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Synthesis and proof of stereostructure of a new (+)-isomenthone-derived homochiral 1,3-diol

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Abstract

Diastereopure (+)-isomenthone-derived ketoalcohol **2** was converted to the homochiral 1,3-diol **6** either by direct reduction or reduction of silyl protected derivatives. The diastereomeric preference of the reduction was the same in all cases. Reduction of **2** with $NaBH_4$ gave essentially a single diastereomer, while reduction with $LiAlH_4$ gave ~6:1 selectivity in favour of the same diastereomer. Reduction of the silyl protected substrates **7** and **8** gave, after column chromatography, 98% yield of a single diastereomer, desilylation of which established this to be the same diastereomer as obtained through hydride reductions of unprotected **2**. The structure of diol **6** was proven through coupling data and NOE experiments at 600 MHz. Overall, two stereochemistry introducing steps have elaborated the two stereogenic centres of (+)-isomenthone to the five contiguous stereogenic centres of **6**.

1. Introduction

Terpenones and terpenols are a valuable source of chiral materials for the synthesis of a range of chiral controllers.[1] While menthone has seen many successful applications, the epimeric isomenthone system has been far less utilized. In 1990 we proposed C_2 or *pseudo*-C_2 chiral cyclic ketones (derived by asymmetric synthesis or from carbohydrate or terpene starting materials) as precursors for asymmetric epoxidation through the intermediacy of dioxiranes derived from such ketones.[2] During the synthesis of one target class of *pseudo*-C_2 chiral cyclic ketones, ketoalcohols **2** and/or **3** were synthesized from (+)-isomenthone **1**. The diastereomeric outcome of the aldol reactions providing these ketoalcohols was shown to be influenced by choice of reaction conditions, with *Si*-face addition being kinetically preferred

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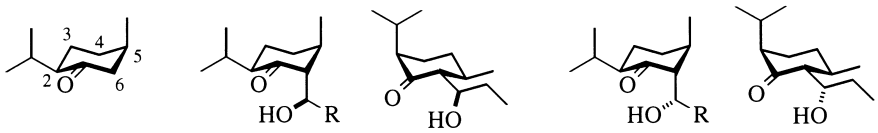
with a range of aldehyde substrates.[3] Since there are relatively few applications of (+)-isomenthone as a chiral pool source of chiral controllers, we are also interested in exploring these aldol derivatives as intermediates for synthesis of various types of novel bifunctional homochiral compounds with potential applications in asymmetric synthesis. We thus considered the elaboration of these ketoalcohols to new chiral 1,3-diols, and report here the synthesis of the diastereopure homochiral 1,3-diol **6** which contains five contiguous stereogenic centres and proof of its stereochemistry through NMR experiments at 600 MHz.



1 **2a** **2b** **3a** **3b**

2. Results and discussion

The reduction of the cyclohexanones of types **2** or **3** (alternate conformers shown) could be influenced by a number of factors, including the ring conformation and the stereoelectronic preferences of axial versus equatorial reduction, coupled with the steric requirements of the C2 (and C6 if present) substituents in the reactive conformation. Additionally, with some reducing agents the influence of the free OH on reagent direction could be considered. X-Ray structures of several of the ketoalcohols of types **2** and **3** all indicate that the ketoalcohols in the solid state adopt the conformation with the isopropyl *equatorial*, as shown for **2a** and **3a**.[3,4] However, NMR analyses indicate a *trans*-diaxial H1–H2 relationship suggesting that in solution the ketoalcohols adopt the alternate cyclohexyl conformer with an axial isopropyl. We proceeded with ketoalcohol **4** (which has the stereochemistry of generic diastereomer **2**) as the substrate for further elaboration through reduction. The NMR-derived conformational evidence for the solution structure of **4** leads to an anticipation of axial hydride delivery being sterically and stereoelectronically preferred *anti* to the (axial) isopropyl, generating a diol product with *trans* disposed C1 hydroxyl and C2 hydroxyalkyl substituents, i.e., diol **6**.

Reduction of ketoalcohol **4** with sodium borohydride (at ambient temperature, MeOH) afforded, with high selectivity, one of the two possible diols **5** or **6** [**6** is represented in the ring conformation with three equatorial groups (related to the NMR-derived conformation of precursor **4** shown) and **5** represents equatorial hydride addition to conformer **4**]. Analogous reduction of **4** with lithium aluminium hydride (between 0°C and r.t., THF) provided a mixture of diol diastereomers but favouring (~6:1 ratio) the *same diastereomer* as obtained by reduction with $NaBH_4$. To evaluate the effect of any free hydroxyl involvement, reductions were also carried out using the two silyl ether protected derivatives **7** and **8**. Reduction of both **7** and **8** provided single diastereomeric products in 98% purified yield, and desilylation provided a diol product which was identical to that formed from reduction of the *unprotected* ketoalcohol with a hydride reagent. We thus wished to establish the diol as being **6** or **5**.

Proof of whether the stereostructure of the diol was not trivial by NMR. There is extensive signal overlap, and the connectivity, *via* the C6 proton, between protons on the two hydroxyl bearing carbons is complicated both by this fact and by the rotational options for the side chain and conformational possibilities for the ring (although *predicted* conformations for **5** and **6** are shown, this is perhaps less certain in **5** than **6**).[5]

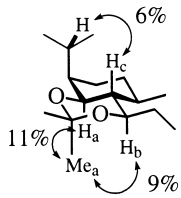
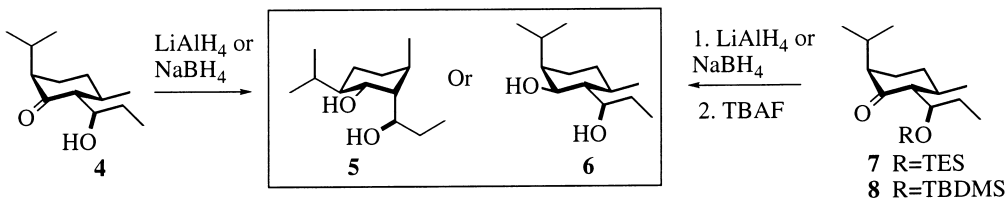
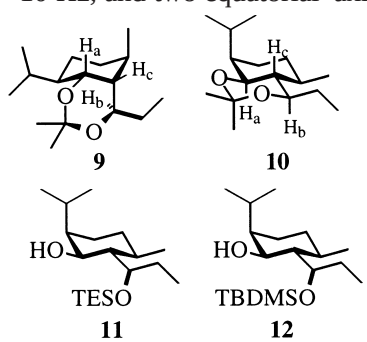


Fig. 1. Key NOE effects establishing diastereostructure



To resolve the diastereomeric assignment by NMR methods, we prepared the isopropylidine acetal derivative of the diol obtained, to freeze out rotational effects about the important C–C bond to C6, and restrict the conformational freedom of the cyclohexyl ring by forming a decalin-type bicycle. Diol **5** would give rise to acetal **9**, and diol **6** to acetal **10**. The isopropylidine acetal derivative is thus either **9** or **10**. Decoupling experiments indicated that both H_a and H_b are coupled to a third proton, H_c (at 1.34 ppm) which appears as a ddd with couplings of 9.5, 10.2 and 10.5 Hz. This is consistent with the three diaxial couplings expected for H_c in **10**, but inconsistent with the expected pattern for H_c in **9** (which would have one diaxial coupling of ~10 Hz, and two equatorial–axial couplings of ~3 Hz).



NOE experiments (Fig. 1) further confirm the structure, with large NOEs between H_a, H_b and the axial isopropylidene acetal methyl group, and a 6% NOE between H_c and the isopropyl hydrogen (Fig. 1). In the alternative diastereomer **9**, H_a and H_b are on *opposite* faces of the bicyclic system, and H_c and the isopropyl group are 1,3-diequatorial, and thus key observed NOEs would be impossible in this alternative. Further confirmation of the structure is provided by all the NMR data (Table 1 and Fig. 2). Thus, NMR unambiguously establishes that reduction of **4**, or its hydroxyl-protected analogues, with $NaBH_4$ or $LiAlH_4$ gives good or essentially complete diastereoselectivity in favour of diastereomeric 1,3-diol **6**. Additionally, the monosilylated diol products from **7** and **8** can thus be unambiguously identified as **11** and **12** respectively.

In summary, overall, the *two stereogenic centres* of (+)-isomenthone have been elaborated to **6** (in two stereochemistry introducing steps) which has *five contiguous stereogenic centres*, the configurations of all centres now unambiguously established through a combination of X-ray determinations[3,4] and NMR. The outcomes are consistent with axial reduction of conformers with an axial isopropyl group. This can

Table 1
^{1}H NMR resonances and assignments for **10**

Site	Proton	δ_H	J_{HH} (Hz)	NOE responses
	Me_a	1.38 (s)		a (11%), b (9%)
	Me_e	1.35 (s)		none
1	a	3.75 (dd)	10.5, 4.1	b (3%), d (2%), Me_a (1%)
2	d	1.44 (m)		
3	e	~1.28 (m)		
3	f	1.78 (dm)†	4†	
4	g	1.38 (m)†		f (3.5%), j (4%)
4	j	1.20 (dq)†	4, 3x10-11†	
5	h	1.26 (m)†		
6	c	1.35 (ddd)	10.5, 10.2, 9.3	$H_{i\text{-Pr}}$ (6%), H_{CH_2} (2%)
7	b	3.49 (ddd)	9.3, 2.8, 7.9	a (2.5%), CH_2 (1%), Me_a (1%)
8p	$H_{(CH_2)}$	1.49 (ddq)	3x7.3, 7.9, 14.3	H_{8q} (5%)
8p	$H_{(CH_2)}$	1.78 (ddq)	3x7.3, 2.8, 14.3	H_{8p} (6%)
9	Me_{ethyl}	0.92 (t)	3x7.3	H_{8p} (1%), H_{8q} (2%), c (1%), j (2%)
	$H_{i\text{-Pr}}$	1.91 (dsept)	3x6.7, 9.0	$Me_{i\text{-Pr}}$ (1%), c (3%), j (1%)
	$Me_{i\text{-Pr}}$	0.88 (d)	6.7	$H_{i\text{-Pr}}$ (4%)
	$Me_{i\text{-Pr}}$	1.06 (d)	6.7	f (2%), $H_{i\text{-Pr}}$ (5%)
	$Me_{(5)}$	0.98 (t)	6.2	c (1.5%), j (3%), $H_{(CH_2)}$ (1%)

†Estimated from NOE difference or spin decoupling difference spectra

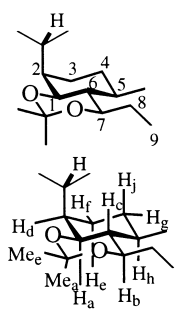


Fig. 2. Site numbers and labels for NMR data in Table 1

be rationalized by considering that the alternate hydride addition on conformer **4** is hindered by an axial isopropyl and two axial hydrogens.

Having established the diastereomeric outcome of the reduction as affording the novel diol **6**, the diol can now be employed for synthesis of chiral controllers, or could be used directly as a 1,3-diol ligand. The use of 1,3-bifunctional ligands such as **6** or derivatives, is of interest because these could form 6-membered chelates which would be able to adopt the *trans*-decalin type conformation seen for the isopropylidine acetal. Functionalization is also available by hydroxyl derivatizations, for example, to provide bifunctional ligands such as bis(diarylphosphinites).[6] The synthesis of other bifunctional ligands from 1,3-diols analogous to **6**, and evaluation as catalysts are planned.

3. Experimental

3.1. General methods and materials

Nuclear magnetic spectra (^{1}H and ^{13}C) were recorded using Bruker AC-200 and AC-300 (UMIST) instruments. 600 MHz NMR data were obtained through the EPSRC Ultra-High Field NMR Service at Edinburgh University. Spectra were recorded in deuterated chloroform ($CDCl_3$) with tetramethylsilane as the internal standard. Chemical shifts (δ) are reported in ppm. ^{13}C substitutions are assigned with the aid of DEPT experiments where indicated. Infrared spectra were obtained using a Perkin–Elmer 1600 FTIR instrument. Chemical ionisation (c.i.) spectra and fast atom bombardment (FAB) spectra were obtained on VG 70/70 Hybrid, or Kratos MS-50TC [FAB] spectrometers. Microanalyses were performed at UMIST microanalysis service. UV spectra were recorded using a Perkin–Elmer Lambda 15 UV/VIS ultraviolet spectrophotometer and infra-red spectra were obtained using Perkin–Elmer 1605 FTIR and 783 instruments. Optical rotations were measured at 589 nm in a 2 mL cell using an AA100 optical activity polarimeter; concentrations are given in g/100 mL of CH_2Cl_2 at 24°C. Thin layer chromatography (tlc) was performed on Merck 60 F_{254} aluminium backed plates and viewed under a UV lamp or visualised by immersion in either *p*-anisaldehyde or phosphomolybdic acid solutions and heating with a hot gun. Flash column chromatography employed Prolabo silica gel (70–230 mesh). THF was distilled from sodium metal/benzophenone immediately prior to use, and dichloromethane and hexane were distilled prior to use in column chromatography.

3.2. (1′R,1S,2R,3R,6R)-2-(1′-Hydroxypropyl)-6-isopropyl-3-methylcyclohexanol **6**

3.2.1. Method (a): reduction of **4** with $NaBH_4$

(1′*R*,2*R*,3*R*,6*R*)-2-(1′-Hydroxypropyl)-6-isopropyl-3-methylcyclohexanone **4** (500 mg, 4.7 mmol) was dissolved in distilled methanol (10 mL), to this was added sodium borohydride (247 mg, 6.5 mmol) and the reaction stirred at room temperature for 24 h. The contents of the flask were then transferred to a separatory funnel and diluted with CH_2Cl_2 (60 mL). The organic layer was washed with saturated sodium chloride solution (3×5 mL) and water (3×5 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the crude diol **6**, which was purified by flash column chromatography (3:1 Hex:Et_2O) to afford 481 mg (95% yield) of the diol as a white solid.

3.2.2. Method (b): reduction of **4** with $LiAlH_4$

A 25 mL round bottomed flask equipped with a stir bar was flame-dried and cooled under a stream of argon. The flask was charged with $LiAlH_4$ (40 mg, 1.05 mmol), sealed and flushed with argon. Freshly distilled THF (10 mL) was added and the flask cooled to 0°C in an ice–water bath. (1′*R*,2*R*,3*R*,6*R*)-2-(1′-Hydroxypropyl)-6-isopropyl-3-methylcyclohexanone **4** (202 mg, 0.95 mmol) was dissolved in THF (5 mL) and added dropwise to the $LiAlH_4$/THF over 10 minutes and the reaction allowed to stir at ambient temperature overnight. The reaction was quenched with water (5 mL) and the contents of the flask transferred to a separatory funnel and diluted with ether (60 mL). The organic layer was washed with water (3×5 mL) and saturated sodium chloride solution (3×5 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the crude diol. Purification by flash column chromatography afforded two diastereomers (R_f 1:1 Hex:Et_2O, 0.23, 0.2; 18 mg (9%) and 120 mg (59%) respectively. The major component being diol **6** (as obtained from $NaBH_4$ reduction).

*3.2.3. Method (c): desilylation of **11** and **12***

The silyl protected diol (**11** or **12**) (100 mg, 0.3 mmol) was dissolved in distilled THF (5 mL) and to this was added *t*-butyl ammonium fluoride (0.6 mL, 0.6 mmol) and the mixture allowed to stir at room temperature for 3 h. The reaction was transferred to a separatory funnel and diluted with ether (30 mL) and washed with saturated NaCl solution (2×5 mL) and water (2×5 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the diol **6** as a white solid (95 mg, 94% yield): mp 52–55°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30–4.28 (m, 1H, C*H*OH), 3.62–3.56 (m, 1H, C*H*OH), 1.71–1.59 (m, 3H), 1.57–1.23 (m, 6H), 1.22–1.18 (m, 4H), 1.08 (d, 3H, *J*=6.6 Hz), 1.0–0.95 (m, 5H), 0.93 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.6 (*C*HOH), 70.2 (*C*HOH), 52.3 (*C*H), 44.6 (*C*H), 29.5 (CH_2), 29.3 (CH_2), 29.2, 28.7, 21.5, 21.4, 21.3, 21.1, 10.2; FAB MS *m*/*z* 214 (M^+), 213 ($M-H^+$), 197 (M–OH); anal. calcd for $C_{13}H_{26}O_2$: C, 72.9; H, 12.2; found: C, 73.0; H, 12.3; IR ν_{max} 3438 (br, OH), 2939, 2876, 1452, 1281, 1053, 912, 732 cm^{-1}; $[\alpha]_D$ −15 (*c* 0.65, CH_2Cl_2, 24°C).

*3.3. (1′R,2R,3R,6R)-(1′-Triethylsilyloxypropyl)-6-isopropyl-3-methyl-2-cyclohexanone **7***

To sodium hydride (101 mg, 4.0 mmol) suspended in freshly distilled THF (10 mL) was added triethylsilyltriflate (710 mg, 2.68 mmol) and the flask cooled to −78°C. To this mixture **4** (570 mg, 2.68 mmol) dissolved in THF (5 mL) was added dropwise and the mixture was stirred at −78°C for 1 h and then allowed to warm to room temperature. The reaction was diluted with ether (60 mL), transferred to a separatory funnel and washed with saturated sodium chloride solution (2×5 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Flash column chromatography (10:1 Hex:Et_2O, 1% Et_3N) yielded the title compound **7** as a colourless oil in 85% yield (760 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (dt, 1H, *J*=5.8, 11.5 Hz, –C*H*OSiEt_3), 2.26–2.10 (m, 1H), 2.05–1.87 (m, 3H), 1.81–1.62 (m, 2H), 1.58–1.38 (m, 5H), 1.35–1.10 (m, 6H), 0.97–0.73 (m, 14H), 0.63–0.47 (m, 6H); ^{13}C NMR (75 MHz $CDCl_3$) δ 207.1 (*C*=O), 73.8 (–*C*HOSiEt_3), 60.7 (*C*H), 55.1 (*C*H), 33.8, 29.0 (CH_2), 27.5 (CH_2), 26.7, 25.2 (CH_2), 21.1, 20.6, 19.0, 8.6, 6.6 (3×CH_3), 5.3 (3×CH_2); HRMS *m*/*z* calcd for $C_{19}H_{38}O_2Si$ (MH^+): 327.2719; found 327.2725; anal. calcd: C, 69.9; H, 11.6; S, 8.6; found: C, 69.7; H, 11.8; S, 8.3; IR ν_{max} 2958, 2923, 1706, 1445, 1388, 1154 1058, 984 cm^{-1}; $[\alpha]_D$ +98 (*c* 0.35, CH_2Cl_2, 24°C).

*3.4. (1′R,2R,3R,6R)-2-(1′-t-Butyldimethylsilyloxypropyl)-6-isopropyl-3-methylcyclohexanone **8***

To a solution of **4** (100 mg, 0.47 mmol) and DMAP (3 mg) in pyridine (5 mL) was added *t*-butyldimethylsilyl triflate (137 mg, 0.52 mmol). The reaction was stirred at room temperature under argon overnight. The reaction was diluted with ether (15 mL) and transferred to a 100 mL separatory funnel and further diluted with ether (60 mL), washed with saturated copper sulphate (4×5 mL) and water (3×5 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the crude product which was purified by flash column chromatography (10:1 Hex:Et_2O) to afford the silylated compound **8** as a colourless oil (130 mg, 85% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05–3.95 (m, 1H, C*H*OTBDMS), 2.22–2.12 (m, 2H), 2.08–1.95 (m, 2H), 1.81–1.62 (m, 3H), 1.55–1.34 (m, 3H), 1.0 (d, 3H, *J*=6.6 Hz), 0.93–0.81 (m, 18H), 0.00 and 0.02 (2 singlets for Si(*Me*)$_2$, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.0 (*C*=O), 73.3 (*C*HOTBDMS), 60.2 (*C*H), 55.2 (*C*H), 33.8, 28.9 (CH_2), 26.9 (CH_2), 26.6, 25.7, 25.1 (CH_2), 21.8, 21.7, 18.9, 17.8, 9.7, −4.6 (CH_3), −4.7 (CH_3); HRMS *m*/*z* calcd for $C_{19}H_{38}O_2Si$ (MH^+): 327.2719; found: 327.2717; IR ν_{max} 2956, 2360, 2348, 1701 (C=O), 1382, 1254, 1167, 1094, 867 cm^{-1}; $[\alpha]_D$ +94 (*c* 0.54, CH_2Cl_2, 24°C).

3.5. (1S,5R,6R,7R,10R)-2,4-Dioxa-5-ethyl-10-isopropyl-3,3,7-trimethyl-trans-bicyclo[4.4.0]decane **10**

To the 1,3 diol **6** (300 mg, 1.4 mmol) in acetone (10 mL) was added CSA (32 mg 0.14 mmol) followed by 2,2-dimethoxypropane (160 mg, 1.54 mmol) and the mixture stirred at room temperature for 24 h. The reaction was quenched with water (5 mL), transferred to a separatory funnel and diluted with ether (60 mL). The organic layer was washed with water (3×5 mL), dried over anhydrous ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the crude product. Flash column chromatography (10:1 Hex:Et_2O) afforded the acetonide **10** in 75% yield (269 mg) as a colourless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.75 (dd, 1H, H_a, *J*=4.1, 10.5 Hz), 3.49 (ddd, 1H, H_b, *J*=2.8, 7.9, 9.3 Hz), 1.91 (ds, 1H, H_{iprop}, *J*=6.7, 9.0 Hz), 1.78 (ddq, 1H, H(CH_2), *J*=2.8, 7.3, 14.3 Hz), 1.78 (dm, 1H, H_f, *J*=4 Hz), 1.49 (ddq, 1H, H(CH_2), *J*=7.3, 7.9, 14.3 Hz), 1.44 (m, 1H, H_d), 1.38 (s, 3H, Me_a), 1.38 (m, 1H, H_g), 1.35 (s, 3H, Me_e), 1.35 (ddd, 1H, H_c, *J*=9.3, 10.2, 10.5 Hz), 1.28 (m, 1H, H_e), 1.26 (m, 1H, H_h), 1.20 (dq, 1H, H_j, *J*=4, 10.5 Hz), 1.06 (d, 3H, $Me_{isoprop}$, *J*=6.7 Hz), 0.98 (t, 3H, Me_5, *J*=6.2 Hz), 0.92 (t, 3H, Me_{ethyl}, *J*=7.3 Hz), 0.88 (d, 3H, $Me_{isoprop}$, *J*=6.7 Hz); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (dd, 1H, *J*=3.9, 10.3 Hz, C*H*OH), 3.53–3.46 (m, 1H, C*H*OH), 1.95–1.73 (m, 3H), 1.58–1.40 (m, 5H), 1.38 (s, 3H), 1.36 (s, 3H), 1.07 (d, 3H, *J*=6.6 Hz), 0.99 (d, 3H, *J*=5.7 Hz), 0.95–0.90 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.5 (*C*HOH), 75.1 (*C*HOH), 43.9, 43.6, 33.9, 31.7 (*C*H_2), 30.3, 28.8 (*C*H_2), 27.2 (*C*H_2), 25.9, 23.2, 22.3, 22.0, 19.6, 9.8; HRMS *m*/*z* for $C_{16}H_{30}O_2$ (MH^+): calcd: 255.2246; found: 255.2247; IR ν_{max} 2939, 2876, 1452, 1281, 1053, 912, 732 cm^{-1}; $[\alpha]_D$ +10 (*c* 0.19, CH_2Cl_2, 24°C).

3.6. (1′R,1S,2R,3R,6R)-2-(1′-Triethylsilyloxypropyl)-6-isopropyl-3-methylcyclohexanol **11**

To **7** (200 mg, 0.6 mmol) in dry methanol (5 mL) was added sodium borohydride (47 mg, 1.2 mmol) and the mixture allowed to stir at room temperature for 2 h. The reaction was diluted with CH_2Cl_2 (50 mL), transferred to a separatory funnel and washed with water (2×5 mL) and saturated sodium chloride solution (2×5 mL). The organic layer was separated, dried over anhydrous magnesium sulphate, filtered and the solvent removed *in vacuo* to afford the crude product which was purified by passing through a pad of silica (CH_2Cl_2, 1% Et_3N) to afford the pure product **11** in 98% yield as a colourless oil (198 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02–3.90 (m, 1H), 3.70–3.61 (m, 1H), 1.83–1.80 (m, 1H), 1.61–1.32 (m, 7H), 1.30–1.11 (m, 3H), 0.98–0.84 (m, 11H), 0.83–0.78 (m, 9H), 0.58–0.42 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.3 (*C*H), 71.4 (*C*H), 50.8 (*C*H), 44.0 (*C*H), 30.3 (*C*H), 29.6 (*C*H_2), 29.5 (*C*H_2), 28.4, 23.2, 21.7, 21.5, 20.8, 9.4, 6.9, 5.5 (*C*H_2); FAB MS *m*/*z* 329 (MH^+), 311 (M^+-OH); anal. calcd for $C_{19}H_{40}O_2Si$: C, 69.9; H, 11.6; Si 8.6; found: C, 69.7; H, 11.8; Si, 8.3; IR ν_{max} 2958, 2923, 1445, 1388, 1154 1058, 984 cm^{-1}; $[\alpha]_D$ +44 (*c* 0.45, CH_2Cl_2, 24°C).

3.7. (1′R,1S,2R,3R,6R)-(1′-t-Butyldimethylsilyloxypropyl)-6-isopropyl-3-methyl-2-cyclohexanol **12**

To **8** (200 mg, 0.6 mmol) dissolved in methanol (5 mL) was added sodium borohydride (47 mg, 1.2 mmol) and the mixture stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), transferred to a separatory funnel and washed with water (2×5 mL) and saturated sodium chloride solution (2×5 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the crude product which was purified by passing through a pad of silica to afford **12** in 98% yield as a colourless oil (198 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (dd, 1H, *J*=3, 5 Hz, –CHC*H*OH), 3.76–3.74 (m, 1H, C*H*OTBDMS), 1.70–1.36 (m, 9H), 1.33–1.18 (m, 3H), 0.96 (d, 3H, *J*=6.4 Hz), 0.91 (d, 3H, *J*=5.0 Hz), 0.90–0.86 (m, 14H), 0.06 (s, 3H, CH_3SiCH_3), 0.05 (s, 3H, CH_3SiCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 74.2 (*C*H), 71.6 (*C*H), 50.9 (*C*H), 44.0 (*C*H), 30.9, 30.3

(CH_2), 29.7 (CH_2), 28.4, 25.9, 23.4, 21.7, 21.5, 18.5 (quat, CCH_3), 9.5, −4.4, −4.7; HRMS *m*/*z* calcd for $C_{19}H_{40}O_2Si$ (MH^+): 329.2876; found: 329.2872; IR (neat) 3512 (OH br), 2973, 2960, 1455, 1334, 1128, 1045, 946 cm^{-1}; $[\alpha]_D$ +20 (*c* 0.6, CH_2Cl_2, 24°C).

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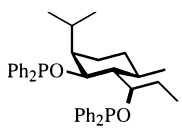
5. In **5** axial hydroxypropyl (branched) and methyl groups would replace the axial isopropyl and hydroxyl groups of compound **6**. Replacing an axial methyl with an axial hydroxyl would be expected to only be favoured by a few (~3.5) KJ mol^{-1}, so the conformational preference for **5** will be largely determined by the direction *and* magnitude of the energy difference between the isopropyl and hydroxyalkyl groups. In the case of **6**, the alternative ring conformer would have three axial groups.
6. Preliminary example: The bisphosphinite derivative **13** has been prepared, and synthetic details and applications will be reported in due course. $[\alpha]_D^{24}$=33 (c 0.34, CH_2Cl_2).



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