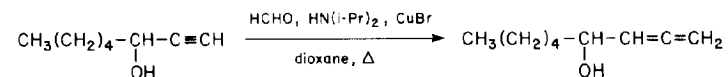
Meldrum's acid: Malonic acid, cyclic isopropylidene ester (8);

1,3-Dioxane-4,6-dione, 2,2-dimethyl- (9); (2033-24-1)

ONE-STEP HOMOLOGATION OF ACETYLENES TO ALLENES:

PREPARATION OF 4-HYDROXYNONA-1,2-DIENE

(1,2-Nonadien-4-ol)



Submitted by Pierre Crabbé, Bahman Nassim and Maria-Teresa Robert-Lopes.¹

Checked by Jeffrey S. Stults and Edwin Vedejs.

1. Procedure

In a 500-mL, three necked flask, equipped with a thermometer, stirrer, and a reflux condenser with drying tube, are placed 12.6 g (0.1 mol) of 1-octyn-3-ol, 154 mL of dioxane, 7.24 g (0.0504 mol) of cuprous bromide, 7.4 g of paraformaldehyde and 18.54 g (0.183 mol) of diisopropylamine (Note 1). The resulting mixture is gently refluxed and stirred for 2 hr, and then cooled to room temperature and filtered through a Celite plug. The dark brown filtrate is concentrated under vacuum (Rotavapor) to a gummy residue and then diluted with 50 mL of water followed by 100 mL of ether and acidified with 6 N hydrochloric acid to pH 2. The ether-water layers are decanted from any residue, the ether layer is separated, and the aqueous solution is extracted with ether (5 x 50 mL). The ether extracts are combined and washed with small portions of water until pH 6.5 is reached. The organic layer is then washed with saturated sodium chloride solution and dried over anhydrous MgSO_4 . After

removal of ether by distillation through a 20-cm Vigreux column (water aspirator vacuum) while heating on a waterbath, $\leq 40^{\circ}\text{C}$, the residual liquid is fractionated under reduced pressure through a 10-cm Vigreux column. The main fraction is collected at $41\text{--}42.5^{\circ}\text{C}$ (0.15 mm) to give 8.65 g of pure allene (Note 2), with additional fractions of a less pure material.

2. Notes

1. Cuprous bromide and 1-octyn-3-ol were used as supplied by the Aldrich Chemical Company, Inc. Dioxane was dried over sodium/benzophenone and distilled, and diisopropylamine was distilled from barium oxide.

2. The spectral properties of 4-hydroxynona-1,2-diene are as follows: IR (neat) cm^{-1} : 3500 (OH), 1960 ($\text{C}=\text{C}$), 850 ($=\text{CH}$), 2900-2850 (CH). ^1H NMR (CDCl_3) δ : 0.65-1.7 (m); 4.15 (1 H, m); 4.8 (2 H, d of d, $J = 2.6$ Hz); 5.22, (1 H, q, $J = 6$ Hz).

3. Discussion

Although allenes were characterized long ago as a distinct class of organic substances, it is only recently that they have received proper attention from chemists, in particular for their potential in organic synthesis.² A number of methods are known for the transformation of acetylenes into allenes,³ but few are known which allow the homologation of an acetylenic group into a propadiene functionality.

A general procedure for the homologation of acetylenic compounds into allenes is described. The reaction conditions are mild and appear to be general, so that they can be applied to plain acetylenic substances as well as

to acetylenic alcohols, ethers, and esters. This procedure is essentially a one-step reaction. As such, it is simpler and faster than the previously reported technique which involves the conversion of an acetylenic compound into the Mannich base, the formation of its quaternary ammonium salt and the reduction of this salt with lithium aluminum hydride.⁴ Of great advantage over previously available methodology are the mild conditions, as well as the clean and fast procedure, which make this a method of choice for an efficient conversion of acetylenes to allenes.⁵

1. Department of Chemistry, University of Missouri, Columbia, MO 65211.
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Appendix

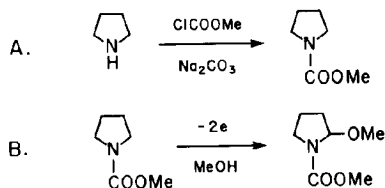
Chemical Abstracts Nomenclature (Collective Index Number): (Registry Number)

4-Hydroxynona-1,2-diene: 1,2-Nonadien-4-ol (10); (73229-28-4)
1-Octyn-3-ol (9); (818-72-4)

ANODIC OXIDATION OF N-CARBOMETHOXPYRROLIDINE:

2-METHOXY-N-CARBOMETHOXPYRROLIDINE

(1-Pyrrolidinecarboxylic acid, 2-methoxy-, methyl ester)



Submitted by T. Shono, Y. Matsumura, and K. Tsubata.¹

Checked by B. Schaer, G. Raymond, V. Toome, and Gabriel Saucy.

1. Procedure

A. *N*-Carbomethoxypyrrolidine. A 1-L, three-necked, round-bottomed flask is equipped with a 200-mL pressure-equalizing dropping funnel, a Graham condenser protected by a calcium chloride tube, and a mechanical stirrer. The flask is charged with 200 g (1.89 mol) of sodium carbonate (Note 1), 400 mL of methylene chloride (Note 2), and 71 g (1 mol) of pyrrolidine (Note 3). The dropping funnel is charged with 103 g (1.1 mol) of methyl chlorocarbonate (Note 3) which is added with stirring over a 2-hr period at a rate which sustains a gentle reflux. After the addition of methyl chlorocarbonate is completed, the reaction mixture is stirred overnight at room temperature. The

white precipitate is filtered with suction through a coarse Buchner funnel and washed three times with 100 mL of methylene chloride. The filtrate is concentrated on a vacuum rotary evaporator at a bath temperature of 30°C. The crude oily product is distilled under reduced pressure through a Claisen flask to yield 119-121 g (92-94%) of *N*-carbomethoxypyrrolidine, bp 64°C/1.3 mm.

B. *2-Methoxy-N-carbomethoxypyrrolidine*. A solution of *N*-carbomethoxypyrrolidine (12.7 g, 0.098 mol) and tetraethylammonium *p*-toluenesulfonate (0.83 g, 0.0027 mol) (Note 3) in 83 mL of methanol (Note 2) is added into an undivided jacketed cell (Note 4) equipped with two graphite-rod anodes and two graphite-rod cathodes, (Note 5) a thermometer, an exit tube for venting purposes, and a magnetic stirring bar. The carbon rods (0.6 cm in diameter, immersed 5.5 cm into the solution, resulting in a working electrode surface of 21.3 cm² and a current density of 46.9 mA/cm²) are spaced 4.5 mm apart. The anode rods and the two cathode rods are connected with #22 copper wire as shown in Figure 1. During the electrolysis (Note 6), the temperature of the reaction mixture is maintained at 10-15°C (Note 7) by cooling with tap water. After 2.34 F/mole of electricity (1A, 6 hr; the voltage between the anode and cathode was 19-24 V for the example in Figure 1) has been passed through, (Note 8) the current is stopped and the solvent is removed under reduced pressure. The residue is dissolved in 120 mL of methylene chloride and washed with aqueous NaCl (20 mL). The aqueous NaCl wash is re-extracted with methylene chloride (2 x 30 mL). The methylene chloride phases are combined and dried over magnesium sulfate. The solvent is evaporated and the residue is distilled, employing a Vigreux column, 5 cm, and an oil bath at 80-90°C (Note 9). The yield is 12.3-13.0 g (78-83%), bp 48-55°C/0.2-0.5 mm (Note 10).

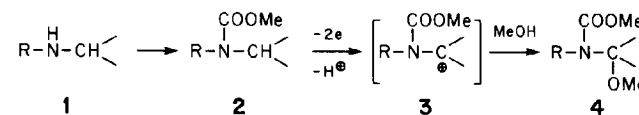
2. Notes

1. Sodium carbonate, anhydrous powder, supplied by J. T. Baker Chemical Company, is used directly.
2. Methylene chloride was purchased from Fisher Scientific Co.
3. Pyrrolidine was purchased from the Aldrich Chemical Company, and used without further purification.
4. The cell is shown in Figure 1.
5. The electrodes were purchased from Princeton Applied Research (PAR); Spectroscopic grade, Lot #174/78. This grade is not necessarily the best type of graphite for electrochemical purposes, but it was the only one immediately available. The submitters used graphite plates, purchased from Tokai Carbon Company, Inc., as electrodes, but they note that these are not the only electrode material usable in this reaction.
6. Princeton Applied Research (PAR) Potentiostat-Galvanostat, Model 173/179 was used.
7. According to the submitters the temperature should be kept below 50°C; otherwise lower yields are observed.
8. According to the submitters, if more than 2.2-2.5 F/mole of electricity is passed N-carbomethoxy-2,5-dimethoxypyrrolidine forms. The by-product can be separated by distillation (bp 64-65°C/1.0 mm).
9. An oil bath temperature higher than 100°C results in the formation of unsaturated carbamate formed by the elimination of methanol from the methoxylated carbamate. Accordingly, in the anodic methoxylation of carbamates having high boiling points, the product must be purified by column chromatography in order to avoid formation of the unsaturated carbamates.

10. The product has the following spectral properties: IR (liquid film) cm^{-1} : 2940, 2880, 1685, 1440, 1370, 1185, 1080, 950, 825, 770; ^1H NMR (CCl_4) δ : 1.48-2.21 (m, 4 H, CH_2 at C_3 and C_4 of pyrrolidine ring), 3.25 (s, 3 H, methoxy CH_3), 3.08-3.52 (m, 2 H, CH_2 at C_5 of pyrrolidine ring), 3.64 (s, 3 H, ester CH_3), 5.06 (m, 1 H, CH at C_2 of pyrrolidine ring).

3. Discussion

This procedure describes anodic α -methoxylation of carbamates (2) which are derived from primary and secondary amines (1).^{2,3}



The intermediate cations (3) are trapped with methanol to yield α -methoxycarbamates, 4, which are sufficiently stable to be stored for a long period. Table I shows other examples of anodic synthesis of 4.

The high regioselectivity in the methoxylation of unsymmetrical carbamates is remarkable (see 2-pipecoline carbamate and N-carbomethoxyproline methyl ester in Table I). The methoxylation always takes place in the order of $\text{CH}_3- > >\text{CH}_2 > -\text{CH}$.

α -Methoxycarbamates (4) are useful intermediates in organic syntheses, since treatment of 4 with Lewis acids or Brønsted acids regenerates 3 which can be trapped with a variety of nucleophiles. Thus, physiologically active compounds such as alkaloids,³ amino acids,⁴ nitrogen-containing phosphorus compounds,⁵ and pyridoxine⁶ can be synthesized using 4 as key starting compounds. Figure 2 summarizes the transformations.³⁻⁷

Figure 1

Electrolysis Cell for Methoxylation

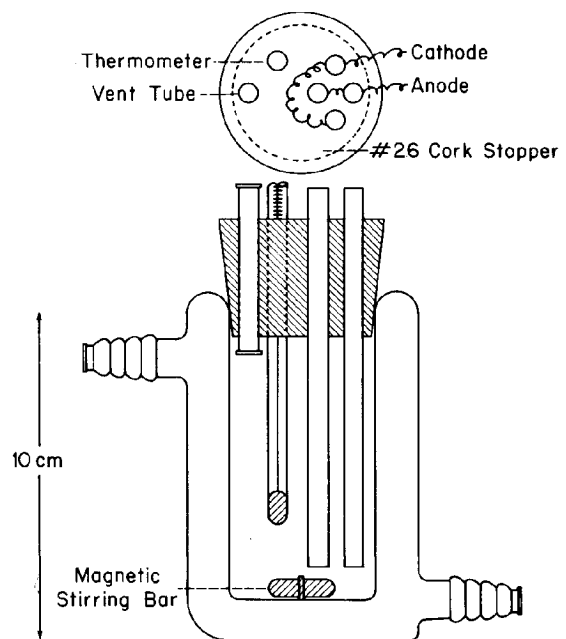


Figure 2

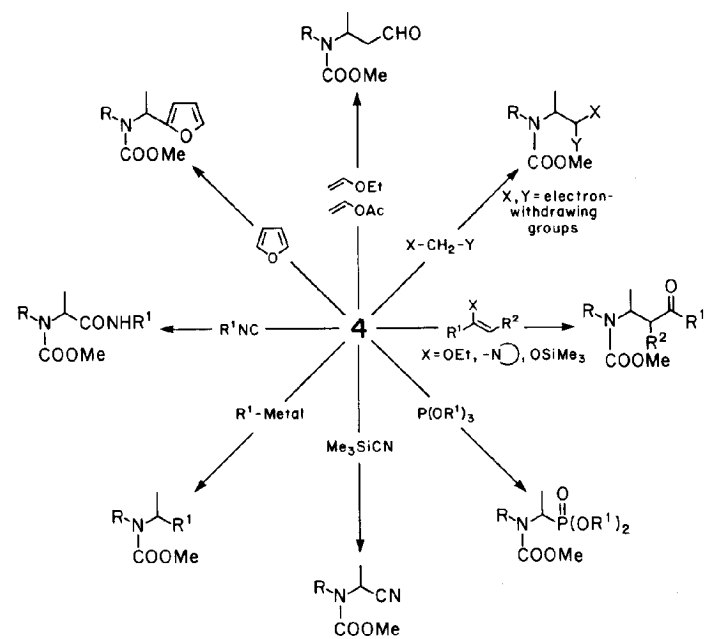




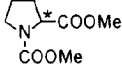
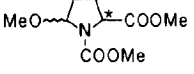

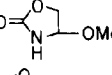



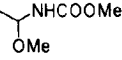
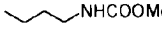
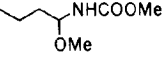
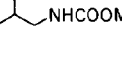
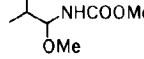
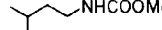
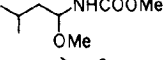


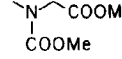
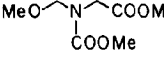


TABLE I
ANODIC SYNTHESIS OF α -METHOXYCARBAMATES

Carbamate	Electricity Passed F/mole	α -Methoxycarbamate	% Yield
	2.7		86
	2.6		69
	2.5		87
	3.0		89
	2.7		55
	4.85		83
	10.2		88
	6.0		70
	7.1		77
	2.1		72
	3.2		94

1. Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Sakyo, Kyoto 606, Japan.
2. Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264.
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Appendix

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

N-Carbomethoxypyrrolidine: 1-Pyrrolidinecarboxylic acid, methyl ester (9); (56475-80-0)

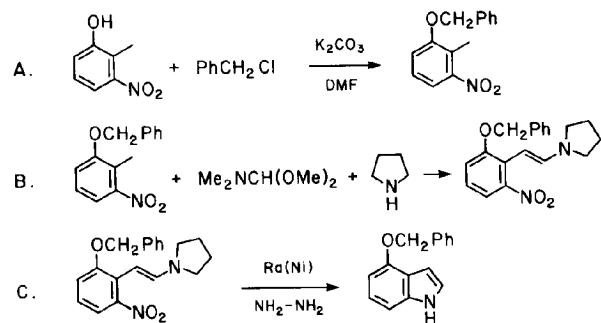
2-Methoxy-N-carbomethoxypyrrolidine: 1-Pyrrolidinecarboxylic acid, 2-methoxy-, methyl ester (9); (56475-88-8)

Pyrrolidine (8,9); (123-75-1)

Methyl chlorocarbonate: Formic acid, chloro-, methyl ester (8); Carbonochloridic acid, methyl ester (9); (79-22-1)

Tetraethylammonium p-toluenesulfonate: Ammonium, tetraethyl-, p-toluenesulfonate (8); Ethanaminium, N,N,N-triethyl-, salt with 4-methylbenzenesulfonic acid (1:1) (9); (733-44-8)

**INDOLES FROM 2-METHYLNITROBENZENES BY CONDENSATION WITH
FORMAMIDE ACETALS FOLLOWED BY REDUCTION: 4-BENZYLOXYINDOLE
(1 H-Indole, 4-(phenylmethoxy)-)**



Submitted by Andrew D. Batcho¹ and Willy Leimgruber.²

Checked by David J. Wustrow and Andrew S. Kende.

1. Procedure

A. 6-Benzyloxy-2-nitrotoluene. A stirred mixture of 124.7 g (0.81 mol) of 2-methyl-3-nitrophenol (Note 1), 113.2 g (0.90 mol) of benzyl chloride, 112.2 g (0.81 mol) of anhydrous potassium carbonate, and 800 mL of dimethylformamide (DMF) is heated at 90°C for 3 hr. Most of the DMF is removed on a rotary evaporator (20 mm) and the oily residue is poured into 400 mL of 1 N sodium hydroxide and extracted with ether (3 x 800 mL). The combined extracts are dried (Na₂SO₄), filtered, and evaporated to give 203.5 g

of yellowish solid. Recrystallization from 1 L of methanol cooled to 0°C affords 177.6 (90%) of 6-benzyloxy-2-nitrotoluene as pale yellow crystals, mp 61-63°C³ (Note 2).

B. (E)-6-Benzyloxy-2-nitro-β-pyrrolidinostyrene. To a solution of 175.4 g (0.72 mol) of 6-benzyloxy-2-nitrotoluene in 400 mL of DMF are added 102.5 g (0.84 mol) of N,N-dimethylformamide dimethyl acetal (Note 3) and 59.8 g (0.84 mol) of pyrrolidine. The solution is heated at reflux (110°C) for 3 hr (Note 4) under nitrogen and allowed to cool to room temperature. The volatile components are removed on a rotary evaporator, and the red residue (Note 5) is dissolved in 200 mL of methylene chloride and 1.60 L of methanol. The solution is concentrated to a volume of about 1.40 L on the steam bath and then is cooled to 5°C. Filtration and washing of the filter cake with 200 mL of cold methanol affords 209.8 g of red crystals, mp 87-89°C (Note 6). The mother liquors are evaporated, and the residue is recrystallized from 50 mL of methanol (5°C) to give an additional 12.30 g of red solid, mp 81-83°C (Note 7). Thus the total yield is 222.1 g (95%) of a 15:1 mixture of (E)-6-benzyloxy-2-nitro-β-pyrrolidinostyrene (Note 8) and (E)-6-benzyloxy-β-dimethylamino-2-nitrostyrene.

C. 4-Benzyloxyindole. To a stirred solution of 162.2 g (0.50 mol) of (E)-6-benzyloxy-2-nitro-β-pyrrolidinostyrene (Note 9) in 1 L of THF and 1 L of methanol at 30°C under nitrogen is added 10 mL of Raney nickel (Note 10) followed by 44 mL (0.75 mol) of 85% hydrazine hydrate. Vigorous gas evolution is observed. The red color turns to dark brown within 10 min and the reaction temperature rises to 46°C. An additional 44 mL of 85% hydrazine hydrate is added after 30 min and again 1 hr later. The temperature is maintained between 45-50°C with a water bath during the reaction and for 2 hr after the last addition. The mixture is cooled to room temperature and the catalyst is

removed by filtration through a bed of Celite (Note 11) and is washed several times with methylene chloride. The filtrate is evaporated and the residue dried by evaporating with 500 mL of toluene. The reddish residue (118.5 g), dissolved in ca. 1 L of toluene-cyclohexane (1:1), is applied to a column of 500 g of silica gel (70-230 mesh, Merck) prepared in the same solvent. Elution with 6.0 L of toluene-cyclohexane (1:1) followed by 3 L of toluene-cyclohexane (1:2) affords 108.3 g of white solid which is crystallized from 150 mL of toluene and 480 mL of cyclohexane (Note 12). A total of 107.3 g (96% yield) of 4-benzyloxyindole (Note 13) is obtained in three crops as white prisms, mp 60-62°C (Note 14).

2. Notes

1. 2-Methyl-3-nitrophenol was obtained from Aldrich Chemical Company, Inc.

2. The ^1H NMR spectrum is as follows δ : 7.35 (m, 5 H), 7.13 (m, 3 H), 5.10 (s, 2 H), 2.42 (s, 3 H).

3. N,N-Dimethylformamide dimethyl acetal was prepared according to a procedure of Bredereck.⁴ N,N-Dimethylformamide diethyl acetal can also be used. Both the dimethyl and the diethyl acetal are commercially available from Aldrich Chemical Company, Inc.

4. The reaction was followed by TLC on silica gel plates developed with ether-pet. ether (1:1).

5. Since it contained non-volatile N-formylpyrrolidine, direct reduction of the crude material was not attempted.

6. This crop contained 5% 6-benzyloxy- β -dimethylamino-2-nitrostyrene (by NMR). Pure 6-benzyloxy-2-nitro- β -pyrrolidinostyrene melts at 91.5-92.5°C.

7. This crop contained 15% 6-benzyloxy- β -dimethylamino-2-nitrostyrene (by NMR).

8. The ^1H NMR spectrum is as follows δ : 7.75 (d, 1 H, $J = 12.2$), 7.25 (m, 6 H), 6.91 (dd, 2 H, $J = 9$), 5.20 (d, 1 H, $J = 12.2$), 5.03 (s, 2 H), 3.08 (m, 4 H), 1.8 (m, 4 H).

9. This compound may contain varying amounts of 6-benzyloxy- β -dimethylamino-2-nitrostyrene.

10. Raney nickel is commercially available as type #28 from the Davison Chemical Division of W. R. Grace and Co.

11. The catalyst is pyrophoric and should not be sucked dry.

12. The material tenaciously holds hydrocarbons, such as pentane, hexane, and petroleum ether, which cannot be removed even under high vacuum. The solvated crystals show hydrocarbon protons in the NMR and exhibit a broad melting point. However, we have found that cyclohexane is not retained in the crystals.

13. The ^1H NMR spectrum is as follows δ : 7.9 (br s, 1 H), 7.32 (m, 5 H), 6.95 (m, 3 H), 6.65 (m, 2 H).

14. We could not reproduce the reported⁵ mp 72-74°C (toluene). The material has the proper microanalysis and is pure by NMR and TLC.

3. Discussion

Through the years, widespread interest in the synthesis of natural products and their analogs bearing the oxygenated indole nucleus has led to the development of several routes to protected hydroxylated indoles. However, 4-benzyloxyindole was first prepared relatively recently in modest overall yield by the Reissert method, which involves condensation of 6-benzyloxy-2-

nitrotoluene with ethyl oxalate, reductive cyclization to the indole-2-carboxylate, hydrolysis to the acid, and decarboxylation.⁵

Although a variety of synthetic methods have been used to prepare indoles^{6,7} many of these lack generality and are somewhat restrictive since they employ conditions, e.g., acid or strongly basic cyclizations or thermal decarboxylations, which are too harsh for labile substituents. This efficient, two-step procedure^{8,9} illustrates a general, simple, and convenient process for preparing a variety of indoles substituted in the carbocyclic ring, as can be seen in Table I. Since many of these examples served to determine the scope of this method, the yields in most cases have not been optimized. In many cases, the starting materials are readily available or can be easily prepared.

As can be seen in Table I, variation of the substituent has a profound effect on the rate of reaction of the o-nitrotoluene derivative with dimethylformamide acetals, but has little effect on the yields, which are often almost quantitative. As can be predicted, electron withdrawing groups accelerate the reaction. To shorten the somewhat lengthy reaction times which are often necessary when electron-donating substituents are present, more reactive aminomethylenating reagents such as pyrrolidine (or piperidine) acetals,⁸ amins,¹⁰ or trisaminomethanes¹¹ can be employed. Alternatively, as described above, simply adding pyrrolidine to the reaction mixture also generates in situ a very effective aminomethylenating reagent.^{12,13} Thus, for example, in the case of 6-benzyloxy-2-nitrotoluene, the reaction with N,N-dimethylformamide dimethyl acetal requires 51 hr versus 3 hr when pyrrolidine is added. Pyrrolidine undergoes exchange reactions with N,N-dimethylformamide acetals to produce an equilibrium mixture of formylpyrrolidine acetal and the mixed pyrrolidine dimethylamine amina (alkoxydimethylaminopyrrolidinomethane)

as well as other trisaminomethane species.¹⁴ (In cases where pyrrolidine reacts with the aromatic substrate, addition of the substrate can be delayed until pyrrolidine exchange is complete.) This mixture of reagents gives rise to condensation products - pyrrolidine enamines which contain 5-10% of the corresponding N,N-dimethylenamines.

The enamine intermediates are usually crystalline, red compounds which can be stored at room temperature for reasonable periods. In cases where the enamines are non-crystalline, it is recommended that the crude product be used directly in the next step, since purification is, in such cases, not practical. Although the more volatile derivatives can be distilled under high vacuum, this entails some risk because of their thermal instability. Moreover, the enamines are not stable to silica gel (TLC or column) chromatography.

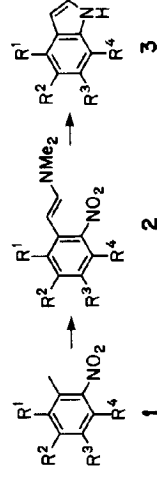
Conversion of the intermediate nitroenamine into the indole requires selective reduction of the nitro group. Catalytic hydrogenation results in spontaneous formation of the indole and is generally the mildest and most convenient method of reduction. Although selectivity does vary with the substituent on the aromatic ring, it is generally highly in favor of the nitro group. However, scale-up requires access to large autoclaves or special equipment. To avoid hydrogenolysis of benzyl or chloro functions, Raney nickel is the catalyst of choice. Excellent yields have been obtained using hydrazine and the appropriate catalyst¹⁵ as, in essence, a hydrogenation process which does not require an autoclave or special equipment and can be easily carried out in the laboratory.

Alternative methods of reduction have also been used: sodium dithionite,¹⁶ iron in acetic acid,¹⁷ stannous chloride,¹⁷ and titanium trichloride.¹⁸

This method has been applied to the preparation of polycyclic indoles^{12,19} and azaindoles^{19,20,21} as well.

TABLE I

INDOLES FROM 2-METHYLNITROBENZENES BY CONDENSATION WITH N,N-DIMETHYLFORMAMIDE ACETALS AND REDUCTION



Interme-

Substituents	diates 2				Purified		Indoles 3		References	
	R ₁	R ₂	R ₃	R ₄	mp or bp/mm	Reaction Time	Yield % (Procedure) ^a	mp or bp/mm		Yield % (Procedure) ^b
----	----	---	---	---	125°/0.03	22 hr	97 (M,E)	52.5 - 53.5°	80 (A)	8,9
OCH ₂ Ph	----	---	---	---	67 - 68°	51 hr	90 (M)	60 - 62°	70 (B)	12
----	OCH ₂ Ph	---	---	---	98 - 99°	29 hr	78 (E)	103 - 105°	45 (B) [64] ^c	8,9,12
----	----	---	OCH ₂ Ph	---	108.5-110°	41 hr	97 (M)	118 - 120°	75 (B) ⁱ	12
----	OCH ₂ Ph	OCH ₂ Ph	---	---	99.5-101°	48 hr	86 (M)	112 - 113°	54 (B) ^j	8,9
----	OCH ₂ Ph	CH ₃	---	---	113 - 134°	31 hr	87 (M)	82 - 83°	84 (B)	12
----	OCH ₃	---	---	---	68.5-70°	16 hr	92 (M)	56.5 - 57.5°	83 (A)	8,9
----	----	OCH ₃	---	---	152°/0.06	70 hr	64 (E)	88 - 90°	63 (A) [62] ^c	8,9,12
----	OCH ₃	OCH ₃	---	---	125 - 126°	48 hr	68 (M)	154 - 155°	28 (A)	8,9
----	OCH ₃	---	---	CH ₃	100 - 101°	8 hr	54 (M)	100 - 110°/0.15	66 (A)	22
----	OCH ₂ O	---	---	---	114 - 116°	18 hr	72 (E)	110 - 111°	50 (A) [52] ^c	8,9,12
Cl	---	---	---	---	111°/0.03	6 hr	89 (E)	90°/0.04	63 (B)	8,9
----	Cl	---	---	---	81.5-82.5°	7 hr	88 (E)	71 - 72°	78 (B)	8,9
----	---	Cl	---	---	44 - 46°	24 hr	57 (M)	86.5 - 88°	52 (B) [75] ^c	8,9,12
----	---	NH ₂ ^d	---	---	173 - 174°	2 hr	82 (E) ^f	77.5 - 78.5°	43 (A)	8,9,12
CN	---	---	---	---	66 - 68°	3 hr	93 (M)	116 - 117°	67 (C)	17
----	---	---	CN	---	134 - 137.5°	2.5 hr	86 (E)	128 - 129°	65 (A)	8,9
----	F	---	---	---	57.5 - 59°	3.5 hr	92 (E)	46.5 - 47°	51 (B)	8,9
----	---	---	F	---	46 - 47°	22 hr	63 (M)	74 - 75°	80 (B) [80] ^c	8,12
CH ₃	---	---	---	---	108°/0.05	24 hr	70 (E)	82°/0.4	57 (A)	8,9
----	---	---	CH ₃	---	41.5 - 43.5°	37 hr	83 (M)	29 - 30.5°	83 (A)	23
----	---	---	---	CH ₃	76 - 76.5°	46 hr	40 (E)	83 - 84°	48 (A)	8,9
----	---	---	CH(CH ₃) ₂	---	138-140°/0.06	42 hr	84 (E)	40 - 41°	51 (A)	8,9
----	---	---	CH(OCH ₃) ₂	---	67 - 68°	8 hr	55 (E)	62 - 63.5°	31 (A)	8,9
COOCH ₃	---	---	---	---	120-130°/0.2	6 hr	86 (M)	63°	82 (A) [63] ^c	17,24
COOC ₂ H ₅	---	---	---	---	(oil)	5 days	93 (E)	67 - 69°	38 (D)	17

----	COOC ₂ H ₅ ^e	----	55 - 56.5°	4.5 hr	70(E)	95 - 96°	39(A)	8,9
----	----	----	COOCH ₃	9 hr	88(M)	46 - 48°	72(A) ^g	12
C1	OCH ₃	----	----	overnight	--(M)	109 - 111°	(B) [59] ^c	25
----	OCH ₃	C1	140 - 141°	overnight	78(M)	126 - 128°	46(B) [45] ^c	25
----	OCH ₃	F	116 - 117°	overnight	64(M)	73 - 74°	54(B)	25
----	----	Br	----	31 hr	--(M)	93°	37(B) ^h	26

^a(M) = N,N-Dimethylformamide dimethyl acetal; (E) = N,N-dimethylformamide diethyl acetal.

^bA = Catalytic hydrogenation in benzene using palladium on charcoal; B = catalytic hydrogenation in benzene using Raney

nickel; C = iron in acetic acid; D = stannous chloride.

yield in brackets represents overall yield without purification of intermediate 2.

^dR₃ = NO₂ in compounds 1 and 2.

^eR₂ = COOH in compound 1.

^fNo solvent was used.

^gMethanol was the solvent.

^hEthanol was the solvent.

ⁱ(M) + pyrrolidine gave a mixture (10:1) of pyrrolidine enamine, mp 108-110° (MeOH), and N,N-dimethylenamine (5 hr reflux, 97% yield) which, on reduction (Raney nickel-hydrazine), gave the indole (93% yield).

^j(M) + pyrrolidine gave a mixture (9:1) of pyrrolidine enamine and N,N-dimethylenamine (5 hr reflux, 95% yield) which, on reduction (Raney nickel-hydrazine), gave the indole (89% yield).

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Appendix

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

4-Benzyloxyindole: Indole, 4-benzyloxy- (8); 1 H-Indole, 4-(phenylmethoxy)-
(9); (20289-26-3)

6-Benzyloxy-2-nitrotoluene: Benzene, 2-methyl-1-nitro-3-(phenylmethoxy)- (9);
(20876-37-3)

2-Methyl-3-nitrophenol: o-Cresol, 3-nitro- (8); Phenol, 2-methyl-3-nitro-
(9); (5460-31-1)

Benzyl chloride: Toluene, α -chloro- (8); Benzene, (chloromethyl)- (9);
(100-44-7)

N,N-Dimethylformamide dimethyl acetal: Trimethylamine, 1,1-dimethoxy- (8);
Methanamine, 1,1-dimethoxy-N,N-dimethyl- (9); (4637-24-5)

Pyrrolidine (8,9); (123-75-1)

(E)-6-Benzyloxy- β -dimethylamino-2-nitrostyrene: Ethenamine, N,N-dimethyl-2-
[2-nitro-6-(phenylmethoxy)phenyl]-, (E)- (10); (78283-29-1)

TETRAMETHYLBIPHOSPHINE DISULFIDE

WARNING

It has been reported^{1,2} that serious explosions have occurred during the preparation of tetramethylbiphosphine disulfide by the method described in *Inorganic Syntheses*.³ No such incidents have been reported in the synthesis of the compound published in this series,⁴ but the two procedures are sufficiently similar that caution is indicated. The following precautions are strongly urged:

- (1) The phosphorus trichloride sulfide (PSCl_3) should be distilled before use.
- (2) The reaction vessel should be cooled with an ice-salt bath (rather than an acetone-dry ice bath as specified in the published procedure) during the addition of the PSCl_3 solution to the Grignard reagent. The reaction temperature should be monitored carefully. If it falls below -5° , the addition should be stopped and the reaction mixture cautiously rewarmed to 0 – 5° before addition is resumed.
- (3) The reaction apparatus should be shielded throughout the addition of the PSCl_3 solution and the subsequent warming of the reaction mixture.

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Unchecked Procedures

Accepted for checking during the period September 1, 1983 through September 1, 1984. An asterisk (*) indicates that the procedure has been subsequently checked.

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Address requests to:

Professor Jeremiah P. Freeman
Organic Syntheses, Inc.
Department of Chemistry
University of Notre Dame
Notre Dame, Indiana 46556

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- 2292* Di-*tert*-Butyl Methylene malonate
P. Ballsteros and B. W. Roberts, Department of Chemistry,
University of Pennsylvania, Philadelphia, PA 19104
- 2293* 1,3-Dimethyl-3-methoxy-4-phenylazetidinone
L. S. Hegedus, M. A. McGuire, and L. M. Schultze, Department of
Chemistry, Colorado State University, Fort Collins, CO 80523
- 2294R* 1,3-Dimethylimidazole-2-thione
B. L. Benac, E. M. Burgess and A. J. Arduengo, III, School of
Chemical Sciences, 270 Roger Adams Laboratory, Box 57, 1209 W.
California Street, Urbana, IL 61801
- 2296 Ring Expansion and Cleavage of Succinoin Derivatives:
Spiro[4.5]decane-1,4-dione and Ethyl 4-Cyclohexyl-4-oxobutanoate
E. Nakamura and I. Kuwajima, Department of Chemistry, Tokyo
Institute of Technology, Meguro, Tokyo 152, Japan
- 2297 Trimethylsilylacetylene
A. B. Holmes and C. N. Sporikou, University Chemical Laboratory,
Lensfield Road, Cambridge, CB2 1EW, United Kingdom
- 2298 1,4-Bis(Trimethylsilyl)buta-1,3-diyne
G. E. Jones, D. A. Kendrick and A. B. Holmes, University Chemical
Laboratory, Lensfield Road, Cambridge, CB2 1EW, United Kingdom
- 2300 Ambient Temperature Ullmann Reaction: 4,5,4',5'-Tetramethoxy-1,1'-
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Department of Chemistry, Yale University, New Haven, CT 06511
- 2302* 2-Pentyl-3-methyl-cyclopent-2-en-1-one (DIHYDROJASMONE)
H. Stetter, H. Kuhlmann and W. Haese, Institut für Organische Chemie
der Rheinisch-Westfälischen Technischen Hochschule Aachen, West
Germany
- 2303* α -Hydroxylation of a Ketone Using o-Iodosylbenzoic Acid: α -
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R. M. Moriarty, K.-C. Hou and S. K. Arora, Department of Chemistry,
University of Illinois at Chicago, Chicago, IL 60680
- 2304 (R)-(+)- and (S)-(-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
(BINAP)
H. Takaya and R. Noyori, Department of Chemistry, Faculty of
Science, Nagoya University, Chikusa-ku, Nagoya 464, Japan
- 2305R* 6-Bromo-6-deoxy Hexose Derivatives by Ring-Opening of Benzylidene
Acetals with N-Bromosuccinimide
S. Hanessian, Department of Chemistry, University of Montreal, C.P.
6210, Succursale A., Montreal (Que.), Canada H3C 3V1
- 2306* 4-Nitroindole
J. Bergman and P. Sand, Department of Chemistry, Royal Institute of
Technology, S-100 44, Stockholm, Sweden
- 2307 (R)-(+)-Citronellal via Asymmetric Isomerization of N,N-
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Japan
- 2308 Telomerization of Isoprene with Dialkylamine: N,N-Diethylnerylamine
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Synthetic Chemistry, Faculty of Engineering, Shizuoka University,
Johoku, Hamamatsu 432, Japan
- 2309 Addition of Dialkylamine to Myrcene: N,N-Diethylgeranylamine
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Shizuoka University, Johoku, Hamamatsu 432, Japan
- 2310 (-)- α -Pinene by Isomerization of (-)- β -Pinene
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- 2311 Chiral 1,3-Oxathiane from (+)-Pulegone [Hexahydro-4,4,7-trimethyl-
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- 2315 Alkoxy carbonylation of Propargyl Chloride: Methyl 4-Chloro-2-
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- 2316 Dibenzothiophene-4-thiol
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- 2318 Synthesis of Macrocyclic Sulfides Using Cesium Thiolates
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- 2320 Methylenation of Carbonyl Compounds: (+)-3-Methylene-cis-p-menthane
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- 2330 Preparation of Optically Pure (-)-8-Phenylmenthol
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- 2334 t-Octyl-t-butylamine
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CUMULATIVE SUBJECT INDEX
FOR VOLUMES 60, 61, 62, AND 63

This index comprises subject matter for Volumes **60**, **61**, **62**, and **63** only. For subjects in previous volumes, see the cumulative indices in Volume **59**, which covers Volumes **55** through **59**, and Volume **54**, which covers Volumes **50** through **54**, and either the indices in Collective Volumes I through V or the single volume entitled *Organic Syntheses, Collective Volumes I, II, III, IV, V, Cumulative Indices*, edited by R. L. Shriner and R. H. Shriner.

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, accompanied by its registry number in brackets. 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, reactions, or methods appearing in the title of the preparation.

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