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ASYMMETRIC SYNTHESIS OF (R)-(+)-ETHYLMETHYL-n-PROPYLCARBINOL IN HIGH ENANTIOMERIC PURITY. A 1,3-OXATHIANE DERIVED FROM (+)-PULEGONE AS CHIRAL ADJUVANT

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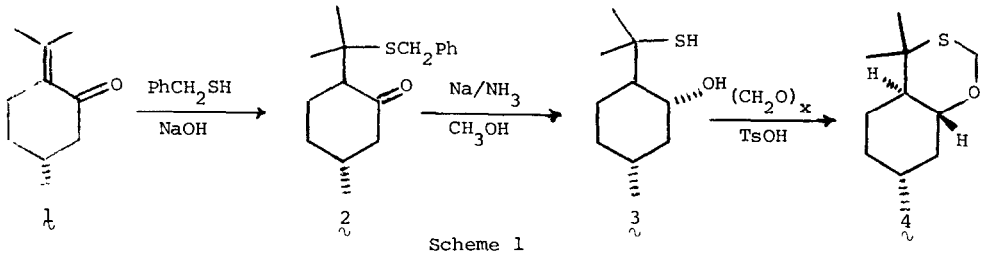
Summary. A chiral, conformationally locked 1,3-oxathiane has been prepared by 1,4-addition of benzyl mercaptan to (+)-pulegone followed by Na/NH_3 reduction and condensation of the resulting hydroxythiol with paraformaldehyde. The utility of this chiral adjuvant is exemplified by the asymmetric synthesis of the title compound in 93% e.e.

In previous publications[1,2] we have described highly (>95% e.e.) stereoselective asymmetric syntheses of $C_6H_5C(CH_3)OHCHO$ (or the methoxy-acid derived therefrom) from a chiral 1,3-oxathiane. However, the syntheses had various shortcomings. 1) Originally[1] the chiral adjuvant (oxathiane) was only 44% enantiomerically pure. In the second synthesis[2] this flaw was overcome by using a 100% enantiomerically pure 1,3-oxathiane derived from camphor-10-sulfonic acid. 2) Both syntheses involved an aryl group next to the chiral center generated; it is generally more difficult to achieve high enantiomeric excess in the synthesis of purely aliphatic compounds and, indeed, initial efforts[3] had yielded e.e.'s of less than 80% in such cases. 3) In neither of the syntheses described[1,2] was the chiral adjuvant recovered - though such recovery is, in general, a necessary condition for a practical asymmetric synthesis.[4] 4) In the synthesis based on camphor-10-sulfonic acid[2] the chiral adjuvant had to be purified by chromatography and the final hydrolysis of the oxathiane to the aldehyde product [by means of CH_3I/H_2O-$CH_3CN/CaCO_3$[5]] did not proceed well in some instances.[6]

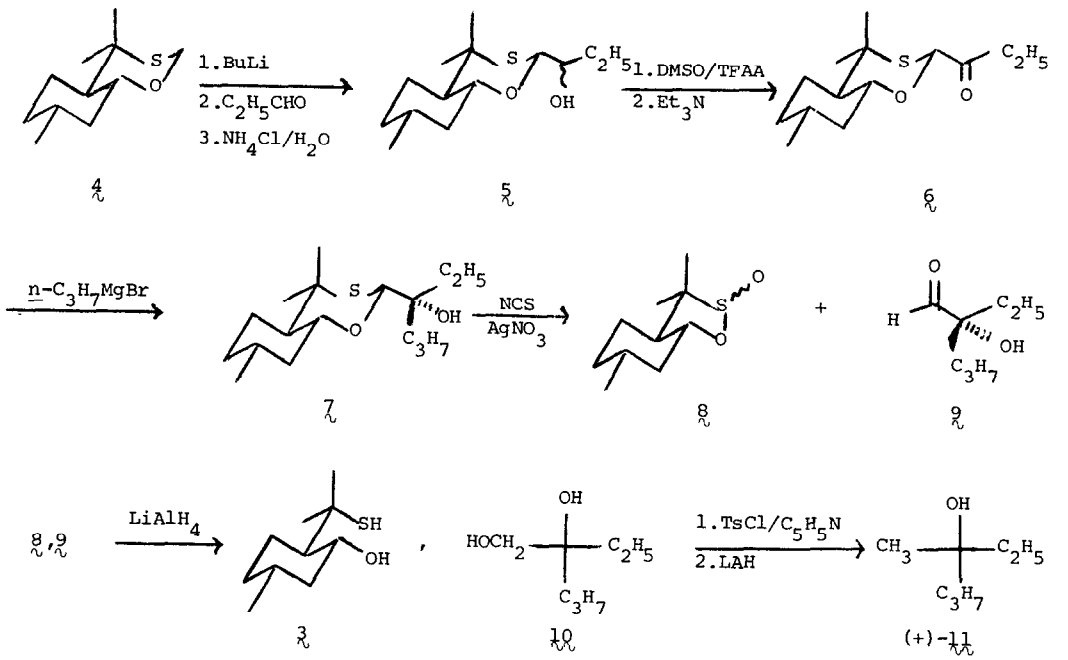
We now describe a variant of our earlier method which avoids all of these shortcomings. The chiral adjuvant 4 is obtained (Scheme 1) from the inexpensive (+)-pulegone (1) (which is readily available in optically pure form) and can be freed of accompanying diastereomers by mere recrystallization. High optical yield of the tertiary carbinol 7 (Scheme 2) is attained even with aliphatic Grignard reagents by operating at low temperatures. And, finally, a smooth hydrolysis



1 2 3 4

Scheme 1

of the oxathiane is achieved by the use of N-chlorosuccinimide/silver nitrate[7] (Scheme 2). The products 8 and 9 were separated by distillation and each in turn was then reduced, by LAH, to 10 and recovered 3, respectively. The optical purity of 10, as determined by ^{1}H-NMR of the MPTA ester[8] [prepared by reaction with (-)-α-methoxyphenyltrifluoroacetyl chloride], was 94%.



Scheme 2

Compound 10 was converted to the monotosylate in the standard way; subsequent reduction with LAH led to the simplest chiral tertiary carbinol, ethylmethyl-n-propylcarbinol (11) whose enantiomeric purity was determined, by a chiral shift reagent, to be 93%.

The overall yield of the pure chiral adjuvant 4 from pulegone was 29%. Yields in subsequent steps were 88% (5), 54% (6), 88% (7), 69% (9), 98% (8), 89% (10), 75% (3), 59% (11).

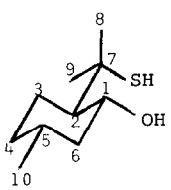
We describe here in detail the preparation of the chiral adjuvant 4 from 1. Details of the subsequent steps will be given in the full publication. All compounds had ^{1}H and, where observed, ^{13}C NMR and IR spectra compatible with the assigned structure (the ^{13}C NMR spectra of 5 and 9 and the IR spectrum of 5 were not recorded). Compound 11 was spectrally identical with an authentic sample of the racemic material prepared from 3-hexanone and CH_3MgI.[9]

2: A solution of pulegone (1) (10 ml, 9.4g, 62 mmol), benzyl mercaptan (10 ml, 9.45g, 76 mmol) and 1 ml 10% aqueous NaOH in 100 ml THF was refluxed under N_2 for 18 hr. After cooling, the solution was washed with 5% aqueous (200 ml) NaOH and the NaOH wash was extracted with 100 ml ether. The combined organic layers were washed with water (100 ml), saturated NaCl soln. (100 ml) and dried over $MgSO_4$. Concentration and distillation yielded, after a small forerun, b.p. 40-60°C/0.5 mm, 14.4g (85%) of product 2, b.p. 122-125°C/0.05 mm. Product 2 is a mixture of 87% trans and 13% cis isomers as determined by integration of ^{13}C signals.

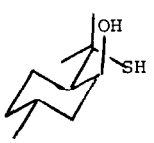
^{1}H NMR ($CDCl_3$), δ(ppm): 7.28 (m, 5H); 3.71 (s, 2H); 1.58 (s, 3H); 1.36 (s, 3H); and others. IR (CCl_4), cm^{-1}: 1708 (s), 1448 (s), 1382 (s), 1363 (s), 1132 (s), 696 (s). ^{13}C NMR ($CDCl_3$), δ (ppm): 192.2, 138.7, 128.9, 128.4, 126.8, 57.8, 52.3, 48.00, 36.6, 34.5, 33.1, 29.6, 27.8, 29.9, 22.2 plus signals due to minor isomer.

3: A solution of 250g (0.906 mol) 2 and 72.5 ml (1.79 mol)methanol in 625 ml ether was added dropwise over 5 hr. to a cold (-78°C) solution of sodium (125g, 5.43 g-atom) in liquid ammonia (3000 ml) under N_2. The solution was stirred for an additional ½ hr., then 150 ml methanol was added dropwise and the mixture was allowed to warm; by the time the temperature reached -42°C, the deep blue color had been discharged. The ammonia was allowed to evaporate and water (700 ml) was cautiously added (exotherm!). The aqueous solution was twice extracted with 200-ml portions of ether which were discarded. The aqueous solution was acidified with 500 ml of conc. aqueous hydrochloric acid while being cooled with ca. 1000g ice and was then extracted with four 200-ml portions of ether. The combined ether extracts were washed with water (200 ml), saturated aqueous NaCl (200 ml) and dried over $MgSO_4$. Concentration of the filtered solution, eventually at 40° under vacuum (0.2 mm) for 1 hr. gave a mixture of isomeric hydroxythiols 3 weighing 137g (80%).

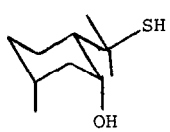
The mixture of hydroxythiols contains 78% equatorial hydroxyl and 22% axial hydroxyl determined by ^{1}H NMR integration. Three isomers (3A-C) were obtained in pure form by HPLC separation (Waters Prep 500A, 3% ethyl acetate in hexanes as eluent). A fourth component was



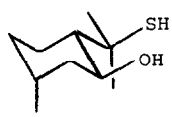
3A



3B



3C



3D

isolated; however, spectral data were not consistent with structure 3D.

3A, ^{1}H NMR ($CDCl_3$), δ(ppm): 3.70 (double triplet J=4 hz, 10 hz, 1H); 3.0-2.9 (s, 1H); 2.14 (s, 1H); 1.56 (s, 3H); 1.45 (s, 3H); 0.95 (d, J=6 hz, 3H). IR (CCl_4), cm^{-1}: 3610 (w), 3465 (m), 2980-2820 (vs), 2575 (vw), 1460 (m), 1450 (m), 1385 (m), 1368 (m), 1140 (m), 1055 (m), 1029 (m). ^{13}C NMR ($CDCl_3$), δ(ppm): 72.9, 54.6, 47.2, 45.4, 34.6, 34.5, 31.3, 29.3, 26.9, 21.9.

3B, ^{1}H NMR ($CDCl_3$), δ(ppm): 3.3 ppm (m, 1H); 3.0 (s, 1H); 1.9 (s, 1H); 1.5 (s, 6H); 0.87 (d, J=7 hz, 3H). ^{13}C NMR ($CDCl_3$), δ(ppm): C_1, 67.8; C_2, 51.7; C_7, 46.9; C_6, 43.0; C_4, 35.1; $C_{8,9}$, 33.6, 31.0; C_5, 29.6; $C_{3,10}$, 22.1, 21.8.

3C, ^{1}H NMR ($CDCl_3$), δ(ppm): 3.35 (m, 1H); 2.75 (s, 1H); 1.93 (s, 1H); 1.48 (s, 6H); 1.19 (d,J=7 hz, 3H). ^{13}C NMR ($CDCl_3$), δ(ppm): C_1, 68.7; C_2, 52.1; C_7, 47.1; C_6, 39.5, $C_{8,9}$, 33.4, 32.3 C_4, 30.8; C_5, 26.3; C_3, 21.2; C_{10}, 17.0.

4: The above mixture of hydroxythiols 3 (165g, 0.878 mol) was dissolved in 350 ml benzene. Paraformaldehyde (30g, 1.0 mol) and p-toluenesulfonic acid (1g) were added and the mixture refluxed for 4 hr., water being removed by a Dean-Stark trap. The solution was allowed to cool, stirred with ca. 5g anhydrous K_2CO_3 overnight, filtered, concentrated and distilled to give 151.6g (89%) of crude product, b.p. 52-98°C/0.25 mm. The distillate was dissolved in 150 ml

pentane, cooled to -25°C and seeded with 4. (The initial seed crystals were obtained by preparative glpc on a 5% FFAP column.) Crystallization was allowed to proceed for 48 hr. and the crystals were then collected, weight 58g (33%). Concentration (to 200 ml) and recooling produced a second crop of 10g (5.7%), further concentration (to 100 ml) a third crop of 7g (4%) Mp 36-40°C, unchanged by further recrystallization from pentane; the material was pure as judged by ^{13}C NMR.

^{1}H NMR ($CDCl_3$), δ(ppm): 5.03 (d, J=10 hz, 1H); 4.65 (d, J=10 hz, 1H); 3.34 (double triplet, J=4 hz, 10 hz, 1H); 1.42 (s, 3H); 1.25 (s, 3H); 0.91 (d, J=7 hz, 3H).

IR (CCl_4), cm^{-1}: 2970-2870 (vs), 1455 (s), 1440 (m), 1388 (m), 1370 (s), 1355 (m), 1305 (s), 1155 (vs), 1095 (vs), 1066 (vs).

^{13}C NMR ($CDCl_3$), δ(ppm): 76.4, 67.1, 51.5, 41.8, 41.5, 34.7, 31.3, 29.4, 24.4, 22.1, 21.8.

Anal. Calc'd for $C_{11}H_{20}OS$: C, 65.95; H, 10.06. Found: C, 65.85; H, 10.11.

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