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New preparation of (3a*R**,6*S**,7a*R**)-6,7,7-trimethylhexahydro-2-benzofuran-1(3*H*)-one: formal synthesis of (±)-γ-irone

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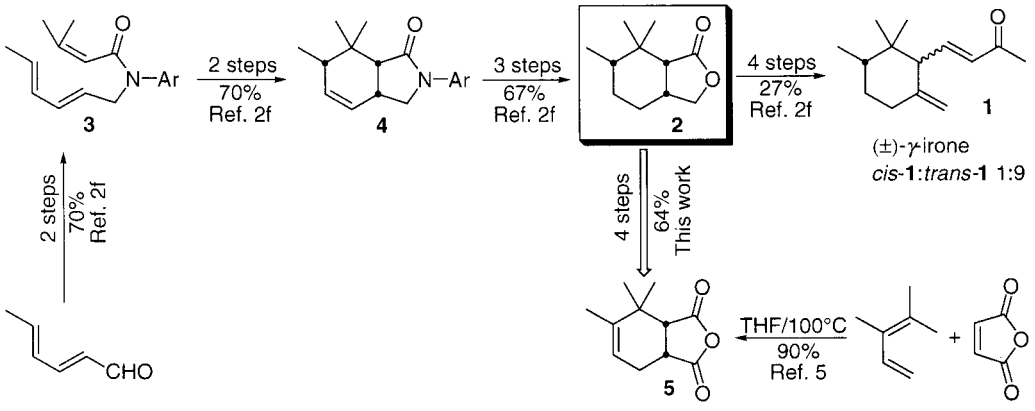
Abstract—A four-step synthesis of (3a*R**,6*S**,7a*R**)-6,7,7-trimethylhexahydro-2-benzofuran-1(3*H*)-one **2** has been developed. Lactone **2** is an intermediate in a synthesis of γ-irone. Opening of the Diels–Alder adduct **5** with ethanol afforded hemiester **6b** with 87:13 regioselectivity. Subsequent chemoselective reduction of the ester group in **6b** yielded hydroxyacid **14** which was lactonized to the *cis*-fused bicyclic lactone **15**. Finally, hydrogenation of **15** into **2** occured with complete diastereoselectivity.

1. Introduction

While many syntheses of α- or β-irones have been reported,[1] only six preparations of *cis*-γ-irone *cis*-**1** have been developed,[2] among which only one is stereoselective.[2c] The difficulty in preventing isomerization of the double bond and the *cis*-relationship between the 6-methyl and the carbonyl side chain may explain the scarcity of these syntheses. However, not only is *cis*-γ-irone one of the main constituents of the iris essential oil,[3] it also exhibits the strongest and finest violet-like odor.[4] New efforts towards the synthesis of **1** are therefore of interest.

A 1:9 mixture of racemic *cis*- and *trans*-γ-irones **1** has been synthesized by Mori et al.[2f] (Scheme 1). The requisite *cis*-fused bicyclic lactone **2** was obtained according to a seven step process: the intramolecular Diels–Alder reaction of the trienoic amide **3** afforded a separable mixture of *cis*- and *trans*-adducts in 22% and 43% isolated yields, respectively. In situ epimerization of the later raised the yield of the *cis*-adduct **4** to 70%. Hydrogenation of **4** yielded a saturated lactam which was treated with nitric acid in acetic acid. Decomposition of the resulting *N*-nitrosolactam with aqueous KOH in THF, followed by heating with *p*-TsOH in benzene finally gave the desired *cis*-lactone **2** in 33% overall yield.

We report herein a new preparation of the key intermediate **2**. Adduct **5** was used as the starting material. According to our recently reported procedure,[5] this anhydride is now readily available in grams quantities by the intermolecular



Scheme 1.

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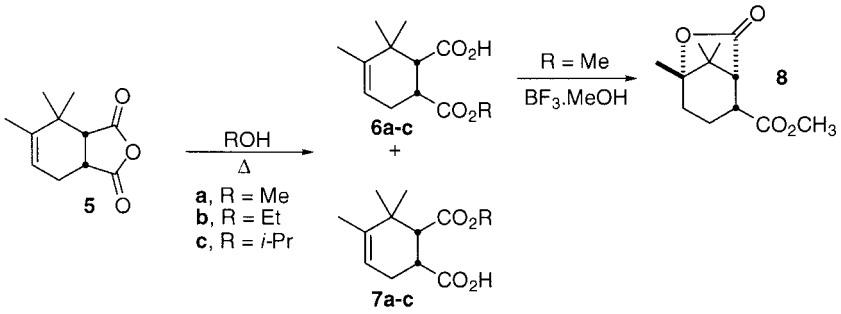
Table 1. Opening of anhydride **5** with various alcohols



	ROH	T (°C)	Time (h)[a]	**6:7**[b]	% conv.[b]	% yield[c]
a	MeOH	70	15	82:18	100	60% **6a** (+10% **7a**)
b	EtOH	75	24	87:13	100	73% **6b** (+2% **7b**)
c	*i*-PrOH	80	72	87:13	90	56% **6c** (+12% **7c**)

[a] Reactions monitored by GC.
[b] Determined by GC of the crude mixture.
[c] Isolated yield of **6** after separation by liquid chromatography on silica-gel.

Diels–Alder reaction of 3,4-dimethylpenta-1,3-diene with maleic anhydride.

2. Results

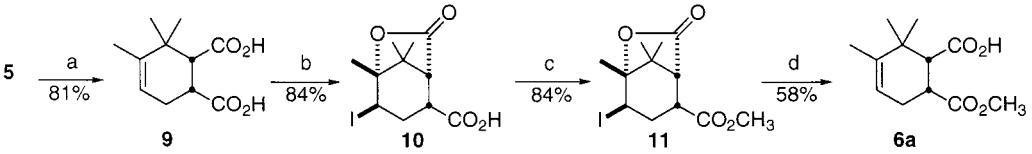
Direct hydride reductions of anhydride **5** ($NaBH_4$,[6] $LiAlH_4$[6b]) were quickly dismissed because of a lack of regioselectivity. Likewise, catalytic reduction of **5** by hydrogenation over Adams platinum oxide,[7] afforded a complex mixture of hydrogenated lactones. Therefore, the regioselectivity of the opening of anhydride **5** by nucleophilic attack of various alcohols was studied. Results are summarized in Table 1.

The best result was thus obtained by refluxing adduct **5** in ethanol for 24 h, affording **6b** in 73% isolated yield contaminated by ca. 2% of the regioisomer **7b**.[8] As expected, the alcohols attacked mainly on the less hindered anhydride carbonyl, as was demonstrated by the transformation of **6a** into the known[9] lactone **8** (Table 1).

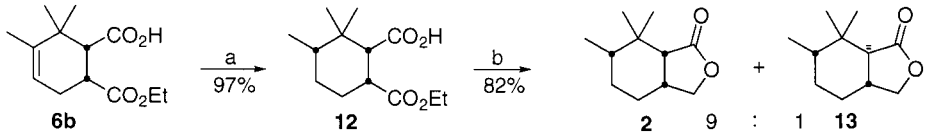
Considering the facile formation of **8**, we also studied a regioselective route to the hemiester **6a**, which involved iodolactonization[10] (Scheme 2).

Mild hydrolysis of adduct **5** with aqueous Na_2CO_3 (2 h, 20°C) afforded diacid **9** in 81% yield after recrystallization from pentane/ether. Iodolactonization[11] of **9** with KI_3 resulted in crystalline iodolactone **10** (84% yield), which was esterified (3% HCl in methanol) to provide iodoester **11** (white crystals, 84% yield after recrystallization from pentane/ether). Zn/AcOH reduction[12] of **11** finally gave the pure hemiester **6a** in 58% yield after recrystallization, identical in all respects with the main product resulting from the direct opening of adduct **5** with methanol (see Table 1). Although less regioselective, we routinely used the direct procedure (i.e. opening of **5** with EtOH) for its convenience.

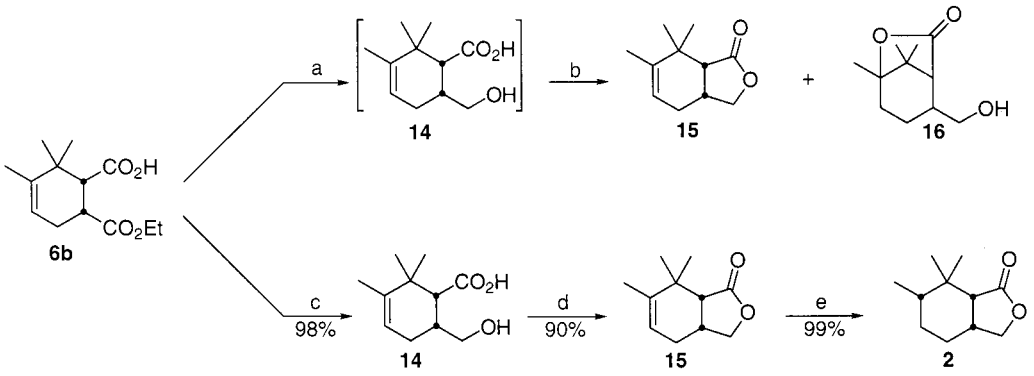
Transformation of hemiester **6b** into lactone **2** involved two steps: reduction of the hemiester into a lactone and hydrogenation of the double bond. We considered both possible sequences of reaction and first examined the



Scheme 2. (a) i. Na_2CO_3, H_2O, ii. 10% aq. HCl. (b) KI, I_2, $NaHCO_3$, H_2O. (c) 3% HCl in MeOH. (d) Zn, AcOH.



Scheme 3. (a) PtO_2 (10%), H_2, AcOH, 24h. (b) i. BuLi 0.9 eq., ii. $LiBH_4$ 2.2 eq., $(MeO)_3B$, Et_2O, reflux, 20h, iii. 5% aq. HCl.



Scheme 4. (a) $LiBH_4$, $(MeO)_3B$, Et_2O or $Ca(BH_4)_2$, EtOH, H_2O. (b) 10% aq. HCl, 20°C, 15h. (c) i. $Ca(BH_4)_2$, EtOH, H_2O, 0°C then 20°C, 6h, ii. 5% aq. HCl (pH 3~4), 0°C. (d) DCC 1.1 eq., DMAP 0.1 eq., CH_2Cl_2, 20°C, 2h. (e) PtO_2 (10%), H_2 3 bar, AcOH or EtOH, 30°C, 6h.

hydrogenation step followed by the chemoselective reduction (Scheme 3).

After the screening of several catalyst/solvent systems,[13] we found that PtO_2 (10%) in acetic acid was most effective (97% yield of 12[14] after 24 h, 3 bar H_2). Chemoselective reduction of the ester functionality in **12** with calcium borohydride (2 eq.) in ethanol[15] gave a ca. 50:50 mixture of **2** and unreacted **12**, as was obtained with $LiBH_4$/ether in the presence of catalytic methanol ($B(OMe)_3$).[16] We then blocked the carboxylic acid group (BuLi, 0.9 eq.) and observed complete conversion. However, the ^{1}H-NMR spectrum showed ca. 10% of C-7a epimerised *trans*-lactone **13**.[2f]

Therefore, the alternate sequence of reactions was investigated (Scheme 4).

When crystalline hydroxyacid **14**, resulting from the reduction of **6b** with either $Ca(BH_4)_2$ or $LiBH_4$, was treated in situ with 10% HCl, a mixture of lactones **15** and **16**[17] was obtained. It was then deemed useful to first isolate hydroxyacid **14** under mild acidic conditions (pH 3~4). $Ca(BH_4)_2$ was found far superior (98% yield) to $LiBH_4$ (60% yield) in this reduction step. DMAP catalyzed[18] lactonization of **14** afforded the desired lactone **15**, under slightly basic conditions. Finally, hydrogenation of **15** over PtO_2 (10%) in either AcOH or EtOH afforded pure lactone **2** (100% GC) in quantitative yield after thorough elimination of the catalyst by filtration.

IR and ^{1}H-NMR data of **2** were identical to those reported for the all-*cis* lactone.[2f]

3. Conclusion

In summary, starting with anhydride **5**, we have described a four step synthesis of the *cis*-lactone **2** in 64% overall yield which represents a significant improvement with regard to the reported synthesis (seven steps, 33% overall yield).[2f] The described transformation of **2** into irones yielded a 1:9 mixture of *cis*- and *trans*-γ-irones **1**, respectively.[2f] Work is now in progress to convert lactone **2** into (±)-*cis*-γ-irone *cis*-**1** in a more stereoselective way.

4. Experimental

4.1. General information

IR spectra were recorded on a Mattson Genesis FTIR spectrometer, in KBr dispersion for solids and thin films on NaCl plates for liquids. NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C on a Bruker AC400 spectrometer, in $CDCl_3$ using TMS for ^{1}H spectra and the solvent for ^{13}C spectra as internal references, unless otherwise noted. Multiplicities in the ^{13}C spectra were determined by DEPT experiments. Low resolution mass measurements were obtained by electron impact at 70 eV with a Finnigan ITD800 ion trap coupled with a Varian 3400 gas chromatograph. High resolution mass measurements were recorded on a Varian MAT 311spectrometer at 70 eV.

4.1.1. (±)-(1*R,6*R**)-6-Methoxycarbonyl-2,2,3-trimethylcyclohex-3-ene-1-carboxylic acid (6a).** Anhydride **5** (1.0 g, 5.15 mmol) was refluxed in methanol (12 mL) for 15 h with stirring, under N_2. Removal of excess methanol in vacuo gave a light-brown oil which was chromatographed over silicagel (25×) with 9:1 cyclohexane: ethylacetate to give 0.815 g (3.60 mmol, 70% yield) of a 90:10 mixture of hemiesters **6a**:**7a**, respectively. An analytically pure sample of **6a** could be prepared by recrystallization from 95:5 pentane:ether:white solid, mp 100–101°C (pentane:ether 95:5); IR (KBr) ν_{max}: 1737 (C=O), 1690 (C=O), 1257, 1198 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.14 and 1.17 (2s, 2×H), 1.67 (s, 3H), 2.26 (m, 1H), 2.63 (m, 1H), 2.85 (d, J=4.0 Hz, 1H), 3.02 (m, 1H), 3.70 (s, 3H), 5.41 (s, 1H) ppm. ^{13}C-NMR ($CDCl_3$) δ: 19.10, 24.58 and 29.51 (3q), 25.16 (t), 36.62 (s), 38.52 and 51.99 (2d), 51.74 (q), 120.48 (d), 137.18 (s), 174.56 (s), 178.30 (s) ppm. MS (GCMS, EI 70 eV) *m*/*z* (%): 180 (29), 166 (14), 151 (3), 121 (100), 107 (54), 91 (42), 79 (25), 65 (10), 53 (8). MS (GCMS, CI^+ iBuH) *m*/*z* (%): 227 (MH^+, 17), 209 (100), 195 (45), 181 (23), 167 (61), 121 (12). Anal. Calcd. for $C_{12}H_{18}O_4$ (226.27): C, 63.70; H, 8.02; O, 28.28. Found: C, 63.86; H, 8.06; O, 28.51.

4.1.2. (±)-(1*R,6*R**)-6-Methoxycarbonyl-4,5,5-trimethylcyclohex-3-ene-1 carboxylic acid (7a).** An enriched sample was obtained from the late fractions of the liquid chromatography of the **6a**:**7a** mixture. IR (film) ν_{max}: 3399 (OH), 1733 (C=O ester), 1708 (C=O acid), 1436, 1376, 1207, 1166, 1064, 1025 cm^{-1}. ^{1}H-NMR δ: 1.07 and 1.17

(2s, 2×3H), 1.42 (s, 3H), 2.30 (m, 1H), 2.68 (m, 1H), 2.85 (d, 1H), 3.02 (m, 1H), 3.70 (s, 3H); 5.43 (m, 1H) ppm. ^{13}C-NMR ($CDCl_3$) δ: 19.11 and 24.58 (2q), 25.22 (t), 29.46 (q), 38.35 (s), 38.48 and 51.36 (2d), 51.15 (t), 120.37 (d), 137.19 (s), 172.95 (s), 179.65 (s) ppm. MS (GCMS, EI 70 eV) *m/z* (%): 166 (25), 151 (4), 121 (31), 107 (100), 91 (54), 79 (23). MS (GCMS, CI^+ iBuH) *m/z* (%): 227 (MH^+, 56), 209 (30), 195 (70), 167 (100), 121 (11).

4.1.3. (±)-(1*R,6*R**)-6-Ethoxycarbonyl-2,2,3-trimethylcyclohex-3-ene-1 carboxylic acid (6b).** Anhydride **5** (2.5 g, 12.9 mmol) was refluxed in abs. ethanol (30 mL) for 24 h with stirring, under N_2. Removal of excess ethanol in vacuo gave a light-brown oil which was chromatographed over silicagel (25×) with cyclohexane: ethylacetate (95:5 to 50:50) to give 2.33 g (9.7 mmol, 75% yield) of a 98:2 mixture of hemiesters **6b**:**7b**, respectively, as a colorless oil. The following data were collected upon this 98:2 mixture. IR (film) ν_{max}: 1735 (C=O), 1710 (C=O), 1463, 1438, 1373, 1303, 1272, 1232, 1193, 1168, 1064, 1033 cm^{-1}. ^{1}H-NMR δ: 1.15 and 1.17 (2s, 2×3H), 1.25 (t, *J*=7.2 Hz, 3H), 1.70 (s, 3H), 2.26 (m, 1H), 2.62 (m, 1H), 2.84 (d, *J*=3.9 Hz, 1H), 2.98 (m, 1H), 4.15 (q, *J*=7.2 Hz, 2H), 5.45 (s, 1H) ppm. ^{13}C-NMR ($CDCl_3$) δ: 14.02 and 19.05 (2q), 24.53 (q), 25.16 (t), 29.47 (q), 36.56 (s), 38.46 and 51.64 (2d), 60.76 (t), 120.52 (d), 137.07 (s), 173.99 and 178.13 (2s) ppm.

4.1.4. Methyl (±)-(1*R,2*R**,5*S**)-5,8,8-trimethyl-7-oxo-6-oxabicyclo[3.2.1]octane-2-carboxylate (8).** A solution of hemiester **6a** (220 mg, 0.97 mmol) in benzene (15 mL) and BF_3.MeOH complex in methanol (15 mL) was stirred at reflux for 1 h. After quenching with water (10 mL), the mixture was diluted with ether (20 mL) and $NaHCO_3$ (aq.) (30 mL). After separation, the aq. layer was extracted with ether (2×75 mL). The combined organic portions were dried over $MgSO_4$ and concentrated in vacuo to yield a brown viscous oil (220 mg). Crystallization from 6:4 pentane:ether afforded white crystals of **8** (67 mg, 30%): mp 109°C (pentane: ether 6:4) (Lit.[9] 112°C). IR (KBr) ν_{max}: 1772 (C=O lactone), 1737 (C=O ester), 1466, 1309, 1216, 1098, 929 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (s, 3H), 1.20 (s, 3H), 1.30 (s, 3H), 1.73 to 2.17 (m, 4H), 2.63 (br. s, 1H), 3.30 (m, 1H), 3.73 (s, 3H) ppm.

4.1.5. (±)-(1*R,2*R**)-3,3,4-Trimethylcyclohex-4-ene-1,2-dicarboxylic acid (9).** A stirred mixture of anhydride **5** (0.45 g, 2.3 mmol), sodium carbonate (0.4 g, 4 mmol) in water (15 mL) was heated during a few minutes until all of the solid had dissolved. The solution was then stirred for 2 h at room temperature then washed with ether (2×25 mL). The ether layer was extracted with water (30 mL) and the combined aqueous layers were acidified to pH ~1 with 10% aq. HCl and extracted with ether (3×20 mL). The combined organic layers were dried ($MgSO_4$), filtered and solvent removed under reduced pressure to afford crude diacid **9** as a white solid which was recrystallized in pentane–ether. Yield 0.397 g (81%): mp 150–151°C (pentane–ether), (Lit.[9] 150–151°C). IR (KBr) ν_{max}: 1731 (C=O), 1626, 1427, 1268, 1233, 1216, 1063, 923, 735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (s, 3H), 1.18 (s, 3H), 1.67 (br. s, 3H), 2.32 (m, 1H), 2.71 (m, 1H), 2.89 (d, 1H, *J*=4.0 Hz), 3.02 (m, 1H), 5.41 (br. s, 1H), ~12 (2H) ppm. ^{13}C-NMR ($CDCl_3$) δ: 19.11, 24.80, 29.68 (3q), 25.01 (t), 36.64 (s), 38.42 and 51.62 (2d), 120.55 (d), 137.03 (s), 179.38 and 180.78 (2s). Anal. Calcd. for $C_{11}H_{16}O_4$ (212.25): C, 62.25; H, 7.60; O, 30.15. Found: C, 62.01; H, 7.78; O, 29.96.

4.1.6. (±)-(1*R,2*R**,4*R**,5*R**)-4-Iodo-5,8,8-trimethyl-7-oxo-6-oxabicyclo[3.2.1]octane-2-carboxylic acid (10).** A solution of I_2 (3.56 g, 14 mmol) and KI (7 g, 42 mmol) in water (21 mL) was added to a magnetically stirred solution of diacid **9** (1.01 g, 5 mmol) in 0.5 M aq. $NaHCO_3$ (40 mL). Stirring was continued for 18 h in the dark. Ether (25 mL) was then added and the brownish solution was washed with sat. aq. Na_2SO_3 (50 mL) then with sat. aq. NaCl (2×75 mL). The combined aqueous layers were acidified with 10% aq. HCl (~60 mL), then extracted with ether (3×100 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed in vacuo affording 1.36 g (84% yield) of iodolactone **10** as light-yellow crystals of sufficient purity for use in the next step. However, analytically pure samples were prepared by recrystallization from pentane–ether: mp 105°C (pentane–ether, dec.). IR (KBr) ν_{max}: 3524 (OH); 1761 (C=O); 1737 (C=O), 1204, 1180, 981, 911 cm^{-1}. ^{1}H-NMR (CD_3COCD_3) δ: 1.15 (s, 3H), 1.56 (s, 3H), 1.62 (s, 3H), 2.49 (m, 1H), 2.72 (m, 1H), 2.75 (br. s, 1H), 3.29 (m, 1H), 4.62 (d, 1H, *J*=7.6 Hz), ~9.8 (br. s, 1H) ppm. ^{13}C-NMR (CD_3COCD_3) δ: 20.76 (q), 22.67 (q), 24.39 (d), 25.32 (q), 34.51 (t), 36.19 (d), 45.17 (s), 53.38 (d), 88.52 (s), 172.90 and 175.12 (2s) ppm. Anal. Calcd. for $C_{11}H_{15}IO_4$ (338.14): C, 39.07; H, 4.47; O, 18.93. Found C, 39.35; H, 4.58; O, 18.88.

4.1.7. Methyl (±)-(1*R,2*R**,4*R**,5*R**)-4-iodo-5,8,8-trimethyl-7-oxo-6-oxabicyclo[3.2.1]octane-2-carboxylate (11).** A solution of iodoacid **10** (1.19 g, 3.5 mmol) in 3% HCl in anhydrous methanol (~21 mL, prepared by adding acetylchloride (1 mL) to anhydrous methanol (20 mL)) was magnetically stirred for 1 h at room temperature, under N_2. Ether (20 mL) was added and the organic layer was washed with saturated aq. $NaHCO_3$ (2×20 mL) and then with brine (2×20 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvents were evaporated to give iodoester **11** as white crystals (1.04 g, 84%) of sufficient purity for use in the next step. Recrystallization from pentane–ether afforded analytical samples. Mp 111–113°C (pentane–ether). IR (KBr) ν_{max}: 1784 (C=O), 1731 (C=O), 1204, 1180, 1063, 911, 846 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (s, 3H), 1.56 (s, 3H), 1.59 (s, 3H), 2.57 (m, 1H), 2.75 (br. s, 1H), 2.80 (m, 1H), 3.21 (m, 1H), 3.75 (s, 3H), 4.44 (d, 1H, *J*=7.5 Hz) ppm. ^{13}C-NMR ($CDCl_3$) δ: 20.44, 22.52, 22.87, 25.37, 33.68, 35.98, 44.57, 52.44, 52.51, 88.24, 171.73, 174.90 ppm.

4.1.8. Preparation of hemiester (6a) from iodoester (11). Powdered zinc (4.2 g, 64 mmol) was added portionwise under N_2, to a stirred solution of iodoester **11** (0.55 g, 1.6 mmol) in acetic acid (15 mL). The mixture was then refluxed for 45 min. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 (20 mL), filtered on celite and the residue rinsed with CH_2Cl_2 (10 mL). The filtrate was washed with water (3×75 mL), then extracted with 5% aq. Na_2CO_3 (3×75 mL). The combined basic

aqueous phases were acidified until pH ~1 with 10% aq. HCl, then extracted with CH_2Cl_2 (4×50 mL). The combined organic layers were dried over $MgSO_4$, then filtered and the solvent removed in vacuo to afford a semi-crystalline residue (0.275 g, 78% crude yield). Crystallization from pentane:ether (95:5) yielded white crystals of pure hemiester **6a** (0.205 g, 58%), identical in all respects with the main product resulting from the opening of adduct **5** with methanol (see above).

4.1.9. (±)-(1*R,3*S**,6*R**)-6-(Ethoxycarbonyl)-2,2,3-trimethylcyclohexanecarboxylic acid (12).** A solution of hemiester **6b** (0.421 g, 1.75 mmol) in AcOH (30 mL) was hydrogenated for 48 h under pressure (H_2, 3 bar), at 30°C and with stirring in the presence of PtO_2 (84 mg, 20% w/w). Filtration and evaporation in vacuo of the solvent left hemiester **12** as an oil (0.414 g, 97% yield) which was used in the next step without further purification. IR (film) ν_{max}: 1747, 1714, 1456, 1377, 1275, 1232, 1201, 1170, 1064, 1016 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (d, J=6.9 Hz, 3H), 0.96 and 1.11 (2s, 2×3H), 1.20 (t, J=7.1 Hz, 3H), 1.27 (m, 1H), 1.53 (m, 3H), 2.24 (m, 1H), 2.50 (d, J=4.8 Hz, 1H), 3.10 (m, 1H), 4.08 (q, J=7.1 Hz, 2H), 11.00 (m, 1H) ppm. ^{13}C-NMR ($CDCl_3$) δ: 13.66 and 15.44 (2q), 17.36 (q), 25.04 and 27.53 (2t), 28.35 (q), 35.77 (s), 41.16 (d), 41.38 and 53.00 (2d), 60.55 (t), 174.27 and 180.31 (2s) ppm.

4.1.10. Reduction–lactonization of hemiester (12). *n*-BuLi (0.9 eq., 0.323 mL of 1.6 M sol. in hexane, 0.517 mmol) was added via syringe, under N_2, to a stirred solution of hemiester **12** (0.139 g, 0.574 mmol) in ether (2 mL), cooled at −78°C. After 30 min stirring at −78°C, a solution of $LiBH_4$/$(MeO)_3B$ prepared by adding one drop of MeOH (~7 mg, 0.2 mmol) to $LiBH_4$ (2.2 eq., 28 mg, 1.26 mmol) in ether (2 mL), was added via syringe. After warming up to room temperature, the solution was heated at reflux for 20 h. After cooling, the mixture was quenched with anhydrous MeOH and diluted with ether (20 mL). 10% aq. HCl (10 mL) was added and the mixture was stirred overnight. The separated aqueous phase was saturated with NaCl then extracted with ether (10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed in vacuo. The oily residue was taken up in $CHCl_3$ and a few precipitated salts removed by filtration over sand. Removal of the solvent in vacuo yielded a colorless oil (0.085 g, 0.522 mmol, 91% combined yield). ^{1}H-NMR analysis of the product showed it to be a mixture of *cis*-lactone **2** (90%) and *trans*-lactone **13** (10%). For the characterization of **2**, see below.

4.1.11. (±)-(3a*R,6*S**,7a*S**)-6,7,7-Trimethylhexahydro-2-benzofuran-1(3*H*)-one (13).** The following signals were extracted from the spectra of the 9:1 mixture of **2** and **13**, respectively. ^{1}H-NMR[2f] ($CDCl_3$) δ: 0.83 (d, 3H, J=6.2 Hz), 0.81 and 1.25 (2s, 2×3H), 1.56 (m, 1H), 1.74 (d, J=13.8 Hz, 1H), 1.84 (m, 1H), 2.24 (m, 1H), 3.67 (dd, J=11.0 et 8.3 Hz, 1H), 4.24 (dd, J=8.3 et 6.8 Hz, 1H) ppm. ^{13}C-NMR ($CDCl_3$) δ: 14.40, 14.64 and 25.41 (3q), 28.15 and 30.56 (2t), 34.47 (s), 38.64 and 42.72 (2d), 54.16 (d), 70.72 (t), 175.88 (s) ppm.

4.1.12. (±)-(1*R,6*R**)-6-(Hydroxymethyl)-2,2,3-trimethylcyclohex-3-ene-1-carboxylic acid (14).** A solution of KOH (0.696 g, 12.4 mmol) and $CaCl_2$ (2.31 g, 20.8 mmol) in abs. EtOH (15 mL) was added under N_2 to a stirred solution of hemiester **6b** (1.36 g, 5.7 mmol) in abs. EtOH (40 mL). The stirred mixture was cooled to 0°C and a suspension of $NaBH_4$ (1.38 g, 36.3 mmol) in EtOH (11.5 mL)/H_2O (1.9 mL) was added dropwise. The ice-bath was removed at the end of the addition and the mixture stirred at room temperature for 6.5 h. 5% aq. HCl was added at 0°C (55 mL, pH ~3–4). Most of the ethanol solvent was removed in vacuo. The residue was taken up in water (30 mL) and the aq. phase saturated with NaCl, extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed in vacuo. The resulting white solid was further dried at 0.07 torr for 2 h affording hydroxyacid **14** as white crystals (1.11 g, 5.6 mmol, 98% yield): mp 126–128°C. IR (film) ν_{max}: 1704 (C=O), 1436, 1214, 1182, 1079, 1043, 1002 cm^{-1}. ^{1}H-NMR (CD_3COCD_3) δ: 1.24 and 1.29 (2s, 2×3H), 1.79 (s, 3H), 2.15 (m, 2H), 2.37 (m, 1H), 2.78 (d, J=4.0 Hz, 1H), 3.62 (dd, J=2.2 and 7.1 Hz, 2H), 5.50 (s, 1H), 10.5 (br. s, 1H) ppm. ^{13}C-NMR (CD_3COCD_3) δ: 19.36 and 24.93 (2q), 26.83 (t), 29.63 (1q), 36.03 (d), 36.87 (s), 53.13 (d), 66.01 (t), 122.21 (d), 137.88 (s), 174.27 (s) ppm.

When more concentrated (10% to 50%) aq. HCl solution was used to quench the reaction and the mixture then stirred overnight in order to induce the in situ lactonization of the intermediate hydroxyacid **14**, a mixture of lactones **15** and **16**[17] was obtained which could be separated by liquid chromatography on silica-gel.

4.1.13. (±)-2-Hydroxymethyl-5,8,8-trimethyl-6-oxabicyclo[3.2.1]octan-7-one (16) (mixture of isomers). IR (film) ν_{max}: 3457 (OH), 1764 (C=O), 1187, 1145, 1099, 1070, 1018, 927 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04, 1.06, 1.14, 1.18, 1.22 and 1.26 (6s, 2×3Me), 2.14 (m), 2.37 (br. s), 2.48 (d, J=8 Hz), 2.70 (m), 3.56 (d, J=6.6 Hz), 3.7 (s), 3.93 (dd, J=7.2 and 8.8 Hz), 4.21 (dd, J=7.2 and 8.8 Hz) ppm. ^{13}C-NMR ($CDCl_3$) δ: 18.15, 18.66, 21.20, 21.32, 23.98, 24.23, 24.98, 26.91, 30.60, 32.15, 33.90, 34.37, 38.82, 43.33, 47.99, 52.76, 64.47, 70.79, 73.20, 77.24, 89.20, 177.99, 178.48 ppm.

4.1.14. (±)-(3a*R,7a*R**)-6,7,7-Trimethyl-3a,4,7,7a-tetrahydro-2-benzofuran-1(3*H*)-one (15).** A solution of dicyclohexylcarbodiimide (DCC, 3.351 g, 16.27 mmol, 1.1 eq.) in anhydrous CH_2Cl_2 (80 mL) was added at room temperature, under N_2, to a stirred solution of hydroxyacid **14** (2.92 g, 14.75 mmol) and 1,4-dimethylaminopyridin (0.18 g, 1.47 mmol, 0.1 eq.) in anhydrous CH_2Cl_2 (70 mL). After 2 h stirring at room temperature, oxalic acid (133 mg, 1.47 mmol, 0.1 eq.) was added and the solvent was removed in vacuo. The residue was taken up in ether (30 mL) and the precipitated DCU eliminated by filtration over sand and washed with ether (30 mL). The combined organic layers were washed with $NaHCO_3$ (2×100 mL), dried over $MgSO_4$, filtered and the solvent removed in vacuo. The residue was taken up in anhydrous ether (5 mL) and the solution filtered over a fritted glass of fine porosity. After rinsing with ether (3 mL), the solvent was removed in vacuo to yield lactone **15** as a colourless oil (2.379 g, 13.2 mmol, 89.5% yield). IR (film) ν_{max}: 1772 (C=O), 1469, 1450, 1371, 1139, 1105, 1035 cm^{-1}. ^{1}H-NMR

($CDCl_3$) δ: 1.17 and 1.31 (2s, 2×3H), 1.68 (s, 3H), 1.96 (m, 1H), 2.35 (m, 1H), 2.40 (d, J=7.6 Hz, 1H), 2.85 (m, 1H), 3.93 (dd, J=8.6 and 3.3 Hz, 1H), 4.25 (dd, J=8.6 and 5.6 Hz, 1H), 5.29 (s, 1H) ppm. ^{13}C-NMR ($CDCl_3$) δ: 19.24 and 23.39 (2q), 26.24 (t), 29.26 (q), 32.42 (d), 34.67 (s), 50.08 (d), 73.11 (t), 119.44 (d), 140.22 (s), 176.81 (s) ppm. MS (GCMS, EI 70 eV) m/z (%): 180 ($M^{+\cdot}$, 32), 165 (36), 121 (100), 105 (66), 93 (64), 91 (42), 85 (33), 81 (35), 73 (33), 77 (26), 41 (36). HRMS (70 eV) calcd. for $C_{11}H_{16}O_2$: 180.11502, found: 180.1153.

4.1.15. (±)-(3a*R,6*S**,7a*R**)-6,7,7-Trimethylhexahydro-2-benzofuran-1(3*H*)-one (2).** A solution of lactone **15** (2.07 g, 11.5 mmol) in AcOH (100 mL) was hydrogenated for 6 h under pressure (H_2, 3 bar), at 30°C and with stirring in the presence of PtO_2 (0.206 g, 10% w/w). Filtration and evaporation of the solvent in vacuo yielded lactone **2** as a colourless oil (2.08 g, 11.4 mmol, 99% yield). IR[2f] (film) ν_{max}: 1766 (C=O), 1463, 1367, 1199, 1186, 1166, 1147, 1139, 1014, 970 cm^{-1}. ^{1}H-NMR[2f] ($CDCl_3$) δ: 0.89 (d, J=6.5 Hz), 0.97 and 1.14 (2s, 2×3H), 1.27 to 1.72 (m, 5H), 2.21 (d, J=8.0 Hz, 1H), 2.67 (m, 1H), 3.94 (t, J=8.7 Hz, 1H), 4.18 (dd, J=8.7 and 8.0 Hz, 1H) ppm. ^{13}C-NMR ($CDCl_3$) δ: 15.64 and 19.22 (2q), 22.63 and 26.01 (2t), 25.47 (s), 29.93 (q), 34.76 and 39.40 (2d), 48.00 (d), 70.75 (t), 178.37 (s) ppm. MS (GCMS, EI 70 eV) *m/z* (%): 183 (70, MH^+), 122 (90), 107 (41), 95 (25), 81 (66), 55 (54), 39 (100). Anal. Calcd. for $C_{11}H_{18}O_2$ (182.26): C, 72.49; H, 9.95; O, 17.56. Found C, 72.32; H, 9.76; O, 17.64.

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