One-Pot Synthesis of Enantiomerically Pure (Methylenecyclopropyl)carbinol: A Key Intermediate to the Synthesis of the Causative Agent of Jamaican Vomiting Sickness

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Enantiomerically pure (*R*)- and (*S*)-(methylenecyclopropyl)carbinol was synthesized in a one-pot operation by the reaction of methylenetriphenylphosphane with (*R*)- and (*S*)-epichlorohydrin followed by the addition of paraformaldehyde (23 and 18% yield). The yields of this compound were improved by the following two-step reaction. The reaction of methylenetriphenylphosphorane with epichlorohydrin afforded the corresponding (3,4-epoxybutyl)triphenylphosphonium iodide in 83% yield. This phosphonium salt further reacted with NaH followed by the addition of paraformaldehyde to give enantiomerically pure (methylenecyclopropyl)carbinol in 71% yield. The present method affords the short-step synthesis of (methylenecyclopropyl)carbinol compared with the known methods.

Numerous studies of the reactions of Wittig reagents with epoxides have been published during the last thirty years.[1] Recently, we reported the general preparation of enantiomerically pure (3-hydroxyalkyl)triphenylphosphonium salts[2] and Liu *et al.*[3] and Baldwin *et al.*[4] reported the total synthesis of (methylenecyclopropyl)acetic acid (1), which is known to be the cause of Jamaican Vomiting Sickness. The key intermediate in the synthesis of 1 is enantiomerically pure methylenecyclopropylcarbinol (2). In this paper, we report a one-pot synthesis of enantiomerically pure (*R*)-(+)- and (*S*)-(−)-2 from methylenetriphenylphosphorane (3).

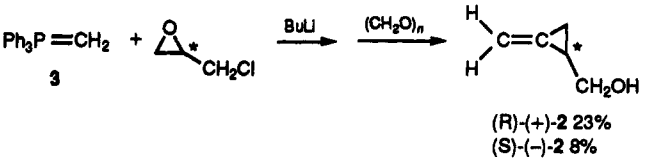
Results and Discussion

Methylenetriphenylphosphorane reacted with optically active (*R*)-(−)- and (*S*)-(+)-epichlorohydrin, followed by the addition of butyllithium and paraformaldehyde, to give the corresponding enantiomerically pure (*R*)-(+)- and (*S*)-(−)-2 in 23% and 18% yields, respectively (Scheme I).

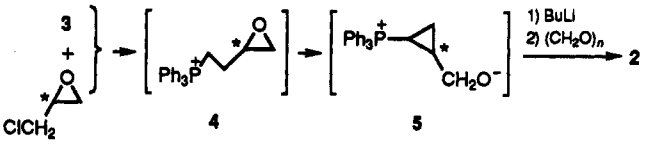
The enantiomeric excess of 2 was confirmed by the ^{1}H NMR spectra of the corresponding (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetates.

We suggest that the reaction proceeds as follows. Methylenetriphenylphosphorane reacts with epichlorohydrin to give (3,4-epoxybutyl)triphenylphosphonium salt (4), which results in the formation of [2-(hydroxymethyl)-cyclopropyl]triphenylphosphonium betaine (5) after the addition of butyllithium. This betaine further reacts with paraformaldehyde to give 2 (Scheme II).

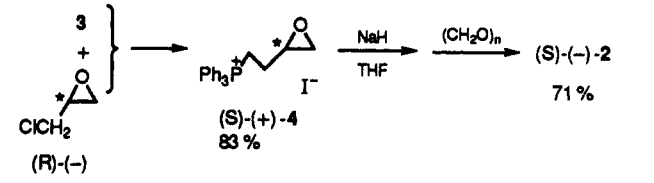
Scheme I



Scheme II



Scheme III



Several attempts to improve the yield of this reaction have led us to believe that excess base and lithium halide prevent the reaction. To avoid this interference, we isolated the (3,4-epoxybutyl)triphenylphosphonium iodide (4). The reaction of 4 with an equivalent amount of sodium hydride would produce the corresponding salt free phosphonium betaine (5), which would react with paraformaldehyde to give the corresponding 2. As shown in Scheme III, the yield of 2 was improved to 71% by this strategy.

Thus, the carbinol 2 was obtained by a two-step sequence starting from 1 and epichlorohydin, in 59% overall yield.

Turcant and Le Corre reported the synthesis of bicyclic oxaphosphorane 6 by the reaction of methylenetriphenylphosphorane with epichlorohydrin.[5] Since optically

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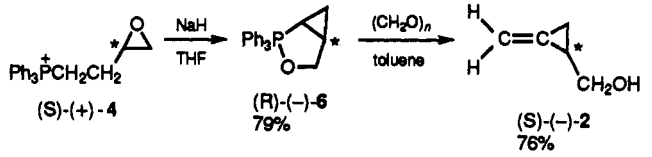
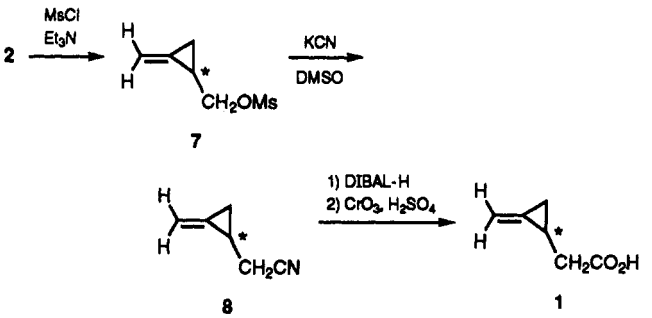
Scheme IV



Scheme V



pure epichlorohydrin is commercially available, we attempted the isolation of enantiomerically pure **6**. Treatment of **4** with sodium hydride afforded oxaphosphorane **6** in 79% yield. The reaction of **6** with paraformaldehyde in refluxing toluene afforded (methylenecyclopropyl)-carbinol (**2**) in 76% yield (Scheme IV).

The reported synthesis of enantiomerically pure **2** required six steps starting from enantiomerically pure glicidol.[3] Baldwin reported the synthesis of racemic **1** from 3-butenol in five steps and then obtained enantiomerically pure **1** by optical resolution of racemic **1**.[4] The present method has advantages over these synthetic methods of **1**: carbinol **2** was prepared through one- or two-step operations from commercially-available enantiomerically pure epichlorohydrin; optical resolution is not required.

Enantiomerically pure **1** was easily prepared from **2** by a method described by Liu *et al.*[3] as shown in Scheme V.

Thus, the present method provides a short synthesis of enantiomerically pure **1** starting from commercially available enantiomerically pure epichlorohydrin.

Experimental Section

Melting points are uncorrected. The NMR spectra were recorded on a JEOL-GSX 400-MHz spectrometer.

Enantiomerically pure epichlorohydrin was purchased from Daiso Co Ltd: (*R*)-(−)-epichlorohydrin, $[\alpha]_D$ −34.0°, (*S*)-(+)-epichlorohydrin, $[\alpha]_D$ +34.0°.

One-Pot Operation of the Reaction of Methylenetriphenylphosphorane with (*R*)-(−)-Epichlorohydrin Followed by the Addition of Paraformaldehyde. To a solution of **3** (10 mmol) derived from methyltriphenylphosphonium iodide (4.04 g, 10 mmol) and butyllithium (1.6 M in hexane, 7.0 mL, 11.5 mmol) in hexane was added a solution of (*R*)-(−)-epichlorohydrin (0.96 g, 10.4 mmol) in THF (10 mL) at −70 °C. After bein stirred for 3 h, the reaction mixture was warmed up to −30 °C. Butyllithium (1.6 M in hexane, 14.0 mL, 23 mmol) in hexane was added to this solution at this temperature and the solution stirred for 1 h. Paraformaldehyde (0.90 g, 30 mmol) was added to this solution in one portion at this temperature. The reaction mixture was warmed up to room temperature and poured into water. The resulting suspension was extracted three times with ether (30 mL), dried over magnesium sulfate, and evaporated to give a pale orange oil. This oil was chromatographed over silica gel by elution with dichloromethane to afford the crude carbinol. The crude carbinol was purified by Kugelrohr distillation to afford the enantiomerically pure (*S*)-(−)-**2** (0.17 g 1.8 mmol, 18%): bp 125–138 °C (lit.[3] bp 138 °C); $[\alpha]_D$ −5.1° (*c* 2.20, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.95–0.99 (m, 1H, C*H*H), 1.33 (tt, *J* = 8.9, 2.1 Hz, 1H, C*H*H), 1.76–1.84 (m, 1H, CH), 3.47–3.53 (m, 1H, C*H*HOH), 3.60–3.66 (m, 1H, CH*H*OH), 5.44 (d, *J* = 1.5 Hz, CHH=); 5.47–5.49 (m, 1H, C*H*H=); ^{13}C NMR ($CDCl_3$) δ 8.07 (CH_2), 18.02 (CH), 65.41 (CH_2OH), 104.23 (CH_2=), 132.85 (C=). These spectral data were identical with the reported values.[3]

(*R*)-(+)-**2** was obtained in a similar manner by using methyltriphenylphosphonium iodide (4.0 g, 11 mmol), butyllithium (1.6 M in hexane, 7 mL, 11.5 mmol), (*S*)-(+)-epichlorohydrin (0.90 g, 10 mmol), butyllithium (1.6 M in hexane, 14 mL, 23 mmol), and paraformaldehyde (0.90 g, 30 mmol). (*S*)-(+)-**2** (0.19 g, 2.3 mmol, 23%): $[\alpha]_D$ +5.1° (c 2.0, CHCl3.)

Preparation of (3,4-Epoxybutyl)triphenylphosphonium Iodide (4). To a THF solution (30 mL) of **3** (20.0 mmol) derived from methyltriphenylphosphonium iodide (8.08 g, 20.0 mmol) and butyllithium (1.6 M in hexane, 14 mL) was added a solution of (*R*)-(−)-epichlorohydrin (2.00 g, 21.6 mmol) in THF (10 mL) with vigorous stirring. After being stirred for 1 h, the reaction mixture was washed with water and extracted three times with dichloromethane (30 mL). The combined extracts were dried over magnesium sulfate and evaporated to give pale yellow crystals. Recrystallization from methanol–ether afforded pure crystals of (*S*)-(+)-(3,4-epoxybutyl)triphenylphosphonium iodide (**4**) (7.60 g, 16.5 mmol, 83%): mp 202–203 °C; $[\alpha]_D$ +6.7° (*c* 2.00, MeOH); ^1H NMR ($CDCl_3$) δ 1.71–1.82 (m, 1H, C*H*H), 2.13–2.24 (m, 1H, CH*H*), 2.69–2.71 (m, 1H, OC*H*H), 2.76–2.78 (m, 1H, OCH*H*), 3.41–3.45 (m, 1H, CH), 3.67–3.78 (m, 1H, PC*H*H), 3.93–4.05 (m, 1H, PCHH), 7.70–7.86 (m, 15H, Ar); ^{13}C NMR ($CDCl_3$) δ 19.48 (d, *J* = 51.5 Hz, PCH_2), 25.37 (CH_2), 47.43 (CH_2), 50.90 (d, *J* = 18.3 Hz, CH), 117.03, 117.89, 130.38, 130.51, 133.44, 133.55, 135.08 (Ar). Anal. Found: C, 57.60; H, 4.83. Calcd for $C_{22}H_{22}OPI$: C, 57.41; H, 4.82.

(*R*)-(−)-**4** was obtained in a similar manner by using methyltriphenylphosphonium iodide (4.04 g, 10.0 mmol), butyllithium (6.3 mL, 1.6 M in hexane, 10.1 mmol), and (*S*)-(+)-epichlorohydrin (0.93 g, 10.0 mmol). (*R*)-(−)-**4** (3.68 g, 8.0 mmol, 80%): mp 192–193 °C; $[\alpha]_D$ −6.3° (*c* 2.00, MeOH).

Reaction of 4 with Sodium Hydride Followed by the Addition of Paraformaldehyde. To a suspension of sodium hydride (1.2 g, 60% mineral oil dispersion, 30 mmol) in THF (30 mL) was added a solution of (*S*)-(+)-**4** (11.9 g, 26 mmol) in THF (20 mL). After being fluxed for 5 h, the resulting suspension was evaporated and extracted three times with ether (30 mL). The combined extracts were evaporated and dissolved in toluene (50 mL), and paraformaldehyde (3.0 g, 100 mmol) was added. After bing refluxed for 1 h, the resulting pale yellow solution was distilled to give the corresponding (*S*)-(−)-**2** (1.55 g, 18.5 mmol, 71%): bp 135–138 °C (lit[3] bp 138 °C).

Preparation of Oxaphosphorane 6. A solution of (*S*)-(+)-**4** (5.96 g, 13.0 mmol) in THF (100 mL) was added to a suspension of sodium hydride (0.60 g, 60% mineral oil dispersion, 15.0 mmol) in THF (5 mL) at room temperature and refluxed for 4 h. The resulting suspension was filtered and evaporated to give pale yellow crystals, which were extracted three times with ether (30 mL). The combined extracts were evaporated and the residue was recrystallized from dichloromethane–hexane to afford the pure crystals of (*R*)-(−)-**6** (4.10 g, 10.3 mmol, 79%): mp 125–126 °C; $[\alpha]_D$ −142.7° (*c* 2.00, $CHCl_3$); ^1H NMR (C_6D_6) δ 0.69–0.77 (m, 1H, C*H*H), 1.01–1.12 (m, 1H, PCH), 1.20–1.33 (m, 2H, CH, CH*H*), 3.08 (dd, *J* = 8.9 Hz, 3.0 Hz, 1H, OC*H*H), 3.58 (dd, *J* = 15.3 Hz, 8.9 Hz, 1H, OCH*H*), 6.98–7.09 (m, 9H, Ar), 7.55–7.64 (m, 6H, Ar); ^{13}C NMR (C_6D_6) δ 7.07 (d, *J* = 5.5 Hz, CH_2), 12.25 (d, *J* = 139.7 Hz, PCH), 14.87 (d, *J* = 3.7 Hz, CH), 58.21 (OCH_2), 127.50, 127.61, 131.78, 131.88 (Ar). Anal. Found: C, 79.44; H, 6.58. Calcd for $C_{22}H_{21}OP$: C, 79.50; H, 6.37.

(*S*)-(+)-**6** was obtained in a similar manner by using (*R*)-(−)-**4** (4.60 g, 10.0 mmol) and sodium hydride (0.44 g, 60 % mineral oil dispersion, 11 mmol). (*S*)-(+)-**6** (1.76 g, 5.3 mmol, 53%): mp 126–127 °C; $[\alpha]_D$ +141.4° (*c* 2.00, $CHCl_3$).

Preparation of 2 from 6. To a solution of (*R*)-(−)-**6** (7.26 g, 21.8 mmol) in toluene (25 mL) was added paraformaldehyde (3.0 g, 100.0 mmol) in one portion. After being refluxed for 1 h, the reaction mixture was distilled to give a colorless oil of (*S*)-(−)-**2** (1.39 g, 16.5 mmol, 76%): $[\alpha]_D$ −5.1° (*c* 2.00, $CHCl_3$).

(*R*)-(+)-**2** was obtained in a similar manner by using (*S*)-(+)-**6** (1.66 g, 5.0 mmol) and paraformaldehyde (0.45 g, 15.0 mmol). (*R*)-(+)-**2** (0.30 g, 3.5 mmol, 70%): $[\alpha]_D$ +5.1° (*c* 2.20, $CHCl_3$).

Preparation of 7. To a solution of (*S*)-(−)-**2** (0.77 g, 9.1 mmol) in dichloromethane (50 mL) was added triethylamine (0.93 g, 9.2 mmol). After the solution was stirred for 30 min, methanesulfonyl chloride (1.05 g, 9.2 mmol) was added via syringe. After 1 h of stirring at room temperature, water was added to this suspension and the mixture was extracted with dichloromethane (20 mL × 3). The combined extracts were washed with 1 N HCl and saturated $NaHCO_3$, dried over magnesium sulfate, and filtered. The solution was evaporated to give the desired (*S*)-(−)-**7** (1.47 g, 9.1 mmol, 99%): $[\alpha]_D$ −33.6° (*c* 2.00, $CHCl_3$). Spectral data of (*S*)-(−)-**7** were identical with those reported.[5]

Preparation of 8. To a suspension of 18-crown-6 (3.60 g, 13.6 mmol) and potassium cyanide (0.89 g, 13.6 mmol) in anhydrous dimethyl sulfoxide (10 mL) was added dropwise a solution of (*S*)-(−)-**7** (1.47 g, 9.1 mmol) in dimethyl sulfoxide (5 mL). After 14 h of stirring, the reaction mixture was poured into water and extracted with dichloromethane (20 mL × 3). The combined extracts were washed with 1 N HCl, aqueous $NaHCO_3$, and water. The solution was dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The resulting oil was chromatographed over silica gel by elution with dichloromethane to give (*R*)-(−)-**8** (0.42 g, 4.5 mmol, 49%): $[\alpha]_D$ −27.3° (*c* 1.50, $CHCl_3$). Spectral data of (*R*)-(−)-**8** were identical with those reported.[5] Since compound **8** is very volatile, careful distillation is required.

Preparation of 1. (*R*)-(−)-Acetic acid **1** was obtained from **8** by the method described by Liu *et al.*[5] $[\alpha]_D$ −8.10° (*c* 0.50, $CHCl_3$), lit.[5] $[\alpha]_D$ +8.60° (*S* form).

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