Bicyclo[2.2.2]octane analogues of patchouli alcohol by Sakurai reaction and Nagata cyclization. Synthesis and olfactory properties of novel isopropyl derivatives†

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Dedicated to Prof. Csaba Szántay on his 80th birthday

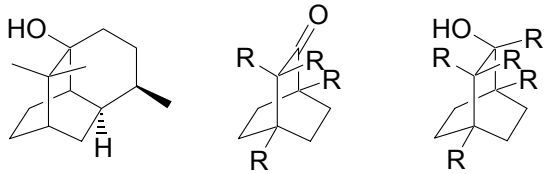
Abstract
The synthesis of bicyclo[2.2.2]octane *patchouli alcohol* analogues by the Sakurai conjugate addition and Nagata cyclization is described. By this approach, complementary to those so far adopted and based on the Diels-Alder addition, known analogues **2**, **3** and **20** and new analogues **8**-**11**, with 1-isopropylbicyclo[2.2.2]octane structure, could be obtained. The olfactory properties of **8** and **10** were also evaluated.

Keywords: 1-isopropylbicyclo[2.2.2]octane derivatives, synthesis, Sakurai allylation, Nagata cyclization, *patchouli alcohol* analogues, olfactory properties

Introduction

The olfactory properties of *patchouli alcohol* **1**, a sesquiterpenoid largely available from natural sources, are well known. Since total synthesis[2] has proven uneconomical, a systematic search for synthetic analogues with simpler structures **I** (R=H, alkyl, alkenyl) and **II** (R=H, alkyl, alkenyl) has been carried out by Spreitzer[3] and Weyerstahl.[4]

† The work described in this paper constitutes part of the Ph.D. Thesis of A.L.B.[1]



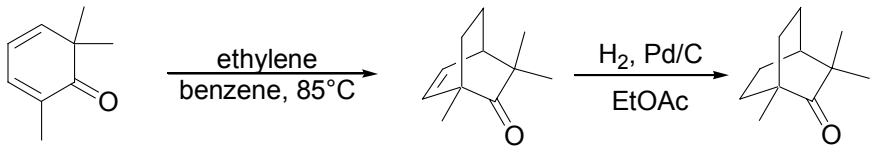
1 **I** **II**

Some compounds of type **I** and **II** display olfactory properties similar to those of **1**.[4] A general requisite for patchouli alcohol-like olfactory properties is a 13-15 C-atoms skeleton.[5] In the case of analogues of type **II**, another requisite is that the *"hydroxyl group should be sterically shielded by a methyl or another group to a large extent but not completely"*.[6]

2 R_1=H, R_2=H, R_3=H, R_4=H
3 R_1=Me, R_2=Me, R_3=H, R_4=H
4 R_1=Me, R_2=*i*-Pr, R_3=H, R_4=H
5 R_1=Me, R_2=H, R_3=Me, R_4=Me
8 R_1=*i*-Pr, R_2=H, R_3=H, R_4=H
9 R_1=*i*-Pr, R_2=H, R_3=Me, R_4=Me

6 R_1=H, R_2=H, R_3=Me, R_4=Me
7 R_1=Me, R_2=Me, R_3=Me, R_4=Me
10 R_1=*i*-Pr, R_2=H, R_3=Me, R_4=Me
11 R_1=*i*-Pr, R_2=H, R_3=H, R_4=H

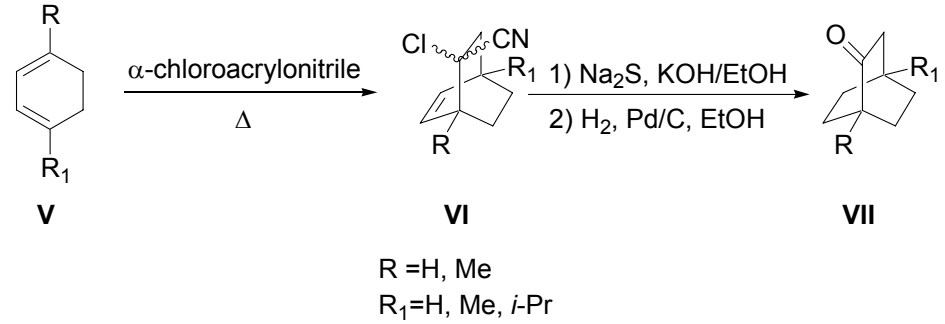
The key intermediate in the Spreitzer approach was the bicyclo[2.2.2]octan-2-one **5**, obtained by catalytic hydrogenation of the Diels-Alder addition product **IV** of ethylene to the unsymmetrical activated diene **III** (2,6,6-trimethylcyclohexadienone). By standard steps **5** was converted into analogues of type **II** (Scheme 1).[3b]



III **IV** **5**

Scheme 1

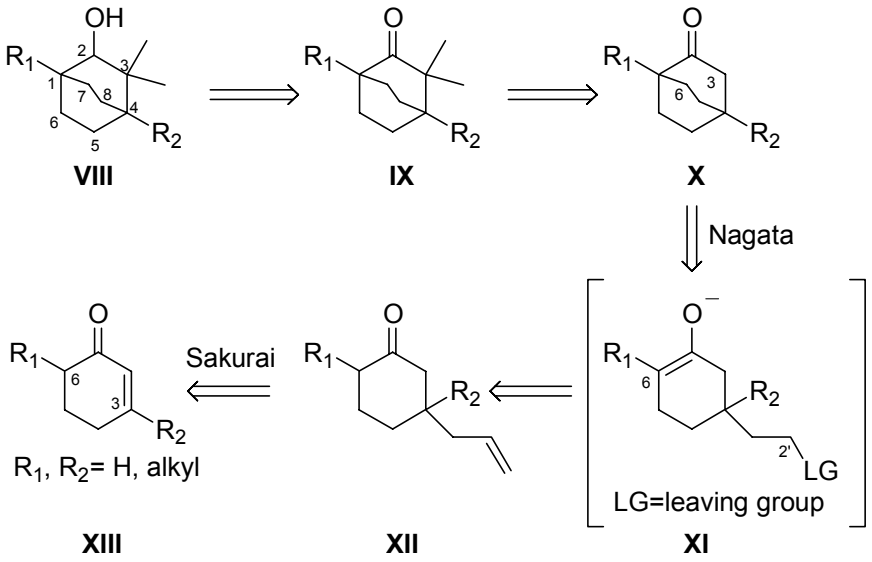
Weyerstahl obtained intermediates **I** *via* catalytic hydrogenation of the Diels-Alder addition product **VI** of an activated unsymmetrical dienophile (α-chloroacrylonitrile) to symmetrically 1,4-disubstituted unactivated dienes (cyclohexadiene or 1,4-dimethylcyclohexadiene) or to readily available α-terpinene (Scheme 2).[4]



Scheme 2

Steric, regiochemical and electronic restrictions of the Diels–Alder reaction as well as the availability of suitable dienes limit the versatility of this approach and the number of analogues **I** and **II** of *patchouli alcohol* obtainable.

In our studies for the synthesis of natural products containing bicyclo[2.2.2]octane systems or *via* intermediates of this type,[7] we have developed a synthetic approach to *patchouli alcohol* analogues, complementary to those so far adopted,[3,4] and based on the Nagata 3-sulfonyloxyethylcyclohexanone cyclization[8] and the Sakurai cyclohex-2-en-1-one conjugate addition[9] (Scheme 3).



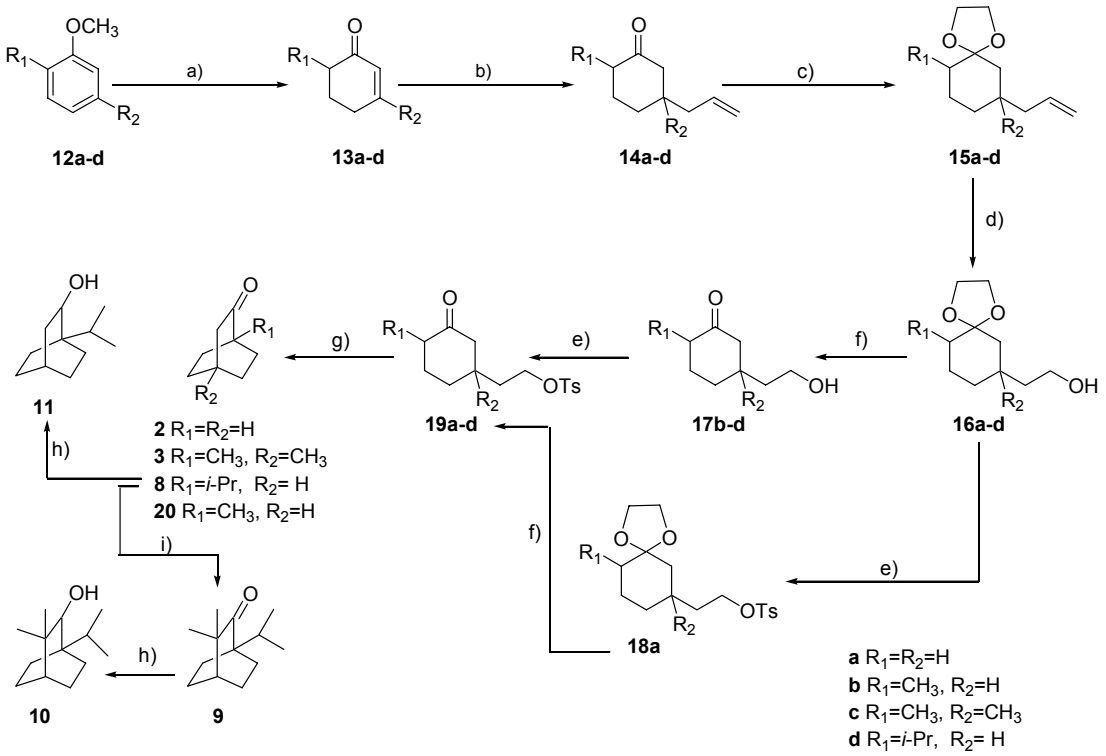
Scheme 3

The targets we selected were the known **2**[4], **3**[4], **20**[10] and the novel 1-isopropylbicyclo[2.2.2]octan-2-one **8**. Compound **8** was selected since its C(4) homologue **4** could be obtained only in trace amounts by the Diels-Alder approach, owing to the "*strong steric influence of the bulky isopropyl group*".[4] In addition 1-isopropylbicyclo[2.2.2]octan-2-one **8** can

be transformed into **9**, a new analogue of type **I**, and into **10** and **11**, new analogues of type **II**. Thus information on the effect of a bulky alkyl group at C(1) on the olfactory properties of analogues of type **I** and **II** could be obtained.

Results and Discussion

The starting materials for this study (Scheme 4) were commercially available anisoles **12** which were converted into α,β-unsaturated ketones **13** by Birch reduction followed by acidic hydrolysis.

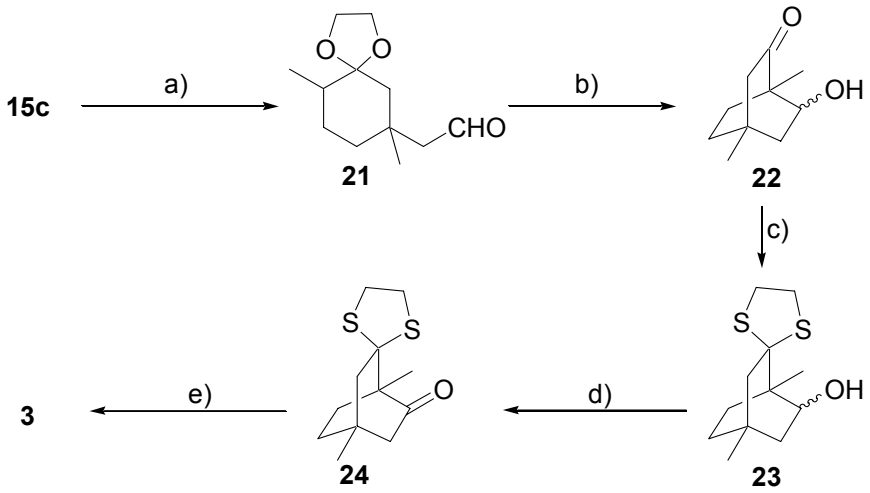


a) i) Li, NH_3, *t*-BuOH, THF, -50°C; ii) HCl; b) $TiCl_4$, CH_2Cl_2, $Me_3SiCH_2CH=CH_2$,-78°C, Ar; c) $HO(CH_2)_2OH$, benzene, TsOH, reflux; d) i) O_3, CH_2Cl_2, -78°C; ii) $NaBH_4$, MeOH, r.t.; e) TsCl, Py, r.t.; f) THF/1N HCl 4/1, r.t.; g) *t*-BuOH/*t*-BuOK, 0°C; h) $LiAlH_4$, THF, r.t.; i) CH_3I, NaH, THF, reflux.

Scheme 4

The latter were allowed to react according to Sakurai[9] with allyltrimethylsilane in the presence of $TiCl_4$ to give **14**. Protection of the carbonyl function of **14** as ethylene glycol acetal gave then **15**. The side chain double bond was cleaved with $O_3/NaBH_4$ to give **16**, which on treatment with 1N HCl/THF gave **17**. The latter were converted into tosylates **19**. In the case of **16a** the transformation into **19a** was also achieved by tosylation of **16a** to **18a**, which was then

deprotected giving **19a**. Exposure of tosylates **19** to *t*-BuOK in *t*-BuOH gave **2**, **3**, **8** and **20**. Previously[1] compound **3** had been obtained from **15c** as reported in Scheme 5.



a) OsO_4, $NaIO_4$, THF, H_2O, r.t.; b) THF/2N HCl 3:1, reflux; c) $HSCH_2CH_2SH$, BF_3-Et_2O, r.t.; d) PDC, CH_2Cl_2, r.t.; e) Raney-Nickel, EtOH, reflux.

Scheme 5

Compound **8** was also converted with MeI and NaH into the highly volatile gem-dimethylated compound **9** which could not be isolated. It was therefore reduced with $LiAlH_4$ to **10**. $LiAlH_4$ reduction of **8** gave then **11**.

Evaluation of olfactory properties.

The evaluation of olfactory properties requires a rather large amount of material. Thus only compounds **8** (type **I**) and **10** (type **II**) were subjected to olfactory evaluation.

Evaluation of analogue **8** revealed a scent reminiscent of eucalyptol and camphor, with the earthy-fruity part of *patchouli* oil. Thus the presence of the isopropyl group at C(1) appears to be sufficient for maintaining the earthy-fruity note of *patchouli* fragrance. In contrast, previously prepared analogues of type **I** having such olfactory properties were substituted at C(1), C(3) and C(4).[4]

The 13 C skeleton analogue **10** gave an earthy, mouldy and harsh odour with a technical and solvent-like note in olfactory evaluation. The HO-C(2) shielding by the isopropyl group at C(1) and by the two methyl groups at C(3) seems therefore to be responsible for the lack of the *patchouli alcohol* note in **10** (see prerequisites noted in the Introduction).

Conclusions

In conclusion, by preparing known analogues **2**, **3** and **20** and new analogues **8-11**, we have shown that the approach based on the Sakurai cyclohex-2-en-1-one conjugate addition and on the Nagata 3-sulfonyloxyethylcyclohexanone cyclization is quite convenient for the preparation of *patchouli alcohol* analogues of type **I** and **II**. Thus optically active *patchouli alcohol* analogues of type **II** can be prepared by performing the last reductive step with an asymmetric reducing reagent.

This approach could be useful for preparing a number of compounds of type **I** and **II** and in evaluating the influence on the olfactory properties of C(1)-substituents different than H and methyl, thus contributing to the knowledge of structure/odour relationships in this class of compounds, a target which deserves considerable attention and efforts.[11]

Acknowledgements

We are grateful to Dr. Philip Kraft and Mr. Jean-Jacques Rouge, *Givaudan Schweiz* AG, Fragrance Research (Ueberlandstrasse 138 CH-8600 Duebendorf, Switzerland) for evaluating the olfactory properties of compounds **8** and **10**.

We are also grateful to Prof. John A. Findlay (University of New Brunswick, Fredericton N. B., Canada) for kindly revising the manuscript.

Financial support by Università degli Studi di Roma "La Sapienza" (Ateneo 60%) and Ministero dell'Istruzione, Università e Ricerca (COFIN 2000 "Sintesi di Sostanze di Comunicazione Chirali" and COFIN 2002 "Aromi e Fragranze") is finally gratefully acknowledged.

Experimental Section

General Procedure: All solvents were anal. grade. TLC: Merck silica gel 60 F_{254}. Column Chromatography (CC): silica gel 60, 70-230 mesh ASTM. IR Spectra: *Shimadzu-470* scanning infrared spectrophotometer; in cm^{-1}. ^{1}H- and ^{13}C NMR: *Varian-Gemini-200*, at 200 and 50 MHz respectively; chemical shifts are on the δ scale and were referenced to residual $CDCl_3$ (at 7.26 for ^{1}H and the center line of the triplet at 77.0 for ^{13}C NMR); δ in ppm; *J* in Hz. Compounds **12** and **13a** are commercially available; compounds **2**,[4,12] **3**,[4,13] **13b**,[14] **13c**,[15] **13d**,[16] **14a**,[9,17] **14b**,[18] **15a**,[19] **16a**,[20] **17b**,[21] **17d**,[22] **18a**,[20a,23] **19a**,[8b] **20**,[10] were already described in the literature. The ^{13}C-NMR spectra of compounds obtained as not easily separable diastereoisomeric mixtures (**14c**, **15c**, **15d**, **16c**, **16d**, **19b**, **19c**, **19d**) are not reported. Olfactory properties of compounds **8** and **10** were evaluated at *Givaudan Schweiz* AG in a 10% dipropylene glycol (DPG) solution.

5-Allyl-2,5-dimethylcyclohexanone (14c). To a solution of enone **13c** (7.9 g, 63 mmol) in anhydrous CH_2Cl_2 (40 mL), cooled to –78°C, a solution of $TiCl_4$ (6.8 mL, 63 mmol) in anhydrous CH_2Cl_2 (13 mL) was added dropwise. To the well stirred mixture a solution of allyltrimethylsilane (11 mL, 69 mmol) in anhydrous CH_2Cl_2 (60 mL) was added dropwise. After 1 h the mixture was allowed to warm slowly to –30°C and stirred for 45 min. The reaction was then quenched at 0°C with H_2O and the whole poured into a separatory funnel. The layers were separated, the aqueous was extracted with CH_2Cl_2 (2x50 mL). The combined organic layers were repeatedly washed with sat. $NaHCO_3$ solution, brine, dried with anhydrous Na_2SO_4 and concentrated at atmospheric pressure distilling off the solvent through a *Vigreux* column. The crude product was then purified by CC (SiO_2: petroleum ether (40-70°)/Et_2O: 8.5/1.5) to afford **14c** as an oil (7.8 g, 50 mmol, 75%). Data of **14c**: IR (CCl_4): 1711 ($\nu_{C=O}$); ^{1}H-NMR ($CDCl_3$): 5.86-5.58 (*m*, 1H), 5.07-4.91 (*m*, 2H), 2.34-1.34 (*m*, 9H), 1.01-0.78 (*m*, 6H).
$C_{11}H_{18}O$ (166.26); Calc. C: 79.46; H: 10.91%. Found C: 79.28; H: 11.18%.

5-Allyl-2-isopropylcyclohexanone (14d). Compound **14d** was prepared from known **13d** (2.7 g, 20 mmol) as described for **14c** from **13c**. The crude product was then purified by CC (SiO_2: petroleum ether (40-70°)/Et_2O: 8.5/1.5) to afford two oily diastereomers. Data of **14d**$_{Rf<}$ (0.9 g, 5 mmol, 25%): IR (CCl_4): 1711 ($\nu_{C=O}$); ^{1}H-NMR ($CDCl_3$): 5.84-5.58 (*m*, 1H), 5.08-4.91 (*m*, 2H), 2.35-1.17 (*m*, 11H), 0.92-0.73 (*m*, 6H); ^{13}C-NMR ($CDCl_3$): 214.0, 135.8, 116.6, 57.3, 45.7, 40.1, 38.9, 27.0, 26.9, 26.7, 20.8, 19.8. $C_{12}H_{20}O$ (180.29); Calc. C: 79.94; H: 11.18 %. Found C: 79.70; H: 11.35%. Data of **14d**$_{Rf>}$ (0.9 g, 5 mmol, 25%): IR (CCl_4): 1710 ($\nu_{C=O}$); ^{1}H-NMR ($CDCl_3$): 5.81-5.55 (*m*, 1H), 5.03-4.90 (*m*, 2H), 2.43-1.20 (*m*, 11H), 0.94-0.78 (*m*, 6H); ^{13}C-NMR ($CDCl_3$): 211.9, 135.6, 116.5, 56.1, 48.4, 41.0, 39.9, 31.3, 27.6, 25.8, 21.0, 18.6. $C_{12}H_{20}O$ (180.29); Calc. C: 79.94; H: 11.18 %. Found C: 79.75; H: 11.50%.

9-Allyl-6,9-dimethyl-1,4-dioxaspiro[4.5]decane (15c). To a solution of ketone **14c** (7.8 g, 50 mmol) in anhydrous benzene (50 mL) an excess of ethylene glycol (0.3 mol) and a catalytic amount of TsOH were added. The mixture was refluxed under Ar with azeotropic removal of H_2O (*Dean-Stark* trap), until the TLC (petroleum ether (40-70°C)/Et_2O: 8.5/1.5, R_f(**14c**)<R_f(**15c**)) indicated the complete disappearance of the starting material. The reaction mixture was then cooled to r.t., diluted with Et_2O, and washed with sat. $NaHCO_3$ solution till neutral, brine, dried with anhydrous Na_2SO_4 and concentrated at atmospheric pressure distilling off the solvent through a *Vigreux* column. The crude product was then purified by CC (SiO_2: petroleum ether (40-70°)/Et_2O: 9/1) affording **15c** as an oil (7.7 g, 36 mmol, 73%). Data of **15c**: ^{1}H-NMR ($CDCl_3$): 5.90-5.67 (*m*, 1H), 5.04-4.92 (*m*, 2H), 3.97-3.80 (*m*, 4H), 2.31-1.10 (*m*, 9H), 0.97-0.81 (*m*, 6H). $C_{13}H_{22}O_2$ (210.31); Calc. C: 74.24; H: 10.54%. Found C: 74.03; H: 10.89%.

9-Allyl-6-isopropyl-1,4-dioxaspiro[4.5]decane (15d). Compound **15d** was prepared from **14d** (1.8 g, 10 mmol), as described for **15c** from **14c**. The crude product was then purified by CC (SiO_2: petroleum ether (40-70°)/Et_2O: 9/1) affording **15d** as an oil (1.9 g, 8.5 mmol, 85%). Data of **15d**: ^{1}H-NMR ($CDCl_3$): 5.88-5.64 (*m*, 1 H), 5.08-4.90 (*m*, 2 H), 4.08-3.77 (*m*, 4H), 2.20-1.19 (*m*, 11 H), 0.95-0.81 (*m*, 6H).
$C_{14}H_{24}O_2$ (224.34); Calc. C: 74.95; H: 10.78%. Found C: 75.18; H: 11.13%.

2-(10-Methyl-1,4-dioxaspiro[4.5]dec-7-yl)-ethanol (16b). Compound **15b** (5.5 g, 28 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to -78°C; a stream of O_3 was then slowly passed through the solution until a faint blue color persisted. $NaBH_4$ (2 g, 54 mmol) was then added portionwise, and the mixture stirred for 4 h at -78°C. After evaporation of the solvent under reduced pressure, the residue was taken up with water, neutralized with 5% HCl solution and extracted with CH_2Cl_2. Combined extracts were washed with water, brine, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was then purified by CC (SiO_2: petroleum ether (40-70°)/Et_2O: 6/4) to afford two oily diastereomers. Data of **16b**$_{Rf>}$ (0.8 g, 4.2 mmol, 15%): IR (CCl_4): 3635 (ν_{OH}); ^{1}H-NMR ($CDCl_3$): 3.97-3.86 (*m*, 4H), 3.73-3.52 (*m*, 2H), 2.08-1.07 (*m*, 11H), 0.89 (*d*, *J*=6.04, 3H); ^{13}C-NMR ($CDCl_3$): 110.8, 64.9, 64.7, 60.9, 44.5, 38.3, 36.7, 34.8, 31.1, 22.7, 10.7. $C_{11}H_{20}O_3$ (200.27); Calc. C: 65.97; H: 10.07%. Found C: 65.85; H: 10.34%. Data of **16b**$_{Rf<}$ (3.4 g, 17 mmol, 60%): IR (CCl_4): 3642 (ν_{OH}); ^{1}H-NMR ($CDCl_3$): 3.98-3.82 (*m*, 4H), 3.73 (*t*, *J*=6.87, 2H), 2.09 (*s*, 1H), 1.85-0.87 (*m*, 10H), 0.83 (*d*, *J*=6.41, 3H); ^{13}C-NMR ($CDCl_3$): 110.6, 65.2, 64.8, 60.5, 42.1, 39.7, 39.6, 32.3, 32.1, 31.8, 13.8. $C_{11}H_{20}O_3$ (200.27); Calc. C: 65.97; H: 10.07%. Found C: 65.78; H: 10.42%.

2-(7,10-Dimethyl-1,4-dioxaspiro[4.5]dec-7-yl)-ethanol (16c). Compound **16c** was prepared from **15c** (7.7 g, 36 mmol), as described for **16b** from **15b**. The crude product was then purified by CC (SiO_2: petroleum ether (40-70°)/Et_2O: 6/4) to afford **16c** as an oil (5.4 g, 25 mmol, 70%). Data of **16c**: IR (CCl_4): 3475 (ν_{OH}); ^{1}H-NMR ($CDCl_3$): 3.96-3.75 (*m*, 4H), 3.67-3.54 (*m*, 2H), 2.16 (*s*, 1H), 1.91-1.03 (*m*, 9H), 0.96-0.79 (*m*, 6H).

$C_{12}H_{22}O_3$ (214.30); Calc. C: 67.26; H: 10.35%. Found C: 66.96; H: 10.72%.

2-(10-Isopropyl-1,4-dioxaspiro[4.5]dec-7-yl)-ethanol (16d). Compound **16d** was prepared from **15d** (1.9 g, 8.5 mmol), as described for **16b** from **15b.** The crude product was then purified by CC (SiO_2: petroleum ether (40-70°)/Et_2O: 6/4) to afford **16d** as an oil (1.5 g, 6.5 mmol, 77%). Data of **16d**: IR (CCl_4): 3422 (ν_{OH}); ^{1}H-NMR ($CDCl_3$): 4.03-3.84 (*m*, 4H), 3.68-3.60 (*m*, 2H), 2.17-0.96 (*m*, 12H), 0.92-0.79 (*m*, 6H).

$C_{13}H_{24}O_3$ (228.33); Calc. C: 68.38; H: 10.59%. Found C: 68.22; H: 10.81%.

5-(2-Hydroxyethyl)-2,5-dimethylcyclohexanone (17c). A 4:1 THF/1N HCl solution (10 mL) of **16c** (5.4 g, 25 mmol) was stirred at r.t. until TLC analysis (SiO_2; petroleum ether (40-70°)/Et_2O: 1/1; R_f(**16c**)>R_f(**17c**)) showed the disappearance of the starting material (about 72 h). The reaction mixture was neutralized with a sat. $NaHCO_3$ solution and diluted with Et_2O; after separation, the aqueous phase was thoroughly extracted with Et_2O and the combined organic extracts were washed with H_2O and brine, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by CC (SiO_2: petroleum ether (40-70°)/Et_2O: 7/3) to afford two oily diastereomers. Data of **17c**$_{Rf<}$ (1.5 g, 8.8 mmol, 35 %): IR (CCl_4): 1715 ($\nu_{C=O}$);^{1}H-NMR ($CDCl_3$): 3.71 (*t*, *J*=7.23, 2H), 2.45-1.33 (*m*, 10H), 1.08-0.77 (*m*, 6H); ^{13}C-NMR ($CDCl_3$): 213.0, 58.7, 53.3, 46.7, 44.5, 38.8, 36.6, 31.3, 23.1, 14.3. $C_{10}H_{18}O_2$ (170.25); Calc. C: 70.55; H: 10.66%. Found C: 70.31; H: 10.90%. Data of **17c**$_{Rf>}$ (2.3 g, 14 mmol, 55%): IR (CCl_4): 1713 ($\nu_{C=O}$); ^{1}H-NMR ($CDCl_3$): 3.74-3.57 (*m*, 2H), 2.45-1.37 (*m*, 10H), 1.09-0.92 (*m*,

6H); ^{13}C-NMR ($CDCl_3$): 213.3, 58.9, 53.6, 44.2, 39.9, 38.8, 36.6, 31.2, 28.2, 14.3. $C_{10}H_{18}O_2$ (170.25); Calc. C: 70.55; H: 10.66%. Found C: 70.24; H: 11.03%.

2-(4-Methyl-3-oxocyclohexyl)ethyl-4-methylbenzenesulfonate (19b). To a stirred solution of **17b** (3.6 g, 23 mmol) in pyridine (5 mL) TsCl (4.4 g, 23 mmol) was added. After stirring for 18 h at r.t. H_2O (5 ml) was added, followed, after additional 10 min, by Et_2O (20 mL). The aqueous layer was separated and the organic one washed with 2N HCl, H_2O, sat. $NaHCO_3$ solution till neutral, brine, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was then purified by CC (SiO_2: petroleum ether (40-70°)/Et_2O: 6/4, R_f(**17b**)<R_f(**19b**)) to afford **19b** as an oil (6.8 g, 22 mmol, 95%). Data of **19b**: IR (CCl_4): 1715 ($\nu_{C=O}$); ^{1}H-NMR ($CDCl_3$): 8.10-7.56 (*m*, 4H), 4.37-4.26 (*m*, 2H), 2.72 (*s*, 3H), 2.66-1.42 (*m*, 10H), 1.32-1.20 (*m*, 3H).

$C_{16}H_{22}SO_4$ (310.41); Calc. C: 61.91; H: 7.14; S: 10.33%. Found C: 61.72; H: 7.39; S: 10.64%.

2-(1,4-Methyl-3-oxocyclohexyl)ethyl-4-methylbenzenesulfonate (19c). Compound **19c** was prepared from **17c** (3.8 g, 22 mmol) as described for **19b** from **17b**. The crude product was then purified by CC (SiO_2: petroleum ether (40-70°)/Et_2O: 6/4) to afford **19c** as an oil (5.2 g, 16 mmol, 73%). Data of **19c**: IR (CCl_4): 1713 ($\nu_{C=O}$); ^{1}H-NMR ($CDCl_3$): 8.09-7.58 (*m*, 4H), 4.43-4.32 (*m*, 2H), 2.74 (*s*, 3H), 2.65-1.53 (*m*, 9H), 1.32-1.07 (*m*, 6H).

$C_{17}H_{24}SO_4$ (324.44); Calc. C: 62.93; H: 7.46; S: 9.88%. Found C: 63.23; H: 7.61; S: 10.11%.

2-(4-Isopropyl-3-oxocyclohexyl)ethyl-4-methylbenzenesulfonate (19d). Compound **19d** was prepared from **17d** (2.1 g, 11 mmol) as described for **19b** from **17b**. The crude product was purified by CC (SiO_2: petroleum ether (40-70°)/Et_2O: 6/4) to afford **19d** as an oil (3.3 g, 9.9 mmol, 90%). Data of **19d**: IR (CCl_4): 1712 ($\nu_{C=O}$); ^{1}H-NMR ($CDCl_3$): 7.78-7.32 (*m*, 4H), 4.06-3.99 (*m*, 2H), 2.43 (*s*, 3H), 2.31-1.13 (*m*, 11H), 1.00-0.76 (*m*, 6H).

$C_{18}H_{26}SO_4$ (338.46); Calc. C: 63.87; H: 7.74; S: 9.47%. Found C: 64.01; H: 8.07; S: 9.82 %.

1-Isopropylbicyclo[2.2.2]octan-2-one (8). To a solution of **19d** (3.3 g, 9.9 mmol) in *t*-BuOH (8 mL), *t*-BuO^-K^+ (1.4 g, 12.5 mmol) was added. The mixture was stirred at r.t. until TLC (petroleum ether (40-70°)/Et_2O: 1/1, R_f(**19d**)<R_f(**8**)) showed the complete disappearance of the starting material (1 h). After careful neutralization with 0.1N HCl, Et_2O (10 mL) was added, the aqueous layer separated, extracted with Et_2O. The combined organic phases were washed with H_2O, brine, dried with anhydrous Na_2SO_4 and evaporated at atmospheric pressure. The crude product was purified by CC (SiO_2: petroleum ether (40-70°)/Et_2O: 8/2, R_f(**19d**)<R_f(**8**)) to afford **8** as an oil (1.4 g, 8.6 mmol, 87%). Data of **8**: IR (CCl_4): 1715 ($\nu_{C=O}$); ^{1}H-NMR ($CDCl_3$): 2.20-2.19 (*m*, 2H), 2.10 (*ps*, 1H), 2.01 (*sept*, *J*=6.87, 1H), 1.77-1.41 (*m*, 8H), 0.80 (*d*, *J*=6.87, 6H); ^{13}C-NMR ($CDCl_3$): 217.7, 47.8, 45.3, 28.9, 27.7, 25.2, 24.6, 17.6.

$C_{11}H_{18}O$ (166.26); Calc. C: 79.46; H: 10.91%. Found C: 79.58; H: 11.12%.

1-Isopropyl-3,3-dimethylbicyclo[2.2.2]octan-2-ol (10). To a stirred solution of **8** (380 mg, 2.3 mmol) in THF (3 mL) NaH (0.8 g, 3.5 mmol) was added portionwise under Ar and the mixture was stirred at r.t. for 40 min. CH_3I (4 mL, 0.07 mol) was then added dropwise and the mixture refluxed under Ar until TLC monitoring (SiO_2; petroleum ether (40-70°)/Et_2O: 9/1, R_f(**8**)<R_f(**9**)) showed the disappearance of the starting material. The reaction mixture was neutralized with

0.5N HCl, washed with H_2O, brine, dried with anhydrous Na_2SO_4 and evaporated at atmospheric pressure. The residue constituted by 1-isopropyl-3,3-dimethyl-bicyclo[2.2.2]octan-2-one (**9**) was used as such in the following step.

A solution of compound **9** in anhydrous THF (10 mL) was treated with $LiAlH_4$ (130 mg, 3.3 mmol). The reaction mixture was stirred at r.t. until TLC analysis (petroleum ether (40-70°)/Et_2O: 9/1, R_f(**10**)<R_f(**9**)) showed the disappearance of the starting material (1h). Excess $LiAlH_4$ was quenched by dropwise addition of H_2O and neutralized with 0.1N HCl. The layers were separated and the aqueous one extracted three times with Et_2O. The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated at atmospheric pressure. The crude residue was purified by CC (SiO_2; petroleum ether (40-70°)/Et_2O: 9.5/0.5) to afford **10** as an oil (350 mg, 1.8 mmol, 77%). Data of **10**: IR (CCl_4): 3516 (ν_{OH}); ^{1}H-NMR ($CDCl_3$): 3.36 (*s*, 1H), 1.89-1.12 (*m*, 11H), 1.01 (*s*, 3H), 0.99 (*s*, 3H), 0.81 (*d*, *J*=6.85, 3H), 0.76 (*d*, *J*=6.92, 3H); ^{13}C-NMR ($CDCl_3$): 78.0, 38.6, 36.4, 36.3, 30.8, 30.0, 23.2, 22.9, 22.2, 21.9, 21.6, 17.2, 16.9.

$C_{13}H_{24}O$ (196.33); Calc. C: 79.53; H: 12.32%. Found C: 79.83; H: 12.56%.

1-Isopropyl-bicyclo[2.2.2]octan-2-ol (11). To a solution of compound **8** (150 mg, 0.9 mmol) in anhydrous THF (5 mL) $LiAlH_4$ (50 mg, 1.3 mmol) was added. The reaction mixture was stirred at r.t. until TLC analysis (SiO_2: petroleum ether (40-70°)/Et_2O: 9/1, R_f(**8**)>R_f(**11**)) showed the disappearance of the starting material (1h). Excess $LiAlH_4$ was quenched by dropwise addition of H_2O and neutralized with 0.1N HCl. The layers were separated, and the aqueous one extracted with Et_2O, washed with brine, dried with anhydrous Na_2SO_4 and concentrated at atmospheric pressure. The crude residue was purified by CC (SiO_2; petroleum ether (40-70°)/Et_2O: 9.5/0.5) to afford **11** as an oil (116 mg, 0.7 mmol, 77%). Data of **11**: IR (CCl_4): 3543 (ν_{OH}); ^{1}H-NMR ($CDCl_3$): 3.91-3.85 (*m*, 1H), 2.05-1.92 (*m*, 1H), 1.71-1.03 (*m*, 12H), 0.83 (*d*, *J*=6.32, 3H), 0.80 (*d*, *J*=6.68, 3H); ^{13}C-NMR ($CDCl_3$): 69.7, 38.3, 36.7, 30.8, 26.1, 25.0, 24.8, 22.9, 21.5, 17.1, 17.0.

$C_{11}H_{20}O$ (168.28); Calc. C: 78.51; H: 11.98%. Found C: 78.68; H: 12.28 %.

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