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 synthesis2 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 Spreitzer3 and Weyerstahl.4

† The work described in this paper constitutes part of the Ph.D. Thesis of A.L.B.1
Some compounds of type I and II display olfactory properties similar to those of I. A general requisite for patchouli alcohol-like olfactory properties is a 13-15 C-atoms skeleton. 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".

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).

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).
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-sulfonfylxyethylcylohexanone cyclization8 and the Sakurai cyclohex-2-en-1-one conjugate addition9 (Scheme 3).

Scheme 3

The targets we selected were the known 24, 34, 2010 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.

![Scheme 4](image)

The latter were allowed to react according to Sakurai with allyltrimethylsilane in the presence of TiCl₄ 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 O₃/NaBH₄ 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.

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 F254. Column Chromatography (CC): silica gel 60, 70-230 mesh ASTM. IR Spectra: Shimadzu-470 scanning infrared spectrophotometer; in cm⁻¹. ¹H- and ¹³C NMR: Varian-Gemini-200, at 200 and 50 MHz respectively; chemical shifts are on the δ scale and were referenced to residual CDCl₃ (at 7.26 for ¹H and the center line of the triplet at 77.0 for ¹³C NMR); δ in ppm; J in Hz. Compounds 12 and 13a are commercially available; compounds 2, 3, 13b, 13c, 13d, 14a, 14b, 15a, 16a, 17b, 17d, 18a, 19, 20, 10 were already described in the literature. The ¹³C-NMR spectra of compounds obtained as not easily separable diastereoisomeric mixtures (14c, 15c, 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 CH₂Cl₂ (40 mL), cooled to −78°C, a solution of TiCl₄ (6.8 mL, 63 mmol) in anhydrous CH₂Cl₂ (13 mL) was added dropwise. To the well stirred mixture a solution of allyltrimethylsilane (11 mL, 69 mmol) in anhydrous CH₂Cl₂ (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 H₂O and the whole poured into a separatory funnel. The layers were separated, the aqueous was extracted with CH₂Cl₂ (2x50 mL). The combined organic layers were repeatedly washed with sat. NaHCO₃ solution, brine, dried with anhydrous Na₂SO₄ and concentrated at atmospheric pressure distilling off the solvent through a Vigreux column. The crude product was then purified by CC (SiO₂: petroleum ether (40-70°C)/Et₂O: 8.5/1.5) to afford 14c as an oil (7.8 g, 50 mmol, 75%). Data of 14c: IR (CCl₄): 1711 (νC=O); ¹H-NMR (CDCl₃): 5.86-5.58 (m, 1H), 5.07-4.91 (m, 2H), 2.34-1.34 (m, 9H), 1.01-0.78 (m, 6H).

C₁₁H₁₈O (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 (SiO₂: petroleum ether (40-70°C)/Et₂O: 8.5/1.5) to afford two oily diastereomers. Data of 14d:<sup>R₁</sup> (0.9 g, 5 mmol, 25%): IR (CCl₄): 1711 (νC=O); ¹H-NMR (CDCl₃): 5.84-5.58 (m, 1H), 5.08-4.91 (m, 2H), 2.35-1.17 (m, 11H), 0.92-0.73 (m, 6H); ¹³C-NMR (CDCl₃): 214.0, 135.8, 116.6, 57.3, 45.7, 40.1, 38.9, 27.0, 26.9, 26.7, 20.8, 19.8. C₁₂H₂₀O (180.29); Calc. C: 79.94; H: 11.18 %. Found C: 79.70; H: 11.35%. Data of 14d:<sup>R₂</sup> (0.9 g, 5 mmol, 25%): IR (CCl₄): 1710 (νC=O); ¹H-NMR (CDCl₃): 5.81-5.55 (m, 1H), 5.03-4.90 (m, 2H), 2.43-1.20 (m, 11H), 0.94-0.78 (m, 6H); ¹³C-NMR (CDCl₃): 211.9, 135.6, 116.5, 56.1, 48.4, 41.0, 39.9, 31.3, 27.6, 25.8, 21.0, 18.6. C₁₂H₂₀O (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 H₂O (Dean-Stark trap), until the TLC (petroleum ether (40-70°C)/Et₂O: 8.5/1.5, R<sub>f(14c)</sub><sub><sub><sup>R</sup> </sub></sub><sub><sub><sup>f(15c)</sup></sub></sub> indicated the complete disappearance of the starting material. The reaction mixture was then cooled to r.t., diluted with Et₂O, and washed with sat. NaHCO₃ solution till neutral, brine, dried with anhydrous Na₂SO₄ and concentrated at atmospheric pressure distilling off the solvent through a Vigreux column. The crude product was then purified by CC (SiO₂: petroleum ether (40-70°C)/Et₂O: 9/1) affording 15c as an oil (7.7 g, 36 mmol, 73%). Data of 15c: ¹H-NMR (CDCl₃): 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). C₁₃H₂₂O₂ (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 known 13d (2.7 g, 20 mmol) as described for 15c from 13c. The crude product was then purified by CC (SiO₂: petroleum ether (40-70°C)/Et₂O: 9/1) affording 15d as an oil (7.7 g, 36 mmol, 73%). Data of 15d: ¹H-NMR (CDCl₃): 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). C₁₃H₂₂O₂ (210.31); Calc. C: 74.24; H: 10.54%. Found C: 74.03; H: 10.89%.

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 H₂O (Dean-Stark trap), until the TLC (petroleum ether (40-70°C)/Et₂O: 8.5/1.5, R<sub>f(14c)</sub><sub><sub><sup>R</sup> </sub></sub><sub><sub><sup>f(15c)</sup></sub></sub> indicated the complete disappearance of the starting material. The reaction mixture was then cooled to r.t., diluted with Et₂O, and washed with sat. NaHCO₃ solution till neutral, brine, dried with anhydrous Na₂SO₄ and concentrated at atmospheric pressure distilling off the solvent through a Vigreux column. The crude product was then purified by CC (SiO₂: petroleum ether (40-70°C)/Et₂O: 9/1) affording 15c as an oil (7.7 g, 36 mmol, 73%). Data of 15c: ¹H-NMR (CDCl₃): 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). C₁₃H₂₂O₂ (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 (SiO₂: petroleum ether (40-70°C)/Et₂O: 9/1) affording 15d as an oil (1.9 g, 8.5 mmol, 85%). Data of 15d: ¹H-NMR (CDCl₃): 5.88-5.64 (m, 1 H), 5.08-4.90 (m, 2 H), 4.08-3.77 (m, 4 H), 2.20-1.19 (m, 11 H), 0.95-0.81 (m, 6 H).

C₁₄H₂₄O₂ (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 CH₂Cl₂ (20 mL) and cooled to -78°C; a stream of O₃ was then slowly passed through the solution until a faint blue color persisted. NaBH₄ (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 CH₂Cl₂. Combined extracts were washed with water, brine, dried with anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude product was then purified by CC (SiO₂: petroleum ether (40-70°)/Et₂O: 6/4) to afford two oily diastereomers. Data of 16b: (0.8 g, 4.2 mmol, 15%): IR (CCl₄): 3635 (νOH); ¹H-NMR (CDCl₃): 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); ¹³C-NMR (CDCl₃): 110.8, 64.9, 64.7, 60.9, 44.5, 38.3, 36.7, 34.8, 31.1, 22.7, 10.7. C₁₁H₂₀O₃ (200.27); Calc. C: 65.97; H: 10.07%. Found C: 65.85; H: 10.34%. Data of 16b: (3.4 g, 17 mmol, 60%): IR (CCl₄): 3642 (νOH); ¹H-NMR (CDCl₃): 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); ¹³C-NMR (CDCl₃): 110.6, 65.2, 64.8, 60.5, 42.1, 39.7, 39.6, 32.3, 32.1, 31.8, 13.8. C₁₁H₂₀O₃ (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 (SiO₂: petroleum ether (40-70°)/Et₂O: 6/4) to afford 16c as an oil (5.4 g, 25 mmol, 70%). Data of 16c: IR (CCl₄): 3475 (νOH); ¹H-NMR (CDCl₃): 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). C₁₂H₂₂O₃ (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 (SiO₂: petroleum ether (40-70°)/Et₂O: 6/4) to afford 16d as an oil (1.5 g, 6.5 mmol, 77%). Data of 16d: IR (CCl₄): 3422 (νOH); ¹H-NMR (CDCl₃): 4.03-3.84 (m, 4H), 3.68-3.60 (m, 2H), 2.17-0.96 (m, 12H), 0.92-0.79 (m, 6H). C₁₃H₂₄O₃ (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 (SiO₂: petroleum ether (40-70°)/Et₂O: 1/1; Rₜ(16c)>Rₜ(17c)) showed the disappearance of the starting material (about 72 h). The reaction mixture was neutralized with a sat. NaHCO₃ solution and diluted with Et₂O; after separation, the aqueous phase was thoroughly extracted with Et₂O and the combined organic extracts were washed with H₂O and brine, dried with anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude product was then purified by CC (SiO₂: petroleum ether (40-70°)/Et₂O: 6/4) to afford two oily diastereomers. Data of 17c: (1.5 g, 8.8 mmol, 35 %): IR (CCl₄): 1715 (νC=O); ¹H-NMR (CDCl₃): 3.71 (t, J=7.23, 2H), 2.45-1.33 (m, 10H), 1.08-0.77 (m, 6H); ¹³C-NMR (CDCl₃): 213.0, 58.7, 53.3, 46.7, 44.5, 38.8, 36.6, 31.3, 23.1, 14.3. C₁₀H₁₈O₂ (170.25); Calc. C: 70.55; H: 10.66%. Found C: 70.31; H: 10.90%. Data of 17c: (2.3 g, 14 mmol, 55%): IR (CCl₄): 1713 (νC=O); ¹H-NMR (CDCl₃): 3.74-3.57 (m, 2H), 2.45-1.37 (m, 10H), 1.09-0.92 (m,
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. H2O (5 ml) was added, followed, after additional 10 min, by Et2O (20 mL). The aqueous layer was separated and the organic one washed with 2N HCl, H2O, sat. NaHCO3 solution till neutral, brine, dried with anhydrous Na2SO4 and evaporated under reduced pressure. The crude product was then purified by CC (SiO2: petroleum ether (40-70°)/Et2O: 6/4) to afford 19b as an oil (6.8 g, 22 mmol, 95%). Data of 19b: IR (CCl4): 1715 (νC=O); 1H-NMR (CDCl3): 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).

C16H22SO4 (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 (SiO2: petroleum ether (40-70°)/Et2O: 6/4) to afford 19c as an oil (5.2 g, 16 mmol, 73%). Data of 19c: IR (CCl4): 1713 (νC=O); 1H-NMR (CDCl3): 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).

C17H24SO4 (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 (SiO2: petroleum ether (40-70°)/Et2O: 6/4) to afford 19d as an oil (3.3 g, 9.9 mmol, 90%). Data of 19d: IR (CCl4): 1712 (νC=O); 1H-NMR (CDCl3): 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).

C18H26SO4 (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°)/Et2O: 1/1, Rf(19d)<Rf(8)) showed the complete disappearance of the starting material (1 h). After careful neutralization with 0.1N HCl, Et2O (10 mL) was added, the aqueous layer separated, extracted with Et2O. The combined organic phases were washed with H2O, brine, dried with anhydrous Na2SO4 and evaporated at atmospheric pressure. The crude product was purified by CC (SiO2: petroleum ether (40-70°)/Et2O: 8/2, Rf(19d)<Rf(8)) to afford 8 as an oil (1.4 g, 8.6 mmol, 87%). Data of 8: IR (CCl4): 1715 (νC=O); 1H-NMR (CDCl3): 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).

C11H18O (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. CH3I (4 mL, 0.07 mol) was then added dropwise and the mixture reflushed under Ar until TLC monitoring (SiO2: petroleum ether (40-70°)/Et2O: 9/1, Rf(8)<Rf(9)) showed the disappearance of the starting material. The reaction mixture was neutralized with...
0.5N HCl, washed with H2O, brine, dried with anhydrous Na2SO4 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 LiAlH4 (130 mg, 3.3 mmol). The reaction mixture was stirred at r.t. until TLC analysis (petroleum ether (40-70°)/Et2O: 9/1, Rf(10)<Rf(9)) showed the disappearance of the starting material (1h). Excess LiAlH4 was quenched by dropwise addition of H2O and neutralized with 0.1N HCl. The layers were separated and the aqueous one extracted three times with Et2O. The combined organic layers were washed with brine, dried with anhydrous Na2SO4 and concentrated at atmospheric pressure. The crude residue was purified by CC (SiO2; petroleum ether (40-70°)/Et2O: 9.5/0.5) to afford 10 as an oil (350 mg, 1.8 mmol, 77%). Data of 10: IR (CCl4): 3516 (νOH); 1H-NMR (CDCl3): 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); 13C-NMR (CDCl3): 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.

C13H24O (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) LiAlH4 (50 mg, 1.3 mmol) was added. The reaction mixture was stirred at r.t. until TLC analysis (SiO2: petroleum ether (40-70°)/Et2O: 9/1, Rf(8)>Rf(11)) showed the disappearance of the starting material (1h). Excess LiAlH4 was quenched by dropwise addition of H2O and neutralized with 0.1N HCl. The layers were separated, and the aqueous one extracted with Et2O, washed with brine, dried with anhydrous Na2SO4 and concentrated at atmospheric pressure. The crude residue was purified by CC (SiO2; petroleum ether (40-70°)/Et2O: 9.5/0.5) to afford 11 as an oil (116 mg, 0.7 mmol, 77%). Data of 11: IR (CCl4): 3543 (νOH); 1H-NMR (CDCl3): 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); 13C-NMR (CDCl3): 69.7, 38.3, 36.7, 30.8, 26.1, 25.0, 24.8, 22.9, 21.5, 17.1, 17.0.

C11H20O (168.28); Calc. C: 78.51; H: 11.98%. Found C: 78.68; H: 12.28 %.

References