A Convenient Stereoselective Synthesis of (1*R*,2*S*,3*R*,4*S*)-3-(Neopentyloxy)isoborneol

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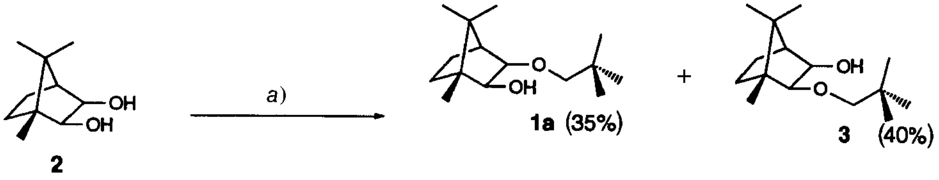
A convenient preparation of (1*R*,2*S*,3*R*,4*S*)-3-(neopentyloxy)isoborneol (= (1*R*,2*S*,3*R*,4*S*)-3-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol; **1a**), a valuable chiral auxiliary, is described. The synthesis involves six steps starting from the readily available camphorquinone (**5**) and gives **1a** in 48% overall yield. The key step is the chemoselective hydrolysis of the less hindered 1,3-dioxolane moiety in the camphorquinone diacetal **4**.

Introduction. – Camphor derivatives lie among the most useful chiral templates in asymmetric synthesis, since they have been extensively used as chiral auxiliaries [1], reagents [2], and ligands [3]. This is mainly due to the rigidity of the bornane skeleton and the easy availability of several enantiomerically pure starting materials such as camphor, camphorsulfonic acid, and borneol.

(1*R*,2*S*,3*R*,4*S*)-3-(Neopentyloxy)isoborneol (= (1*R*,2*S*,3*R*,4*S*)-3-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol; **1a**) is a chiral auxiliary developed in 1982 by *Oppolzer* and coworkers in the course of a study on the use of chiral acrylates in *Diels-Alder* reactions [4]. It was prepared by alkylation of hydroxyisoborneol (**2**) with neopentyl bromide (*Scheme 1*). This procedure, however, suffers from several drawbacks that hampered its synthesis at a convenient preparative scale and probably made difficult its application to enantioselective synthesis: The preparation of the starting material **2** is difficult to scale-up [5], the alkylation is not regioselective [4] affording a nearly 1:1 mixture of alcohols **1a** and **3**, and moreover, the chromatographic separation of these alcohols is tedious due to the small difference in polarity between them.

Alcohol **3** has been much more widely used than **1a** as a chiral auxiliary [1][6], probably because an efficient regio- and stereoselective route to **3** has been reported [7]. However, when both alcohols were tested as chiral inductors in the same reaction

Scheme 1

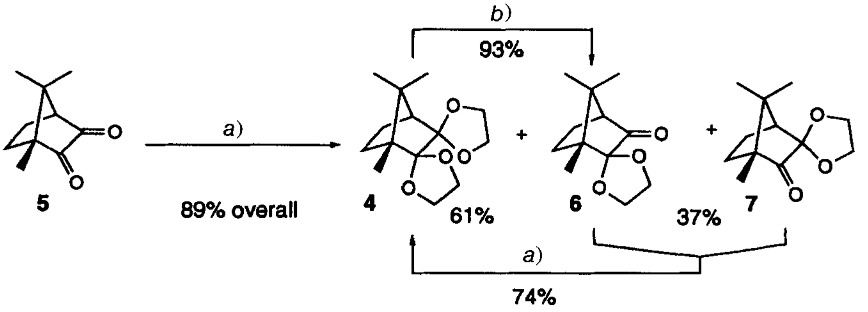


a) NaH, DMF, ^{t}BuCH$_2$Br.

[4][8–11], the results obtained with alcohol **1a** were usually superior to those with alcohol **3**. That is the case, *e.g.*, in the synthesis of cyclopentanones by intramolecular conjugate addition [9], in the [2+2] cycloadditions between dichloroketene and chiral enol ethers [10], and in the asymmetric metal carbene insertion into the Si–H bond [11]. In recent years, we have been involved in the development of asymmetric versions of the *Pauson-Khand* reaction and in its application to the synthesis of natural products [12–15]. Some of our approaches involve the use of chiral acetylenic ethers and esters derived from chiral alcohols. During these studies, many different alcohols have been tested as inductors with the result that alcohol **1a** was in general [14][15] far superior to **3**, and one of the most efficient controllers in this process. An additional advantage derived from the use of **1a** is the generally easy chromatographic separation of the diastereoisomeric pairs of *Pauson-Khand* adducts containing it [14][15]. This condition, being fundamental to the ultimate goal of obtaining enantiomerically pure compounds, is not generally fulfilled by **3**. Our need of multigram quantities of alcohol **1a** prompted us to develop an efficient preparation of this important compound. We report here the first regio- and stereoselective synthesis of (1*R*,2*S*,3*R*,4*S*)-3-(neopentyloxy)isoborneol (**1a**).

Results. – Our synthesis of the target alcohol **1a** started with the preparation of camphorquinone diacetal **4** from the readily available camphorquinone (**5**) [7] (*Scheme 2*). The preparation of diacetal **4** in high yield turned out to be more difficult than expected due to the steric congestion of the molecule. Attempted acetalization of **5** with ethylene glycol in a *Dean-Stark* device using benzene as the solvent afforded a 1:1 mixture of diacetal **4** and monoacetals **6** and **7** after 4 days of reflux. Although the azeotropic removal of H_2O should, in principle, shift the equilibrium towards the desired product **4**, the reaction could not be driven to completion, probably because of the competing polymerization of ethylene glycol which delivered H_2O to the medium. After extensive experimentation, we found that the best reaction conditions involved performing the acetalization in cyclohexane. After an initial reaction in a *Dean-Stark* device, diacetal **4** was separated by chromatography from the mixture of monoacetals which was submitted again to the acetalization protocol. In this way, the preparation of diacetal **4** can be achieved in a 89% combined yield.

Scheme 2

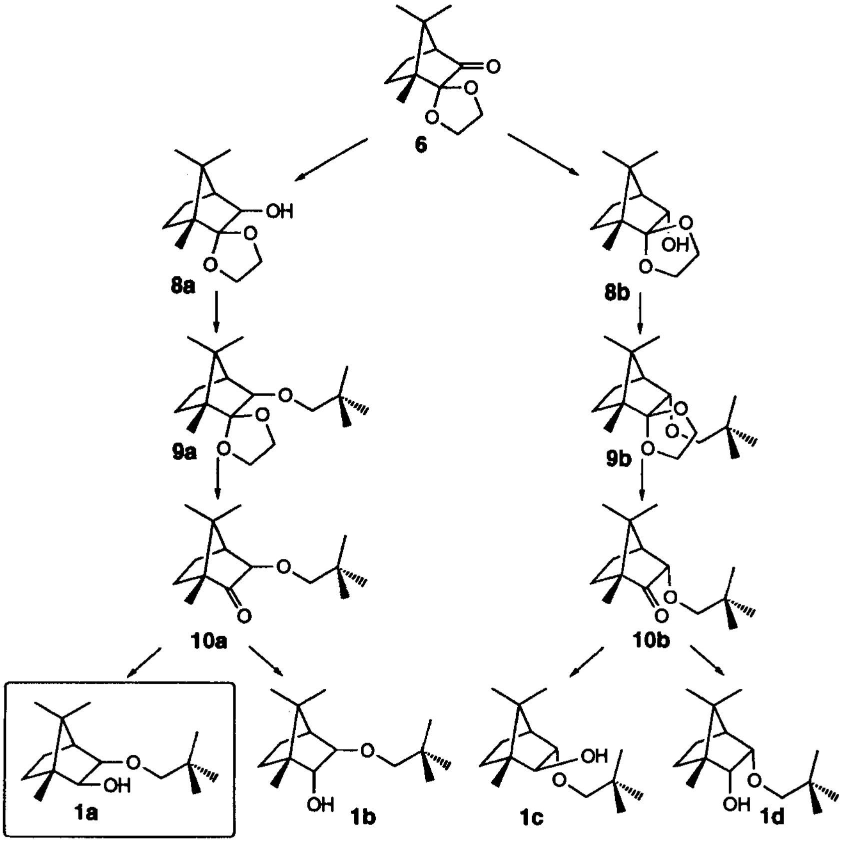


a) Ethylene glycol, TsOH, cyclohexane, *b*) 4M HCl/EtOH, reflux.

The key step in our approach is the chemoselective hydrolysis of diacetal **4** which, by acidic treatment (aqueous HCl solution, EtOH), afforded monoacetal **6** in 93% yield. It is important to notice that the hydrolysis of the less sterically shielded 1,3-dioxolane moiety was very selective yielding < 5% of the regioisomeric monoacetal **7** (*Scheme 2*)1).

With monoacetal **6** in hand, the synthesis of the target alcohol **1a** is, in principle, straightforward: stereoselective reduction of the carbonyl group (→ **8**), *O*-alkylation (→ **9**), hydrolysis of the acetal (→ **10**), and reduction of the second carbonyl group (→ **1**; *Scheme 3*). It is important to notice that four diastereoisomers of compound **1** can be obtained depending on the selectivity of the two carbonyl reductions. Success of the projected synthesis depends then on both stereocontrol in carbonyl reductions and facility of separation of unwanted stereoisomers.

Scheme 3



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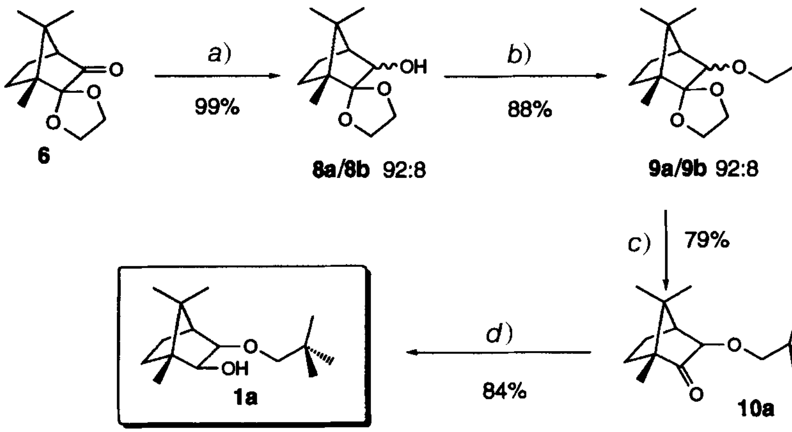
1) Alcohol **3** arising from regioisomeric monoacetal **7** can be removed in the final chromatography. The reduction of monoacetal **6** must be done immediately after its preparation since trace amounts of acid can isomerize it leading to a mixture of regioisomers **6** and **7**.

The reduction of **6** with $NaBH_4$ in MeOH (*Scheme 4*) afforded the alcohol **8** in excellent yield. The stereoselectivity of the reaction, however, was not complete yielding a hardly separable 92:8 mixture of *exo*- and *endo*-alcohols **8a** and **8b**, respectively. This selectivity could not be substantially increased by using *L-Selectride*® as a reducing agent. The *O*-alkylation of the sodium alkoxide of **8** with neopentyl bromide in *N*-methylpyrrolidin-2-one and the acid hydrolysis of the intermediate acetal **9** took place in good yields (88 and 79%, resp.) affording 3-(neopentyloxy)camphor (**10**) as a 92:8 mixture of *exo*- and *endo*-isomers **10a** and **10b**. At this stage, the minor stereoisomer **10b** had to be removed by chromatography since its subsequent reduction afforded as a by-product compound **1d** which co-eluted with the desired final product **1a**. The reduction of ketone **10a** was performed with several reducing agents. Although with *L-Selectride*® the reduction took place with excellent yield and complete stereoselectivity, $LiAlH_4$ and $NaBH_4$ could also be used. In these cases, only minor amounts (2–3%) of **1b** were detected[2]) and easily separated in the final chromatographic purification. Consequently, (1*R*,2*S*,3*R*,4*S*)-3-(neopentyloxy)isoborneol (**1a**) was obtained in pure form.

Scheme 4



a) $NaBH_4$, MeOH. *b*) NaH, *N*-methylpyrrolidin-2-one, ^{t}BuCH$_2$Br. *c*) H_2SO_4/H_2O 1:1. *d*) *L-Selectride*®, THF.

In summary, we have developed the first regio- and stereoselective synthesis of (1*R*,2*S*,3*R*,4*S*)-3-(neopentyloxy)isoborneol (**1a**), a valuable chiral auxiliary, in six steps from the readily available camphorquinone (**5**) and in 48% overall yield.

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Experimental Part

General. Neopentyl bromide [16] and camphorquinone (**5**) [7] were prepared from neopentyl alcohol and camphor, resp., following the described procedures. THF and Et_2O were distilled from sodium diphenylketyl. All reactions were performed in oven-dried glassware under N_2. TLC: 'DC-Alufolien Kieselgel' *60 F254* from *Merck*.

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[2]) Isomer **1b** was independently obtained by reduction of **10a** with Li/NH_3.

Column chromatography (CC): SiO_2 (230–400 mesh) or Et_3N-pretreated (2.5% (*v*/*v*)) SiO_2 (230–400 mesh) in the case of acid-labile substrates. M.p.: open capillary tube; uncorrected. Optical rotations: *Perkin-Elmer-241-MC* polarimeter; at 22–25°; *c* in g/100 ml. IR Spectra: *Perkin-Elmer-681* or *Nicolet-510-FT-IR* spectrophotometer in cm^{-1}. NMR Spectra: *Varian-XL-200* or *Varian-Unity-300* instruments; ^1H at 200 or 300 MHz, ^{13}C at 50.3 or 73.4 MHz; C multiplicities; by DEPT experiments; chemical shifts δ in ppm downfield of $SiMe_4$ (internal standard). Mass spectra: *Hewlett-Packard-5890* instrument at 70 eV ionizing voltage; ammonia or methane were used for chemical ionization (CI); *m*/*z* (rel. %). Elemental analyses were performed by the 'Servei d'Anàlisis Elementals del CSIC de Barcelona'.

(1R,4S)-2,2,3,3-Bis(ethylenedioxy)-1,7,7-trimethylbicyclo[2.2.1]heptane (= *(1'R,4'S)-1',7',7'-Trimethyldispiro[1,3-dioxolane-2,2'-bicyclo[2.2.1]heptane-3',2''-[1,3]dioxolane]*; **4**). To a stirred soln. of **5** (20.0 g, 0.12 mol; $[\alpha]_D^{23} = +103.3$ (*c* = 2.1, EtOH)) and *p*-toluenesulfonic acid (TsOH; 1.25 g, 6.6 mmol) in cyclohexane (100 ml), ethylene glycol (33 ml, 0.59 mol) was added at r.t. The resulting mixture was heated at 110° using a *Dean-Stark* device (TLC monitoring). Additional quantities of ethylene glycol (20 ml after 24 h and 27 ml after 72 h) and TsOH (0.5 g after 72 h) were added to the mixture. After 4 days, the org. layer was washed with 10% aq. NaOH soln. and brine, dried (Na_2SO_4), and evaporated to afford a crude that was chromatographed (Et_3N-pretreated silica gel, hexane/AcOEt 10 → 40%) to afford 18.8 g (61%) of **4** and 9.4 g (37%) of **6**/**7**. The mixture **6**/**7** (9.4 g, 45 mmol) was resubmitted to the procedure described above yielding 8.4 g (74%) of **4** and 2.4 g (26%) of starting material. Overall yield of **4**, 89%.

Data of **4**: M.p. 62–63° (hexanes/AcOEt). $[\alpha]_D^{23} = +1.17$ (*c* = 1.5, MeOH). IR (KBr): 2980, 2890, 1480, 1400, 1380, 1310, 1210, 1150, 1110, 1025, 1000, 980. ^1H-NMR (200 MHz, $CDCl_3$): 4.03–3.71 (*m*, 8 H); 2.05–1.21 (*m*, 5 H); 1.18 (*s*, 3 H); 0.87 (*s*, 3 H); 0.80 (*s*, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 114.7 (*s*); 113.8 (*s*); 65.9 (*t*); 65.0 (*t*); 64.6 (*t*); 64.3 (*t*); 53.3 (*d*); 52.7 (*s*); 44.5 (*s*); 29.3 (*t*); 21.1 (*q*); 21.0 (*t*); 20.7 (*q*); 9.9 (*q*). EI-MS: 254 (5, M^+), 141 (23), 113 (100).

Data of **7**: See [7].

(1S,4R)-3,3-(Ethylenedioxy)-4,7,7-trimethylbicyclo[2.2.1]heptan-2-one (= *(1R,4S)-1,7,7-Trimethylspiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolan]-3-one*; **6**). To 4M aq. HCl (40 ml) a soln. of **4** (13.0 g, 0.051 mol) in EtOH (150 ml) was added at r.t., and the resulting mixture was heated at 110° (TLC monitoring). When **4** was consumed (after 15–30 min), the solvent was evaporated, hexane/Et_2O 1:1 (100 ml) was added to the residue. The resulting org. layer was washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated: 10.0 g (93%) of **6** as white solid which was used in the next step without further purification. M.p. 47–48° (hexanes/Et_2O): $[\alpha]_D^{23} = -66.7$ (*c* = 1, EtOH). IR (film, NaCl): 2970, 2900, 1760, 1480, 1400, 1378, 1200, 1110, 1020, 910. ^1H-NMR (200 MHz, $CDCl_3$): 4.38–3.89 (*m*, 4 H); 2.18 (*s*, *J* = 5, 1 H); 2.16–1.82 (*m*, 2 H); 1.67–1.48 (*m*, 2 H); 1.04 (*s*, 3 H); 0.95 (*s*, 3 H); 0.90 (*s*, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 216.6 (*s*); 107.3 (*s*); 66.3 (*t*); 64.8 (*t*); 59.1 (*d*); 51.3 (*s*); 43.6 (*s*); 29.1 (*t*); 22.8 (*t*); 21.5 (*q*); 18.2 (*q*); 8.7 (*q*). CI-MS (NH_3): 245 (12, $[M + 35]^+$), 228 (100, $[M + 18]$), 211 (6, $[M + 1]^+$).

(1S,2R,4R)/(1S,2S,4R)-3,3-(Ethylenedioxy)-4,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (= *(1R,3R,4S)/(1R,3S,4S)-1,7,7-Trimethylspiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolan]-3-ol*; **8a**/**8b**). To a stirred soln. of **6** (10.0 g, 0.047 mol) in MeOH (100 ml) at –20°, $NaBH_4$ (1.9 g, 0.05 mol) was added portionwise. The resulting mixture was allowed to warm to r.t. (TLC monitoring). When **6** was consumed sat. aq. $NaHCO_3$ soln. was added, the MeOH was evaporated, and Et_2O and H_2O were added until clear phases were formed. The aq. layer was extracted with Et_2O and the combined org. phase washed with brine, dried (Na_2SO_4), and evaporated: 10 g (99%) of **8a**/**8b** 92:8 as a white solid. An anal. sample of **8a** was obtained by CC (AcOEt/hexanes). **8a**: M.p. 46–47° (hexanes/AcOEt). $[\alpha]_D^{23} = -41.7$ (*c* = 1, MeOH). IR (film, NaCl): 3450, 2970, 2890, 1480, 1395, 1375, 1290, 1210, 1150, 1120, 1080, 1010, 960, 820, 760, 725. ^1H-NMR (200 MHz, $CDCl_3$): 4.12–3.69 (*m*, 4 H); 3.44 (*s*, 1 H); 2.64 (*s*, 1 H); 1.87–0.77 (*m*, 5 H); 1.09 (*s*, 3 H); 0.83 (*s*, 3 H); 0.82 (*s*, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 116.9 (*s*); 83.0 (*d*); 66.6 (*t*); 64.0 (*t*); 51.8 (*s*); 51.6 (*d*); 47.7 (*s*); 29.1 (*t*); 24.6 (*t*); 21.7 (*q*); 21.2 (*q*); 9.3 (*q*). EI-MS: 212 (13, M^+), 155 (78), 141 (100), 113 (48). Anal. calc. for $C_{12}H_{20}O_3$: C 67.92, H 9.43; found: C 67.95, H 9.50.

(1R,3R,4S)/(1R,3S,4S)-3-(2,2-Dimethylpropoxy)-2,2-(ethylenedioxy)-1,7,7-trimethylbicyclo[2.2.1]heptane (= *(1R,3R,4S)/(1R,3S,4S)-3-(2,2-Dimethylpropoxy)-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,2'-[1,3]-dioxolane]*; **9a**/**9b**). To a stirred suspension of NaH (2.1 g, 0.07 mol; 80% in oil) in *N*-methylpyrrolidin-2-one (20 ml), a soln. of **8a**/**8b** 92:8 (10 g, 0.045 mol) in *N*-methylpyrrolidin-2-one (20 ml) was added at –20°. After 30 min of stirring at r.t. the mixture was heated to 110°, and a soln. of neopentyl bromide (21.2 g, 0.141 mol) in *N*-methylpyrrolidin-2-one (15 ml) was added. The mixture was stirred for *ca.* 12 h at 110° (TLC monitoring). Then, the mixture was allowed to cool to r.t., H_2O (5 ml) was slowly added, and the mixture was diluted with hexane (100 ml). The org. layer was washed with sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated. The crude product (13.6 g) was purified by filtration through a short pad of silica gel, eluting with hexane/AcOEt 95:5: 11.7 g

(88%) of **9a/9b** 92:8. Colourless oil. $[\alpha]_D^{23} = -32.4$ ($c = 1.5$, MeOH). IR (film, NaCl): 2950, 2870, 1480, 1390, 1370, 1200, 1160, 1120, 1070, 1040, 970, 850. ^{1}H-NMR (200 MHz, CDCl$_3$; **9a/9b**): **9a**: 4.08–3.67 (*m*, 4 H); 3.09, 2.94 (*AB*, $J = 8$, 2 H); 3.07 (*s*, 1 H); 1.95–0.82 (*m*, 5 H); 1.15 (*s*, 3 H); 0.90 (*s*, 9 H); 0.81 (*s*, 3 H); 0.80 (*s*, 3 H). ^{13}C-NMR (50 MHz, CDCl$_3$; **9a/9b**): **9a**: 116.7 (*s*); 91.7 (*d*), 80.3 (*t*); 66.2 (*t*); 63.1 (*t*); 51.4 (*s*); 47.9 (*d*), 31.9 (*s*); 30.0 (*s*); 29.4 (*t*); 26.8 (*q*); 24.8 (*t*); 21.2 (*t*); 20.7 (*q*); 9.5 (*q*).

(1R,3R,4S)-3-(2,2-Dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**10a**). To 50% aq. sulfuric acid (125 ml), **9a/9b** (11.7 g, 0.041 mol) was added, and the two-phase system was vigourously stirred at 60°. When **9a/9b** was consumed (*ca.* 24 h; TLC monitoring), the aq. layer was extracted with hexane (3 × 50 ml) and the combined org. phase washed with sat. aq. NaHCO$_3$ soln. and brine, dried (MgSO$_4$), and evaporated. The crude product (9.8 g) afforded, after flash chromatography (hexane/CH$_2$Cl$_2$ 70:30), ratio 7.8 g (79%) of **10a**, 0.63 g of **10b**, and 0.93 g of **10a/10b**.

Data of **10a**: Colourless oil. $[\alpha]_D^{23} = +89.8$ ($c = 1.5$, EtOH). IR (film, NaCl): 2960, 2890, 1750, 1480, 1395, 1360, 1270, 1130, 1090, 1010, 960, 870, 720. ^{1}H-NMR (200 MHz, CDCl$_3$): 3.47, 3.14 (*AB*, $J = 8$, 2 H); 3.33 (*s*, 1 H); 2.12–1.15 (*m*, 5 H); 0.99 (*s*, 3 H); 0.92 (*s*, 3 H); 0.91 (*s*, 3 H); 0.86 (*s*, 9 H). ^{13}C-NMR (50 MHz, CDCl$_3$): 214.6 (*s*); 84.6 (*d*); 81.6 (*t*); 56.8 (*s*); 47.7 (*d*); 46.3 (*s*); 31.5 (*s*); 29.0 (*t*); 26.5 (*q*); 24.7 (*t*); 20.9 (*q*); 19.8 (*q*); 8.8 (*q*). CI-MS (NH$_3$): 256 (100, $[M + 18]^+$), 239 (5, $[M + 1]^+$).

Data of **10b**: $[\alpha]_D^{23} = +14.87$ ($c = 1.19$, EtOH). IR (film, NaCl): 2958, 2871, 1758, 1480, 1393, 1364, 1319, 1125, 1044, 1015, 812. ^{1}H-NMR (200 MHz, CDCl$_3$): 3.75 (*d*, $J = 4.8$, 1 H); 3.39, 3.07 (*AB*, $J = 8.4$, 2 H); 2.23 (*t*, $J = 4$, 1 H); 1.9–1.1 (*m*, 5 H); 0.96 (*s*, 3 H); 0.89 (*s*, 9 H); 0.87 (*s*, 3 H); 0.81 (*s*, 3 H). ^{13}C-NMR (50 MHz, CDCl$_3$): 217.25 (*s*); 81.00 (*d*); 80.80 (*t*); 58.18 (*s*); 47.12 (*d*); 42.68 (*s*); 32.09 (*s*); 31.65 (*t*); 26.63 (*q*); 19.75 (*q*); 18.99 (*q*); 18.40 (*t*); 9.41 (*q*). CI-MS (CH$_4$): 239 (100, $[M + 1]^+$), 223 (14), 169 (38).

(1R,2S,3R,4S)-3-(2,2-Dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (**1a**). To a stirred soln. of **10a** (7.8 g, 0.033 mol) in THF (50 ml), *L-Selectride®* (50 ml, 1M in THF) was added at −78°. The mixture was stirred for 1 h at −78°, slowly allowed to warm to r.t. and the stirring was continued for 18 h. After cooling to 0°, H$_2$O (2.5 ml), 4M NaOH (20 ml), and 30% H$_2$O$_2$ soln. (21 ml) were consecutively added. The resulting mixture was stirred at 0° for 1 h. Then the aq. layer was extracted with hexane (2 × 50 ml), the combined org. phase washed with brine, dried (MgSO$_4$), and evaporated and the crude product (8.0 g), purified by CC (silica gel, 1 → 10% hexane/*t*BuOMe): 6.6 g (84%) of **1a**. Colourless oil. $[\alpha]_D^{23} = -18.3$ ($c = 1.4$, EtOH) ([4]: $[\alpha]_D^{25} = -18.79$ ($c = 1.1$, EtOH)). IR (film, NaCl): 3450, 2960, 2880, 1480, 1390, 1360, 1290, 1140, 1105, 1075, 1050, 960, 870, 760, 720. ^{1}H-NMR (200 MHz, CDCl$_3$): 3.61, 3.42 (*AB*, $J = 7$, 2 H); 3.26, 3.12 (*AB*, $J = 8.5$, 2 H); 3.09 (*s*, 1 H); 1.85 (*d*, $J = 5$, 1 H); 1.79–1.15 (*m*, 4 H); 1.06 (*s*, 3 H); 0.95 (*s*, 3 H); 0.93 (*s*, 9 H); 0.80 (*s*, 3 H). ^{13}C-NMR (50 MHz, CDCl$_3$): 83.8 (*d*); 81.3 (*t*); 79.9 (*d*); 48.7 (*s*); 47.7 (*d*); 46.5 (*s*); 33.0 (*t*); 32.1 (*s*); 26.8 (*q*); 24.0 (*t*); 21.9 (*q*); 20.8 (*q*); 10.9 (*q*). CI-MS (NH$_3$): 258 (100, $[M + 18]^+$), 241 (11, $[M + 1]^+$), 223 (29, $[M - 17]^+$), 153 (51, $[M - 87]^+$).

(1R,2R,3R,4S)-Isomer **1b**. The reduction of **10a** with LiAlH$_4$ afforded **1a** in 80% yield besides small amounts (2–3%) of **1b** (by NMR). Independently, **1b** was prepared as follows: A soln. of **10a** (0.5 g, 2 mmol) in dry Et$_2$O (4 ml) and solid NH$_4$Cl (0.4 g, 7 mmol) were added to liq. NH$_3$ (50 ml). Then Li (0.06 g, 7 mmol) was added in small pieces over 20 min. The mixture was stirred for 15 min and a sat. NH$_4$Cl soln. was added to destroy the excess of Li. When the blue colour disappeared, the NH$_3$ was allowed to evaporate, and the mixture was extracted with Et$_2$O. The combined org. phase was dried (MgSO$_4$) and evaporated. The TLC of the crude showed a complex product mixture. CC (hexane/Et$_2$O of increasing polarity) gave 80 mg (16%) of **1b**. Colourless oil. $[\alpha]_D^{23} = +6.2$ ($c = 1.87$, EtOH). IR (film, NaCl): 3365, 2954, 2869, 1495, 1478, 1451, 1389, 1362, 1190, 1099, 1068, 1016, 967, 806, 745, 693. ^{1}H-NMR (200 MHz, CDCl$_3$): 3.93 (*s*, 1 H); 3.12, 3.02 (*AB*, $J = 8.3$, 2 H); 3.04 (*d*, $J = 2.6$, 1 H); 1.8–1.0 (*m*, 6 H); 1.01 (*s*, 3 H); 0.89 (*s*, 9 H); 0.87 (*s*, 3 H); 0.83 (*s*, 3 H). ^{13}C-NMR (50 MHz, CDCl$_3$): 91.72 (*d*); 84.33 (*d*); 79.4 (*t*); 49.74 (*s*); 48.62 (*d*); 47.17 (*s*); 31.82 (*s*); 26.87 (*q*); 25.48 (*t*); 25.41 (*t*); 21.00 (*q*); 19.00 (*q*); 12.85 (*q*). CI-MS (CH$_4$): 269 (1, $[M + 29]^+$), 241 (11, $[M + 1]^+$), 223 (29, $M - 17]^+$), 153 (51, $[M - 87]^+$).

(1R,2S,3S,4S)-Isomer **1c** *and (1R,2R,3S,4S)-Isomer* **1d**. To a stirred suspension of NaBH$_4$ (38 mg, 1 mmol) in EtOH (1 ml), a soln. of **10b** (120 mg, 0.5 mmol) in EtOH (2 ml) was added at 0°. When **10b** was consumed (TLC monitoring), the mixture was allowed to warm to r.t. and sat. aq. NaHCO$_3$ soln. (1 ml) was added. EtOH was evaporated, and hexane/Et$_2$O 1:1 (20 ml) was added. The resulting org. layer was washed with sat. aq. NaHCO$_3$ and sat. aq. NaCl soln., dried (Na$_2$SO$_4$), and evaporated to afford 100 mg (84%) of **1c/1d** 3:7 which were separated by CC.

Data of **1c**: $[\alpha]_D^{23} = +24.1$ ($c = 0.7$, CHCl$_3$). IR (film, NaCl): 3487, 2954, 2871, 1725, 1480, 1393, 1362, 1223, 1119, 1099, 1007, 806. ^{1}H-NMR (200 MHz, CDCl$_3$): 3.83 (*m*, 1 H); 3.35 (*d*, $J = 2.6$, 1 H); 3.05 (*s*, 2 H); 1.89 (*t*, $J = 4$, 1 H); 1.8–1.1 (*m*, 5 H); 1.02 (*s*, 3 H); 0.91 (*s*, 9 H); 0.85 (*s*, 3 H); 0.83 (*s*, 3 H). ^{13}C-NMR (50 MHz, CDCl$_3$): 87.91 (*d*); 85.25 (*d*); 79.33 (*t*); 49.39 (*s*); 48.27 (*d*); 46.63 (*s*); 34.57 (*t*); 31.96 (*s*); 26.76 (*q*); 20.81 (*q*); 19.82 (*q*); 18.15 (*t*); 11.27 (*q*). CI-MS (CH$_4$): 241 (19, $[M + 1]^+$), 223 (100, $[M - 17]^+$), 153 (15, $[M - 87]^+$).

Data of **1d**: $[\alpha]_D^{23} = +58.1$ ($c = 1.4$, $CHCl_3$). IR (film, NaCl): 3544, 2956, 1480, 1395, 1364, 1289, 1260, 1190, 1105, 1059, 1021, 965. ^1H-NMR (200 MHz, $CDCl_3$): 3.78 (*m*, 2 H); 3.1–3.0 (*AB*, $J = 8.4$, 2 H); 2.86 (*m*, 1 H); 1.88 (*m*, 1 H); 1.8–1.0 (*m*, 4 H); 0.93 (*s*, 9 H); 0.89 (*s*, 3 H); 0.85 (*s*, 3 H); 0.84 (*m*, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 80.26 (*t*); 75.47 (*d*); 73.85 (*d*); 49.32 (*s*); 48.16 (*d*); 44.35 (*s*); 32.14 (*s*); 26.77 (*q*); 25.54 (*t*); 20.13 (*q*); 18.20 (*q*); 18.20 (*t*); 14.09 (*q*). CI-MS (CH_4): 241 (94, $[M + 1]^+$), 223 (28, $[M - 17]^+$), 153 (42, $[M - 87]^+$).

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