New Convenient Access to Optically Active Methylidenecyclopropylcarbinols

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The recent publication of two papers concerning the synthesis of methylidenecyclopropylmethanol[1] and methylidenecyclopropylcarbinols[2] prompted us to report our work in this area.

Alkylidenecyclopropylcarbinols **3** and particularly the first term (R = H) are very important intermediates in synthesis. Some years ago, we published a short synthesis of this family,[3] starting from oxaphospholane **2** (Scheme 1).

In a recent paper,[1] Okuma *et al.* applied our method to the preparation of homochiral methylidenecyclopropylmethanol using optically active epichlorohydrin. They mentioned the first part of our work (access to **2**) but apparently overlooked the second (access to **3**).

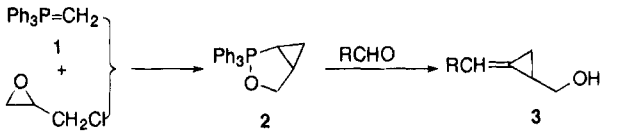
We have already used optically active epichlorohydrin in the synthesis of asymmetric phosphines via oxaphospholane **2**.[4] In a program for the multigram synthesis of optically active alkylidenecyclopropylcarbinols, we have investigated other more economical routes to compounds **3**.

We present in this paper another alternative using a simple resolution of oxaphospholane **2** by tartaric acid (TA) (Scheme 2). Reaction of oxaphospholane **2** with 1 equiv of tartaric acid gave phosphonium salt **4**. Three recrystallizations of this salt in ethanol afforded diastereomerically pure (−)-**4**: $[\alpha]^{20}_D$ −71.92° (*c* 1, MeOH). The other diastereomer could be obtained by recrystallization of the residue in acetonitrile: $[\alpha]^{20}_D$ +71.42° (*c* 1, MeOH). Yields of optically pure products are, respectively, 65% and 64%. Conversion of phosphonium salt **4** to oxaphospholane was realized in a two-phase system by action of aqueous NaOH on a dichloromethane solution of **4**. The absolute configuration of oxaphospholane **2** was obtained by comparison with the product resulting from the condensation of optically active epichlorohydrin with methylenetriphenylphosphorane.

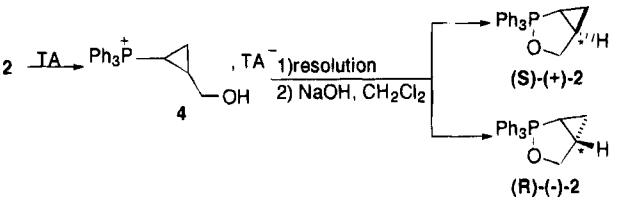
Access to methylidenecyclopropylmethanol from oxaphospholane **2** and paraformaldehyde is difficult. Without solvent, yields are variable, and in an usual solvent like toluene, separation is not easy because of the great volatility of the alcohol (bp = 136 °C). We found that the best procedure was to realize the condensation in a high boiling point solvent such as sulfolane (bp = 284 °C). Thus, optically pure methylidenecyclopropylmethanol **3a** could be obtained directly (Scheme 3). The optical purity of both enantiomers (>95%) was checked by ^{19}F NMR of their corresponding Mosher's esters.

Oxidation of alcohol **3a** under the standard Swern reaction conditions permits the first synthesis of the C_5 aldehyde **5**. This unstable compound was allowed to react with Grignard reagents to afford a new route to methylidenecyclopropylcarbinols **6** and **7**. Assignment of the relative stereochemistry of the generated asymmetric center was achieved by comparison with literature data.[2,5]

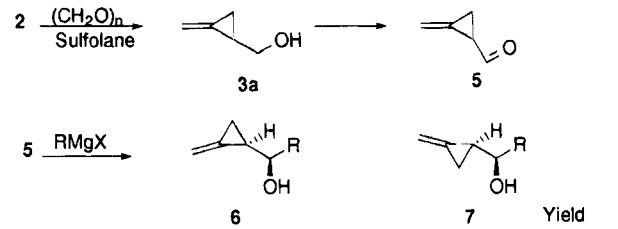
Scheme 1



Scheme 2



Scheme 3



6a	R = n-butyl	1.2	1	58%
6b	R = c-hexyl	6	1	42%
6c	R = phenyl	>50	<1	53%

Experimental Section

Preparation of 2,2-Dihydro-2,2,2-triphenyl-3,4-methano-1,2-oxaphospholane (2). To a refluxing toluene solution (360 mL) of **1** derived from methyltriphenylphosphonium iodide (80.8 g, 0.20 mol) and potassiun *tert*-butoxide (22.44 g, 0.20 mol) was added a solution of epichlorohydrin (9.25 g, 0.10 mol) in toluene (20 mL) with vigorous mechanical stirring. After being stirred for 30 min, the resulting suspension was cooled and filtered, and solvents were evaporated. Recrystallization from dry acetonitrile afforded pure crystals of **2** (27.88 g, 0.084 mol, 84%): mp 127–128 °C; ^1H NMR (300 MHz, C_6D_6) δ 0.70–0.73 (m, 1H,), 1.01–1.13 (m, 1H), 1.12–1.30 (m, 2H), 3.08 (dd, *J* = 8.8, 2.9 Hz, 1H), 3.57 (dd, *J* = 8.8, 15.2 Hz, 1H), 6.99–7.08 (m, 9H), and 7.54–7.61 ppm (m, 6H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 6.86 (d, *J* = 5.5 Hz), 12.05 (d, *J* = 138.4 Hz,), 14.66 (d, *J* = 3.34 Hz), 58.02, 127.29–127.82 and 131.58–131.69 ppm. Anal. Calcd for $C_{22}H_{21}OP$: C, 79.49; H, 6.37; O, 4.81. Found: C, 79.49; H, 6.30; O, 4.68.

Preparation and Resolution of Phosphonium Salt 4. To a toluene solution (220 mL) of racemic **2** (33.20 g, 0.10 mol) was slowly added with vigorous stirring a solution of *L*-tartaric acid (15.00 g, 0.10 mol) in dry acetone (250 mL) . The precipitate was filtered and dried under reduced pressure (47.70 g, 0.099 mol, 99%). Phosphonium salt **4** was recrystallized three times in ethanol (8 mL per g) to afford pure diastereomer **4** as white crystals (15.50 g, 0.032 mol, 65%); $[\alpha]^{20}_D$ −71.92° (*c* 1, MeOH). Anal. Calcd for $C_{26}H_{27}O_7P$: C, 64.72; H, 5.64; O, 23.21. Found: C, 64.56; H, 5.51; O, 23.06.

The other diastereomer **4** was obtained in a similar manner after evaporation of the mother liquor and three recrystalliza-

(1) Okuma, K.; Tanaka, Y.; Yoshihra, K.; Ezaki, A.; Koda, G.; Otha, H.; Hara, K.; Kashimura, S. *J. Org. Chem.* **1993**, 58, 5915–5917.
(2) Lautens, M.; Delanghe P. H. M. *J. Org. Chem.* **1993**, 58, 5037–5039.
(3) Turcant, A.; Le Corre, M. *Tetrahedron Lett.* **1976**, 1277–1280.
(4) Hercouet, A.; Le Corre, M. *Phosphorus, Sulfur Silicon* **1993**, 77, 212.
(5) Maurin, R.; Bertrand, M. *Bull. Soc. Chim. Fr.* **1970**, 2261.

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tions in acetonitrile (7 mL per g) (15.42 g, 0.032 mol, 64%): $[\alpha]^{20}_D$ +71.42° (*c* 1, MeOH).

Conversion of Salt 4 to Oxaphospholane 2. To a suspension of optically active **4** (48.20 g, 0.10 mol) in dichloromethane (200mL) was added a 2 N solution of sodium hydroxide (150 mL). After being stirred for 15 min the organic layer was decanted, dried over magnesium sulfate, and evaporated to give crystals of optically pure oxaphospholane **2**. (*R*)-(−)-**2** (31.20 g, 0.094 mol, 94%): $[\alpha]_D$ −131.9° (*c* 1, $CHCl_3$). (*S*)-(+)-**2** (30.85 g, 0.093 mol, 93%): $[\alpha]^{20}_D$ +129.5° (*c* 1, $CHCl_3$).

Preparation of Methylenecyclopropylcarbinol 3 (R = H). The reaction mixture of (*R*)-(−)-**2** (33.20 g, 0.10 mol) and paraformaldehyde (6.00 g, 0.20 mol) in sulfolane (18 mL) was heated to 100 °C for 15 min. Alcohol **3** was distilled out under reduced pressure (bp 45−65 °C/2 mmHg). A second distillation afforded optically pure (*S*)-(−)-**3** (6.88 g, 0.82 mol, 82%): bp 136 °C; $[\alpha]^{20}_D$ −6.98° (*c* 2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.93−0.99 (m, 1H), 1.28−1.35 (m, 1H), 1.75−1.80 (m, 1H), 2.19−2.29 (m, 1H), 3.41−3.48 (m, 1H), 3.59−3.67 (m, 1H), 5.30-5.47 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.14, 17.98, 65.34, 104.15, and 133.02 ppm. Anal. Calcd for C_5H_8O: C, 71.39; H, 9.58. Found: C, 71.12; H, 9.37.

Enantiomerically pure (*R*)-(+)-**3** was obtained in a similar manner from (*S*)-(+)-**2** (6.55 g, 0.78 mol,78%): bp 136 °C; $[\alpha]^{20}_D$ +6.75° (*c* 2, $CHCl_3$).

Preparation of Aldehyde 5. To a solution of oxalyl chloride (1.5 mL, 17.0 mmol) in CH_2Cl_2 (20 mL) at −60 °C was successively added a solution of DMSO (2.5 mL, 35.0 mmol) in CH_2Cl_2 (5 mL) and after 2 min of stirring, a solution of **3** (0.84 g, 10.0 mmol) in CH_2Cl_2 (5 mL) was added within 5 min. Stirring was continued for 15 min and triethylamine (7 mL, 50.0 mmol) was added dropwise, and the reaction mixture was allowed to warm to room temperature. A 1 N hydrochloric acid solution (55 mL) saturated with sodium chloride was added and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined and dried over magnesium sulfate. After most of the CH_2Cl_2 was removed at atmospheric pressure, *tert*-butyl methyl ether (40 mL) was added to precipitate the ammonium salts. After filtration and removal of the solvent, this unstable product could be used for the following steps or distilled, with some decompositon (0.53 g, 6.5 mmol, 65%): bp 84−86 °C/200 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68−1.71 (m, 2H), 2.24−2.29 (m, 1H), 5.49−5.54 (m, 2H), 8.50 (d, J = 6.1 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.61, 27.91, 107.30, 127.57, and 195.78 ppm.

General Procedure for Preparation of Secondary Alcohols 6. To a stirred solution of racemic aldehyde **5** (0.41 g, 5.0 mmol) in dry Et_2O (10 mL) was added the Grignard reagent (6 mmol) in dry Et_2O (10 mL). Stirring was continued for 2 h at room temperature, the reaction mixture was poured in saturated ammonium chloride solution (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were combined, dried over magnesium sulfate, and evaporated to give an oil. This oil was chromatographed over silica gel.

(*R*)-[(1*S*)-(Methylidenecyclopropyl)]-*n*-pentanol (or (*S*)-[(1*R*)]) (6a) (major diastereomer): R_f = 0.67 on silica gel (Et_2O:toluene 4:1) (0.22 g, 1.6 mmol, 32%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85−1.56 (m, 12H), 2.28 (br s, 1H), 3.09 (dd, J = 5.6 and 6.9 Hz, 1H), 5.35−5.38 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 7.63, 14.04, 22.60, 22.72, 27.73, 36.83, 74.33, 104.04, and 133.02 ppm. Anal. Calcd for $C_9H_{16}O$: C, 77.08; H, 11.50. Found: C, 77.12; H, 11.67.

(*R*)-[(1*R*)-(Methylidenecyclopropyl)]-*n*-pentanol (or (*S*)-[(1*S*)]) (7a) (minor diastereomer): R_f = 0.77 on silica gel (Et_2O:toluene 4:1) (0.18 g, 1.3 mmol, 26%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.80−1.59 (m, 13H), 3.21 (dd, J = 5.2 and 7.2 Hz, 1H), 5.41−5.50 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 7.57, 14.10, 21.85, 22.79, 27.85, 36.87, 74.34, 104.02, and 133.35 ppm.

(*R*)-[(1*S*)-(Methylidenecyclopropyl)]cyclohexylmethanol (or (*S*)-[(1*R*)]) (6b) (major diastereomer): R_f = 0.37 on silica gel (petroleum ether:Et_2O 3:2) (0.30 g, 1.8 mmol, 36%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.81−1.86 (m, 15H), 2.76−2.81 (m, 1H), 5.33−5.38 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 7.29, 20.84, 26.17, 26.31, 26.56, 28.92, 29.00, 44.12, 78.75, 104.31, and 133.41 ppm.

(*R*)-[(1*R*)-(Methylidenecyclopropyl)]cyclohexylmethanol (or (*S*)-[(1*S*)]) (7b) (minor diastereomer): R_f = 0.46 on silica gel (petroleum ether:Et_2O 3:2) (0.05 g, 0.3 mmol, 6%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90−1.94 (m, 15H), 2.92−2.96 (m, 1H), 5.43−5.51 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 8.20, 19.64, 26.22, 26.33, 26.56, 28.67, 29.02, 44.49, 78.60, 104.28, and 133.28 ppm.

(*R*)-[(1*S*)-(Methylidenecyclopropyl)]phenylmethanol (or (*S*)-[(1*R*)]) (6c). NMR spectra (^1H, ^{13}C) show the presence of only one diastereomer: R_f = 0.48 on silica gel (petroleum ether: Et_2O 3:2) (0.55 g, 3.4 mmol, 53%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.93−0.99 (m, 1H), 1.08−1.14 (m, 1H), 1.29−1.37 (m, 1H), 1.89−1.94 (m, 1H,), 2.95 (br s, 1H), 4.28 (d, J = 7.3 Hz, 1H), 5.53−5.68 (m, 2H), 7.33−7.45 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 7.81, 22.82, 76.37, 104.78, 126.23, 127.74, 128.49, 133.36, and 143.50 ppm.

Supplementary Material Available: ^{13}C NMR spectrum for compound **5** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.