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ASYMMETRIC SYNTHESIS OF (R)-(+)- AND (S)-(-)-2,2,4-TRIMETHYL--4-(HYDROXYMETHYL)-1,3-DIOXOLANE OF HIGH ENANTIOMERIC PURITY

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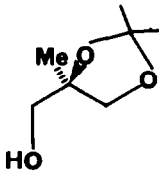
Abstract - The title compounds, 1 and 1', are readily available in four steps from 2-benzyloxymethyl-2-propen-1-ol, the key step being Sharpless asymmetric epoxidation to give the chiral epoxides 5 or 5'. The total chemical yield of 1 or 1' is 50%, the final products being obtained essentially optically pure. By suitable protecting group manipulation, both title enantiomers can be produced from either of the antipodal epoxides 5 or 5'.

As part of a larger synthetic project we required quantities of the title compounds 1 and 1'. In 1983, Williams and Anderson[1] published two routes to these enantiomers, one involving resolution of the racemate and the other employing Sharpless asymmetric epoxidation of 2-methyl-2-propen-1-ol. The former procedure allowed isolation of the optically pure compounds, but only on a small scale (ca. 6 mg) while the latter route afforded, after several operations, material of ca. 85% enantiomeric excess (e.e.) in up to 10% overall chemical yield.



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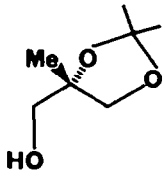
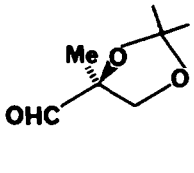


1'



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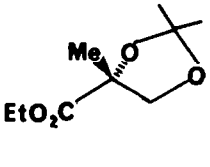

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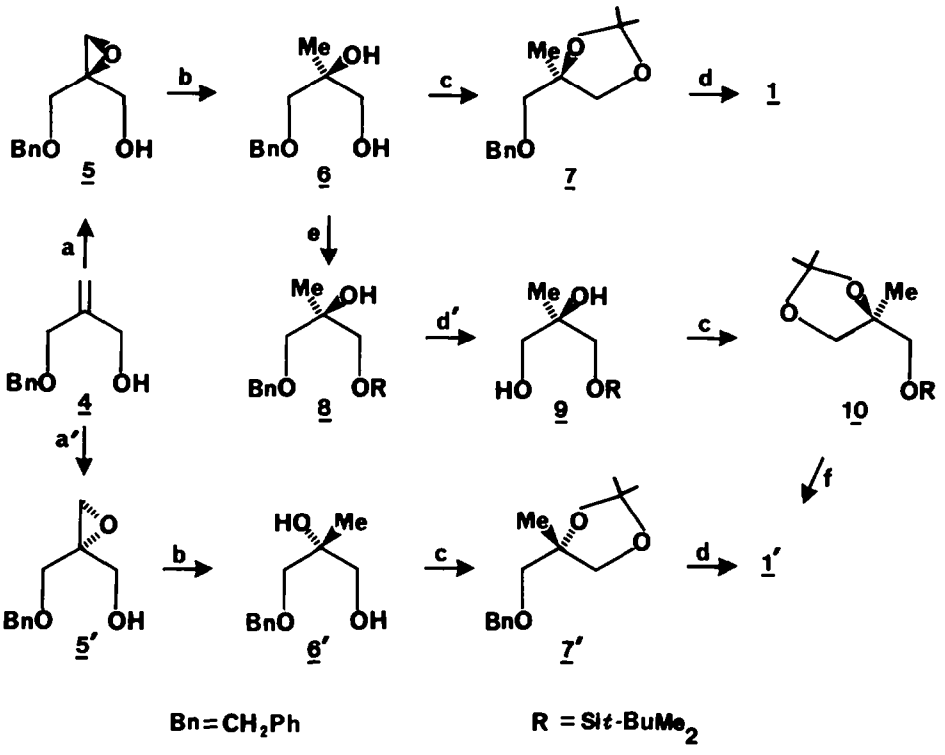
Alcohol 1 is the immediate precursor of the (S)-aldehyde 2 which Williams and Anderson required[1] for a total synthesis of optically active bicyclomycin, and these authors pointed out that materials such as 1 and 2 should represent convenient chiral "building blocks" for total synthesis. Earlier, Barner and Schmid[2] had obtained optically pure (R)-ester 3 in larger quantities (starting with a resolution of the half-ester of 2-benzyloxy-2-methylmalonic acid) and had converted 3, by careful DIBAL reduction, to the antipode of 2 which was used in a total synthesis of α-tocopherol.

Our own synthesis of the alcohols 1 and 1' is shown in Scheme 1.



Scheme 1

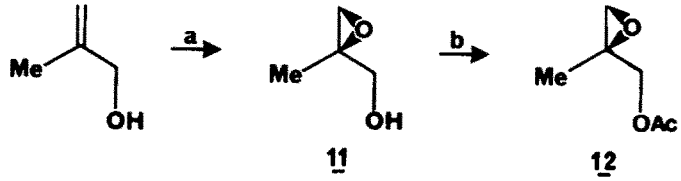
(a) (-)-DET,Ti(O^tBu)$_4$,^{t}BuOOH,molecular sieves,CH_2Cl_2,75% yield (a') as for (a) but (+)-DET used (b) LAH,THF,82% (c) 2,2-dimethoxypropane, CSA cat.,100% (d) H_2,Pd(OH)$_2$/C,pentane-EtOAc,82% (d') as for (d) but EtOH solvent,93% (e) t-$BuMe_2SiCl$,DMAP,NEt_3,CH_2Cl_2,100% (f) Bu_4NF,THF,96%.

The recently published[3] modified version of the Sharpless asymmetric epoxidation reaction, which allows the use of catalytic amounts of titanium(IV) alkoxide and the appropriate chiral tartrate ester, was the key to success. This procedure allowed isolation of the optically active epoxy-alcohols 5 and 5' (75% chemical yield) from the allylic alcohol 4. Epoxide ring-scission (LAH) cleanly gave the crystalline mono-protected 1,2,3-triols 6 or 6' which were quantitatively converted to the acetonides 7 or 7', and final catalytic hydrogenolysis of the benzyl ether moieties furnished 1 or 1'. The total yield for four steps was 50%, all intermediates having spectral data in full accord with the proposed structures and the spectra of the final products closely matching the published data[1]. As for the optical purity of the final products, our synthetic samples of 1 and 1' showed $[\alpha]_D$ = +5.25 and -5.25°, respectively (c 0.3, CH_2Cl_2) these values being in excellent agreement with those reported for the optically pure materials obtained via resolution[1]: +5.2 and -5.33°, respectively.

The reaction sequences depicted in Scheme 1 underscore one of the great advantages of the Sharpless asymmetric epoxidation reaction, viz. that for a given prochiral allylic alcohol both enantiomers of the corresponding chiral epoxy-alcohol are equally easily available, but it can also be seen that both enantiomers 1 and 1' can be obtained at will from either of the chiral epoxides 5 or 5'. This is illustrated by the sequence which transforms 6 to 1' via 8, 9 and

10. Thus, selective protection of the primary hydroxyl of 6 as the TBDMS ether was followed by debenzylation to 9. After acetonide formation, the silyl ether was cleaved to give 1', identical in all respects with material synthesised from 5'. The total yield of 1' by this six-step sequence from 4 was a pleasing 55%.

The difficulties encountered by Williams and Anderson[1] lay in the epoxidation of 2-methyl-2-propen-1-ol, the antipodal epoxides of which could not be isolated. However, the newer asymmetric epoxidation technique used in the present work does allow the epoxide 11 (Scheme 2) to be isolated, by careful kugelrohr distillation followed by flash chromatography, as an NMR-spectroscopically pure,colourless oil (ca. 50% chemical yield). The $[\alpha]_D$ value of the purified material obtained using (-)-DET as the chiral auxiliary was +10.62° (c 1.733, CH_2Cl_2) and the e.e. was determined by use of the chiral NMR-shift reagent $Eu(tfc)_3$ on the corresponding acetate 12, a control experiment being first performed on the racemic acetate. As shown in FIG. 1(a) the shift reagent induced a clean doubling of both types of methyl signal in the racemate, and by this technique the chiral epoxy-alcohol 11 was shown to be of >95% e.e. (see FIG. 1(b)).



11 12

Scheme 2

(a) (-)-DET,$Ti(O^iPr)_4$,^tBuOOH,molecular sieves,CH_2Cl_2, 47% yield
(b) Ac_2O,pyridine, 100%.

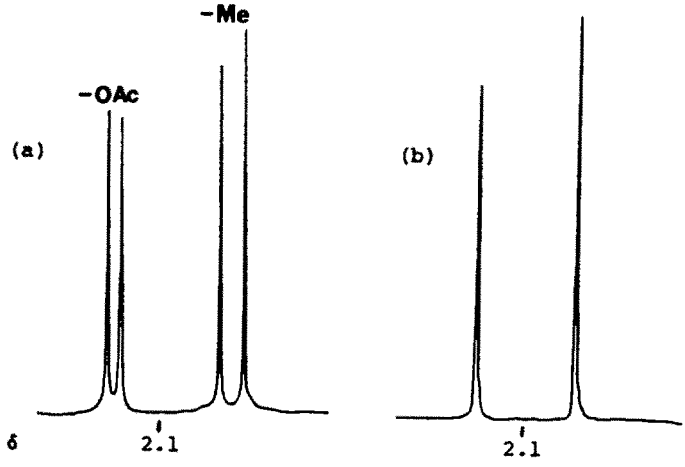


FIG. 1

Highest-field portion of the 270 MHz ^1H NMR spectrum of 12 (C_6D_6) recorded in the presence of $Eu(tfc)_3$.
(a) Racemic 12 (b) (R)-(+)-12, e.e. >95%.

While epoxy-alcohol 11 or its antipode could, of course,be subjected to the procedure of Williams and Anderson[1] to give 1' or 1, respectively, or perhaps converted to the desired acetonides using Colvin's methodology[4], we prefer the routes shown in Scheme 1 since the epoxides 5 and 5' are obtained in considerably higher chemical yields and are easier to handle.

EXPERIMENTAL

^{1}H NMR spectra were obtained at 270 MHz (Bruker WH-270) using $CDCl_3$ as solvent and TMS (δ=0) as internal standard unless otherwise stated. The following abbreviations are used: s,singlet, d,doublet, t,triplet, m,multiplet, b,broad, J,coupling constant in Hz. IR spectra were run on a Perkin-Elmer 197 spectrophotometer and only the strongest/structurally most important peaks (ν_{max},cm^{-1}) are listed. Mass spectra were run on a Finnigan 1020 GC/MS instrument. Optical rotations, $[\alpha]_D$ were measured on a Perkin-Elmer 241 polarimeter at the sodium D line and ambient temperature. Flash chromatography employed Merck silica gel 60 (230-400 mesh). Methylene chloride,pyridine and triethylamine were distilled from calcium hydride immediately before use; tetrahydrofuran (THF) was distilled under nitrogen from sodium-benzophenone ketyl. 1M solutions of lithium aluminium hydride (LAH) and tetrabutylammonium fluoride in THF were purchased from Aldrich. Unless stated otherwise,reactions were run in septum-capped,flame- or oven-dried flasks under balloon pressure of argon,solvents,reactant solutions and liquid reagents being transferred *via* oven-dried (140°C) syringes.

Epoxide 5: Activated 4Å molecular sieves were powdered and slurried under argon in CH_2Cl_2 (300 mg sieves in 50 ml). The stirred mixture was cooled to -10°C and a solution of (-)-diethyl tartrate (DET, 0.271g, 1.3mmol) in CH_2Cl_2 was added, followed by $Ti(O\underline{t}\text{-}Bu)_4$ (0.34ml, 1mmol) and t-BuOOH (7.6ml of a 4.3M toluene solution, 32.6mmol). The resultant mixture was stirred at -10°C for 15min,cooled to -45°C, and stirred during addition of allylic alcohol 4 (2.340g, 13.1mmol) dissolved in CH_2Cl_2 (2ml). The reaction temperature was allowed to reach -20°C and the sealed flask placed in the freezer overnight. Water (10ml) was then added and the resultant mixture stirred at RT for 30min and then cooled to 0°C. Addition of 30% aqueous NaOH saturated with NaCl (1ml) yielded a mixture which was stirred at 0°C for 10min and then filtered through a Celite pad. The organics were separated and the aqueous phase back-extracted with three 10-ml portions of CH_2Cl_2. The combined organics were dried over Na_2SO_4 and the solvents removed to give an oil which was purified by flash chromatography (80% ether/pentane). There was obtained 1.858g (74%) of 5 as a colourless oil. ^{1}H NMR: δ 1.93 (1H, bs, -OH) 2.75 (1H, d, J=4.5, epoxy) 2.91 (1H, d, J=4.5, epoxy) 3.66 (2H, AB-type m, J=11) 3.76 (1H, bd, J=13) 3.94 (1H, d, J=13) 4.57 (2H, AB-m, J=7.5, benzylic) 7.16-7.40 (5H, m, aromatic). IR: 3450(b) 3150, 3050, 2980, 2900, 2850, 1200, 1100, 920cm^{-1}. MS: m/z 107($M-C_7H_7O$, 60%) 91(100).

$[\alpha]_D$ +11.0° (c 1.867, CH_2Cl_2).

Epoxide 5' was synthesised by the same procedure, using (+)-DET as the chiral auxiliary. The purified material showed $[\alpha]_D$ -10.9° (c 1.200, CH_2Cl_2).

Diol 6: To a stirred ice-cooled solution of 5 (0.093g, 0.5mmol) in THF (6ml) under argon was added a solution of LAH in THF (0.18ml of 1M, 0.18mmol). The reaction mixture was stirred at 0°C for 2h then quenched by careful addition of water (0.5ml). The precipitated aluminates were filtered off onto Celite and the filter-cake washed thoroughly with ether. Removal of solvents and flash chromatography (ether) afforded diol 6 (0.077g, 82%) as an oil which crystallised in the refrigerator. M.p. 29-30°C.
^{1}H NMR: 1.15 (3H, s, Me) 3.43 (1H, d, J=9) 3.46 (1H, d, J=10.5) 3.51 (1H, d, J=9) 3.78 (1H, d, J=10.5) 4.56 (2H, s, benzylic) 7.26-7.42 (5H, m, aromatic).
IR: 3400(b,vs) 3100, 3050, 2970, 2910, 2850, 1100(s).
MS: m/z 196(M^+, 1%) 165(3) 91(100).

$[\alpha]_D$ +6.53° (c 1.33, CH_2Cl_2).

Diol 6' showed $[\alpha]_D$ -6.30° (c 0.87, CH_2Cl_2).

Acetonide 7: Diol 6 (0.070g, 0.4mmol) was dissolved with stirring in 2,2-dimethoxypropane (3ml) and a catalytic amount of camphorsulphonic acid was added. The reaction mixture was stirred at RT for 3h and then filtered through a small plug of glass wool. The filtrate was diluted with ether (5ml) and the mixture refiltered. Removal of solvents and flash chromatography (20% ether/pentane) yielded the acetonide as an oil (0.084g, 100%). ^{1}H NMR: 1.33 (3H, s, Me) 1.38 (3H, s, acetonide Me) 1.39 (3H, s, acetonide Me) 3.39 (1H, dd, J=8.9 and 0.9(long-range "W" coupling)) 3.44 (1H, d, J=8.9) 3.70 (1H, dd, J=9 and 0.9) 4.03 (1H, d, J=9) 4.56 (2H, s, benzylic) 7.36 (5H, m, aromatic).
IR: 3100, 3050, 2975, 2930, 2850, 1360, 1200, 1100.
MS: m/z 236(M^+, 2%) 221(M-Me, 6%) 178(2) 116(70) 92(100) 58(80).

$[\alpha]_D$ -2.27° (c 0.67, CH_2Cl_2).

Acetonide 7: $[\alpha]_D$ +2.30° (c 1.73, CH_2Cl_2).

(R)-(+)-2,2,4-Trimethyl-4-(hydroxymethyl)-1,3-dioxolane, 1: Acetonide 7 (0.110g, 0.5 mmol) was dissolved with stirring in 9:1 pentane/ethyl acetate (10ml) and $Pd(OH)_2/C$ (15mg) was added. The reaction vessel was evacuated (aspirator) and then flushed with argon via a three-way stopcock. The flask was then alternately evacuated and flushed with H_2 several times and finally placed under balloon pressure of hydrogen. The reaction was complete (TLC) after 3h at RT. The reaction vessel was then evacuated and flushed with argon and the mixture filtered through a pad of Celite. The filter-cake was washed thrice with ether and the combined filtrate and washings concentrated at 0°C to minimise loss of the volatile product. The residue was purified by flash chromatography (66% ether/pentane) to yield the title compound as a clear, colourless oil (0.056g, 82%).
^{1}H NMR: 1.29 (3H, s, Me) 1.42 (3H, s, acetonide Me) 1.43 (3H, s, acetonide Me) 1.85 (1H, bm, -OH) 3.50 (2H, bAB-m, J=13, $-CH_2OH$) 3.74 (1H, d, J=8.5) 3.98 (1H, d,J=8.5)
IR: 3450(b,s) 2975, 2925, 2850, 1380, 1200,1060.
MS: m/z 131 (M-Me, 58%) 115(55) 97(40) 71(85) 57(100).
$[\alpha]_D$ +5.25° (c 0.30, CH_2Cl_2). Lit. +5.2° (c 0.5, CH_2Cl_2, see ref. 1).

The (S)-(-)-enantiomer, 1', showed $[\alpha]_D$ -5.25° (c 0.30, CH_2Cl_2)

Silyl ether 8: To a stirred ice-cooled solution of 6 (0.312g, 1.6mmol) in CH_2Cl_2 (10ml) was added 4-dimethylaminopyridine (0.010g) and triethylamine (0.23ml, 1.7mmol). The resultant mixture was stirred at 0°C for 10min before addition of t-butyldimethylsilyl chloride (0.400g, 2.6mmol). The reaction mixture was allowed to reach RT, stirred overnight, and poured into water/CH_2Cl_2. The layers were separated and the aqueous phase extracted once with CH_2Cl_2. The combined organics were washed with NH_4Cl(aq.) and then dried over Na_2SO_4. Removal of solvent and flash chromatography yielded 8 as an oil (0.491g, 100%).
^{1}H NMR: 0.06 (6H, s, $-SiMe_2$) 0.90 (9H, s, t-Bu) 1.17 (3H, s, Me) 2.58(1H, bs, -OH) 3.38 (2H, AB-m, J=9) 3.53 (2H, AB-m, J=9.5) 4.56 (2H, s, benzylic) 7.31 (5H, m, aromatic).
IR: 3450(b) 3100, 3050, 3025, 2950, 2925, 2850, 1100(s, -O-Si).
MS: m/z 253(M - t-Bu, 1%) 161(5) 146(45) 92(85) 76(100) 59(78).
$[\alpha]_D$ +1.22° (c 1.80, CH_2Cl_2).

Diol 9: The silyl ether 8 (0.445g, 1.4mmol) was dissolved in abs. EtOH and hydrogenolysis of the benzyl ether was carried out as described for compounds 7 and 7'. The usual work-up was followed by flash chromatography (60% ether/pentane) to yield 9 as a viscous oil (0.293g, 93%).
^{1}H NMR: 0.10 (6H, s, $-SiMe_2$) 0.92 (9H, s, t-Bu) 1.11 (3H, s, Me) 3.56 (4H, two AB-m, J=10 and 11).
IR: 3400(b, vs) 2950, 2925, 2850, 1100(s).
MS: m/z 145(M - t-Bu and H_2O, 50%) 76(100).
$[\alpha]_D$ -1.28° (c 1.33, CH_2Cl_2).

Acetonide 10: The procedure described for the preparation of acetonides 7 and 7' was followed. From 0.270g (1.2mmol) of 9 was obtained 0.320g (100%) of 10 as an oil.
^{1}H NMR: 0.05 (6H, s, $-SiMe_2$) 0.89 (9H, s, t-Bu) 1.28 (3H, s, Me) 1.39 (6H, bs, acetonide Me) 3.39 (1H, dd, J=10 and 1, "W" coupling) 3.54 (1H, d, J=10) 3.64 (1H, dd, J=9 and 1) 4.04 (1H, d, J=9).
IR: 2975, 2950, 2925, 2850, 1260, 1200, 1100.
MS: m/z 245(M - Me, 3%) 203(M - t-Bu, 1) 185(10) 146(55) 116(65) 75(100) 59(83).
$[\alpha]_D$ +1.63° (c 1.60, CH_2Cl_2).

(S)-(-)-2,2,4-Trimethyl-4-(hydroxymethyl)-1,3-dioxolane, 1': Acetonide 10 (0.268g, 1.0mmol) was dissolved with stirring in THF (10ml). The solution was cooled to 0°C and a solution of tetrabutylammonium fluoride in THF (1.5ml of 1M, 1.5mmol) was added dropwise. The reaction mixture was allowed to warm up to RT and then stirred for 2h. After dilution with ether, the mixture was washed with water and the organics dried over Na_2SO_4. Removal of solvents and flash chromatography yielded the title compound as an oil (0.129g, 96%) which was identical in all respects with the material synthesised from epoxide 5'.

Epoxide 11: The general procedure described for the synthesis of 5 and 5' was followed. Thus 2-methyl-2-propen-1-ol was epoxidised using (-)-DET as the chiral auxiliary in conjunction with $Ti(Oi\text{-}Pr)_4$. After admixture of all the reactants, the solution was allowed to stir for ten hours at -45°C before being warmed to -20°C. The reaction vessel was then sealed and placed in the freezer overnight. After the usual work-up, the oily residue was purified first by kugelrohr distillation and then by flash chromatography (50% to 80% gradient of ether/pentane). From 1.000g (13.9mmol) of 2-methyl-2-propen-1-ol there was obtained 0.570g (47%) of pure epoxide 11 as a colourless, volatile oil. The yield of crude epoxide (ca. 80% purity) was 70%.
^{1}H NMR (after D_2O shake): 1.38 (3H, s, Me) 2.67 (1H, d, J=4.9, epoxy) 2.93 (1H, d,

J=4.9, epoxy) 3.68 (2H, AB-m, J=13).
IR: 3400(b) 2975, 2925, 2850, 1210, 890.
MS: m/z 73(M - Me, 15%) 59(100).

$[\alpha]_D$ +10.62° (c 1.733, CH_2Cl_2). This material was shown to be >95% optically pure by ^{1}H NMR analysis of the acetate 12, using the chiral shift reagent Eu(tfc)$_3$ (vide infra and FIG. 1).

Acetate 12: The epoxy-alcohol 11 (0.088g, 1.0mmol) was dissolved in pyridine (1ml) and the solution cooled to 0°C. Acetic anhydride (0.13ml, 1.4mmol) was added and the resultant mixture stirred overnight at RT. The reaction mixture was then diluted with ether (15ml) and the pyridine removed by washing with three 5-ml portions of dilute aqueous $CuSO_4$ solution. The ethereal phase was then washed once with water and once with brine and dried over Na_2SO_4. Removal of solvent and flash chromatography yielded 0.130g (100%) of the acetate 12 as an oil.
^{1}H NMR: 1.39 (3H, s, Me) 2.10 (3H, s, acetate Me) 2.68 (1H, d, J=4, epoxy) 2.79 (1H, d, J=4, epoxy) 3.98 (1H, d, J=12) 4.27 (1H, d, J=12).
IR: 3000, 2950, 1740(s) 1240(s).
MS: m/z 115(1%) 100(20) 87(10) 72(70) 58(100).

$[\alpha]_D$ +4.59 (c 2.270, CH_2Cl_2).

This material was chromatographically and spectroscopically identical to a sample of racemic material prepared by mCPBA epoxidation of the acetate of 2-methyl-2-propen-1-ol.
The racemic acetate was then examined by ^{1}H NMR (C_6D_6 solution) in the presence of the chiral shift reagent Eu(tfc)$_3$. The shift reagent induced a doubling of all sets of protons, the shift differences being greatest for the two methyl groups (see FIG. 1(a)). When the optically active epoxy-acetate 12 was examined in the same way, only one set of signals could be observed. We estimate that 5% of the minor enantiomer, if present, could easily have been detected.

Acknowledgements. We thank the Swedish Natural Science Research Council for financial support.

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