

# Synthesis of Decaline Analogues of Isovelleral

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Decaline analogues of the bioactive fungal sesquiterpene (+)-isovelleral (**1a**), retaining the bicyclo[4,1,0]hept-2-en-1,2-dicarbaldehyde system, were prepared, and their cytotoxic and antimicrobial activities were compared with those of the natural product. While the two isomers ( $\pm$ )-**2** and ( $\pm$ )-**3** were as active as isovelleral (**1a**), the isomer ( $\pm$ )-**4** was approximately 10 times less potent.

**Key words:** Bioactive Sesquiterpenoids, Unsaturated 1,4-Dialdehydes, Isovelleral

## Introduction

Isovelleral (**1a**), an extremely pungent sesquiterpene isolated from the fruit bodies of *Lactarius vellereus*, possesses several potent biological activities [1]. It is formed enzymatically from an inactive precursor in seconds as a response to injury to the fruit body, apparently to protect it from parasites [2]. The unsaturated 1,4-dialdehyde moiety, which also is present in a number of other terpenoids claimed to be part of natural defence systems, is thought to be responsible for the biological activities of **1a** [3]. However, the cyclopropane ring of **1a** may also be involved in the biological activity. When **1a** was allowed to react with a primary amine in ethanol the dialdehyde was transformed to a pyrrol ring and the cyclopropane was opened by the solvent as it is slightly activated towards nucleophilic attack [4]. When the activities of the two previously prepared bicyclic analogues **5** and **6** were compared, **5**, with the methyl group attached to the cyclopropane ring, was approximately 10 times less potent than **6**, lacking this methyl [4]. The structures are shown in Fig. 1.

This would be expected if a nucleophilic attack on the methylated cyclopropane carbon (C3) is part of the molecular mechanism by which isovelleral (**1a**) exerts its activity. The isovelleral analogue lacking the methyl groups, tridemethylisovelleral (**1b**) was consequently prepared and found to be approximately 10 times as cytotoxic towards common tumour cell lines as isovelleral itself [5]. In addition, as **1a** is considerably more potent than **5**, the cyclopentane ring of isovelleral also appears to contribute to the biologi-

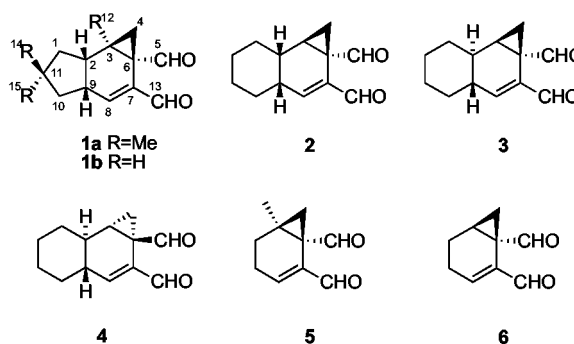
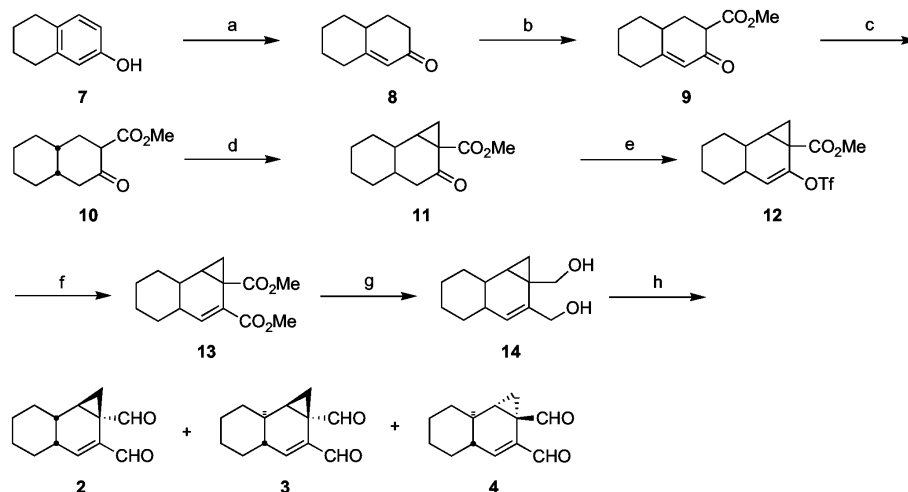


Fig. 1. Analogues of isovelleral.

cal activity. It has been shown for other terpenoid unsaturated dialdehydes that the dihedral angle between the two aldehyde groups in the unsaturated dialdehyde moiety is correlated with the antimicrobial activity [6]. The cyclopentane ring of **1a** would certainly affect the positioning of the aldehyde groups in space by altering the conformation of the six-membered ring, however, it is not evident that the best effect is accomplished with a cyclopentane ring. The purpose of this study was therefore to prepare and assay decalin analogues of isovelleral (e. g. **2**), with a cyclohexane ring instead of a cyclopentane and lacking methyl groups.

## Results and Discussion

The decalin analogues **2**, **3**, and **4** were synthesized according to the procedure described in Scheme 1, starting from commercially available hydroxytetralin **7**.



Scheme 1. Reaction conditions: (a) i) MeI,  $K_2CO_3$ , DMF, 55 °C; ii) Li,  $NH_3$ , EtOH, THF, -78 °C; iii) 10% HCl, MeOH, 66% (3 steps); (b) DIPA, *n*-BuLi,  $MeO_2CCN$ , THF, -78 °C, 69%; (c)  $HCO_2NH_4$ , 10% Pd/C, MeOH, reflux; (d) i) PhSeCl, pyridine, 30%  $H_2O_2$ ,  $CH_2Cl_2$ ; ii)  $Me_2SOCH_2$ , THF, 20 °C, 54%; (e) DIPA, *n*-BuLi, PhNTf<sub>2</sub>, THF, 77%; (f) Pd(OAc)<sub>2</sub>, PPh<sub>3</sub>, CO, MeOH, Et<sub>3</sub>N, DMF, 20 °C, 90%; (g) DIBAL-H, THF, 75%; (h) oxalyl chloride, DMSO, Et<sub>3</sub>N,  $CH_2Cl_2$ , -78 °C, 78%.

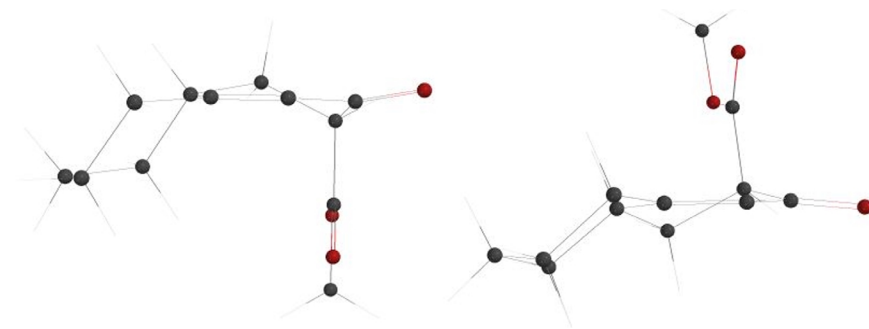


Fig. 2. Lowest energy conformers of the two epimers of **9**.

Birch reduction of the methyl ether and acidic hydrolysis afforded the bicyclic enone **8** [7, 8], which was transformed into an epimeric mixture of the ester **9** after treatment with LDA followed by reaction with methylcyanoformate [9]. Hydrogenation of **9** resulted in a *cis/trans* mixture of the saturated  $\beta$ -keto ester from which the major *cis* isomers (**10**) could be obtained in 48% yield after chromatography on silica gel. The lack of selectivity, which is in contrast to the hydrogenation of indanes, can be explained by the reversed facial discrimination of the two epimers, and the lowest energy conformers of both epimers are shown in Fig. 2.

The oxidation of **10** to the  $\alpha,\beta$ -unsaturated  $\beta$ -keto ester with PhSeCl and hydrogen peroxide, preceding the cyclopropanation, also generated isomeric mixtures [10,11], as the allylic bridgehead proton was prone to epimerisation and the initially desired *cis*

compound was to some degree transformed to the thermodynamically more stable *trans* compound ( $\Delta E = 6$  kJ/mol)\*. However, this was not considered a problem as we desired several stereoisomers of the final products for determining structure-activity relations. By not isolating the  $\alpha,\beta$ -unsaturated  $\beta$ -keto ester, but instead treating it immediately with the cyclopropanation reagent [12], the epimerisation gave approximately a 1:1 mixture of *cis* and *trans* decalines, and while the cyclopropanation of the *cis* compound was stereoselective, as expected, adding from the least hin-

\*The lowest energy conformer of each compound was determined by a conformational search. Calculations were performed using MacroModel v8.6 (Force field: MMFFs; Solvent: Octanol (using the analytical Generalized Born/Surface-Area (GB/SA) model); Minimization method: TNCG; Conformational search: MonteCarlo (MCMC); Steps: 2000). The energy was then determined by equilibrium geometry *ab initio* calculation (6-31G\*\*) using MacSpartan-Pro.

Table 1. Dihedral angles and distances of relevant conformers of **1a–4**<sup>a,b</sup>.

Compound (conformer)	$\Delta E^c$	Dihedral angle <sup>d</sup>
<b>1a(1)</b>	0	29.2
<b>1a(2)</b>	4.21	34.2
<b>2(1)</b>	0	54.5
<b>2(2)</b>	11.68	30.7
<b>3(1)</b>	0	30.8
<b>3(2)</b>	15.49	31.9
<b>4(1)</b>	0	56.3
<b>4(2)</b>	23.93	53.9

<sup>a</sup> Calculations were performed using MacroModel v8.6 (Force field: MMFFs; Solvent: Water (using the analytical Generalized Born/Surface-Area (GB/SA) model); Minimization method: TNCG; Conformational search: MonteCarlo (MCM); Steps: 2000); <sup>b</sup> the two lowest conformers, no rotamers, were taken into consideration; <sup>c</sup> energy is given in kJ/mol; <sup>d</sup> the dihedral angle between the two carbonyl carbons.

dered side, the cyclopropanation of the *trans* compound gave a 1:1 mixture of cyclopropane stereoisomers. This resulted in a 2:1:1 mixture of cyclopropanes (as determined by NMR), and the remaining steps were carried out without separating the isomers. Introduction of the second ester group [13] and the oxidation/reduction sequence to transform the ester groups to aldehyde groups [14, 15] followed essentially a previously described procedure developed for the total synthesis of ( $\pm$ )-isovelleral (**1a**) [16], affording a mixture of the three decalin-type dialdehydes **2**, **3** and **4** as racemates. Final purification with HPLC gave the pure compounds for characterisation and biological assays. The structure and relative stereochemistry of each dialdehyde was determined by NMR spectroscopy.

The cytotoxic and antimicrobial activity of the new dialdehydes **2**, **3** and **4** were compared with those of **1a**. Previously, it has been shown that the antimicrobial and cytotoxic activities of the two enantiomers of isovelleral (**1**) are comparable [17], and it is reasonable to compare the potency of the racemic compounds **2**, **3** and **4** with the natural product (+)-isovelleral (**1a**). The *in vitro* cytotoxicity towards the two cell lines L1210 (lymphocytic leukaemia mouse) and Colo 320 (human colon adenocarcinoma) showed that the *cis* isomer **2** and the *trans* isomer **3** are as potent as the natural product (IC<sub>50</sub>-values 0.1  $\mu$ g/ml towards L1210 and 1  $\mu$ g/ml towards Colo 320), while the *trans* isomer **5** was 10 times less potent. The antimicrobial activity towards the bacteria *Bacillus subtilis*, *B. brevis*, *Micrococcus luteus* and *Enterobacter dissolvens*, and the fungi *Mucor miehi*, *Paecilomyces varioti*, *Penicillium notatum* and *Nematospora coryli* was comparable for compounds **1a**, **2** and **3**, and in agreement with

those already reported for isovelleral (**1a**) [4], while compound **4** was significantly less potent. The reason for this difference is not clear, but it has been shown that the dihedral angle between the aldehyde groups is important for the antimicrobial activity of other terpenoid unsaturated 1,4-dialdehydes [6]. The dihedral angles of the most stable conformers of compounds **1a–4** were calculated with MacroModel, and the results are shown in Table 1. Isovelleral (**1a**) has several low energy conformers below 12 kJ/mol, compound **2** has two while compounds **3** and **4** have only one (excluding rotamers). The more active compounds **1a–3** all have at least one low energy conformer in which the dihedral angle between the two aldehyde groups is approximately 30°, while this angle is almost doubled in the less active compound (**4**).

## Conclusion

Decaline analogues of the fungal sesquiterpene isovelleral (**1a**) were synthesised and shown to be cytotoxic and antimicrobial agents, two of them as potent as isovelleral itself. However, the removal of the methyl group adjacent to the cyclopropane did not result in a 10-fold increase in the activity, as observed for **6** compared to **5** and **1b** compared to **1a**. Obviously, the six-six-three fused system of the compounds investigated here is less suitable for isovelleraloids with high activity, compared to the natural five-six-three fused variant.

## Experimental Section

Materials were obtained from commercial suppliers and were used without further purification unless otherwise noted. THF was dried by refluxing over sodium/benzophenone ketyl immediately prior to use. CH<sub>2</sub>Cl<sub>2</sub> and triethylamine were distilled from calcium hydride prior to use. DMF and DMSO were distilled under reduced pressure and kept over 4 Å MS. MeOH was dried by distilling from magnesium/iodine. All moisture and air-sensitive reactions were carried out under an atmosphere of dry nitrogen using oven-dried glassware. ESIMS spectra (H<sub>3</sub>PO<sub>4</sub> for calibration and as internal standard) were recorded with a Micromass Q-ToF Micro spectrometer, while EIMS (direct inlet, 70 eV) and CI spectra (direct inlet, methane) were recorded with a JEOL SX102 spectrometer. The NMR spectra (in CDCl<sub>3</sub>) were recorded with a Bruker DRX 400 spectrometer at 400 MHz (<sup>1</sup>H) and at 100 MHz (<sup>13</sup>C) and with a Bruker DRX 500 spectrometer at 500 MHz (<sup>1</sup>H) and at 125 MHz (<sup>13</sup>C), in CDCl<sub>3</sub> or C<sub>6</sub>D<sub>6</sub>. Chemical shifts are given in ppm relative to TMS us-

ing the residual  $\text{CHCl}_3$  peak in  $\text{CDCl}_3$  solution as internal standard (7.26 and 77.00 ppm, respectively relative to TMS) or using the residual  $\text{C}_6\text{HD}_5$  peak in  $\text{C}_6\text{D}_6$  solution (7.16 and 128.06 ppm, respectively). Organic extracts were dried over  $\text{MgSO}_4$ . All flash chromatography was performed on 60 Å 35–70  $\mu\text{m}$  Matrex silica gel (Grace Amicon). TLC analyses were made on Silica Gel 60 F<sub>254</sub> (Merck) plates and visualised with anisaldehyde/sulphuric acid and heating. HPLC separations were performed using a Dynamax SD-200 solvent delivery pump system with a Varian Microsorb 100 Si (particle size, 5  $\mu\text{m}$ ) column and a Dynamax UV-1 detector (254 nm) with hexane/isopropanol 99:1 to 90:10 gradient with a flow of 4 ml/min. The biological assays for antimicrobial and cytotoxic activities were carried out as described previously [3, 18, 19]. Calculations were performed using MacroModel v8.6 (Force field: MMFFs; Solvent: Water (using the analytical Generalized Born/Surface-Area (GB/SA) model); Minimization method: TNCG; Conformational search: MonteCarlo (MCM); Steps: 2000).

**4,4a,5,6,7,8-Hexahydronaphthalen-2(3H)-one (8).** To a solution of 20.1 g (0.14 mol) of 5,6,7,8-tetrahydro-naphthol (7) in 140 ml DMF was added 12.7 ml (0.20 mol) of methyl iodide and 29.9 g (0.22 mol) of anhydrous  $\text{K}_2\text{CO}_3$ . The solution was stirred at 55 °C for 22 h. 200 ml water and 160 ml ether were added and the phases were separated and the aqueous phases extracted with two portions (200 ml) of ether. The combined organic layers were washed with 200 ml 5% NaOH and 200 ml brine, dried and concentrated to give 18.8 g as a pale brown oil.

The crude product was dissolved in 600 ml liquid ammonia with 100 ml of THF and 100 ml of EtOH at –78 °C under nitrogen. 3.46 g (0.50 mol) of lithium was carefully added in small pieces to the solution that turned dark blue upon addition. After 1 h the dark blue colour had disappeared and the ammonia was allowed to evaporate over night. 400 ml water was added to the remainder and extracted with three 400 ml portions of ether. The combined ether layers were washed with 400 ml 5% aqueous NaOH and 400 ml brine, dried and concentrated to give 17.0 g as a pale yellow oil.

17.0 g of the pale yellow oil was dissolved in 455 ml MeOH and 137 ml 10% aqueous HCl was carefully added and the solution was stirred at room temperature for 2 h. The solution was concentrated and 350 ml water and 350 ml  $\text{CH}_2\text{Cl}_2$  was added. The layers were separated and the water layer was extracted with 350 ml  $\text{CH}_2\text{Cl}_2$ . The combined extracts were washed with saturated aqueous  $\text{NaHCO}_3$  and brine, dried and concentrated. The crude product was purified by vacuum distillation to give 13.5 g (89.6 mmol, 66% from 7) of **8** (75–77 °C, 0.15 mm Hg) as a colourless oil:  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.12 (dq,  $J$  = 12.9, 3.6 Hz, 1H), 1.25–1.45 (m, 2H), 1.48–1.59 (m, 1H), 1.70–1.91 (m, 3H), 2.00 (dq,  $J$  = 13.5, 5.0 Hz, 1H), 2.05–2.40 (m, 5H), 5.71 (s, 1H). –  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):

$\delta$  = 25.90, 27.30, 29.53, 34.80, 35.90, 36.87, 38.23, 124.61, 167.74, 200.36. – MS (EI, 70 eV):  $m/z$  (%) = 150 (61)  $[\text{M}]^+$ , 122 (100), 79 (34), 77 (13). – HRMS (EI):  $\text{C}_{10}\text{H}_{14}\text{O}$  calcd. 150.1045  $[\text{M}]^+$ , found 150.1047.

**3-Oxo-1,2,3,5,6,7,8,8a-octahydronaphthalene-2-carboxylic acid methyl ester (9).** To a solution of 10.8 ml (76.2 mmol) of diisopropylamine in 55 ml of THF, cooled to –78 °C, was added drop wise 7.8 ml (73.1 mmol, 9.4 M in hexanes) of *n*-BuLi. After 20 min a solution of 9.30 g (61.9 mmol) of the enone **8** in 40 ml of THF was added slowly. The solution was warmed to 0 °C after 20 min and stirred for 1 h at 0 °C. The solution was cooled to –78 °C and 7.95 ml (103.4 mmol) methylcyanofornate was added quickly. The solution was allowed to warm to room temperature and stirred for 40 min. 100 ml brine and 100 ml of ether were added and the layers separated. The water layer was extracted with 100 ml ether and the combined ether layers were washed with 250 ml brine, dried and concentrated. The oil was purified with flash chromatography (H/E 10:1) to give 8.90 g (42.7 mmol, 69%) of a 3:1 epimeric mixture of the ester **9**:  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ , major isomer):  $\delta$  = 1.20 (m, 1H), 1.44 (m, 2H), 1.91 (m, 3H), 2.20 (m, 2H), 2.43 (m, 2H), 3.37 (m, 1H), 3.76 (s, 3H), 5.84 (s, 1H). –  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ , major isomer):  $\delta$  = 25.73, 26.91, 32.50, 34.91, 35.51, 37.62, 52.57, 53.49, 167.78, 171.46, 194.50. – MS (EI, 70 eV):  $m/z$  (%) = 208 (55)  $[\text{M}]^+$ , 177 (18), 148 (42), 122 (100), 94 (26), 91 (23). – HRMS (EI):  $\text{C}_{12}\text{H}_{16}\text{O}_3$  calcd. 208.1099  $[\text{M}]^+$ , found 208.1102.

**3-Oxodecahydronaphthalene-2-carboxylic acid methyl ester (10).** 6.3 g (30.3 mmol) of the methyl ester **9** was dissolved in 580 ml of MeOH with 315 mg of 10% palladium on carbon. 9.55 g (151.5 mmol) of ammonium formate was added and the reaction mixture was refluxed under  $\text{N}_2$  for 30 min and then allowed to cool to room temperature. The reaction mixture was filtered through a bed of celite which was washed with MeOH. The solvent was removed under reduced pressure and the remains were dissolved in 500 ml ether and 500 ml water. The layers were separated and the aqueous layer was extracted with 500 ml of ether. The combined organic layers were dried and concentrated. Recrystallisation from heptane gave 3.08 g (14.5 mmol, 44%) of the *trans* isomers. The *cis* isomers were purified with flash chromatography to give 2.80 g (13.3 mmol, 40%):  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ , major *cis* isomer):  $\delta$  = 0.94 (m, 1H), 0.99 (m, 1H), 1.14 (m, 1H), 1.27 (m, 2H), 1.27 (m, 1H), 1.73 (m, 2H), 1.76 (m, 2H), 1.78 (m, 1H), 2.00 (dd,  $J$  = 16.9, 11.2 Hz, 1H), 2.09 (dd,  $J$  = 17.0, 5.1 Hz, 1H), 2.41 (dd,  $J$  = 17.0, 5.3 Hz, 1H), 3.68 (s, 3H), 12.1 (s, 1H). –  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ , major *cis* isomer):  $\delta$  = 26.03, 26.22, 31.62, 33.37, 33.41, 37.50, 38.33, 38.86, 50.41, 91.59, 156.23, 170.52.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ , major *trans* isomer):  $\delta$  = 0.99 (m, 1H), 1.15 (m, 1H), 1.27

(m, 3H), 1.76 (m, 3H), 2.02 (ddd,  $J = 17.0, 11.1, 1.2$  Hz, 1H), 2.11 (dd,  $J = 17.0, 5.3$  Hz, 1H), 2.42 (dd,  $J = 15.7, 5.3$  Hz, 1H), 3.68 (s, 3H), 12.1 (s, 1H). –  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ , major *trans* isomer):  $\delta = 26.56, 26.70, 32.03, 33.88, 33.81, 37.94, 38.78, 39.23, 50.99, 91.95, 156.75, 171.07$ . – HRMS (ESI):  $\text{C}_{12}\text{H}_{19}\text{O}_3$  calcd. 211.1334  $[\text{M}+\text{H}]^+$ , found 211.1331.

*2-Oxodecahydro-1aH-cyclopropa[a]naphthalene-1a-carboxylic acid methyl ester (11)*. 1.60 g (8.32 mmol) of  $\text{PhSeCl}$  was dissolved in 80 ml of  $\text{CH}_2\text{Cl}_2$  under  $\text{N}_2$  and cooled to 0 °C. To the cooled solution was added 732  $\mu\text{l}$  (9.07 mmol) of pyridine and after 20 min of stirring 1.55 g (7.56 mmol) of **10** in 16 ml of  $\text{CH}_2\text{Cl}_2$  was added drop wise. After 30 min the reaction mixture was extracted with  $2 \times 40$  ml of 10% aqueous HCl and cooled in an ice-bath. A solution of 30% aqueous  $\text{H}_2\text{O}_2$  was added in 515  $\mu\text{l}$  portions with 10 min intervals. 10 min after the last  $\text{H}_2\text{O}_2$  addition 40 ml of water was added and the phases were separated. The organic phase was washed with saturated aqueous  $\text{NaHCO}_3$ , dried and concentrated giving 1.71 g of crude product, which was used without further purification in the next step.

To 100 mg of the crude product was added 800  $\mu\text{l}$  (0.04 mmol, 0.5 M in THF) of dimethylsulfoxonium methylide. The cloudy white-yellowish solution was stirred at room temperature under nitrogen atmosphere for 40 min. The solution was diluted with both ether and water and the phases were separated. The aqueous phase was extracted with ether and the combined ethereal phases were washed with brine, dried and concentrated. The crude product was purified by flash chromatography (H/E 4:1) to give 43 mg (0.19 mmol, 43% from **10**) of an isomeric mixture of **11**. – MS (EI, 70 eV):  $m/z$  (%) = 222 (87)  $[\text{M}]^+$ , 190 (64), 134 (100), 95 (66), 79 (50). – HRMS (EI):  $\text{C}_{13}\text{H}_{18}\text{O}_3$  calcd. 222.1256  $[\text{M}]^+$ , found 222.1255.

*2-Trifluoromethanesulfonyloxy-1,3a,4,5,6,7,7a,7b-octahydro-1aH-cyclopropa[a]naphthalene-1a-carboxylic acid methyl ester (12)*. To an ice-cold solution of 237  $\mu\text{l}$  (1.68 mmol) of diisopropylamine in 1.25 ml of THF was added drop wise 800  $\mu\text{l}$  (1.9 M in cyclohexane) of *n*-BuLi under a nitrogen atmosphere. After 10 min the solution was cooled to –78 °C and 308 mg (1.39 mmol) of **11** dissolved in 0.63 ml of THF was added drop wise. The reaction mixture was stirred for 40 min at –78 °C when 536 mg (1.50 mmol) of *N*-phenyltrifluoromethanesulfonimide in 1.5 ml of THF was added. The resulting solution was allowed to reach room temperature and stirred for 1 h. The reaction mixture was then diluted with 10 ml saturated aqueous  $\text{NaHCO}_3$  and extracted with 10 ml of ether. The organic phase was washed with water, brine, dried and concentrated. The crude product was purified by flash chromatography (H/E 4:1, 1% EtOH) to give 379 mg (1.07 mmol, 77%) of **12**. – MS (EI, 70 eV):  $m/z$  (%) = 354 (35)  $[\text{M}]^+$ , 323 (19), 297 (8), 253 (6),

221 (52), 189 (100), 161 (48), 145 (22), 91 (38), 79 (22). – HRMS (EI):  $\text{C}_{14}\text{H}_{17}\text{F}_3\text{O}_5\text{S}$  calcd. 354.0749  $[\text{M}]^+$ , found 354.0758.

*1,3a,4,5,6,7,7a,7b-Octahydro-1aH-cyclopropa[a]naphthalene-1a,2-dicarboxylic acid dimethyl ester (13)*. 348 mg (0.94 mmol) of **12**, 272  $\mu\text{l}$  (1.96 mmol) of triethylamine, 1.59 ml (39.2 mmol) MeOH, 6.6 mg (0.03 mmol) of palladium acetate and 15.4 mg (0.06 mmol) of triphenylphosphine were dissolved in 4 ml of DMF. CO was bubbled through the solution and the reaction mixture was stirred for 2 h under a CO atmosphere at room temperature. The mixture was diluted with 40 ml of ether, washed with 40 ml of water and 40 ml brine, dried and concentrated. Flash chromatography (H/E 4:1, 1% EtOH) gave 282 mg (quant) of **13**. – MS (EI, 70 eV):  $m/z$  (%) = 264 (73)  $[\text{M}]^+$ , 232 (100), 200 (36), 173 (37), 145 (60), 91 (19), 83 (22). – HRMS (EI):  $\text{C}_{15}\text{H}_{20}\text{O}_4$  calcd. 264.1362  $[\text{M}]^+$ , found 264.1351.

*(2-Hydroxymethyl-1,3a,4,5,6,7,7a,7b-octahydro-1aH-cyclopropa[a]naphthalen-1a-yl)-methanol (14)*. 100 mg (0.38 mmol) of **13** was dissolved in 1 ml of THF under a nitrogen atmosphere and cooled to –78 °C and 3.0 ml (1.0 M in hexane) of DIBAL-H was added dropwise. The solution was stirred at room temperature for 30 min and then cooled to 0 °C. 510 mg (12.16 mmol) of NaF followed by 3 ml of water were added to the cooled solution. The reaction mixture was diluted with 30 ml of water and extracted twice with 30 ml of ethyl acetate. The combined organic extracts were dried and concentrated. Flash chromatography (H/E 1:1, 0.1% MeOH) afforded 59 mg (75%) of **14**. – MS (EI, 70 eV):  $m/z$  (%) = 208 (18)  $[\text{M}]^+$ , 159 (100), 105 (100), 91 (100), 79 (62). – HRMS (EI): for  $\text{C}_{13}\text{H}_{20}\text{O}_2$  calcd. 208.1463  $[\text{M}]^+$ , found 208.1470.

*1,3a,4,5,6,7,7a,7b-Octahydro-1aH-cyclopropa[a]naphthalene-1a-2-dicarbaldehyde (2, 3 and 4)*. To a solution of 54  $\mu\text{l}$  (0.76 mmol) of DMSO in 1 ml of  $\text{CH}_2\text{Cl}_2$  at –78 °C was added 26  $\mu\text{l}$  (0.30 mmol) of oxalyl chloride. The solution was stirred for 15 min when 15.8 mg (0.08 mmol) of **14** in 1 ml of  $\text{CH}_2\text{Cl}_2$  was added. After 30 min stirring at –78 °C, 254  $\mu\text{l}$  (1.82 mmol) of triethylamine was added. The stirring was continued for an additional 30 min before the reaction mixture was allowed to reach room temperature. After 20 min stirring at room temperature the mixture was diluted with 10 ml of water and 10 ml of ether. The phases were separated and the aqueous phase was extracted with 10 ml of ether. The combined ether extracts were dried and concentrated. Flash chromatography (H/E 8:1) afforded 12 mg (80%) of the isomeric mixture. The isomers were separated on normal phase HPLC in the same system, to afford 5 mg of **2**, 2.5 mg of **3** and 2.5 mg of **4**.

**2**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.09$  (dd,  $J = 7.2, 4.6$  Hz, 1H), 1.24 (m, 1H), 1.34 (m, 1H), 1.59 (m, 3H), 1.67 (m, 3H), 1.79 (m, 2H), 2.08 (dd,  $J = 8.9, 4.6$  Hz, 1H), 2.11

(m, 1H), 2.38 (m, 1H), 6.87 (d,  $J = 1.9$  Hz, 1H), 9.58 (s, 1H), 9.80 (s, 1H). –  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta = 20.11, 23.34, 24.87, 26.12, 29.85, 30.12, 30.39, 33.45, 33.81, 142.04, 153.82, 192.48, 199.40$ . – HRMS (CI):  $\text{C}_{13}\text{H}_{17}\text{O}_2$   $[\text{M}+\text{H}]^+$ , calcd. 205.1229, found 205.1223.

**3**:  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta = 0.53$  (dd,  $J = 7.0, 4.4$  Hz, 1H), 0.65 (m, 1H), 0.78 (m, 2H), 0.87 (m, 2H), 0.94 (m, 1H), 0.99 (m, 1H), 1.33 (m, 2H), 1.50 (m, 2H), 1.92 (dd,  $J = 8.8, 4.4$  Hz, 1H), 6.50 (d,  $J = 2.0$  Hz, 1H), 9.56 (s, 1H), 9.96 (s, 1H). –  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta = 18.28, 20.13, 26.41, 30.65, 31.73, 35.07, 36.11, 37.95, 45.53, 139.92, 153.16, 192.69, 199.60$ . – HRMS (CI):  $\text{C}_{13}\text{H}_{17}\text{O}_2$   $[\text{M}+\text{H}]^+$ , calcd. 205.1229, found 205.1235.

**4**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 0.76$  (dd,  $J_1 = 5.9, 4.9$  Hz, 1H), 1.02 (m, 1H), 1.16 (dt,  $J = 12.6, 2.9$  Hz, 1H), 1.24 (m, 1H), 1.35 (m, 1H), 1.37 (m, 1H), 1.50 (dt,  $J = 8.6, 6.1$  Hz, 1H), 1.81 (m, 2H), 1.99 (dd,  $J = 8.3, 4.4$  Hz, 1H), 2.02 (m, 1H), 2.07 (m, 1H), 2.12 (m, 1H), 6.87 (d,  $J = 2.2$  Hz, 1H), 9.09 (s, 1H), 9.57 (s, 1H). –  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta = 26.03, 26.16, 27.62, 28.28, 30.84, 31.31, 33.11, 40.76, 46.14, 139.52, 160.48, 191.96, 198.51$ . – HRMS (CI):  $\text{C}_{13}\text{H}_{17}\text{O}_2$   $[\text{M}+\text{H}]^+$ , calcd. 205.1229, found 205.1227.

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