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Anthracyclines. XII*
The Preparation of (−)-(7*R*)-7-Acetyl-7-(t-butyldimethylsilyloxy)-4,4-dimethoxy-5,6,7,8-tetrahydronaphthalene-1(4*H*)-one and (+)-(6*R*)-6-Acetyl-6-(t-butyldimethylsilyloxy)-4,4-dimethoxy-5,6,7,8-tetrahydronaphthalene-1(4*H*)-one: an Improved Route to Chiral AB Synthons for 7-Deoxydaunomycinone

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Abstract

The title dienones (2) and (5) were prepared from the chiral alcohols (7a) and (7b) respectively. These key starting materials were in turn available from the reduction of 3-acetyl-5-benzyloxy-8-methoxy-1,2-dihydronaphthalene (6a) and 3-acetyl-8-benzyloxy-5-methoxy-1,2-dihydronaphthalene (6b) with lithium aluminium hydride modified with (−)-*N*-methylephedrine and *N*-ethylaniline. Chiral phase high-pressure liquid chromatography was used to analyse the enantioselectivity of these reductions which were shown to yield variable results depending upon the origin of the reducing agent.

Introduction

We recently described[1] an enantiospecific synthesis of (−)-7-deoxydaunomycinone (3) based upon the use of chiral type 1 and type 2 dienones as synthons (see Scheme 1) for the A and B rings. Our early work in this area involved the preparation of the type 1 dienone (2),[2,3] by the bromolactonization route,[4] but that approach could not readily be extended to dienones required for the type 2 synthetic strategy[1] which proceeds with superior yield. In this paper, we describe a common enantiospecific route to either type of chiral dienone, illustrated by the preparation of dienones (2) and (5) from the isomeric chiral alcohols (7a) and (7b) respectively. These latter compounds are prepared by the enantiospecific reduction of the 3-acetyl-1,2-dihydro-

* Part XI, *Aust. J. Chem.*, 1984, **37**, 1721.

[1] Russell, R. A., Krauss, A. S., Warrener, R. N., and Irvine, R. W., *Tetrahedron Lett.*, 1984, 1517.
[2] Warrener, R. N., Gee, P. S., and Russell, R. A., *J. Chem. Soc., Chem. Commun.*, 1981, 1100.
[3] Russell, R. A., Gee, P. S., Irvine, R. W., and Warrener, R. N., *Aust. J. Chem.*, 1984, **37**, 1709.
[4] Jew, S. S., Terashima, S., and Koga, K., *Chem. Pharm. Bull.*, 1979, **27**, 235.

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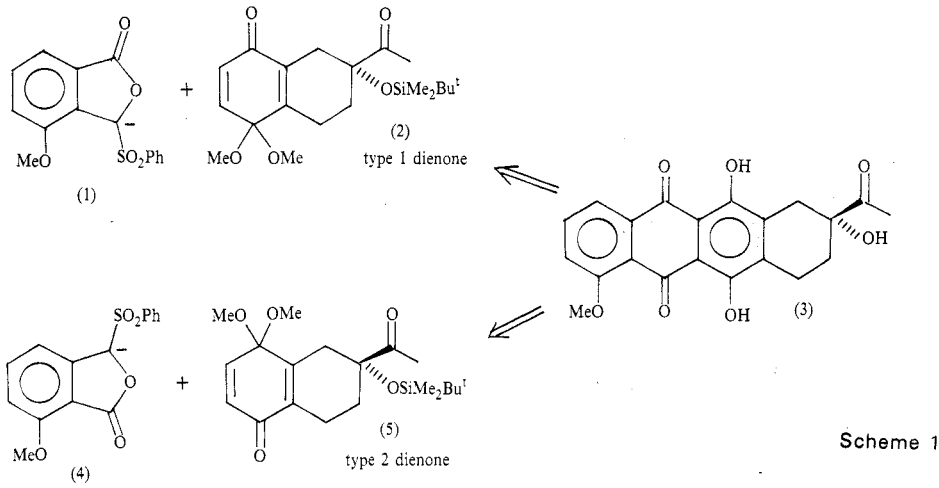
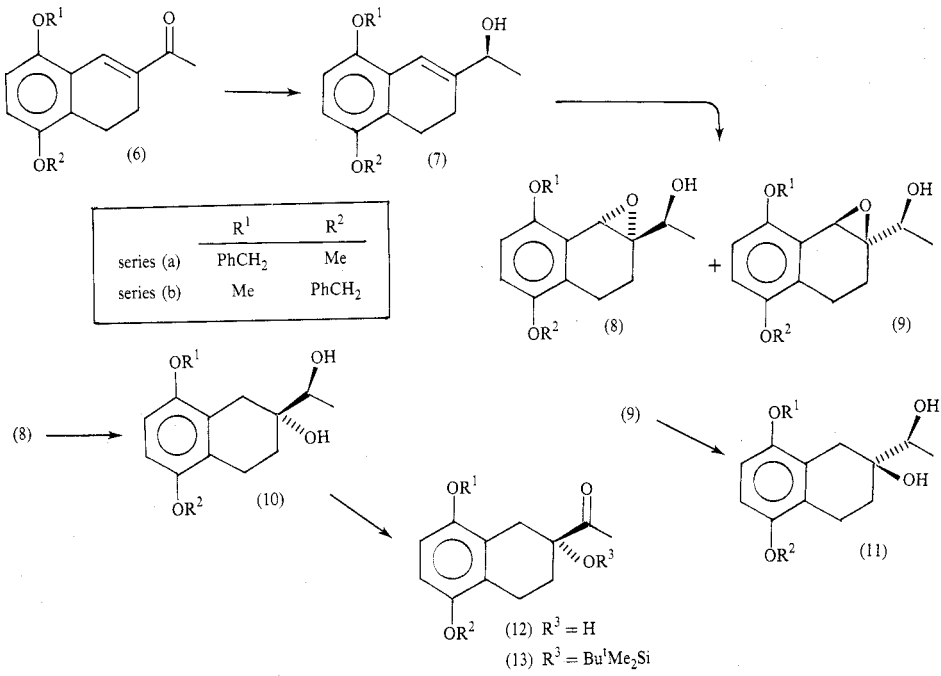
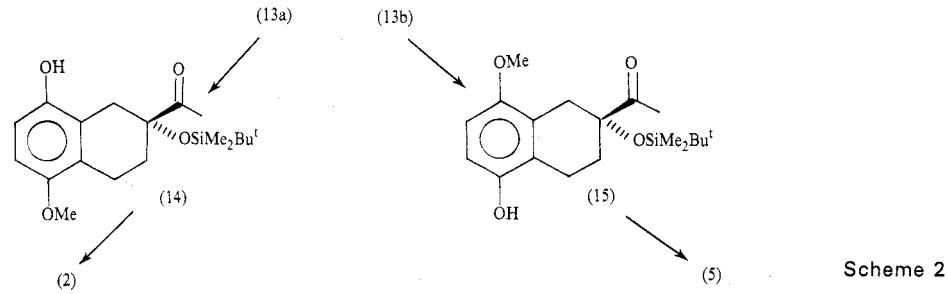


Scheme 1



	R^1	R^2
series (a)	$PhCH_2$	Me
series (b)	Me	$PhCH_2$



Scheme 2

naphthalenes* (6a,b) which we have shown to be readily available from *p*-benzoquinone and buta-1,3-diene.[5,6]

Results and Discussion

Chiral Reduction of Ketones (6a,b)

The reduction of ketones by chiral reagents has been investigated by a number of workers.[7,8] One of the most successful reagents reported to date is that devised by Terashima who has modified lithium aluminium hydride with (−)-*N*-methylephedrine and *N*-ethylaniline.[9,10] This reagent is claimed to exhibit a chiral reaction efficiency[11] comparable with enzymatic reductions, and has already been exploited[10] in the synthesis of optically enriched (+)-4-demethoxydaunomycinone.[12]

We have examined the reduction of ketones (6a,b) with this chiral hydride reagent and have found that, even under the 'optimum conditions' (i.e., an aged reagent prepared from 1 equiv. lithium aluminium hydride, 1 equiv. (−)-*N*-methylephedrine and 2 equiv. *N*-ethylaniline) reported by Tanno and Terashima,[9] the optical yields obtained are variable. The degree of success of this reagent is found to depend on the type of lithium aluminium hydride used in the reaction. Thus highly reactive samples of the hydride (e.g., Alfa pellets) frequently gave low optical yields (*c.* 50% enantiomeric excess) even at −100° whereas less active samples of hydride (e.g., Merck, Metallgesellschaft) at −78° gave high optical yields (*c.* 88% enantiomeric excess). Some variation was also found amongst different batches of lithium aluminium hydride from the same source. Optimization of optical yield was important; this was best achieved by examining the crude reduction products by h.p.l.c. on a chiral phase column and adjusting the mole ratio of reagents and the reaction conditions accordingly (see Experimental). Under these carefully established conditions, the chiral (*S*) alcohol (7a) could be obtained in high optical yield (88% enantiomeric excess). Similarly, (7b) could be obtained in comparable optical yield in small-scale reactions; however, in larger-scale preparations (*c.* 10 g) the optical yield dropped (average 75% enantiomeric excess). It should be noted that, in reactions where the optical yield in the initial reaction was poor, this resulted in an automatic drop in the chemical yield of the isolated chiral (*S*) alcohol since the optical purity was only improved by repeated crystallization.

Synthesis of Dienones (2) and (4) (Scheme 2)

Epoxidation of the enantiomerically pure α,β-unsaturated alcohol (7a) or (7b) with t-butyl hydroperoxide and vanadium(IV) bis(pentane-2,4-dionate) oxide in

* Named in accordance with common usage. For systematic naming (as naphthalenylethanones) see Part XI.[5]

[5] Russell, R. A., Collin, G. J., Crane, M. P., Gee, P. S., Krauss, A. S., and Warrener, R. N., *Aust. J. Chem.*, 1984, **37**, 1721.

[6] Russell, R. A., Collin, G. J., Gee, P. S., and Warrener, R. N., *J. Chem. Soc., Chem. Commun.*, 1983, 994.

[7] Kagan, H. B., and Fiand J. C., 'Topics in Stereochemistry' (Eds E. L. Eliel and N. L. Allinger) Vol. 10 (John Wiley: New York 1978).

[8] Noyari, R., Tomino, I., and Nishazawa, M., *J. Am. Chem. Soc.*, 1979, **101**, 5843.

[9] Tanno, N., and Terashima, S., *Chem. Pharm. Bull.*, 1983, **31**, 837.

[10] Tanno, N., and Terashima, S., *Chem. Pharm. Bull.*, 1983, **31**, 852.

[11] Wilson, J. M., and Cram, D. J., *J. Am. Chem. Soc.*, 1982, **104**, 881.

[12] Tanno, N., and Terashima, S., *Chem. Pharm. Bull.*, 1983, **31**, 821.

benzene according to the method developed by Sharpless proceeded stereoselectively[12,13] to yield, as the major product, the corresponding epoxide (8a) or (8b). These epoxides were immediately reduced with lithium aluminium hydride, without isolation, to yield the derived diols, (10a) or (10b). In the case of the alcohol (7a), this two-step sequence afforded the optically pure (−)-(2*R*,1′*S*)-diol (10a) in 77% yield isolated by direct crystallization. The mother liquors from the crystallization were shown to contain predominantly the (2*S*,1′*S*) diastereomer (11a) (7%) and partly racemized starting material (7a). The production of racemized starting material is considered to arise from competitive oxidation of the chiral alcohol (7a) to the related achiral ketone (6a) by t-butyl hydroperoxide in the first step of the sequence, a reaction with literature precedent.[14] The resulting achiral α,β-unsaturated ketone is slow to epoxidize and so remains largely unchanged at the time of the second step of the sequence, and is accordingly reduced to afford a racemic mixture of alcohol (7a) and its epimer. This side reaction could be minimized, but not entirely eliminated, by conducting the epoxidation of (7a) at as low a temperature as the solvent would permit (*c.* 5°). Similar results were obtained with the chiral alcohol (7b).

Oxidation of the diol (10a) or (10b) was best achieved with silver carbonate supported on Celite.[15] The use of silver carbonate alone resulted in lower yields and, contrary to the literature report, no oxidation was observed with commercial sulfur trioxide–pyridine complex.[16] Oxidation with bromine and bis(tributyltin) oxide was successful, but the product was difficult to free from tin by-products.[17,18] Numerous other oxidants either failed to effect oxidation or resulted in side-chain cleavage, which was also observed, to a minor extent, in the oxidation of (10b) with silver carbonate. The optical purity of the hydroxy ketone, (12a) or (12b), was assessed by h.p.l.c. on a chiral phase column (see Experimental).

Conversion of the hydroxy ketone (12a) or (12b) into the corresponding t-butyldimethylsilyl ether (13a) or (13b) was very slow when a mixture of t-butyldimethylsilyl chloride and imidazole in dimethylformamide was used as reagent.[19] A more efficient procedure was to use the corresponding silyl trifluoromethanesulfonate in the presence of 2,6-dimethylpyridine as catalyst.[20] This latter method initially afforded the bis-silyl derivative from which the enol silyl group could be selectively hydrolysed (methanol/acid resin) *in situ* to afford the desired ketone.

Protection of the tertiary alcohol group in either (12a) or (12b) was, as expected, achieved with complete retention of stereochemistry. The chiral integrity of (13a) could not be evaluated by chiral phase h.p.l.c. since racemic samples of (13a) could not be separated on the available column. The chiral specificity of these reactions was established by treating a sample of the optically pure (−)-hydroxy ketone (12a) with t-butyldimethylsilyl trifluoromethanesulfonate, and subsequently desilylating the resultant product, whereupon no loss of optical purity was detectable by chiral phase h.p.l.c.

[13] Tanaka, S., Yamamoto, H., Nozaki, H., Sharpless, K. B., Michaelson, R. C., and Cutting, J. D., *J. Am. Chem. Soc.*, 1974, **96**, 5254.
[14] Kaneda, K., Kawanishi, Y., Jitsukawa, K., and Teranishi, S., *Tetrahedron Let.*, 1983, 5009.
[15] Fetizon, M., and Golfier, M., *C. R. Acad. Sci.*, 1968, **267**, 900.
[16] Ogilvie, K. K., and Iwacha, D. J., *Tetrahedron Lett.*, 1973, 317.
[17] Ueno, Y., and Okawaro, M., *Tetrahedron Lett.*, 1976, 4597.
[18] Del Nero, S., and Lombardi, P., *Gazz. Chim. Ital.*, 1983, **113**, 125.
[19] Del Nero, S., Gandolfi, C., Lombardi, P., and Arcamone, F., *Chem. Ind.* (*London*), 1981, 810.
[20] Corey, E. J., Cho, H., Rucker, C., and Hua, D. H., *Tetrahedron Lett.*, 1981, 3455.

Hydrogenolysis of the benzyl ether group in (13a) or (13b) afforded the phenol (14) or (15) respectively; the phenols (14) and (15) were oxidized, by our previously reported modification of the thallium(III) nitrate procedure, to form the dienones (2) and (4) respectively, in excellent chemical yield (>95%), with no loss in enantiomeric purity.

Finally, it should be noted that the diols (10a,b) provide access to a variety of dienones with side chains related to anthracyclines other than daunomycin. Work in this area will be reported in subsequent papers.

Experimental

General methods have been reported previously.[5] Chiral phase h.p.l.c. was conducted on Baker DNBPG (ionic or covalent) columns with mixtures of propan-2-ol and hexane as eluents. Flash chromatography was performed on silica (70–230 mesh) from Merck.

(−)-(1′S)-5-Benzyloxy-3-(1′hydroxyethyl)-8-methoxy-1,2-dihydronaphthalene (7a)*

To a stirred suspension of lithium aluminium hydride (760 mg, 20·1 mmol) in ether (50 ml) under a nitrogen atmosphere was added (−)-*N*-methylephedrine (3·68 g, 20·5 mmol), and the mixture heated under reflux for 1 h. *N*-Ethylaniline (5·2 ml, 42·8 mmol) was added, and, after refluxing for a further 1 h, the stirred suspension was cooled to −78° and a solution of 3-acetyl-5-benzyloxy-8-methoxy-1,2-dihydronaphthalene (6a) (1·97 g, 6·4 mmol) in ether (300 ml) introduced dropwise. After a further 1·5 h at −78°, the mixture was warmed to 20° and the excess hydride neutralized with ethyl acetate (50 ml). The mixture was poured into brine (200 ml), and the aqueous phase extracted with ether (2 × 100 ml). The combined organic phases were washed successively with brine (2 × 100 ml), dilute hydrochloric acid (0·1 M, to neutrality), and water (100 ml), then dried, and the solvent was removed in vacuum. The residue was purified by column chromatography on silica (ethyl acetate/light petroleum 1:3) to afford a colourless solid (1·95 g, 98%), $[\alpha]_D$ −20·9°, which was recrystallized once from a mixture of ethyl acetate and light petroleum to afford the title *compound (7a)* as colourless needles (1·79 g, 90%), m.p. 92·5–93·5°, $[\alpha]_D$ −23·7° (*c*, 1·8) (Found: C, 77·3; H, 7·1. $C_{20}H_{22}O_3$ requires C, 77·4; H, 7·2%). I.r. ($CHCl_3$) ν_{max} 3590w, 2940m, 2890m, 2840m, 1590w, 1480s, 1255m, 1095s, 1050m, 880m cm^{-1}. ^1H n.m.r. δ 1·30, d, *J* 7·5 Hz, 3H, H2′; 1·62, br s, 1H, OH; 2·16–2·40, m, 2H, H1; 2·70–2·96, m, 2H, H2; 3·90, s, OCH_3; 4·46, q, 1H, H1′; 5·06, s, 2H, $PhCH_2O$; 6·74, s, 2H, H6,7; 6·90, s, 1H, H4; 7·24–7·60, aromatics. ^{13}C {^1H} n.m.r. δ 20·9, C3 or C4; 21·4, C2′; 21·9, C4 or C3; 56·0, OCH_3; 71·0, $PhCH_2O$; 71·3, C1′; 109·7, 110·6, C6 and C7; 115·6, C1; 124·5, 2C, C4a, C8a; 127·3, 2C, aromatic; 127·7, 1C, aromatic; 128·4, 2C, aromatic; 137·5, aromatic; 143·9, C2; 148·7, 150·5, C5 and C8. Mass spectrum *m/z* 311 (14%), 310 (M, 63), 266 (16), 220 (22), 203 (13), 202 (10), 177 (42), 176 (19), 162 (16), 115 (14), 91 (79), 43 (100).

In subsequent preparations the chromatography step was omitted and the product purified by two recrystallizations from a mixture of ether and light petroleum.

(−)-(2R,1′S)-8-Benzyloxy-2-(1′-hydroxyethyl)-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-ol (10a)

A stirred solution of alcohol (7a) (1·80 g) and vanadium(IV) bis(pentane-2,4-dionate) oxide (18 mg) in benzene (20 ml) was cooled to incipient crystallization and a solution of t-butyl hydroperoxide in benzene (4·2 ml, 3 M) added. The mixture was stirred for 0·7 h and then added dropwise to a stirred suspension of lithium aluminium hydride (1·10 g) in ether (300 ml) under a nitrogen atmosphere. After stirring at room temperature for 1 h, the mixture was refluxed for a further 1 h, cooled, and the excess hydride destroyed by slow addition of ethyl acetate (50 ml). The mixture was poured into brine (150 ml), and extracted with ethyl acetate (2 × 100 ml). The combined organic phase was washed with brine (100 ml) and water (100 ml), dried, and the solvent removed in vacuum. Crystallization of the residue from a mixture of acetone and light petroleum afforded colourless needles (1·63 g, 85%), $[\alpha]_D$ −34·8°. A further recrystallization from propan-2-ol afforded the pure *diastereomer (10a)* as colourless needles (1·46 g, 77%), m.p. 178–179°, $[\alpha]_D$ −38·6° (*c*, 1·4) (Found:

* Systematic name: (−)-(1*S*)-1-(8′-benzyloxy-5′-methoxy-3′,4′-dihydronaphthalen-2′-yl)ethanol.

C, 73·2; H, 7·4. $C_{20}H_{24}O_4$ requires C, 73·2; H, 7·4%). I.r. ($CHCl_3$) ν_{max} 3570w, 2940m, 2834w, 1710w, 1600w, 1460s, 1380m, 1328m, 1257m, 1089s cm^{-1}. ^1H n.m.r. δ 1·26, d, J 6·0 Hz, 3H, H2′; 1·90, br s, 2H, OH; 1·90–2·10, m, 2H, H3; 2·66–2·94, m, 4H, H1,4; 3·74, q, J 6·0 Hz, 1H, H1′; 3·77, s, 3H, OCH_3; 5·02, s 2H, $PhCH_2O$; 6·67, m, 2H, H6,7; 7·18–7·55, m, 5H, aromatics. ^{13}C {^1H} n.m.r. δ 17·2, C2′; 19·9, C3; 29·6, C4; 30·8, C1; 55·6, OCH_3; 70·4, $PhCH_2O$; 72·3, C2; 73·4, C1′; 107·1, 108·9, C6 and C7; 124·5, 126·2, C4a and C8a; 127·1, 2C, aromatic; 127·6, aromatic; 128·5, 2C, aromatic; 137·6, aromatic; 151·0, 151·4, C5 and C8. Mass spectrum m/z 329 (11%), 328 (M, 46), 238 (11), 193 (10), 192 (13), 191 (10), 176 (11), 175 (19), 151 (51), 149 (19), 91 (100), 65 (10), 45 (13), 43 (17).

Column chromatography on silica (ethyl acetate/light petroleum 1:1) of the residue from the mother liquors (0·38 g) yielded, in order of increasing polarity: partly racemized starting material (0·08 g, $[\alpha]_D$ −8·0°); a 9:1 mixture of the (2*S*,1′*S*) and (2*R*,1′*R*) isomers (0·15 g, 8%), m.p. 130–137° (from ether), $[\alpha]_D$ +12·7°; and a 3:1 mixture of the (2*R*,1′*S*) and (2*S*,1′*R*) isomers (0·15 g, 8%), $[\alpha]_D$ −20·4°.

(−)-(2R)-2-Acetyl-8-benzyloxy-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-ol (12a)

A mixture of Fetizon's reagent[15] (7·6 g) and the alcohol (10a) (500 mg) was heated under reflux in benzene (50 ml), and 5 ml distilled off to azeotropically remove water. The mixture was stirred under reflux for 1 h, filtered through Celite, and the solvent evaporated. The residue was decolorized with charcoal in methanol, filtered, and the solvent removed to give a solid (478 mg, 96%). A sample was recrystallized from aqueous methanol to afford the optically pure product (12a) as colourless needles, m.p. 86–87°, $[\alpha]_D$ −24·3° (*c*, 1·11) (lit.[2] m.p. 84·5–85°, $[\alpha]_D$ −22·9°), which had properties identical to those of an authentic sample.[2]

(−)-(2R)-2-Acetyl-8-benzyloxy-2-(t-butyldimethylsilyloxy)-5-methoxy-1,2,3,4-tetrahydronaphthalene (13a)

To a solution of hydroxy ketone (12a) (175 mg) in dry dichloromethane (2 ml) under argon were added 2,6-dimethylpyridine (256 μl, 4 equiv.) and t-butyldimethylsilyl trifluoromethanesulfonate[18] (372 μl, 3 equiv.), and the mixture was stirred for 1 h at 15°. Methanol (2·5 ml) and Bio-Rad AG 50W-X4 (H^+ form) resin (50 mg) were added, and stirring was continued for a further 10 min. The solution was filtered through Celite; the filtrate was diluted with dichloromethane (50 ml) and washed successively with water (2 × 20 ml), dilute hydrochloric acid (20 ml, 0·01 M) and water (20 ml), then dried and the solvent evaporated. Flash chromatography of the residue on silica (ethyl acetate/hexane 1:33) afforded the title *compound (13a)* as a colourless oil (225 mg, 96%) which crystallized upon trituration with light petroleum. Recrystallization of a sample of the resulting solid afforded colourless needles, m.p. 93–94°, $[\alpha]_D$ −13·0° (*c*, 1·23) (Found: C, 70·9; H, 8·3. $C_{26}H_{36}O_4Si$ requires C, 70·9; H, 8·2%). I.r. (neat) ν_{max} 2950s, 2855m, 1715s, 1604m, 1470s 1386m, 1350m, 1332m, 1250s, 1205m, 1158w, 1100(br)s, 1040s, 835m, 780m, 732m, 695m cm^{-1}. ^1H n.m.r. δ −0·20, s, 3H, $SiCH_3$; 0·08, s, 3H, $SiCH_3$; 0·87, s, 9H, $SiC(CH_3)_3$; 1·90, m, 2H, H3; 2·10, s, 3H, $COCH_3$; 2·70–3·42, m, 4H, H1,4; 3·79, s, 3H, OCH_3; 5·06, s, 2H, $PhCH_2O$; 6·67, m, 2H, H6,7; 7·25–7·53, m, 5H, aromatics. ^{13}C {^1H} n.m.r. δ −3·4, $SiCH_3$; −3·0, $SiCH_3$; 18·3, $SiC(CH_3)_3$; 20·1, C3; 24·3, C2′; 25·9, 3C, $SiC(CH_3)_3$; 31·7, 2C, C1, C4; 55·6, OCH_3; 70·2, $PhCH_2O$; 79·5, C2; 106·9, 108·6, C6 and C7: 124·9, 125·5, C4a and C8a; 127·0, 2C, aromatics; 127·6, 1C, aromatic; 128·4, 2C, aromatics; 137·7, 1C, aromatics; 150·5, 151·1, C5 and C8; 210·9, C1′. Mass spectrum m/z 440 (M, <1%), 394 (11), 393 (37), 384 (31), 383 (100), 306 (28), 292 (22), 277 (11), 143 (19), 91 (74), 75 (19), 73 (47).

(−)-(7R)-7-Acetyl-7-(t-butyldimethylsilyloxy)-4-methoxy-5,6,7,8-tetrahydronaphthalene-1-ol (14)

A solution of the ether (13a) (400 mg) in ethyl acetate (5 ml) and acetic acid (1 drop) was stirred with 10% palladium on charcoal (100 mg) under hydrogen at 1 atm and ambient temperature for 16 h. The catalyst was removed by filtration and the filtrate evaporated to afford the title *compound (14)* as an unstable colourless syrup (315 mg, 99%). Column chromatography on silica (ethyl acetate/light petroleum 1:3) afforded a heart fraction with $[\alpha]_D$ −3·3° (*c*, 1·10) which decomposed slowly. I.r. (neat) ν_{max} 3400m, 2960s, 2935s, 2900m, 2865m, 1717s, 1614m, 1495s, 1468s, 1442s, 1364m, 1355m, 1333m, 1265s, 1095s, 1042m, 991m, 838s, 779s cm^{-1}. ^1H n.m.r. δ −0·20, s, 3H, $SiCH_3$;

0·09, s, 3H, $SiCH_3$; 0·85, s, 9H, $SiC(CH_3)_3$; 1·94, m, 2H, H 6; 2·10, s, 3H, $COCH_3$; 2·68–3·36, m, 4H, H 5,8; 3·76, s, 3H, OCH_3; 5·70, br s, 1H, OH; 6·56, s, 2H, H 2,3. ^{13}C {^1H} n.m.r. δ −3·4, $SiCH_3$; −3·1, $SiCH_3$; 18·2, $SiC(CH_3)_3$; 20·1 C 6; 24·2, C 2′; 25·7, $SiC(CH_3)_3$; 31·6, 2C, C 5, C 8; 55·7, OCH_3; 79·4, C 7; 107·9, C 3; 111·6, C 2; 122·5, 125·5, C 4a and C 8a; 147·4, C 1; 151·0, C 4; 211·4, C 1′. Mass spectrum *m/z* 350 (M, <1%), 335 (M−15, <5) (Found: 335·168. $C_{18}H_{27}O_4Si$ requires 335·168), 308 (14), 307 (55), 294 (23), 293 (100), 177 (19), 175 (21), 143 (24), 75 (31), 73 (83).

(−)-(7R)-7-Acetyl-7-(t-butyldimethylsilyloxy)-4,4-dimethoxy-5,6,7,8-tetrahydronaphthalene-1(4H)-one (2)

A mixture of the phenol (14) (160 mg) and sodium bicarbonate (160 mg) in a mixture of methanol (6 ml), tetrahydrofuran (3 ml) and trimethyl orthoformate (3 ml) was stirred at 0°, and thallium(III) nitrate trihydrate (208 mg) added. The mixture was stirred at 0° for 0·25 h, poured into water (50 ml), and extracted with dichloromethane (2 × 25 ml). The combined organic phases were washed with water (2 × 20 ml), dried, and the solvent was removed in vacuum to give a pale yellow syrup which was column chromatographed on silica (acetone/petroleum 1:4) to yield the title *compound (2)* as a colourless syrup (161 mg, 93%), $[\alpha]_D$ +10·8° (*c*, 3·56). I.r. (neat) ν_{max} 2950s, 2900m, 2860s, 1720s, 1675s, 1650s, 1625s, 1463s, 1430m, 1400m, 1361s, 1300s, 1286s, 1260s, 1208m, 1122s, 1100s, 1065s, 1030s, 964s, 915m, 872m, 838s, 823s, 775s, 732s cm^{-1}. ^1H n.m.r. δ −0·08, s, 3H, $SiCH_3$; −0·05, s, 3H, $SiCH_3$; 0·80, s, 9H, $SiC(CH_3)_3$; 1·80, m, 2H, H 6; 2·18, s, 3H, $COCH_3$; 2·20–3·00, m, 4H, H 5,8; 3·08, s, 3H, OCH_3; 3·18, s, 3H, OCH_3; 6·40, d, *J* 10 Hz, 1H, H 3; 6·73, d, *J* 10 Hz, 1H, H 2. Mass spectrum *m/z* 380 (M, <1%), 338 (27), 337 (M−43, 100) (Found: 337·185. $C_{18}H_{29}O_4Si$ requires 337·183), 324 (17), 323 (69), 308 (15), 307 (48), 306 (13), 263 (15), 217 (14), 205 (26), 143 (45), 75 (38), 73 (93).

(−)-(1S)-8-Benzyloxy-3-(1′-hydroxyethyl)-5-methoxy-1,2-dihydronaphthalene (7b)*

(−)-*N*-Methylephedrine (20·94 g, 116·8 mmol) was added in small portions (of *c.* 1 g) to a stirred suspension of lithium aluminium hydride (4·28 g, 113 mmol) in ether (500 ml), under an atmosphere of argon, and the mixture refluxed for 2 h. A solution of *N*-ethylaniline (28·26 g, 233·2 mmol) in ether (150 ml) was then added slowly so as to maintain gentle reflux.

After heating under reflux for a further 80 min, the mixture was cooled to −78°, and a solution of 3-acetyl-8-benzyloxy-5-methoxy-1,2-dihydronaphthalene (6b) (5·90 g, 19·1 mmol) in ether (600 ml) added dropwise over a period of 1·25 h. The reaction mixture was stirred for a further 1 h at −78°, and the reaction quenched by the addition of ethyl acetate (200 ml). The mixture was poured onto brine (400 ml), and acidified with dilute hydrochloric acid (6·5%, 400 ml). The organic layer was separated, and washed successively with dilute hydrochloric acid (6·5%, 100 ml), water (500 ml), saturated sodium bicarbonate solution (500 ml) and brine (500 ml). The dry ethereal solution was freed of solvent to afford a colourless solid (5·80 g), $[\alpha]_D$ −21·4° (*c*, 0·98), which was recrystallized twice from a mixture of dichloromethane, ether and light petroleum to yield the optically pure *alcohol (7b)* as colourless needles (4·55 g, 77%), m.p. 119–121°, $[\alpha]_D$ −23·9° (*c*, 0·90) (Found: C, 77·7; H, 7·3. $C_{20}H_{22}O_3$ requires C, 77·4; H, 7·1%). I.r. ν_{max} 3230(br)w, 1255m, 1090w, 875w, 790w cm^{-1}. ^1H n.m.r. (270 MHz) δ 1·35, d, *J* 6·5 Hz, 3H, H 2′; 1·69, br s, 1H, OH; 2·13–2·38, m, 2H, H 2; 2·72–2·97, m, 2H, H 1; 3·78, s, 3H, OCH_3; 4·46, dq, *J* 6·5, 1·3 Hz, 1H, H 1′; 5·01, s, 2H, $PhCH_2O$; 6·63, 6·75, d, *J* 8·9 Hz, 1H each, H 6,7; 6·79, dd, *J* 2·5, 1·3 Hz, 1H, H 4; 7·26–7·46, m, 5H, ArH. ^{13}C {^1H} n.m.r. δ 21·2, C 3 or C 4; 21·5, C 2′; 22·1, C 4 or C 3; 56·0, OCH_3; 71·1, $PhCH_2O$; 71·4, C 1′; 108·7, 111·9, C 6 and C 7; 115·4, C 1; 124·1, 125·4, C 4a and C 8a; 127·3, 2C, aromatic; 127·8, 1C, aromatic; 128·5, 2C, aromatic; 137·7, 1C, aromatic; 144·0, C 2; 149·6, 150·0, C 5 and C 8. Mass spectrum *m/z* 310 (M, 4%), 293 (11), 292 (46), 202 (19), 201 (100), 200 (14), 199 (10), 186 (23), 185 (12), 173 (13), 171 (10), 170 (17), 169 (13), 158 (10), 141 (24), 128 (11), 115 (13), 91 (84), 77 (11), 70 (10), 65 (11).

(−)-(2R,1′S)-5-Benzyloxy-2-(1′-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydronaphthalen-2-ol (10b)

A stirred solution of the (−)-alcohol (7b) (8·30 g) and vanadium(IV) bis(pentane-2,4-dionate) oxide (83 mg) in benzene (160 ml) was cooled to incipient crystallization, and a solution of t-butyl

* Systematic name: (−)-(1*S*)-1-(5′-benzyloxy-8′-methoxy-3′,4′-dihydronaphthalen-2′-yl)ethanol.

hydroperoxide in benzene (20 ml, 3 M) added. The resulting mixture was stirred for 1·5 h, and added dropwise to a stirred suspension of lithium aluminium hydride (5·0 g) in ether (800 ml), under argon. After stirring at room temperature overnight, the excess hydride was destroyed with ethyl acetate (150 ml). Brine (100 ml) was then added, and the mixture filtered. The organic layer was separated, washed successively with water (1 l.) and brine (1 l.), dried, filtered and evaporated under reduced pressure. The crude product was precipitated from a hot mixture of acetone (20 ml) and light petroleum (200 ml). Recrystallization from propan-2-ol gave the optically pure *diol* (*10b*) as colourless needles (6·72 g, 77%), m.p. 148–150°, $[\alpha]_D$ −34·4° (*c*, 1·02) (Found: C, 73·2; H, 7·3. $C_{20}H_{24}O_4$ requires C 73·2; H, 7·4%). I.r. (Nujol) ν_{max} 3290(br)w, 1225w, 1084w, 1030w, 795w cm^{-1}. ^1H n.m.r. (270 MHz) δ 1·27, d, *J* 6·4 Hz, 3H, H2′; 1·62, ddd, *J* 13· 6, 11·5 Hz, 1H, H3*ax*; 1·94, dddd, *J* 13, 6, 3, 2·5 Hz, 1H, H3*eq*; 1·98, s, 2H, OH; 2·57, d, *J* 18 Hz, 1H, H1*ax*; 2·70–2·85, m, 1H, H4*ax*; 2·81, dd, *J* 18, 2·5 Hz, 1H, H1*eq*; 3·00, ddd, 1H, *J* 18, 6, 3 Hz, 1H, H4*eq*; 3·72, q, *J* 6·4 Hz, 1H, H1′; 3·76, s, 3H, OCH_3; 5·02, s, 2H, $PhCH_2O$; 6·65, AB q, *J* 8·8 Hz, 2H, H6,7; 7·26–7·46, m, 5H, ArH. ^{13}C {^1H} n.m.r. δ 17·2, C2′; 20·1, C3; 29·6, C4 or C1; 30·6, C1 or C4; 55·5, OCH_3; 70·4, $PhCH_2O$; 72·3, C2; 73·6, C1′; 107·0, 108·8, C6 and C7; 124·1, 126·7, C4a and 8a; 127·2, 2C, aromatic; 127·7, 1C, aromatic; 128·5, 2C, aromatic; 137·8, 1C, aromatic; 150·3, 152·2, C5 and C8. Mass spectrum *m*/*z* 328 (M, 4%), 310 (14), 292 (11), 219 (10), 201 (23), 191 (10), 175 (44), 160 (12), 92 (11), 91 (100).

(−)-(2R)-*2-Acetyl-5-benzyloxy-8-methoxy-1,2,3,4-tetrahydronaphthalen-2-ol* (*12b*)

A stirred mixture of the (−)-diol (10b) (5·85 g) and Fetizon's reagent (55 g) in benzene (420 ml) was distilled until 70 ml of distillate were collected. The mixture was stirred under reflux for a further 1 h, cooled, filtered through Celite, and the solvent evaporated. The residue was flash-chromatographed on silica (ethyl acetate/light petroleum 1:60) to give the *hydroxy ketone* (*12b*) (4·66 g, 80%), a sample of which was recrystallized from ether/cyclohexane as colourless prisms, m.p. 109–110°, $[\alpha]_D$ −34·1° (*c*, 1·06) (Found: C, 73·3; H, 7·0. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%). I.r. ν_{max} 3470(br)w, 1715s, 1605w, 1255s, 1200w, 1120m, 1100s, 1075m, 975w, 955w, 807s, 745s cm^{-1}. ^1H n.m.r. (270 MHz) δ 1·79–2·01, m, 2H, H3; 2·30, s, 3H, $COCH_3$; 2·77, dd, *J* 17, 2·5 Hz, 1H, H1*eq*; 2·78–3·11, m, 1H, H4*ax*; 2·95, d, *J* 17 Hz, 1H, H1*ax*; 3·05, ddd, *J* 17, 6, 2·5 Hz, 1H, H4*eq*; 3·38, br s, 1H, OH; 3·74, s, 3H, OCH_3; 5·01, s, 2H, $PhCH_2O$; 6·66, AB q, *J* 8·8 Hz, 2H, H6,7; 7·25–7·45, m, 5H, ArH. ^{13}C {^1H} n.m.r. δ 19·5, C3; 23·9, C2′; 29·8, 32·5, C1 and C4; 55·5, OCH_3; 70·4, $PhCH_2O$; 76·5, C2; 107·1, 109·1, C6 and C7; 123·0, 126·2, C4a and C8a; 127·2, 2C, aromatic; 127·7, 1C, aromatic; 128·5, 2C, aromatic; 137·7, 1C, aromatic; 150·3, 151·9, C5 and C8; 212·3, C1′. Mass spectrum *m*/*z* 326 (M, 12%), 217 (11), 215 (10), 175 (47), 160 (12), 92 (10), 91 (100), 65 (10).

(+)-(2R)-*2-Acetyl-5-benzyloxy-2-(t-butyldimethylsilyloxy)-8-methoxy-1,2,3,4-tetrahydronaphthalene* (*13b*)

t-Butyldimethylsilyl trifluoromethanesulfonate (5·0 ml) was added to a stirred solution of the (−)-hydroxy ketone (12b) (2·60 g) and 2,6-dimethylpyridine (3·9 ml) in dichloromethane (40 ml) under argon, and the resulting mixture was stirred for 2 h. Methanol (75 ml) and Bio-Rad AG 50W-X4 (H^+ form) (6 g) were added, and stirring was continued for a further 2 h. The mixture was filtered, and the filtrate partitioned between dichloromethane (200 ml) and saturated sodium bicarbonate solution (100 ml). The organic layer was separated, and the aqueous phase extracted with dichloromethane (100 ml). The combined organic extracts were washed successively with dilute hydrochloric acid (500 ml, 0·1 M), water (500 ml) and brine (500 ml), and dried. The residue recovered from the organic extract was subject to flash chromatography on silica (ethyl acetate/light petroleum 3:97) to afford the pure *ether* (*13b*) as a colourless syrup (3·25 g, 93%), $[\alpha]_D$ +1·4°, $[\alpha]_{365}$ −27·0° (*c*, 0·99) (Found: C, 71·1; H, 6·4. $C_{26}H_{36}O_4Si$ requires C, 70·9; H, 8·2%). I.r. (neat) ν_{max} 2915s, 2850s, 1715s, 1600m, 1465s, 1435s, 1380m, 1345m, 1245s, 1200m, 1090s, 1025s, 825s, 770s, 725s, 684s cm^{-1}. ^1H n.m.r. (270 MHz) δ −0·25, s, 3H, $SiCH_3$; 0·07, s, 3H, $SiCH_3$; 0·83, s, 9H, $SiC(CH_3)_3$; 1·73–2·04, m, 2H, H3; 2·28, s, 3H, $COCH_3$; 2·74–2·91, m, 2H, H4; 2·80, dd, *J* 18, 2 Hz, 1H, H1*eq*; 3·18, d, *J* 18 Hz, 1H, H1*ax*; 3·77, s, 3H, OCH_3; 5·02, AB q, *J* 12 Hz, 2H, $PhCH_2O$; 6·63, AB q, *J* 8·8 Hz, 2H, H6,7; 7·30–7·44, m, 5H, ArH. ^{13}C {^1H} n.m.r. δ −3·4, $SiCH_3$; −3·0, $SiCH_3$; 18·4, $SiC(CH_3)_3$; 20·4, C3; 24·2, C2′; 25·9, 3C $SiC(CH_3)$; 31·6, 2C, C1, C4; 55·6, OCH_3; 70·4, $PhCH_2O$; 79·5, C2; 107·0, 109·0, C6 and C7; 125·0, 126·2,

C4a and C 8a; 127·1, 2C, aromatic; 127·6, 1C, aromatic; 128·4, 2C, aromatic; 137·8, 1C, aromatic; 150·1, 151·7, C 5 and C 8; 210·8, C 1′. Mass spectrum *m/z* 398 (M, 14%), 397 (43), 385 (10), 384 (23), 383 (92), 268 (11), 267 (44), 175 (14), 143 (28), 92 (11), 91 (100), 75 (28), 74 (12), 73 (93).

(−)-(6R)-*6-Acetyl-6-(t-butyldimethylsilyloxy)-4-methoxy-5,6,7,8-tetrahydronaphthalen-1-ol* (*15*)

A mixture of the (+)-benzyl ether (13b) (3·25 g), 10% palladium on charcoal (200 mg) and acetic acid (8 drops) in ethyl acetate (180 ml) was stirred under hydrogen for 65 h. The residue obtained after filtration and evaporation was flash-chromatographed on silica (ethyl acetate/light petroleum 1:12) to give the pure *phenol* (*15*) as a colourless syrup (2·57 g, 99%) which slowly decomposed, $[\alpha]_D$ −13·8°, $[\alpha]_{365}$ −82·6° (*c*, 0·98) (Found: C, 65·2; H, 8·7. $C_{19}H_{30}O_4Si$ requires C, 65·1; H, 8·6%). I.r. ν_{max} 3350s, 1710s, 1615w, 1495m, 1265s, 1160m, 1125m, 1080s, 1020m, 885w, 865w, 840s, 815s, 780s cm^{-1}. ^1H n.m.r. (270 MHz) δ −0·26, s, 3H, $SiCH_3$; 0·08, s, 3H, $SiCH_3$; 0·82, s, 9H, $SiC(CH_3)_3$; 1·74–2·06, m, 2H, H 7; 2·29, s, 3H, $COCH_3$; 2·66–2·90, m, 2H, H 8; 2·80, dd, *J* 18, 2 Hz, 1H H 5*eq*; 3·16, d, *J* 18 Hz, 1H, H 5*ax*; 3·76, s, 3H, OCH_3; 5·52, br s, 1H, OH; 6·58, AB q, *J* 8·7 Hz, 2H, H 2,3. ^{13}C {^1H} n.m.r. δ −3·5, $SiCH_3$; −3·1, $SiCH_3$; 18·3, $SiC(CH_3)_3$; 20·0, C 7; 24·3, C 2′; 25·8, 3C, $SiC(CH_3)_3$; 31·4, 31·5, C 5 and C 8; 55·7, OCH_3; 79·3, C 6; 107·8, C 3; 111·7, C 2; 123·3, 124·2, C 4a and C 8a; 146·8, C 1; 151·4, C 4; 211·3, C 1′. Mass spectrum *m/z* 308 (M, 19%), 307 (63), 294 (24), 293 (100), 249 (12), 177 (42), 175 (15), 163 (13), 143 (24), 117 (10), 84 (34), 78 (34), 75 (31), 73 (94), 69 (45), 58 (23), 57 (98), 56 (38).

(+)-(6R)-*6-Acetyl-6-(t-butyldimethylsilyloxy)-4,4-dimethoxy-5,6,7,8-tetrahydronaphthalene-1*(4H)-*one* (*5*)

A stirred mixture of the (−)-phenol (15) (2·55 g) and sodium bicarbonate (2·55 g) in methanol (100 ml), tetrahydrofuran (65 ml) and trimethyl orthoformate (65 ml) was cooled to 0°. Thallium(III) nitrate trihydrate (3·50 g) was added and the mixture stirred at 0° for 1·5 h. The reaction mixture was poured into water (600 ml), and extracted with dichloromethane (1 × 300 ml, 1 × 150 ml). The combined extracts were washed with water (500 ml) and brine (500 ml), then dried and freed of solvent. Flash chromatography on silica (ethyl acetate/light petroleum 4:50) of the residue afforded the *dienone* (*5*) as a pale yellow syrup (2·64 g, 95%), $[\alpha]_D$ +52·9° (*c*, 1·08) (Found: C, 63·2; H, 8·6. $C_{20}H_{32}SiO_5$ requires C, 63·1; H, 8·5%). I.r. (neat) ν_{max} 2950s, 2860s, 1720s, 1675s, 1650s, 1625s, 1462m, 1400m, 1360m, 1294m, 1255s, 1206m, 1100s, 1062s, 968m, 938m, 871m, 833s, 775s, 727w, 670m, 640w cm^{-1}. ^1H n.m.r. (270 MHz) δ 0·12, s, 6H, $Si(CH_3)_2$; 0·89, s, 9H, $SiC(CH_3)_3$; 1·77–2·02, m, 2H, H 7; 2·16–1·84, m, 4H, H 5,8; 2·25, s, 3H, $COCH_3$; 3·27, s, 3H, OCH_3; 3·29, s, 3H, OCH_3; 6·41, d, *J* 10·3 Hz, 1H, H 3; 6·78, d, *J* 10·3 Hz, 1H, H 2. Mass spectrum *m/z* 338 (M, 10%), 337 (36), 308 (12), 307 (43), 306 (29), 305 (100), 294 (15), 293 (60), 292 (15), 291 (52), 278 (12), 277 (51), 264 (10), 263 (31), 240 (16), 247 (14), 234 (10), 231 (12), 217 (12), 201 (10), 193 (12), 177 (44), 175 (53), 163 (21), 160 (11), 146 (10), 143 (44), 131 (21), 117 (20), 115 (16), 89 (17), 77 (10), 75 (87), 74 (23), 73 (72), 50 (22).

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