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Camphor-derived amber/woody odorants: 1,7,7-trimethyl-2′-*iso*-propylspiro[bicyclo[2.2.1]heptane-2,4′-(1,3-dioxanes)]

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Abstract—Six stereoisomers of a new camphor-derived 1,7,7-trimethyl-2′-*iso*-propylspiro[bicyclo[2.2.1]heptane-2,4′-(1,3-dioxane)] odorant were prepared. Their design with the help of an amber *olfactophore* model and structure–odour relationship are reported. The (1*R*,2*S*,4*R*,2′*S*) isomer has by far the strongest and the most characteristic amber-like odour. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Most perfumery raw materials[1] contain chiral molecules,[2] many of which are structurally elaborated starting from natural terpenoids, already having several asymmetric centres, and are commercialised as more or less complex mixtures of stereoisomers. Following the development of pharmaceutical research, fragrance chemistry has also begun to look more carefully into structure–activity (in our case odour) relationships among stereoisomers.[2,3] *Chiral switch* patents claim main odour vectors of products[4] and, where economically justified, stereomerically pure or enriched odorants are being used. This increases the odour quantity available for a given weight of a perfuming composition and should allow significant reduction of the amount of chemicals necessary to elicit the desired olfactory sensation.

The amber scent, almost always coexistent with some woody aspects, is one of the most noble odour notes, usually long-lasting and used in both fine and functional perfumery. Amberketal **A** and Ambrox®[†] **B**, prepared from natural sclareol, are still benchmarks in this odour note (depicted in Fig. 1 together with other important perfumery raw materials of similar olfactory

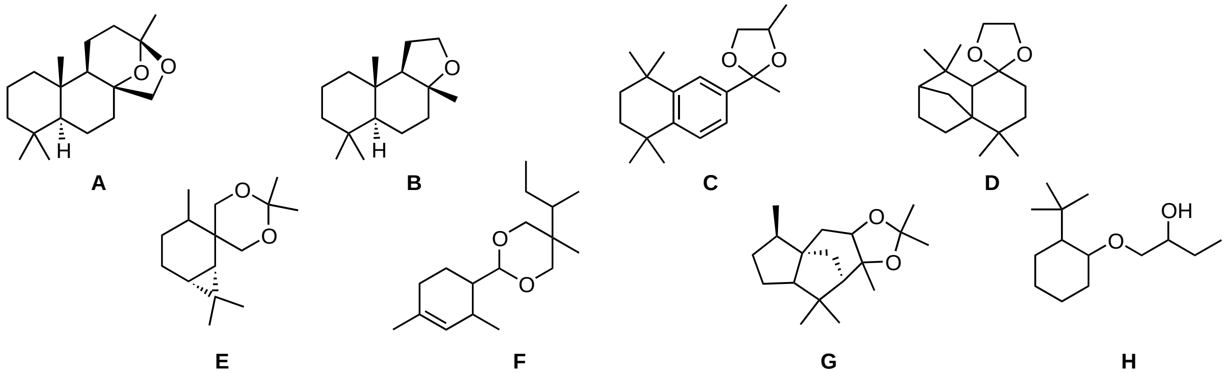

Figure 1. Important amber-type odorants used in perfumery.

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[†] Also used under the names of Amberiff, Amberlyn, Ambermor, Ambrofix, Ambroxan, Ambroxid(e), Sylvamber, etc. (trade marks).

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profile). The high price of these two chiral products prompted us to look for less expensive amber-smelling molecules.

2. Results and discussion

Several olfactophore[‡] models for the amber scent have been proposed.[2,3] To the best of our knowledge their predictive power does not allow significant discrimination between very similar structures, which often have dramatic differences in their olfactory properties.[5] However, they can still prove useful in the design of new odorants.[6] We used a hypothesis generated[5] with CATALYST software,[7] which consists of one oriented hydrogen-bond-acceptor (HBA) function;[8] (corresponding to the osmophoric[‡] group of an odoriferous ligand), four hydrophobic functions A–D and six excluded volumes (Fig. 2). The latter should roughly delimit the hypothetical binding site of the relevant odorant receptor. Of several possible bulky fragments that could map the lipophilic fragment (*hydrophobes* A and B) of the odorant we finally selected the bornyl entity, readily available from inexpensive camphor or (iso)borneol building blocks. It was connected in a preparatively straightforward way to a polar cyclic ketal residue, present in many amber-type odorants[2a] (cf. Fig. 1), to give the spiro[bornane-2,4′-(1,3-dioxane)] system. Different substituents were tried on the 1,3-dioxane ring and the 14 best mapping structures[9] were then synthesised, initially as racemates or racemic mixtures of epimers.

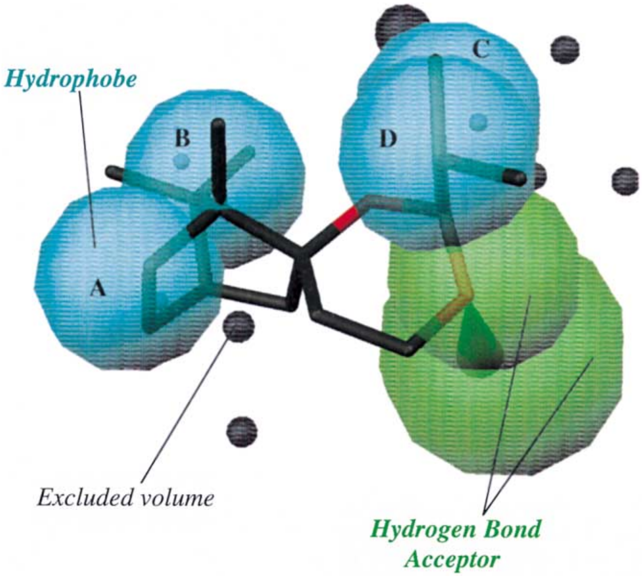
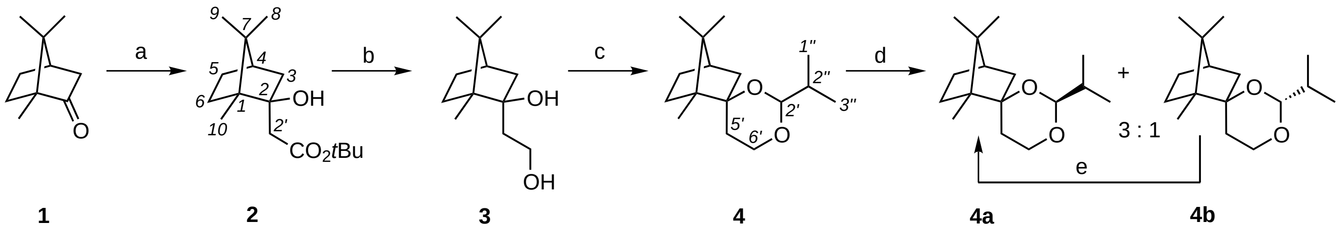


Figure 2. Compound **4a** mapping the amber olfactophore model.

As expected, the racemic mixture of 2′-*iso*-propyl epimers **4a** and **4b** that best fitted to the amber hypothesis, also possessed the most appreciated olfactory properties. Using our olfactophore model it was difficult to discriminate between the four stereoisomers of the mixture, because of the globular form of the bornyl system and a relative flexibility of their dioxane ring. Therefore, although the best mapping was observed for **4a** (Fig. 2), all four stereoisomers were prepared starting from enantiomerically pure (+)- and (–)-camphor **1** and *ent*-**1**. The industrially viable, three step synthesis of 2 diastereoisomer mixtures **4a**+**4b** and *ent*-**4a**+*ent*-**4b**, depicted in Scheme 1, is based on addition of the *tert*-butyl acetate enolate anion to camphor as developed by Maroni-Barnaud, Perry et al.[10] The anion could be generated with *iso*-propylmagnesium chloride,[§] which avoids the use of expensive (by fragrance and flavour industry standards) LDA or lithium hexamethyldisilazide, necessary when enolates derived from acetic acid[12] or ethyl acetate,[13] respectively, were used, and to circumvent the failure of the Reformatsky reaction with camphor. An alternative preparation of diol **3** by hydroboration of the allylic or propargylic alcohol obtained by addition of vinyl Grignard or lithium acetylide to camphor was found to be less efficient, as was the method described recently by Dimitrov et al.[14] via an industrially difficult ozonolysis of the corresponding allylisoborneol. Another synthetic



Scheme 1. Preparation of **4a** and **4b**: (a) *iso*-PrMgCl, AcO*tert*-Bu, –20°C, 78%; (b) LAH, ~100% (crude); (c) Me_2CHCHO, *p*-TsOH, 83%; (d) flash chromatography and recrystallisation from $EtOH/H_2O$; (e) *p*-TsOH, Δ.

[‡] For definition cf. Ref. 2a, p. 7637.

[§] In the case of the less hindered *iso*-propyl acetate, dialkylaminomagnesium halogenide bases[11] also proved effective, but the yields were lower (at best 34%).

route to **4**, via an astonishingly selective Prins reaction of 2-methylenebornane, leading to unsubstituted spiro[bornane-2,4′-(1,3-dioxane)], is currently being investigated.[15] Single stereoisomers of **4** were isolated from each pair of diastereomers by flash chromatography separation followed by repeated recrystallisations.

The assignment of absolute configuration proved easy. Among each pair of diastereoisomers obtained via acid-catalysed ketalisation, the major product should correspond to the thermodynamically more favourable one (cf. free energy values[16] in Fig. 3); **4a** should therefore have the configuration (1*R*,2*S*,4*R*,2′*S*). NOESY experiments (Fig. 4) were in line with this hypothesis and indicated a chair conformation for **4a** and a boat-like, twisted conformation for **4b**, compatible with the molecular modelling[16] results shown in Fig. 3. The crystallographic analysis finally confirmed these conformations, with a slightly different twist for **4b**, even in the solid state (Fig. 5).

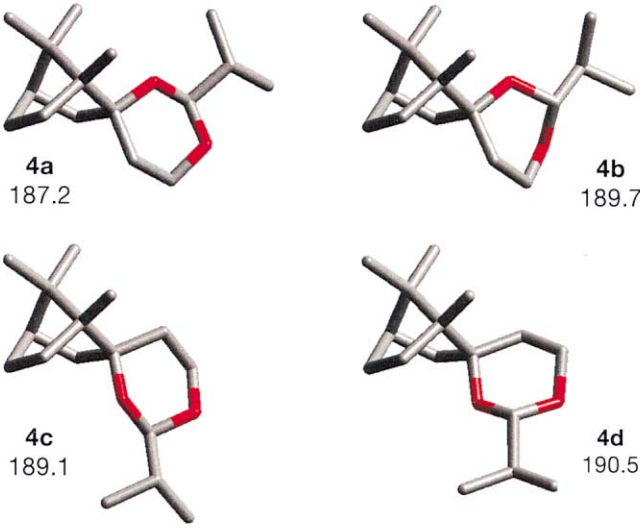


Figure 3. Lowest free energy conformers of **4a**–**d** modelled using MacroModel[16a] and MINTA;[16b] free energy in [kcal/mol].

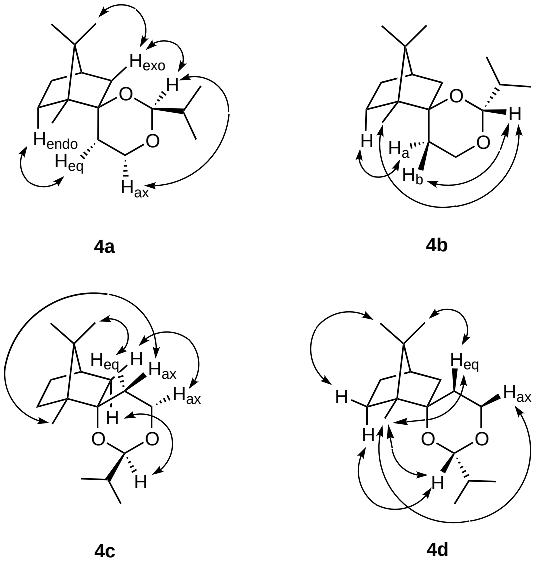


Figure 4. Important NOEs in **4a**–**d**.

The odours of all four prepared stereoisomers of **4** presented some amber/woody aspects, but the scent of **4a** was by far the strongest and the most amber-like (Table 1). To our satisfaction, **4a** was the isomer best fitting our model and prepared starting from the natural, less expensive (1*R*)-(+)-camphor **1**.

Despite the high diastereoselectivity of the *endo*-addition of *tert*-butyl acetate enolate anion to camphor (d.e. ~93%), the final product still contained up to 2%[¶] of each of the two other epimers **4c** and **4d**, resulting from *exo*-attack. We had to know the olfactory contribution of these minor isomers and subjected the mixture to the usual GC-olfactometry[17] analysis. Unfortunately, under our best conditions one of these minor isomers **4c** eluted very closely to the main amber odour vector **4a**. Therefore, although both **4c** and **4d** were judged weaker and less amber/woody than **4a**, a more irrefutable proof was required. After fruitless attempts to isolate **4c** by chromatographic methods we decided to prepare it independently. The synthesis, however simple at a first glance (Scheme 2), proved to be not so trivial.

Firstly, the dehydration of **5** was accompanied by Wagner–Meerwein rearrangement of the camphane skeleton to the isocamphanic and finally the camphenic one[18,19] and gave mixtures[20] of isomeric esters **6** and **11**.[||] Subjected to the reaction sequence shown in Scheme 2, the rearranged dehydration product **11** led to isomeric dioxepanes **13**, the formation of which is rationalised in Scheme 3. After several trials we could reduce the formation of **11** to <1% by using an excess of boron trifluoride etherate. Secondly, the epoxidation of the allylic alcohol **7** occurred with poor stereoselectivity, such that after LAH reduction a 7:2 mixture of diols **9** and **3** was obtained. The unwanted **3** had to be carefully eliminated via repeated flash chromatography and recrystallisation from hexane, in order to avoid significant contamination of the target new epimers of **4** with the strong smelling **4a**; diol **9** was obtained with d.e. of >98.5% (LC/MS). The pure **4c** could finally be prepared by *p*-TsOH-catalysed equilibration of the *quasi*-equimolar **4c**/**4d** kinetic ketalisation mixture, followed by flash chromatography. After the epimerisation, the **4c**/**4d** ratio was 92:8, which can be explained by the very small free energy[16b] gap (1.4 kcal/mol) between the most stable conformers of these two epimers (Fig. 3). It corresponds to a calculated (Boltzmann distribution) ratio of 91.5:8.5. A pure sample of **4d** needed for odour

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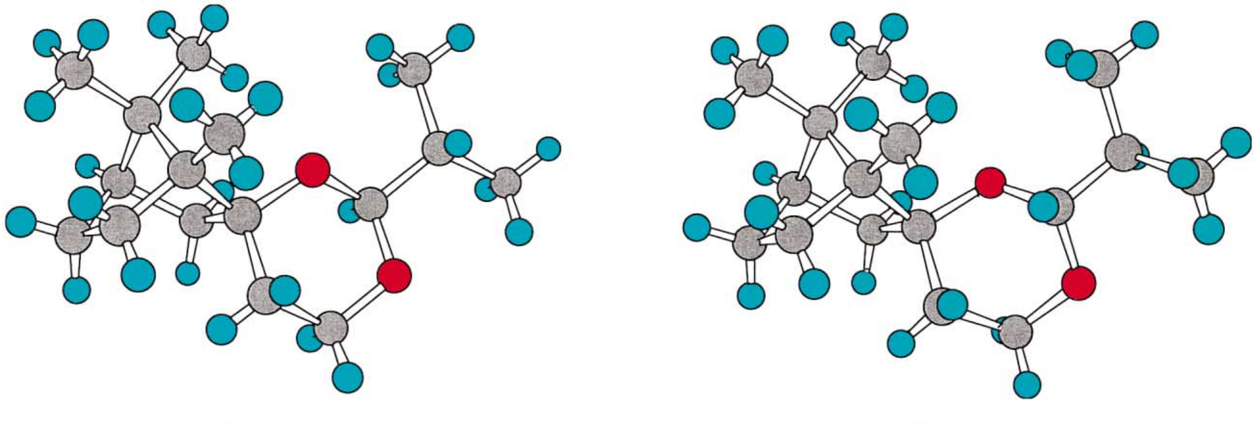
[¶] Significantly the same percentage of **4c** and **4d** was found in **4** prepared via ethynylation of camphor.

[||] Among the different dehydration conditions we investigated, heating with oxalic acid gave the greatest amounts (~35%) of the unwanted camphenyl acetate **11** (cf. Section 4), whilst the analogous isobornylacetone seems to give under similar conditions only the simple dehydration product.[21] In our very recent trials to exploit this rearrangement to the synthesis of natural product analogues we observed that the content of the rearranged product depends very strongly on the ester type.[15]



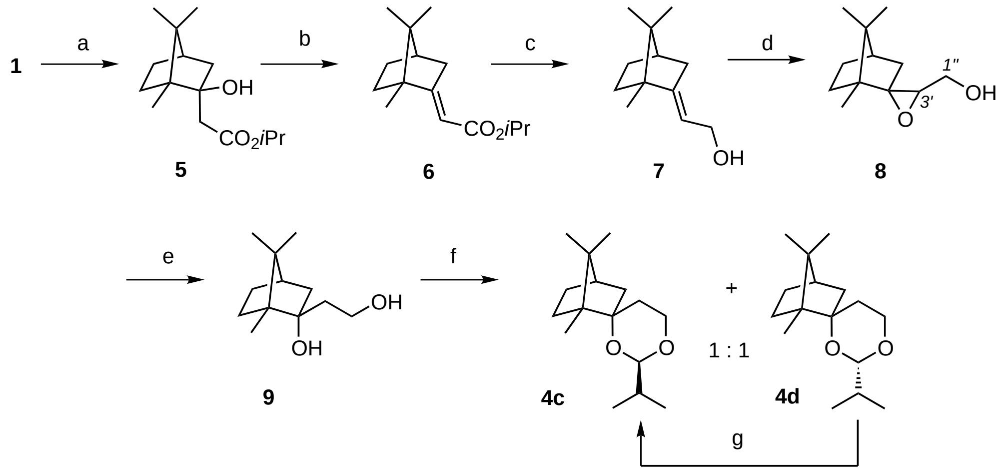
4a **4b**

Figure 5. Crystal structures of **4a** and **4b**.

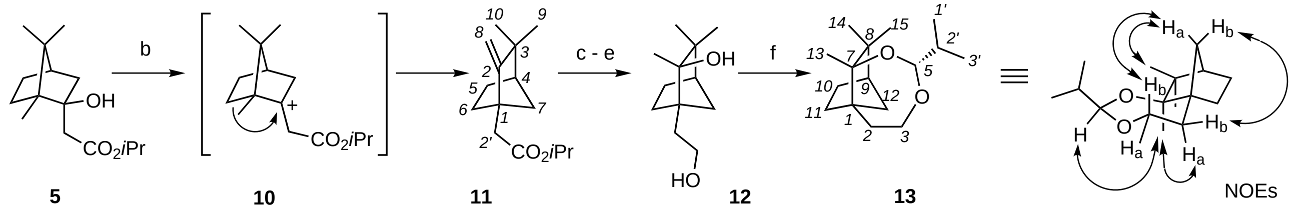
Table 1. Olfactory properties of 1,7,7-trimethyl-2′-*iso*-propylspiro[bicyclo[2.2.1]heptane-2,4′-(1,3-dioxanes)] **4**

Cpd	From camphor	Configuration	GC Odour threshold [ng/l][a]	Odour description
4a	**1** [(1*R*)-(+)]	(1*R*,2*S*,4*R*,2′*S*)	0.2	Amber, woody, cedarwood, animal, strong
4b	**1**	(1*R*,2*S*,4*R*,2′*R*)	40	Woody, cedarwood, rosy, spicy, weak
ent-**4a**	*ent*-**1** [(1*S*)-(−)]	(1*S*,2*R*,4*S*,2′*R*)	88	Woody, camphoraceous, amber, spicy, weak
ent-**4b**	*ent*-**1**	(1*S*,2*R*,4*S*,2′*S*)	40	Woody, piney, slightly amber, weak
4c	**1**	(1*R*,2*R*,4*R*,2′*R*)	4	Camphoraceous, fruity, amber, woody, creamy
4d	**1**	(1*R*,2*R*,4*R*,2′*S*)	250	Woody, cedarwood, drier than **4c**

[a] Measured using a GC/sniffing technique[17] on a DB™-WAX 15 m×0.53 mm/1.0 μm column by four panellists.



Scheme 2. Preparation of **4c** and **4d**: (a) *iso*-PrMgCl, *iso*-Pr_2NH, AcO*iso*-Pr, −20°C, 34%; (b) $BF_3·Et_2O$, 86%; (c) LAH, ~100% (crude); (d) MCPBA, $NaHCO_3$, 86%; (e) LAH, 25%; (f) Me_2CHCHO, *p*-TsOH, 42%; (g) *p*-TsOH, Δ.



Scheme 3. Formation pathway and the main NOEs of one of the by-products in the synthesis of **4c**+**4d**. For the reaction conditions cf. Scheme 2. **11** was prepared independently: (b) oxalic acid, Δ, followed by steam distillation and repeated fractional distillation.

evaluation had to be isolated by preparative GC. The absolute configurations of **4c** and **4d** were attributed by NOESY experiments (Fig. 4).

3. Conclusion

Odour threshold measurements and olfactory evaluation of all the prepared six stereoisomers **4a**–**d**, *ent*-**4a** and *ent*-**4b**, reported in Table 1, confirmed the overwhelming superiority of **4a**. Luckily, all of the stereoisomers present some woody/amber aspect without any detrimental effect on the main amber-like note. Moreover, probably due to its lower free energy compared to **4b**, the main odour vector **4a** is formed as the major product during the last ketalisation step (65.5 versus 29.5%). The minor stereoisomer can also be transformed into the desired one by acid-catalysed epimerisation.

4. Experimental

4.1. General methods

All reagents and solvents were commercially available and were used without any purification. (1*R*)-(+) and (1*S*)-(−)-Camphor of e.e. 98.5 and 97.4%, respectively, were purchased from Fluka.

GC: BGB-178 (20% 2,3-diethyl-6-TBDMS-β-CD in BGB-15: 15% phenyl-, 85%-methylpolysiloxane) for optical purity of camphors, SUPELCOWAX™10 and DB™-WAX in separation of diastereomers of **4**, and DB™-1701 columns. Flash chromatography: Merck silica gel 60 (230–400 mesh). TLC: Merck silica gel 60 F_{254} anal. plates. Melting points were measured on a Büchi Melting Point B-545 apparatus and are uncorrected. Optical rotation: Perkin–Elmer 241. IR spectra: Bruker Vector 22 with Harrick ATR SplitPea™ device; neat (ATR); in cm^{-1}. NMR: Bruker DPX-400; ^{1}H at 400 and ^{13}C at 100 MHz; in $CDCl_3$ if not otherwise stated; chemical shifts (δ) in ppm downfield from TMS; coupling constants J in Hz; NOESY, and GRASP COSY-DQF, HMBC, HMQC and INADEQUATE ($Cr(Acac)_3$; with **4c** and **13**) data were used in signal attributions; for clarity, the numberings of C-atoms (corresponding to the usual numbering of the camphane system and otherwise to the systematic names of compounds), and the necessary arbitrary designation of protons of some CH_2 groups are indicated in schemes and in Fig. 3. MS and GC/MS: Finnigan MAT 212 and Hewlett–Packard MSD 5973 (EI, 70 eV) with HP-5MS column; intensities (in brackets) in % rel. to the base peak. HRMS: Finnigan MAT 95 (EI, 70 eV). Optical rotation: Perkin–Elmer 241. Molecular modelling: on SGI Octane R12000 workstation; conformational analyses (in chloroform; GB/SA solvation model) using MacroModel[16a] software package; free energy calculations with MINTA[16b] algorithm. Crystallographic analysis: at 150(2)K on a STOE STADIP diffractometer with graphite-monochromated Mo Kα radiation; the structure was solved using direct methods (SHELX-93) and refined against F^2 by full-matrix least-squares methods using SHELX-93.[22] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 165196 and 165197. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.2. [(1*R*,2*S*,4*R*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]acetic acid *tert*-butyl ester[10a] 2

Prepared by a modified procedure of Maroni-Barnaud et al.:[10] *iso*-Propyl chloride (5 mL, 0.055 mol) was added to a suspension of Mg turnings (48.6 g, 2.0 mol) in MTBE (50 mL). The reaction was initiated by addition of a small crystal of iodine and a solution of *iso*-propyl chloride (168 g, 2.14 mol) in MTBE (1 L) was added under reflux over 1.5 h. After stirring the mixture under reflux for a further 0.5 h, a solution of *tert*-butyl acetate (232 g, 2.0 mol) in MTBE (200 mL) was added dropwise (1.7 h) at −20°C and the mixture was stirred for a further 20 min at −20°C. (1*R*)-(+)-Camphor (152 g, 1 mol) dissolved in MTBE (250 mL) was added at the same temperature and stirring continued for 2 h at −20°C and at rt overnight. The reaction mixture was poured into a mixture of ice-water (1 kg) and acetic acid (250 mL). The phases were separated and the aqueous layer extracted with MTBE (100 mL). The combined organic phases were washed with water (600 mL), 10% $NaHCO_3$ solution (2×500 mL) and water (600 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was distilled using a short (5 cm) Vigreux column to give **2** as colourless oil (208 g, 77.5%); d.e. 93%; bp 95–96°C/0.05 torr; $[\alpha]_D^{22}$ −11.5 (*c* 1.1, EtOH); IR: ν_{max} 3492, 2957, 2876, 1709, 1457, 1369, 1214, 1155, 1077; ^{1}H NMR: δ 0.85 (Me(9)), 0.855 (Me(10)), 0.95–1.04 (m, H_{endo}-C(5)), 1.12, (Me(8)), 1.27–1.34 (m, H_{endo}-C(6)), 1.38–1.4 (H_{exo}-C(6)), 1.39 (d, J=13.3, H_{endo}-C(3)), 1.47 (s, *t*-Bu), 1.67–1.76 (m, H_{exo}-C(5)), 1.71 (dd, J=3.5, 1.9, H-C(4)), 2.10 (br. dt, J=13.3, 3.8, H_{exo}-(C3)), 2.42 (d, J_{AB}=15.3, H-(C2′)), 2.48 (d, J_{AB}=15.3, H-(C2′)), 3.91 (br. s, HO-C(2)); ^{13}C NMR: δ 10.6 (q, Me(10)), 20.9 (q, Me(9)), 21.3 (q, Me(8)), 26.8 (t, C(5), 28.0 (3q, *t*-Bu), 30.5 (t, C(6)), 44.0 (t, C(2′)), 44.9 (d, C(4)), 46.8 (t, C(3)), 49.1 (s, C(7)), 52.2 (s, C(1)), 79.0 (s, C(2)), 81.3 (s, *t*-Bu), 173.2 (s, C(1′)); MS: 268 (0.2, M$^+$), 212 (12), 194 (28), 152 (8), 139 (11), 135 (11), 123 (9), 110 (46), 109 (39), 108 (18), 95 (100), 57 (34), 55 (21), 41 (46).

4.3. (1*R*,2*S*,4*R*)-2-(2-Hydroxyethyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol 3

Prepared[10a] by reduction of **2** (17.6 g, 66 mmol) with LAH (2.7 g, 71 mmol). The crude product (quantitative yield) was used in the next step without further purification. An analytical sample was recrystallised from hexane to afford white crystals; MS: 199 (0.3), 198 (3, M$^+$), 180 (5), 165 (4), 162 (7), 153 (3), 147 (8), 135 (8), 119 (25), 108 (45), 95 (100), 93 (25), 91 (24), 79 (20), 69 (23), 55 (21), 43 (21), 41 (33). Anal. calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.78; H, 11.22%. Mp, $[\alpha]_D^{22}$, IR and NMR in agreement with the literature data.[10,14]

4.4. General procedure for preparation of *iso*-butyraldehyde cyclic ketals: (1*R*,2*S*,4*R*,2′*S*)- and (1*R*,2*S*,4*R*,2′*R*)-1,7,7-trimethyl-2′-(1-methylethyl)spiro[bicyclo-[2.2.1]heptane-2,4′-(1,3-dioxane)] 4a and 4b

A solution of crude diol **3** (13.0 g, 65.5 mmol), *iso*-butyraldehyde (5.26 g, 73 mmol) and *p*-toluenesulfonic acid monohydrate (0.69 g, 3.6 mmol) in anhydrous THF (100 mL) was stirred under nitrogen at rt for 5 h, then poured into ice-cold aqueous $NaHCO_3$ solution (10%, 200 mL) and extracted with MTBE (2×150 mL). The combined organic phases were washed with brine (2×150 mL), dried ($MgSO_4$) and concentrated in vacuo to give 17.1 g of crude product (GC purity 88%). Fractional distillation at 0.08 torr yielded a 65.5+29.5% mixture of **4a**+**4b** as a colourless oil (13.45 g, 83%); bp 84°C/0.08 torr. The two epimers were separated by flash chromatography (hexane/Et_2O 15:1) and recrystallised from aqueous ethanol.

Compound **4a**: white crystals; mp 35–36°C; $[\alpha]_D^{22}$ −61.5 (*c* 1.1, EtOH); IR: ν_{max} 2952, 1451, 1392, 1126, 1110, 1061, 1038, 889; ^1H NMR: δ 0.85 (s, Me(9)), 0.86 (s, Me(10)), 0.88 (d, *J*=6.9, Me(1″)), 0.89 (d, *J*=6.9, Me(3″)), 0.91–0.98 (m, H_{endo}-C(5)), 1.01 (s, Me(8)), 1.11 (br. dt, *J*=12.7, 2.0, H_{eq}-C(5′)), 1.29–1.42 (m, 2H-C(6)), 1.32 (d, *J*=12.8, H_{endo}-C(3)), 1.65–1.74 (m, H_{exo}-C(5) and H-C(2″)), 1.75 (br. t, *J*=4.5 H-C(4)), 1.92 (br. td, *J*=12.8, 5.2, H_{ax}-C(5′)), 2.13 (br. dt, *J*=12.8, 3.7, H_{exo}-C(3)), 3.76 (ddd, *J*=12.8, 11.4, 2.4, H_{ax}-C(6′)), 4.04 (ddd, *J*=11.4, 5.2, 1.7, H_{eq}-C(6′)), 4.33 (d, *J*=4.8, H-C(2′)); ^{13}C NMR: δ 9.9 (q, Me(10)), 16.7 (q, Me(1″)), 17.5 (q, Me(3″)), 20.8 (q, Me(9)), 21.2 (q, Me(8)), 26.7 (t, C(5)), 29.2 (t, C(6)), 32.2 (t, C(5′)), 32.7 (d, C(2″)), 40.7 (t, C(3)), 45.2 (d, C(4)), 48.6 (s, C(7)), 52.6 (s, C(1)), 64.1 (t, C(6′)), 82.1 (s, C(2)), 98.3 (d, C(2′)); MS: 253 (2), 252 (14, M^+), 209 (5), 181 (11), 180 (11), 165 (37), 163 (89), 142 (28), 123 (30), 109 (58), 108 (100), 107 (44), 95 (66), 93 (28), 81 (26), 79 (26), 69 (28), 55 (26), 43 (31), 41 (49). Anal. calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 75.88; H, 11.21%. X-Ray crystal structure (CCDC 165197): colourless needle, 0.5×0.3×0.15 mm, monoclinic, space group *P*2(1), *a*=8.7242(17), *b*=7.7176(15), *c*=11.194(2) Å, β=97.73(3)°, *Z*=2, ρ_{calcd}=1.122 g/cm³, μ=0.071 mm⁻¹, *F*(000)=280; the final residuals for 168 parameters (with anisotropic *B*-factors for all non-hydrogen atoms) without restraints refined against all 2817 unique data were R=0.0467 and R_w=0.1056.

Compound **4b**: white crystals; mp 43–45°C; $[\alpha]_D^{22}$ +3.5 (*c* 0.8, EtOH); IR: ν_{max} 2965, 2937, 1475, 1461, 1392, 1134, 1110, 1033, 1012, 877; ^1H NMR: δ 0.83 (s, Me(9)), 0.88 (d, *J*=6.8, Me(1″)), 0.89 (d, *J*=6.8, Me(3″)), 0.90 (s, Me(10)), 0.92–0.99 (m, H_{endo}-C(5)), 1.09 (s, Me(8)), 1.29–1.37 (m, 2H-C(6)), 1.41 (ddd, *J*=14.0, 3.4, 2.4, H_a-C(5′)), 1.48 (d, *J*=13.2, H_{endo}-C(3)), 1.58–1.68 (m, H-C(2″)), 1.65–1.73 (m, H_{exo}-C(5)), 1.71 (br. t, *J*=4.5, H-C(4)), 2.16 (br. dt, *J*=13.2, 3.8, H_{exo}-C(3)), 2.41 (ddd, *J*=14.0, 13.0, 5.5, H_b-C(5′)), 3.95 (ddd, *J*=13.0, 9.8, 3.4, H_a-C(6′)), 4.03 (ddd, *J*=9.8, 5.5, 2.4, H_b-C(6′)), 4.72 (d, *J*=4.9, H-C(2′)); ^{13}C NMR: δ 10.8 (q, Me(10)), 16.4 (q, Me(1″)), 17.3 (q, Me(3″), 20.7 (q, Me(9)), 20.9 (q, Me(8)), 26.7 (t, C(5)), 29.6 (t, C6)), 29.7 (t, C(5′)), 33.4 (d, C(2″)), 44.9 (d, C(4)), 47.0 (t, C(3)), 49.0 (s, C(7)), 53.1 (s, C(1)), 60.6 (t, C(6′)), 82.8 (s, C(2)), 97.1 (d, C(2′)); MS: 253 (2), 252 (13, M^+), 209 (4), 181 (10), 180 (11), 165 (42), 163 (69), 142 (26), 123 (35), 109 (64), 108 (100), 107 (45), 99 (30), 95 (79), 93 (33), 79 (31), 69 (26), 55 (29), 43 (40), 41 (61). Anal. calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 75.85; H, 10.89%. X-Ray crystal structure (CCDC 165196): colourless needle, 0.4×0.17×0.02 mm, monoclinic, space group *P*2(1), *a*=8.6693(17), *b*=7.5806(15), *c*=11.033(2) Å, β=95.22(3)°, *Z*=2, ρ_{calcd}=1.161 g/cm³, μ=0.074 mm⁻¹, *F*(000)=280; the final residuals for 168 parameters (with anisotropic *B*-factors for all non-hydrogen atoms) without restraints refined against all 2771 unique data were *R*=0.0682 and R_w=0.1377.

4.5. (1*S*,2*R*,4*S*,2′*R*)- and (1*S*,2*R*,4*S*,2′*S*)-1,7,7-Trimethyl-2′-(1-methylethyl)spiro[bicyclo[2.2.1]heptane-2,4′-(1,3-dioxane)] *ent*-4a and *ent*-4b

Prepared from (1*S*)-(−)-camphor via *ent*-**2** and *ent*-**3** according to the procedures described for their enantiomers. *ent*-**4a**: mp 35–36°C; $[\alpha]_D^{22}$ +61.5 (*c* 1.1, EtOH). Anal. calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 75.85; H, 10.89%. *ent*-**4b**: white crystals; mp 44–45°C; $[\alpha]_D^{22}$ −2.5 (*c* 0.8, EtOH). Anal. calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.05; H, 11.23%. Spectral data identical with those of **4a** and **4b**, respectively.

4.6. (1*R*,2*R*,4*R*,2′*R*)- and (1*R*,2*R*,4*R*,2′*S*)-1,7,7-Trimethyl-2′-(1-methylethyl)spiro[bicyclo[2.2.1]heptane-2,4′-(1,3-dioxane)] 4c and 4d

Prepared according to the above general procedure as a **4c**/**4d**=54+45% mixture starting from **9** (0.76 g, 3.8 mmol): colourless oil (42%). Prolonged stirring (96 h) with more *p*-toluenesulfonic acid monohydrate (0.2 mol. equiv.) led to a 92:8 mixture (58% yield), which was further enriched in **4c** by repeated flash chromatography (hexane/MTBE 15:1). An analytical sample of **4d** was isolated by preparative GC using in line connected DB™-WAX and DB™-1 columns. **4c** (contains 3.5% of **4d**): colourless oil; GC on the chiral BGB-178 column showed that no detectable racemisation occurred during the whole synthetic route from (1*R*)-(+)-camphor; $[\alpha]_D^{22}$ +12.5 (*c* 1.15, EtOH); IR: ν_{max} 2954, 2873, 1473, 1389, 1111, 1049, 1035, 1005; ^1H NMR: δ 0.84 (s, Me(10)), 0.88 (s, Me(8)), 0.90 (s, Me(9)), 0.91 (2d, *J*=6.8, Me(1″) and Me(3″)), 1.09–1.19 (m, H_{endo}-C(5) and H_{exo}-C(6)), 1.36 (dt, *J*=13.3, 2.0, H_{eq}-C(5′)), 1.54 (br. d, *J*=13.2, H_{endo}-C(3)), 1.64–1.74 (m, H_{exo}-C(5)), 1.72–1.78 (m, H-C(2″)), 1.74 (br. t, *J*=4.1, H-C(4)), 1.82 (br. ddd, *J*=13.2, 4.3, 3.1, H_{exo}-C(3)), 1.97 (br. dt, *J*=13.2, 4.7, H_{ax}-C(5′)), 2.21–2.27 (m, H_{endo}-C(6)), 3.70 (ddd, *J*=12.8, 11.3, 1.9, H_{ax}-C(6′)), 3.89 (ddd, *J*=11.3, 4.7, 2.2, H_{eq}-C(6′)), 4.39 (d, *J*=5.6, H-C(2′)); ^{13}C NMR: δ 11.6 (q, Me(10)), 16.8 (q, Me(1″)), 17.4 (q, Me(3″)), 21.3 (2q, Me(8) and Me(9)), 27.1 (t, C(5)), 28.0 (t, C(6)), 33.0 (d, C(2″)), 35.1 (t, C(5′)), 38.1 (t, C(3)), 44.8 (d, C(4)), 48.1 (s, C(7)), 53.1 (s, C(1)), 62.6 (t, C(6′)), 81.5 (s, C(2)), 101.2 (d, C(2′)); MS: 253 (0.3), 252 (3, M^+), 209 (2), 181 (4), 180 (4), 165 (24), 163 (60), 142 (24), 123 (35), 109 (62), 108 (100), 107 (44), 99 (30), 95 (80), 93 (31), 81 (30), 79 (32), 69 (35), 55 (48), 43 (73), 41 (84). Anal. calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 75.92; H, 11.15%.

Compound **4d**: colourless oil; $[\alpha]_{\mathrm{D}}^{22}$ −51 (*c* 0.2, EtOH); IR: ν_{max} 2956, 2876, 1474, 1458, 1392, 1258, 1130, 1109, 1090 1052, 1032, 884; ^{1}H NMR (C_6D_6): δ 0.75 (s, Me(8)), 0.81 (s, Me(9)), 0.99 (s, Me(10)), 1.14 (d, J=7.0, Me(1″)), 1.16 (d, J=7.0, Me(3″)), 1.29 (td, J=11.8, 5.3, H_{exo}-C(6)), 1.46 (ddd, J=12.2, 9.2, 5.3, H_{endo}-C(5)), 1.52 (br. t, J=4.5, H-C(4)), 1.58 (ddd, J=13.8, 3.0, 2.0, H_{eq}-C(5′)), 1.66 (br. d, J=13.3, H_{endo}-C(3)), 1.60–1.78 (m, H_{exo}-C(5)), 1.85 (ddd, J=13.6, 12.1, 6.3, H_{ax}-C(5′)), 1.88 (ddd, J=13.3, 4.0, 3.0, H_{exo}-C(3)), 1.98 (sepd, J=6.9, 5.0, H-C(2″)), 2.20 (ddd, J=12.1, 9.2, 3.2, H_{endo}-C(6)), 3.75 (ddd, J=11.6, 6.3, 2.3, H_{eq}-C(6′)), 3.82 (ddd, J=12.1, 11.6, 3.0, H_{ax}-C(6′)), 4.57 (d, J=5.0, H-C(2′)); ^{13}C NMR: δ 16.4 (q, Me(10)), 16.9 (q, Me(1″)), 17.3 (q, Me(3″)), 20.9 (q, Me(8)), 21.3 (q, Me(9)), 26.6 (t, C(5)), 29.0 (t, C(6)), 33.6 (d, C(2″)), 35.8 (t, C(5′)), 43.9 (d, C(4)), 48.8 (t, C(3)), 51.2 (s, C(1 or 7)), 53.1 (s, C(1 or 7)), 63.6 (t, C(6′)), 81.0 (s, C(2)), 101.0 (d, C(2′)); MS: 253 (1), 252 (9, M^+), 234 (2), 209 (3), 181 (8), 180 (8), 165 (32), 163 (49), 142 (20), 123 (34), 109 (34), 108 (100), 107 (36), 99 (24), 95 (66), 93 (25), 81 (20), 79 (22), 69 (21), 43 (25), 41 (42); HRMS: (M^+) calcd for $C_{16}H_{28}O_2$: 252.2089. Found: 252.2088.

4.7. [(1*R*,2*S*,4*R*)-(2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)]acetic acid *iso*-propyl ester 5

A solution of di-isopropylamine (282 mL, 2.0 mol) in MTBE (350 mL) was added to the Grignard reagent prepared as in the synthesis of **2** (from 2 mol of Mg), at 0°C over 10 min. The reaction mixture was stirred at 0°C for 0.7 h and diluted with MTBE (250 mL). *iso*-Propyl acetate (204 g, 2.0 mol) in MTBE (200 mL) was added dropwise over 20 min at −20°C and stirring continued for a further 20 min at −20°C. (1*R*)-(+)-Camphor (152 g, 1 mol) dissolved in MTBE (250 mL) was added at the same temperature and stirring continued for 3 h at −20°C. After the usual work-up the crude product was purified by sublimation of the unreacted camphor (80°C/0.2 torr) and distillation using a short (5 cm) Vigreux column to give **5** as colourless oil (86.5 g, 34%); bp 104°C/0.06 torr; $[\alpha]_{\mathrm{D}}^{22}$ −12.5 (*c* 0.97, EtOH); IR: ν_{max} 3502, 2937, 1709, 1455, 1389, 1373, 1323, 1197, 1106, 1077, 959, 814; ^{1}H NMR: δ 0.85 (Me(10)), 0.855 (Me(9)), 0.96–1.05 (m, H_{endo}-C(5)), 1.12, (Me(8)), 1.25–1.36 (m, H_{endo}-C(6)), 1.26, (d, J=6.3 Me(1″)), 1.27, (d, J=6.3 Me (3″)), 1.39–1.48 (H_{exo}-C(6)), 1.41 (d, J=13.3, H_{endo}-C(3)), 1.68–1.77 (m, H_{exo}-C(5)), 1.72 (dd, J=3.3, 2.0, H-C(4)), 2.11 (br. dt, J=13.3, 3.8, H_{exo}-(C3)), 2.47 (d, J_{AB}=15.3, H-(C2′)), 2.54 (d, J_{AB}=15.3, H-(C2′)), 3.81 (br. s, OH), 5.06 (sep, J=6.3, H-C(2″)); ^{13}C NMR: δ 10.5 (q, Me(10)), 20.9 (q, Me(9)), 21.3 (q, Me(8)), 21.7 (2q, Me(1″) and Me(3″)), 26.8 (t, C(5), 30.5 (t, C(6)), 43.2 (t, C(2′)), 44.8 (d, C(4)), 46.7 (t, C(3)), 49.0 (s, C(7)), 52.2 (s, C(1)), 68.1 (d, C(2″)), 79.1 (s, C(2)), 173.3 (s, C(1′)); MS: 255 (0.1), 254 (0.7, M^+), 236 (3), 195 (2), 179 (2), 152 (13), 144 (20), 109 (26), 108 (38), 102 (19), 95 (100), 81 (28), 69 (23), 55 (23), 43 (62), 41 (43). Anal. calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.88; H, 10.29%.

4.8. (*E*)-[(1*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-ylidene]acetic acid *iso*-propyl ester 6

Boron trifluoride etherate (25.0 g, 0.18 mol) was added to a solution of **5** (19.5 g, 0.077 mol) in acetic acid (125 mL) at 10–12°C (ice bath). The reaction mixture was stirred at rt for 8 h and, as conversion was incomplete (75%), more boron trifluoride etherate (25.0 g, 0.18 mol) was added and the mixture stirred at rt for a further 20 h. The mixture was poured into ice-water (200 g) and extracted with MTBE (2×300 mL). The combined extracts were washed with water (3×500 mL), dried ($MgSO_4$), concentrated in vacuo and purified by bulb-to-bulb distillation to give **6** (15.6 g, 86%) as a colourless oil; R_f (hexane/MTBE 2:1) 0.81; $[\alpha]_{\mathrm{D}}^{22}$ −45.5 (*c* 1.0, EtOH); IR: ν_{max} 2955, 1709, 1651, 1360, 1306, 1177, 979; ^{1}H NMR: δ 0.74 (Me(8)), 0.92 (Me(9)), 0.96, (Me(10)), 1.26, (2d, J=6.3 Me(1″) and Me (3″)), 1.17–1.25 (m, H_{endo}-C(5)), 1.21–1.30 (m, H_{endo}-C(6)), 1.66–1.72 (H_{exo}-C(6)), 1.76–1.85 (m, H_{exo}-C(5)), 1.86 (br. t, J=4.3, H-C(4)), 2.40 (dd, J=19.0, 2.2, H_{endo}-C(3)), 2.84 (ddd, J=19.0, 3.0, 2.8, H_{exo}-(C3)), 5.03 (sep, J=6.2, H-C(2″)), 5.55 (br. t H-C(2′)); ^{13}C NMR: δ 12.5 (q, Me(10)), 18.8 (q, Me(9)), 19.6 (q, Me(8)), 22.0 (q, Me(1″)), 22.1 (q, Me(3″)), 27.3 (t, C(5), 34.1 (t, C(6)), 38.3 (t, C(3)), 44.4 (d, C(4)), 48.0 (s, C(7)), 53.6 (s, C(1)), 66.5 (d, C(2″)), 108.4 (d, C(2″)), 166.9 (s, C(2)), 174.9 (s, C(1′)); MS: 237 (2), 236 (12, M^+), 194 (17), 179 (14), 177 (22), 151 (100), 138 (57), 133 (19), 105 (31), 93 (30), 91 (26), 79 (17), 43 (29), 41 (37). Anal. calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.04; H, 10.26%.

4.9. (*E*)-2-[(1*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-ylidene]ethanol** 7

Ester **6** (13.5 g, 57 mmol) was added dropwise to a suspension of LAH (2.2 g, 57 mmol) in Et_2O (150 mL) and the resulting suspension was stirred for 2 h under reflux. The reaction mixture was cooled to 10°C and hydrolysed with 2N aqueous NaOH (15 mL). After filtration, the organic phase was dried ($MgSO_4$), concentrated in vacuo and purified by high-vacuum drying to give **7** as a colourless oil (10.5 g, 100%). An analytical sample was purified by flash chromatography (hexane/MTBE 4:1); R_f (hexane/MTBE 2:1) 0.27; $[\alpha]_{\mathrm{D}}^{22}$ −33 (*c* 1.0, EtOH); IR: ν_{max} 3313, 2950, 2870, 1681, 1448, 1386, 1053, 1010, 979; ^{1}H NMR: δ 0.73 (s, Me(8)), 0.89 (s, Me(9)), 0.92 (s, Me(10)), 1.12–1.28 (m, H_{endo}-C(5) and H_{endo}-C(6)), 1.34 (br. s, OH), 1.59–1.68 (m, H_{exo}-C(6)), 1.74–1.82 (m, H-C(4) and H_{exo}-C(5)), 1.87 (br.

** The isomer prepared by Kostova et al.[14a] has slightly different spectral data and it probably has (*Z*)-configuration.

dd, $J=16.3$, 1.4, H$_{\text{endo}}$-C(3)), 2.37 (dq, $J=16.3$, 2.8, H$_{\text{exo}}$-C(3)), 4.07–4.16 (m, 2H-C(1′)), 5.28 (tt, $J=6.9$, 2.4, H-C(2′)); ^{13}C NMR: δ 12.6 (q, Me(10)), 18.7 (q, Me(9)), 19.4 (q, Me(8)), 27.7 (t, C(5)), 34.1 (t, C(3)), 34.8 (t, C(6)), 44.4 (d, C(4)), 47.2 (s, C(7)), 51.0 (s, C(1)), 60.1 (t, C(1′), 115.0 (d, C(2′)), 153.8 (s, C(2)); MS: 180 (2, M$^+$), 162 (64), 147 (41), 119 (100), 109 (20), 107 (28), 105 (37), 95 (44), 93 (63), 91 (62), 79 (37), 77 (31), 67 (24), 55 (31), 41 (67), 39 (32). Anal. calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.83; H, 11.24%.

4.10. (1*R*,2*S*,4*R*,3′*S*)-3′-Hydroxymethyl-1,7,7-trimethylspiro[bicyclo[2.2.1]heptane-2,2′-oxirane)] 8

Sodium bicarbonate (8.0 g, 95 mmol) and MCPBA (12.1 g, 70 mmol; portionwise) were added to a solution of **7** (10.0 g, 55 mmol) in cyclohexane (250 mL) at 5–10°C. After stirring at 10°C for 1 h, the reaction mixture was filtered and the filtrate concentrated in vacuo to give crude **8** as a colourless oil (9.4 g, ~86%), used in the next step without further purification (relatively unstable). An analytical sample was purified by flash chromatography (AcOEt/hexane 7:3): colourless oil containing 82% of **8** and 9% of its [tentatively assigned] (1*R*,2*R*,4*R*,3′*R*) diastereoisomer; R_f (AcOEt/hexane 7:3) 0.42; $[\alpha]_D^{22}$ −13.5 (*c* 1.0, EtOH); IR: ν_{max} 3420, 2875, 1452, 1389, 1370, 1056, 1037, 966, 793; ^{1}H NMR (C_6D_6; major product): δ 0.61 (s, Me(10)), 0.77 (s, Me(9)), 0.80 (s, Me(8)), 1.21 (d, $J=13.7$, H$_{\text{exo}}$-C(6)), 1.21 (d, $J=13.7$ H$_{\text{endo}}$-C(3)), 1.31–1.42 (m, H$_{\text{endo}}$-C(5) and H$_{\text{exo}}$-C(6)), 1.58 (t, $J=4.5$ H-C(4)), 1.62–1.77 (m, H$_{\text{exo}}$-C(5)), 1.97 (ddd, $J=13.7$, 4.6, 3.3, H$_{\text{exo}}$-C(3)), 2.01 (ddd, $J=12.6$, 9.0, 3.2, H$_{\text{endo}}$-C(6)), 3.11 (dd, $J_{AX}=6.1$, $J_{BX}=4.1$, H-C(3′)), 3.52 (dd, $J_{AB}=12.0$, $J_{AX}=6.1$, H-C(1″), 3.62 (dd, $J_{AB}=12.0$, $J_{BX}=4.1$, H-C(1″)); ^{13}C NMR (C_6D_6; major product): δ 10.3 (q, Me(10)), 19.2 (2q, Me(8) and Me(9)), 27.6 (t, C(5)), 30.3 (t, C(6)), 34.0 (t, C(3)), 44.5 (d, C(4)), 47.3 (s, C(1 or 7)), 47.6 (s, C(1 or 7)), 60.9 (d, C(3′)), 61.8 (t, C(1″)), 71.3 (s, C(2)); MS (major product): 196 (1, M$^+$), 181 (3), 178 (3), 166 (12), 165 (12), 153 (29), 151 (26), 137 (25), 123 (39), 121 (98), 109 (44), 107 (41), 95 (100), 93 (80), 91 (44), 81 (74), 79 (43), 67 (46), 55 (61), 43 (52), 41 (99), 29 (46). Anal. calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.17; H, 10.27%.

4.11. (1*R*,2*R*,4*R*)-2-(2-Hydroxyethyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol 9

A solution of crude **8** (8.0 g, ~41 mmol) in Et_2O (10 mL) was added dropwise to a suspension of LAH (1.92 g, 50 mmol) in the same solvent (150 mL). After stirring the mixture under reflux for 2 h, the reaction was worked-up as usual (cf. **7**). The crude **9** (8.2 g, colourless oil) was purified by flash chromatography (MTBE/hexane 1:1) and 3 recrystallisations from hexane to give **9** (2.0 g, ~25%), containing only 0.7% of **3** (LC/MS on ZORBAX® Eclipse XDB column, eluent: MeOH/H_2O 3:2), as white crystals; mp 79.5–80.5°C; $[\alpha]_D^{22}$ −14 (*c* 1.0, EtOH); IR: ν_{max} 3322, 2995, 2952, 1467, 1385, 1121, 1075, 1039, 1018, 962; ^{1}H NMR (C_6D_6): δ 0.75 (s, Me(8)), 0.87 (br. s, Me(9) and Me(10)), 1.31 (ddd, $J=12.4$, 12.1, 5.3, H$_{\text{exo}}$-C(6)), 1.35 (d, $J=13.4$ H$_{\text{endo}}$-C(3)), 1.47 (ddd, $J=12.0$, 9.4, 5.3, H$_{\text{endo}}$-C(5)), 1.48 (dt, $J=14.8$, 3.2, H-C(2′)), 1.65 (t, $J=4.5$ H-C(4)), 1.72–1.82 (m, H$_{\text{exo}}$-C(5)), 1.80 (ddd t, $J=14.8$, 9.1, 4.0, H-C(2′)), 2.07 (dt, $J=13.3$, 3.5, H$_{\text{exo}}$-C(3)), 2.45 (ddd, $J=12.4$, 9.4, 3.2, H$_{\text{endo}}$-C(6)), 3.40 (br. s, HO-C(1′)), 3.66 (br. s, 2H-C(1′)), 3.67 (br. s, HO-C(2)), 3.86 (br. t, $J=10.1$, H-C(1′)); ^{13}C NMR (C_6D_6): δ 10.8 (q, Me(10)), 21.1 (q, Me(8)), 21.4 (q, Me(9)), 26.8 (t, C(5)), 29.0 (t, C(6)), 40.2 (t, C(2′)), 42.5 (t, C(3)), 44.9 (d, C(4)), 48.8 (s, C(7)), 52.9 (s, C(1)), 58.8 (t, C(1′)), 80.9 (s, C(2)); MS: 199 (0.2), 198 (1, M$^+$), 180 (3), 165 (4), 153 (3), 147 (6), 135 (12), 119 (18), 108 (46), 95 (100), 93 (27), 91 (21), 79 (21), 69 (23), 55 (23), 43 (25), 41 (42). Anal. calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.69; H, 11.20%.

4.12. [(1*S*,4*R*)-(3,3-Dimethyl-2-methylenebicyclo[2.2.1]-hept-1-yl)]acetic acid *iso*-propyl ester 11

A suspension of hydroxyester **5** (25.4 g, 0.10 mol) and oxalic acid (27 g, 0.30 mol) in water (150 mL) was stirred under reflux for 2 h, then steam distilled for 8 h to yield a 19:22 mixture of **6**/**11** (14.1 g) that was enriched in **11** by repeated distillation over a short (5 cm) Vigreux column (1st: **11**/**6**=4:1, 2nd 87:4);[††] colourless oil; bp 77°C/0.1 torr; $[\alpha]_D^{22}$ +21.5 (*c* 1.0, EtOH); IR: ν_{max} 3070, 2975, 1731, 1655, 1468, 1373, 1181, 1109, 1076, 878; ^{1}H NMR (C_6D_6): δ 1.11 (Me(9)), 1.03, (Me(10)), 1.06, (d, $J=6.3$ Me(1″) and Me (3″)), 1.18–1.25 (m, H$_{\text{endo}}$-C(6)), 1.36–1.44 (m, H$_{\text{exo}}$-C(5)), 1.41–1.45 (H$_b$-C(7)), 1.61–1.72 (m, H$_{\text{endo}}$-C(5)), 1.66–1.75 (m, H$_{\text{exo}}$-C(6)), 1.71–1.74 (m, H-C(4)), 1.92 (ddd, $J=9.9$, 4.2, 2.2, H$_a$-C(7)), 2.48 (d, $J_{AB}=14.5$, H-(C2′)), 2.55 (d, $J_{AB}=14.5$, H-(C2′)), 4.61, (s, H$_{\text{anti}}$-C(8)), 4.71 (s, H$_{\text{syn}}$-C(8)), 5.01 (sep, $J=6.3$, H-C(2″)); ^{13}C NMR (C_6D_6): δ 21.5 (2q, Me(1″) and Me(3″)), 24.8 (t, C(5)), 25.7 (q, Me(10)), 29.2 (q, Me(9)), 33.6 (t, C(6)), 37.5 (t, C(2′), 41.6 (t, C(7)), 42.8 (s, C(3)), 46.9 (d, C(4)), 51.3 (s, C(1)), 66.6 (d, C(2″)), 98.2 (t, C(8)), 166.6 (s, C(2)), 170.6 (s, C(1′)); MS: 237 (3), 236 (18, M$^+$), 221 (4), 193 (22), 179 (21), 177 (22), 151 (83), 133 (60), 119 (61), 107 (37), 105 (100), 93 (33), 91 (47), 79 (26), 43 (62), 41 (57). Anal. calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.26; H, 10.39%.

4.13. (1*S*,5*R*,7*S*,9*R*)-5-(1-Methylethyl)-7,8,8-trimethyl-4,6-dioxatricyclo[7.2.1.0^{1,7}]dodecane 13

Isolated from a crude reaction mixture of **4**, obtained through the above experimental procedure starting from **6** that contained ~20% of **11**, by repeated flash chromatography (hexane/Et_2O 15:1), as colourless oil; R_f (hexane/Et_2O 15:1) 0.42; IR: ν_{max} 2956, 2930, 2875, 1460, 1388, 1375, 1129, 1118, 1056, 1021, 882; ^{1}H NMR: δ 0.77 (dd, $J=9.4$, 1.3, H$_b$-C(12)), 0.87 (d, $J=6.8$, Me(1′)), 0.88 (s, Me(14)), 0.89 (d, $J=6.7$, Me(3′)), 0.98 (s, Me(15)), 1.15–1.21 (m, H$_{\text{endo}}$-C(11)), 1.18 (s, Me(13)), 1.27–1.36 (m, H$_{\text{exo}}$-C(10) and H$_{\text{exo}}$-C(11)), 1.43 (ddd, $J=15.1$, 3.2, 1.2 H$_b$-C(2)), 1.52–1.61

[††] An attempt to further purify the sample by flash chromatography on silica gel led to partial isomerisation to **6**.

(m, H_{endo}-C(10)), 1.64–1.67 (m, H-C(9)), 1.78 (oct, $J=6.8$ H-C(2′)), 1.85 (ddd, $J=15.1$, 12.0, 3.3, H_a-C(2)), 2.29 (ddd, $J=9.4$, 4.3, 2.2, H_a-C(12)), 3.51 (ddd, $J=11.9$, 3.3, 3.2, H_a-C(3)), 3.77 (ddd, $J=12.0$, 11.9, 1.2, H_b-C(3)), 4.43 (d, $J=6.9$ H-C(5)); ^{13}C NMR: δ 12.3 (q, Me(13)), 18.0 (q, Me(1′)), 18.3 (q, Me(3′)), 24.1 (q, Me(14)), 25.1 (t, C(2′)), 26.1 (q, Me(15)), 30.8 (t, C(11)), 32.6 (d, C(2′)), 35.8 (t, C(2)), 38.5 (t, C(12)), 46.6 (s, C(8)), 48.3 (d, C(9)), 55.8 (s, C(1)), 59.9 (t, C(5)), 85.4 (s, C(7)), 99.5 (d, C(5)); MS: 252 (0.1, M^+), 209 (19), 180 (7), 163 (61), 137 (16), 123 (34), 110 (17), 107 (42), 97 (36), 95 (43), 94 (43), 93 (37), 86 (100), 79 (55), 43 (71), 41 (55); HRMS: ($M^+-C_3H_7$) calcd for $C_{13}H_{21}O_2$: 209.1542. Found: 209.1556.

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