# 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.

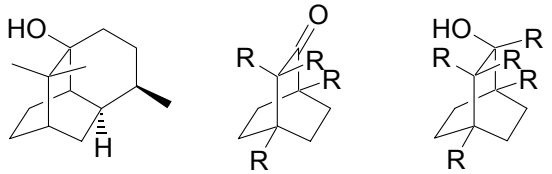
**Keywords:** 1-isopropylbicyclo[2.2.2]octane derivatives, synthesis, Sakurai allylation, Nagata cyclization, *patchouli alcohol* analogues, olfactory properties

## 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]



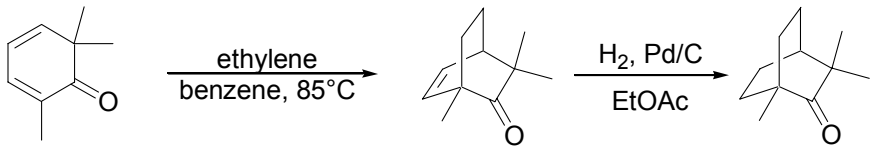

**1** **I** **II**

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

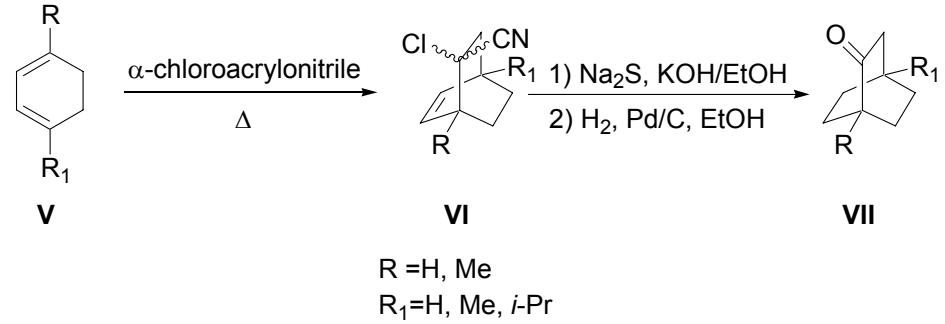
The key intermediate in the Spreitzer approach was the bicyclo[2.2.2]octan-2-one **5**, obtained by catalytic hydrogenation of the Diels-Alder addition product **IV** of ethylene to the unsymmetrical activated diene **III** (2,6,6-trimethylcyclohexadienone). By standard steps **5** was converted into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




**III** **IV** **5**

**Scheme 1**

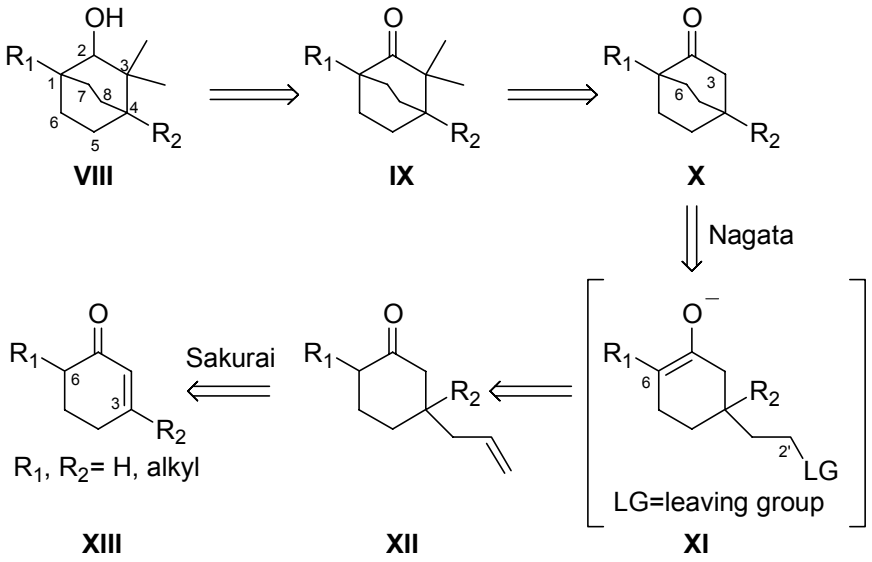
Weyerstahl obtained intermediates **I** *via* catalytic hydrogenation of the Diels-Alder addition product **VI** of an activated unsymmetrical dienophile (α-chloroacrylonitrile) to symmetrically 1,4-disubstituted unactivated dienes (cyclohexadiene or 1,4-dimethylcyclohexadiene) or to readily available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



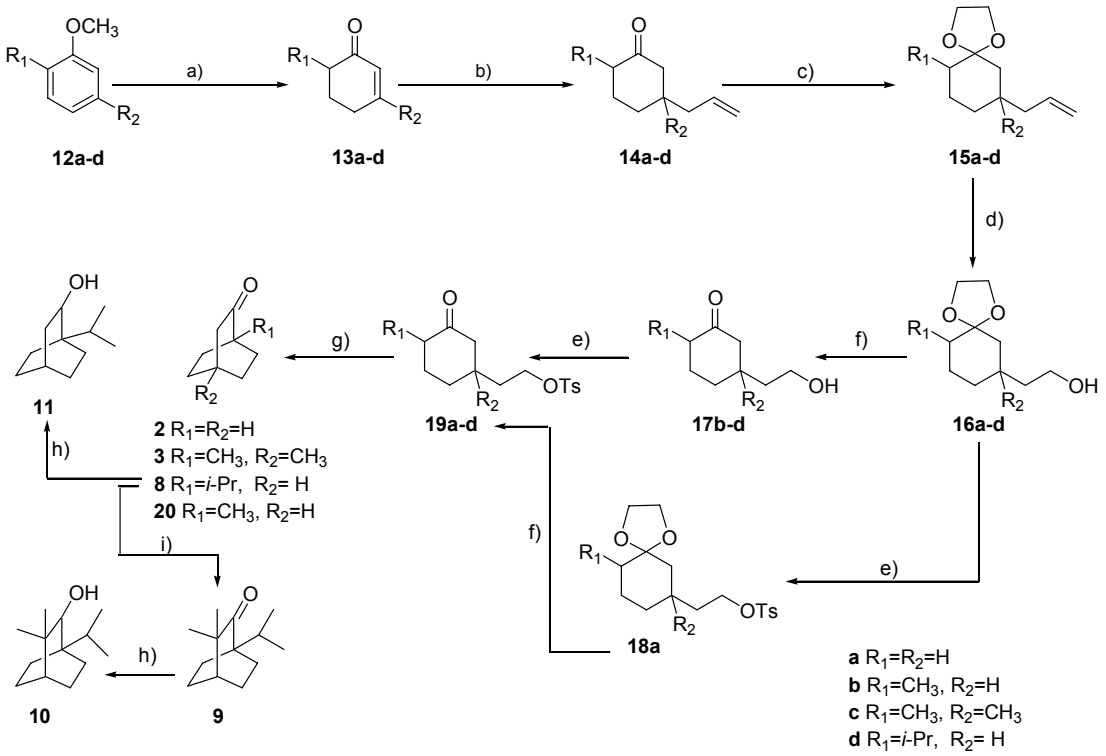

**Scheme 3**

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.

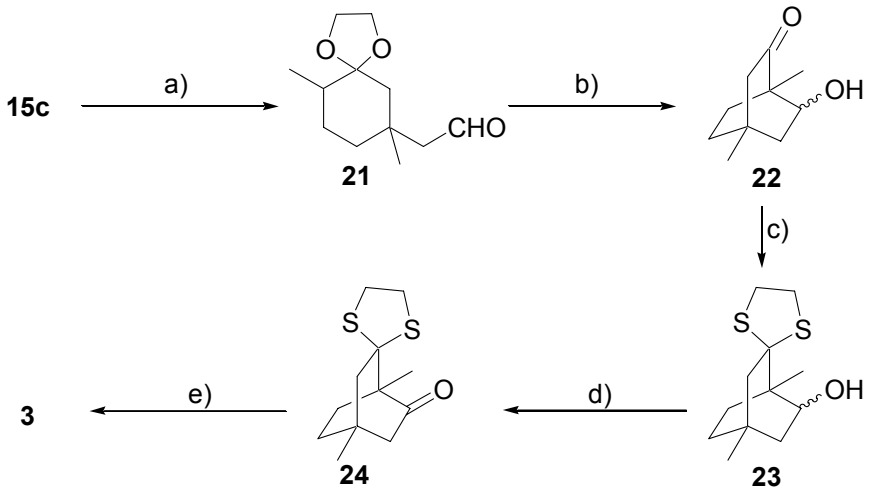



a) i) Li, $NH_3$, *t*-BuOH, THF, -50°C; ii) HCl; b) $TiCl_4$, $CH_2Cl_2$, $Me_3SiCH_2CH=CH_2$,-78°C, Ar; c) $HO(CH_2)_2OH$, benzene, TsOH, reflux; d) i) $O_3$, $CH_2Cl_2$, -78°C; ii) $NaBH_4$, MeOH, r.t.; e) TsCl, Py, r.t.; f) THF/1N HCl 4/1, r.t.; g) *t*-BuOH/*t*-BuOK, 0°C; h) $LiAlH_4$, THF, r.t.;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

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## 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 ($\nu_{OH}$); $^1$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 ($\nu_{OH}$); $^1$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 ($\nu_{OH}$); $^1$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 ($\nu_{OH}$); $^1$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 ($\nu_{OH}$); $^1$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 ($\nu_{OH}$); $^1$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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