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Efficient, Large-Scale Preparation of (*R*)- and (*S*)-1-(2,4,6-Triisopropylphenyl)ethanol, Versatile Chiral Auxiliary for Cyclopentenone, γ-Butyrolactone, and γ-Butyrolactam Synthesis

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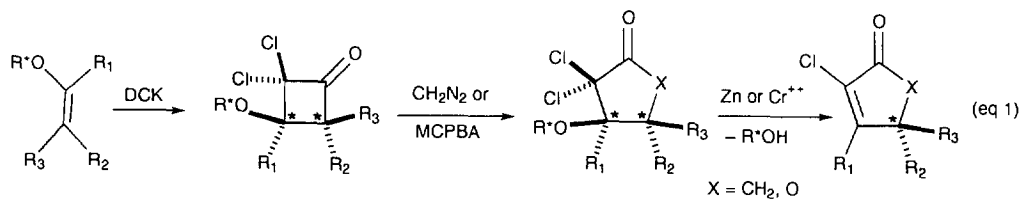
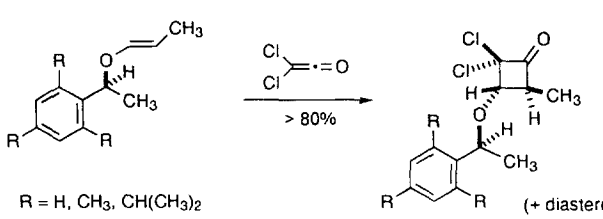
Abstract: **A particularly efficacious, low-cost preparation of both (*R*)- and (*S*)-triisopropylphenyl)-ethanol, useful chiral controllers in the dichloroketene—enol ether cycloaddition reaction, has been developed.** Copyright © 1996 Elsevier Science Ltd

Diastereomerically enriched α,α-dichlorocyclobutanones can be prepared by [2 + 2] cycloaddition of dichloroketene (DCK) with chiral *O*-alkyl enol ethers.[1-3] As a consequence of inherent ring stain and favorable electronic effects, these cyclobutanones on reaction with diazomethane and *m*-chloroperbenzoic acid (MCPBA) readily yield the corresponding α,α-dichlorocyclopentanones and α,α-dichloro-γ-butyrolactones, respectively. These in turn can afford auxiliary-free cyclopentenones[1,2] and butenolides[3] through reductive elimination (eq 1).



(eq 1)

In a program designed to access β-hydroxy-γ-butyrolactones and β-hydroxy-γ-butyrolactams, we sought an alcohol inductor that: a) would generate high diastereomeric excesses in the cycloaddition and b) could be cleaved to leave a hydroxyl residue. An obvious choice were chiral benzylic alcohols. Posner and co-workers[4] had earlier found that the vinyl ethers derived from 1-phenylethanol and 1-(2,4,6-trimethylphenyl)ethanol underwent facially selective cycloaddition in an inverse electron demand Diels-Alder reaction and, furthermore, that benzylic C–O cleavage in a cycloadduct could be cleanly accomplished with trifluoroacetic acid. While, in the present context, these particular chiral inductors provided only moderate diastereoselection, a new inductor, 1-(2,4,6-triisopropylphenyl)ethanol, produced excellent results (eq 2).[5]

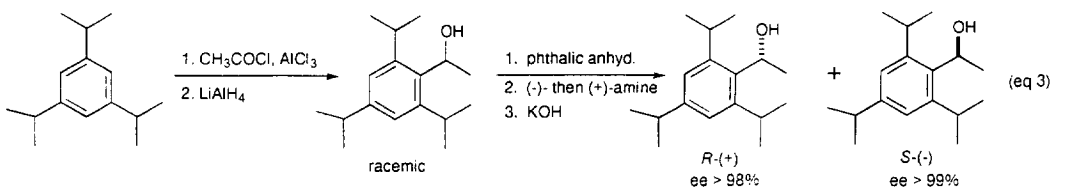


R	Approx. Diast. ratio
H	75 : 25
CH_3	85 : 15
$CH(CH_3)_2$	95 : 5

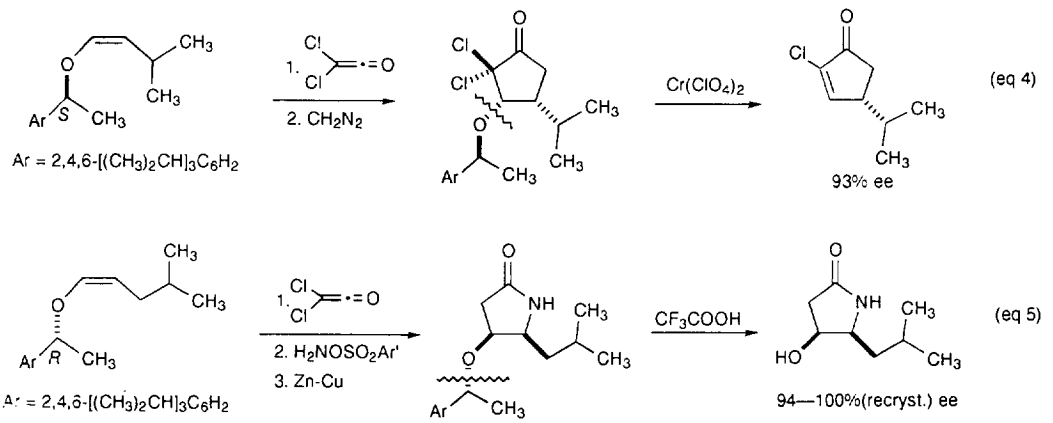
(eq 2)

With the multitude of methods now available for the asymmetric preparation of *sec*-phenethyl alcohol derivatives, it was incorrectly assumed that, in spite of the considerable steric crowding around the benzylic carbon, the synthesis of enantiopure (*R*)- and (*S*)-1-(2,4,6-triisopropylphenyl)ethanol would be straightforward. Much to our chagrin, however, it was found that Corey's CBS,[6] Brown's DIP-Cl,[7] and Noyori's BINAL-H[8] ketone reduction procedures, chiral $Zn(CH_3)_2$-based aldehyde methylation methods,[9] and an enzymatic kinetic resolution technique[10] all provided much less than satisfactory enantiomeric excesses and/or were too sluggish to be practical. In addition, less direct approaches based on the Sharpless asymmetric dihydroxylation[11] and the Jacobsen epoxidation[12] methods were unrewarding.[13]

Fortunately, though, an excellent procedure has been found that involves resolution of the derived acid phthalate with α-methylbenzylamine.[14] While perhaps unspectacular, it is undeniably simple, efficient (ca. 80% theoretical yield), and effective on a 100-g scale (no chromatographic purifications are required). An additional advantage of this approach over several others is that *both of the antipodes are obtained at low cost.* The starting racemic alcohol is readily secured in high yield from commercially available 1,3,5-triisopropylbenzene (ca. $30/100 g) by acylation with acetyl chloride in the presence of aluminum chloride[15] followed by lithium aluminum hydride reduction of the resulting ketone, and can be used without purification (purified yield 91%).



Recent work carried out in our laboratory highlights both the effectiveness of this inductor in the cycloaddition with dichloroketene and the subsequent cleavage option (eqs 4,5).[16,17]



Now readily available, (*R*)- and (*S*)-1-(2,4,6-triisopropylphenyl)ethanol should find expanded application in asymmetric synthesis.

Preparation of (R)- and (S)-1-(2,4,6-triisopropylphenyl)ethanol.[18]

To a stirred mixture of 100 mL (84.5 g, 0.413 mol) of 1,3,5-triisopropylbenzene and 60.0 g (0.450 mol) of aluminum chloride in 180 mL of carbon sulfide at 20 °C was added dropwise a solution of 29.0 mL (32.0 g, 0.408 mol) of acetyl chloride in 50 mL of carbon sulfide at a rate so as to give a controlled gas evolution through an attached bubbler. Following the addition, the reaction mixture was heated at reflux for 1h and then poured into a mixture of 500 g of ice and 200 mL of conc HCl and thoroughly extracted with ether. The organic phase was washed with saturated aqueous sodium bicarbonate solution, water, and brine, dried over sodium sulfate, and concentrated to leave 99.6 g of (2,4,6-triisopropylphenyl)ethanone[15] as a white solid: mp 86-88 °C (lit[15] 87.5-88 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21 (d, J = 6.8 Hz, 12 H), 1.23 (d, J = 7.0 Hz, 6 H), 2.45 (s, 3 H), 2.71 (sept, J = 6.8 Hz, 2 H), 2.87 (sept, J = 7.0 Hz, 1 H), 7.0 (s, 2 H); IR 3052, 2971, 2937, 2868, 1696, 1615, 1466, 1357, 1276 cm^{-1}.

To a stirred solution of the above ketone in 800 mL of dry ether was added portion-wise 16.0 g (0.422 mol) of lithium aluminum hydride. The reaction mixture was heated to reflux for 2 h, after which at 0 °C it was carefully hydrolysed with 32 mL of water and 26 mL of 10% NaOH solution. The solid material was filtered off and then thoroughly washed with ether. The ether filtrates were combined and concentrated under reduced pressure to give 100.1 g of crude (±)-1-(2,4,6-triisopropylphenyl)ethanol as a white solid: mp 92-93 °C (SiO_2).

A stirred solution of the above alcohol and 0.4 g of *N*,*N*-dimethylaminopyridine in 400 mL of dry pyridine was treated in one portion with 68.8 g (0.464 mol) of solid phthalic anhydride and then heated at 100-110 °C for 2 h. The resulting clear yellow solution was concentrated under reduced pressure to about 1/3 its initial volume, diluted with 800 mL of ether, and then washed with 6 N HCl, water, and brine, and dried over sodium sulfate. Evaporation of the solvent under reduced pressure provided 165.0 g of racemic acid as a white foam: mp 140-141 °C (hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.05-1.35 (m, 18 H), 1.79 (d, J = 6.8 Hz, 3 H), 2.87 (sept, J = 6.9 Hz, 1 H), 3.54 (br s, 2 H), 6.81 (q, J = 6.8 Hz, 1 H), 7.04 (s, 2 H), 7.51-7.57 (m, 2 H), 7.59-7.68 (m, 1 H), 7.92-7.95 (m, 1 H), 8.68 (br s, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.3, 167.6, 148.1, 134.0, 132.0, 131.7, 130.6, 129.8, 128.7, 121.3 (br), 70.2, 34.0, 29.4, 24.6, 24.3, 23.5; IR 3408, 2960, 2928, 2868, 1741, 1724, 1704, 1605, 1291 cm^{-1}; mass spectrum (EI), m/z 396 (M^+, 0.7), 215 (84), 43 (100). Anal. Calcd for $C_{25}H_{32}O_4$: C, 75.73; H, 8.13. Found: C, 75.44; H, 8.03.

To a vigorously stirred solution of the above acid in 3.4 L of ether was added 52.0 mL (48.9 g, 0.403 mol) of (*S*)-(-)-α-methylbenzylamine and stirring was continued 3 h, whereupon the white solid was filtered off and washed with ether to give 114.5 g of crude salt. This salt was dissolved in 4.2 L of boiling methanol and to the boiling solution 910 mL of water was added dropwise. After being allowed to cool to 20 °C overnight, the mixture was filtered and the cotton-like solid (mp 192-193 °C) was treated with a mixture of ether and 2 N HCl until complete dissolution. The ether layer was separated, washed with 2 N HCl, water, and brine, dried, and concentrated under reduced pressure to give 61.4 g of the (*S*)-(+)-acid as a white solid (99.6% ee by HPLC[19a]): mp 92-93 °C (hexane); $[\alpha]_D^{22}$ +73.1 (*c* 3.0, CH_3OH).

The ethereal solution from the precipitation of salt was thoroughly washed with 2 N HCl, water, and brine, dried, and concentrated to provide 83.8 g of acid. This acid was treated with (*R*)-(+)-α-methylbenzylamine in ether to give a precipitate, which as above was recrystallized from methanol–water and then converted to the free (*R*)-(-)-acid (45.5 g, 99.8% ee by HPLC[19a]): mp 93-94 °C (hexane); $[\alpha]_D^{22}$ -73.0 (*c* 3.0, CH_3OH).

The mother liquor from each recrystallization was concentrated under reduced pressure to remove the methanol and treated with a mixture of ether and 2 N HCl. The organic layer was separated, washed with 2 N HCl, water, and brine, dried, and concentrated to give a mixture of enantiomeric acids. The mixture was analyzed by HPLC[19a] and/or by its optical rotation and then recycled as above with (*R*)-(+) or (*S*)-(-)-α-methylbenzylamine, as appropriate. Three cycles provided a total of ca. 67 g of each free acid (ee ca. 99%[19a]).

Each enantiomer was dissolved in a mixture of 433 mL of methanol and 300 mL of 4 N KOH and refluxed for 2.5 h. After being allowed to cool to 20 °C, the mixture was filtered and the solid was dissolved in ether. The filtrate was partially concentrated under reduced pressure to remove the methanol and then thoroughly extracted with ether. The ether solutions were combined, washed with 10% aqueous NaOH, water, and brine, dried, and filtered. Removal of the solvent under reduced pressure gave for (*R*)-(+)-1-(2,4,6-triisopropylphenyl)ethanol 40.1 g (39% overall, 98.4% ee[19b]) and for (*S*)-(-)-1-(2,4,6-triisopropylphenyl)ethanol 41.1 g (40% overall, 99.2% ee[19b]): mp 84-85 °C; $[\alpha]_D^{22}$ +46.2 and $[\alpha]_D^{22}$ -46.0 (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.28 (d, *J* = 7.1 Hz, 12 H), 1.30 (d, *J* = 7.1 Hz, 6 H), 1.62 (d, *J* = 7.1 Hz, 3 H), 1.94 (br s, 1 H), 2.90 (sept, *J* = 7.1 Hz, 1 H), 3.61 (br s, 2 H), 5.55 (q, *J* = 7.1 Hz, 1 H), 7.05 (s, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 147.5, 146.8 (br), 135.8, 122.0, 66.0, 34.0, 29.0, 24.6, 23.9, 23.5; IR 3408, 2971, 2868, 1609, 1460, 1360, 1264, 1052 cm^{-1}; mass spectrum (EI), m/z 248 (M^+, 8.5), 215 (47), 43 (100). Anal. Calcd for $C_{17}H_{28}O_1$: C, 82.20; H, 11.36. Found: C, 82.32; H, 11.14.

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13. The enantiopure *levo* isomer was initially secured by using Corey's CBS method with costly (*R*)-(+)-α,α-diphenyl-2-pyrrolidinemethanol),[6] followed by up-grading through recrystallization of the menthoxycarbonyl derivative (B. M. de Azevedo, M.; Murta, M. M.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 4940-4942). The absolute stereochemistry was assigned by using the Horeau (Horeau, A. In "Stereochemistry"; Kagan, H. B., Ed.; Georg Thieme: Stuttgart, 1977; Vol. III, Chapter 3) and Trost (Trost, B.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370-2374) procedures, and was consistent with that expected to result from the CBS method.[6]
14. This procedure is a modification of that described for *sec*-phenethyl alcohol by Reyes and Juaristi (Reyes, A.; Juaristi, E.; *Synth. Commun.* **1995**, *25*, 1053-1058).
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18. For a description of the experimental techniques and apparatus, see reference 3.
19. a) Merck (*R,R*)-Whelk-O 1, 5 μm, acetic acid:isopropanol:hexane = 0.5:10:89.5, 1 mL/min.
b) Chiracel OD-H, 5 μm, isopropanol:hexane = 2:98, 0.5 mL/min.

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