Synthesis of biomimetic precursors of isovelleral analogues

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Dedicated to Prof. Torbjörn Norin on the occasion of his 75th birthday

Abstract
Based on how the mushroom *Lactarius vellereus* converts an inactive precursor into the cytotoxic dialdehyde isovelleral (**1**) via a cyclic enol ether, as part of a binary chemical defense system that protects the fruit bodies against parasites, a synthetic way to obtain analogous dialdehydes masked in the same way has been developed. As isovelleral analogues (e.g. **2** and **3**) possess extremely potent cytotoxic activity, but display low selectivity as their biological activity is linked to their reactivity, suitably masked isovelleraloids that are converted to the corresponding dialdehyde under specific conditions, may constitute a way to utilize these potent compounds. Specifically, compounds **4** and **5**, biomimetic precursors of the isovelleral analogues **2** and **3**, but trapped as the stable methyl acetals, have been prepared.

Keywords: Biomimetic, isovelleral analogues, cytotoxic dialdehyde, methyl acetal

Introduction

In the fruit bodies of the pungent *Lactarius* species, an ingenious binary chemical defense system has evolved.[1] It is based on the rapid (seconds) enzymatic conversion of inactive precursors to pungent and antibiotic sesquiterpenes with an unsaturated 1,4-dialdehyde moiety, as a response to physical injury to the fruit body. For example, in fruit bodies of *Lactarius vellereus* stearoylvelutinal (**6c**) is converted to the dialdehyde isovelleral (**1**) (see Scheme 1). The conversion is so fast that **1** actually was believed to be a normal metabolite of *L. vellereus* fruit bodies, however, the investigation of specimens frozen in liquid nitrogen at their natural habitat showed that the truly intact mushroom does not contain **1**. It is a binary chemical weapon in the sense that the precursor **6c** is present as an emulsion in special pressurized hyphae in the intact fruit body, and only brought in contact with the enzymes responsible for the conversion by an injury that disrupts these hyphae. The dialdehydes are consequently only formed at the site of an injury, not in the entire mushroom. They not only deter parasites from consuming the fruit

bodies, but also inhibit infections of the fruit body caused by bacteria and other fungi. In a second slower step, that will take minutes, the dialdehydes are reduced (isovelleral (**1**) to isovellerol (**7**)) to form less active compounds in the injured tissue, ensuring that the time the fruit body is exposed to the reactive dialdehyde is limited.

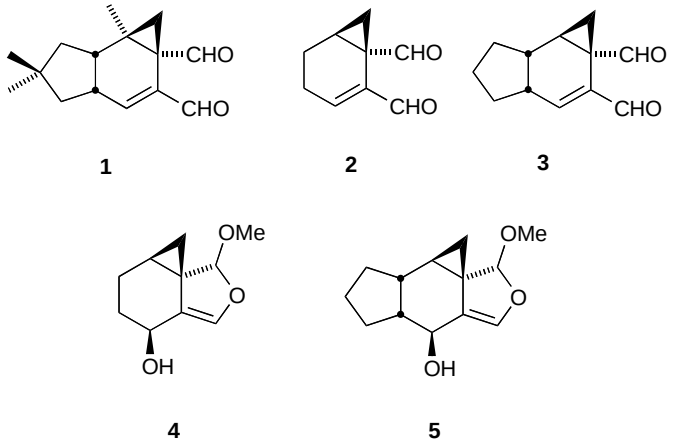
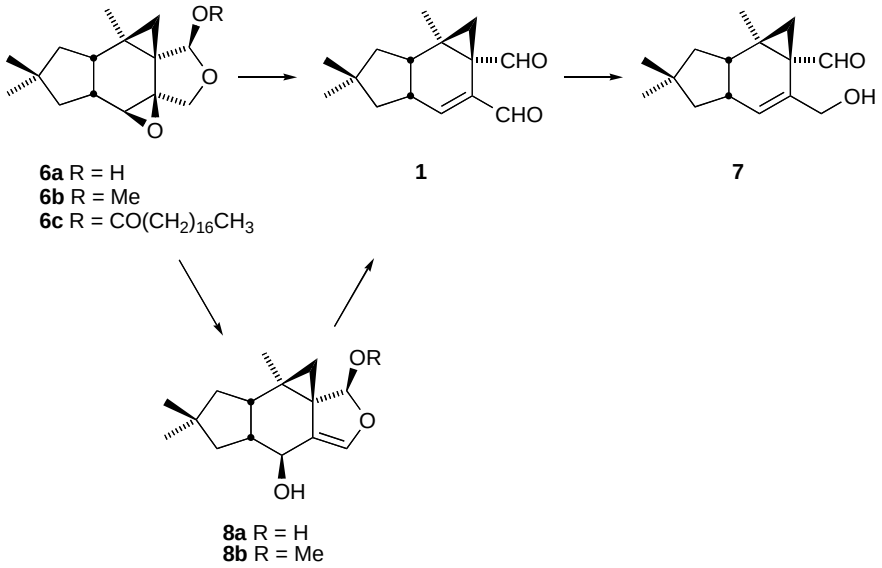


Figure 1

The mechanism for the conversion of stearoylvelutinal (**6c**) to isovelleral (**1**) in *L. vellereus* has been shown to proceed *via* ester hydrolysis to give the hemiacetal velutinal (**6a**).[2] This is followed by an enzymatic β-elimination of the epoxide in **6a** to yield the proposed intermediate **8a**, that spontaneously would be converted to isovelleral (**1**).[3,4] The formation of **8a**, which should be highly unstable, was never demonstrated, but feeding the injured mushroom tissue methylvelutinal (**6b**), obtained by solvolysis of **6c** in methanol, resulted in the formation of **8b,** which could be isolated and characterized.



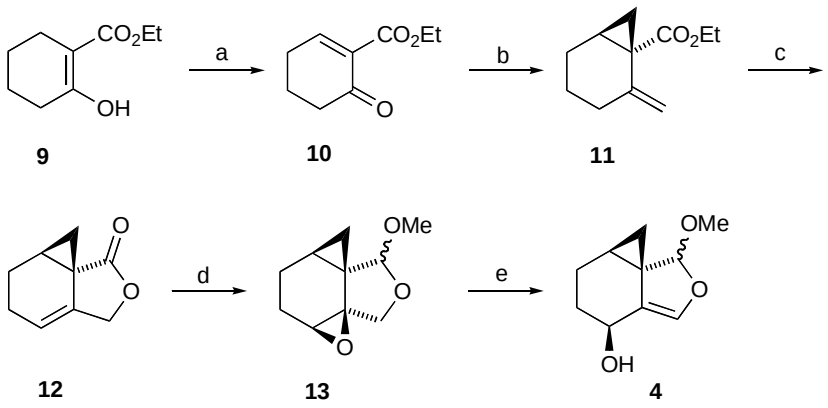
Scheme 1

During an investigation of QSARs of the isovelleraloids,[5] the synthetic analogues **2**[6] and **3**[7] (see Figure 1) were prepared and shown to be even more potent than isovelleral (**1**). Especially **3,** which cytotoxicity towards tumor cells is approximately 10 times that of **1**.[7] However, the general reactivity of the unsaturated dialdehydes prohibits any practical uses, as they will be toxic to all cells and tissues. Nonetheless, utilizing a pro-drug strategy whereby by the reactive functionality is protected in a way that a) makes it is less reactive and b) is deprotected by the conditions (chemical or enzymatical) encountered in certain cells (e.g. tumor cells) or organisms (e.g. pests), the selectivity could increase dramatically. For example, tumor cells are known to be more acidic compared to normal cells due to accelerated metabolism, and may overexpress certain enzymes significantly. As we have noted that the methyl acetal **8b** is rapidly hydrolysed to isovelleral in the presence of traces of acid, we decided to prepare the corresponding derivatives of the two isovelleral analogues **2** and **3**, the cyclic enol methyl acetals **4** and **5** (see Figure 1).

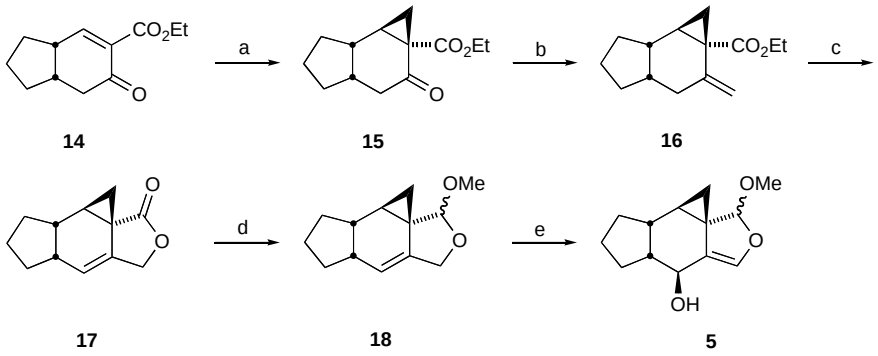
Results and Discussion

The syntheses of acetals **4** and **5** are presented in Schemes 2 and 3. The oxidation of β-keto ester **9** to the corresponding α,β-unsaturated keto ester **10** was carried out with DDQ in good yield,[8] and a stereoselective Corey-Chaykovsky cyclopropantion of **10** in DMF[9] followed by a standard "salt-free" Wittig reaction[10] afforded **11**. Alkene **11** was epoxidized with *m*-CPBA[10] in the presence of $NaHCO_3$, the epoxide was not isolated but was opened directly by the addition of catalytic amount of *p*-TsOH in $CHCl_3$ which also effected the formation of the lactone ring to yield **12**.[10] The lactone was reduced to the corresponding lactol with DIBAL-H in toluene,[11] the resulting hemiacetal was converted to the more stable methyl acetal with a catalytic amount of *p*-TsOH in pentane/MeOH (9:1), where after the allylic lactol was stereoselectively epoxidized with dimethyldioxirane (DMDO) in acetone[11,12] yielding **13**. The final regioselective epoxide opening was carried out with an excess of diisopropyl amine and n-BuLi (1:1), which produced the desired regioisomer **4**.

The synthesis of **5** followed the same procedure, the α,β–unsaturated β-keto ester **14**[7] was cyclopropanated using the same protocol as for **10** and was immediately subjected to Wittig conditions to give **16**. The epoxidation of **16** was carried out with DMDO in acetone[8] at 0°C, and the resulting epoxide was opened *in situ* to yield the lactone **17** by addition of a catalytic amount of *p*-TsOH. **17** was subsequently reduced with DIBAL-H and transformed to the methyl-acetal **18**, which was epoxidized with DMDO and then opened to **5** by an excess of diisopropyl amine and *t*-BuLi (1:1.3) in THF.[6,13] Note that the last step of both Scheme 2 and 3 is sensitive to the relative amounts of diisopropyl amine and organolithium reagent (*t*-BuLi), changing the reported relationship result in mixtures of regioisomers.



Scheme 2. Reaction conditions: (a) DDQ, AcOH, dioxane, rt, 1.75 h (67%); (b) i) NaH (oil free), Me_3SOI, DMF, -15°C, 7 min; ii) $NaNH_2$, Ph_3PCH_2Br, toluene, ~100→20°C, 1.5 h (39%, 2 steps); (c) i) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0°C, 3 h; ii) *p*-TsOH (catalytic), $CHCl_3$, Δ, 3 h (43%, 2 steps); (d) i) DIBAL-H, toluene, -78°C, 3 h; ii) *p*-TsOH (catalytic), pentane/MeOH (9:1), rt, 10 min; iii) DMDO, acetone, 0°C, 1 h (18%, 3 steps); (e) diisopropyl amine, *n*-BuLi, THF, 4 h (60%).



Scheme 3. Reaction conditions: (a) NaH (oil free), Me_3SOI, DMF, -15°C, 7 min (69%); (b) $NaNH_2$, Ph_3PCH_2Br, toluene, ~100→20°C, 1.5 h (69%); c) i) DMDO, acetone, 0°C, 1 h; ii) *p*-TsOH (catalytic), $CHCl_3$, Δ, 3 h (84%, 2 steps); (d) i) DIBAL-H, toluene, -78°C, 3 h; ii) *p*-TsOH (catalytic), pentane/MeOH (9:1), rt, 10 min (53%, 2 steps); (e) i) DMDO, acetone, 0°C, 1 h; ii) diisopropyl amine, *t*-BuLi, THF, 4 h (63%, 2 steps).

The biological activity of the acetals **4** and **5** will be reported elsewhere.

Acknowledgements

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Experimental Section

General procedures. Materials were obtained from commercial suppliers and were used without further purification unless otherwise noted. THF and dioxane were dried by refluxing over sodium/benzophenone ketyl immediately prior to use. CH_2Cl_2, DMF and Et_3N were distilled from CaH_2 prior to use. DMSO and MeOH were dried by sequential drying over 3Å MS and DMSO was then distilled under reduced pressure prior to use. Toluene was dried with Al_2O_3 (neutral, activity I). All moisture and air-sensitive reactions were carried out under an atmosphere of dry nitrogen using oven-dried glassware. Ozonolysis was carried out using an O.S.G. Ozonegenerator NG-5. ESIMS spectra (H_3PO_4 for calibration and as internal standard) were recorded with a Micromass Q-Tof Micro spectrometer and FABMS spectra were recorded with a Jeol SX102 spectrometer. NMR spectra were recorded with a Bruker ARX 300 spectrometer at 300 MHz (^{1}H) and at 75 MHz (^{13}C), Bruker DRX 400 spectrometer at 400 MHz (^{1}H) and at 100 MHz (^{13}C) and with a Bruker DRX 500 spectrometer at 500 MHz (^{1}H) and at 125 MHz (^{13}C). Chemical shifts are given in ppm relative to TMS using the residual $CHCl_3$ peak in $CDCl_3$ solution as internal standard (7.26 and 77.0 ppm, respectively relative to TMS) or using the residual C_6H_6 peak in C_6D_6 solution (7.16 and 128.06 ppm, respectively). Organic extracts were dried over $MgSO_4$. All chromatography was performed on 60 Å 35-70 mm Matrex silica gel (Grace Amicon). TLC analyses were made on Silica Gel 60 F_{254} (Merck) plates and visualized with anisaldehyde-, Seebach- or permanganate visualization reagent and heating.

Ethyl 2-oxocyclohexenecarboxylate (10). Glacial acetic acid (5 ml) was added to a stirred solution of **9** (4.28 g, 25.17 mmol) in dry 1,4-dioxane (137 ml) at room temperature. DDQ (10.00 g, 44.05 mmol) was added, under a blanket of nitrogen, in four portions with intervals of 20 min to the mixture. The mixture was stirred at room temperature for 45 min, diluted with $CHCl_3$ (100 ml) and filtered through celite. The filter-cake was washed with $CHCl_3$ (3x50 ml). The combined filtrate and washings were washed several times with saturated aqueous $NaHCO_3$ until the washings became colorless. The organic fraction was dried, concentrated and chromatographed to give **10** (2.60 g, 15.50 mmol, 61.6%) as a colorless liquid: ^{1}H NMR (300 MHz) δ 7.66 (1H, t, *J*=4.1 Hz), 4.26 (2H, q, *J*=7.1 Hz), 2.52 (4H, m), 2.05 (2H, m), 1.31 (3H, t, *J*=7.1 Hz); ^{13}C NMR δ 194.6, 164.7, 155.7, 133.3, 61.1, 38.7, 26.1, 22.1, 14.1; HRMS (FAB): for $C_9H_{13}O_3$ calcd 169.0865 $[M+H]^+$; found 169.0863.

Ethyl-2-methylenebicyclo[4.1.0]heptane-1-carboxylate (11). To a flask containing fresh NaH (0.30 g, 12.52 mmol, oil free) and trimethylsulfoxonium iodide (2.76 g, 12.52 mmol) was added dry DMF (50 ml) slowly via a syringe and the hydrogen gas generated was ventilated. The mixture was stirred at room temperature until it became clear and all hydride was consumed. The flask was cooled in an acetone-ice bath to –15°C and a solution of **10** (2.00 g, 11.92 mmol) in DMF (5 ml) was added in one portion to the flask via a syringe and the solution turned orange. After 7 minutes TLC indicated complete consumption of starting material **10**, and the reaction was quenched by addition of H_2O (150 ml). The mixture was extracted with Et_2O (3x100 ml),

and the combined extracts were washed with large amounts of water, dried, and concentrated to give the crude cyclopropanated product (1.60 g) as a slightly green oil, which was used directly without further purification. Ph_3PMeBr (4.11 g, 11.50 mmol) was added to a suspension of $NaNH_2$ (1.14 g, 14.70 mmol, 50% w/w in toluene) in dry toluene (40 ml). The mixture was refluxed for 3 h. The warm clear bright yellow liquid was decanted into a solution of crude cyclopropanated β-keto ester (1.05 g) in toluene (10 ml) after the suspension had settled. The reaction was stirred at room temperature for 1 h. (Further ylide was extracted with dry toluene (15 ml) by refluxing the residue of the settled suspension for 1 h, and then poured into the solution of the β-keto ester). Stirring was continued until the starting material disappeared (determined by TLC). The reaction mixture was washed twice with water, dried and concentrated. Triphenylphosphine oxide was removed as a precipitate, by treatment of the residue twice with warm PE (25 ml). After evaporation of the solvent the crude product was chromatographed to give a colorless oil of **11** (0.58 g, 3.22 mmol, 39%): ^{1}H NMR (300 MHz) δ 5.10 (1H, brs), 5.06 (1H, brs), 4.11 (2H, m), 2.14 (1H, dt, *J*= 14.0, 3.8 Hz), 1.96 (1H, m), 1.86 (2H, m), 1.63 (3H, m), 1.23 (3H, t, *J*= 7.1 Hz), 1.12 (1H, m), 0.75 (1H, dd, *J*= 6.1, 3.5 Hz); ^{13}C NMR δ 174.0, 143.3, 114.8, 60.6, 32.6, 27.4, 23.4, 22.5, 20.4, 19.9, 14.2; HRMS (ESI): for $C_{11}H_{16}O_2$ calcd 180.1150 $[M]^+$; found 180.1149.

4,4a,5,6-Tetrahydro-1*H*-cyclopropa[1,6]benzo[1,2-*c*]furan-3-one (12). A solution of **11** (1.48 g, 8.20 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a stirred solution of *m*-CPBA (2.40 g, 9.90 mmol, 70-75% in H_2O) and $NaHCO_3$ (1.00 g, 12.3 mmol) in CH_2Cl_2 (40 ml) at 0°C. Stirring was continued for 3 h. The mixture was washed with 1% aqueous Na_2SO_3 (2x25 ml), 5% aqueous $NaHCO_3$ (2x25 ml) and with water until neutral. The organic layer was dried with Na_2SO_4, filtered and concentrated to afford the crude epoxide, which was used directly without further purification. The epoxide was refluxed in $CHCl_3$ (50 ml) with a catalytic amount *p*-TsOH for 3 h. After cooling, the mixture was washed twice with water, dried, concentrated and chromatographed to give **12** (0.53 g, 3.55 mmol, 43%): ^{1}H NMR (400 MHz) δ 5.45 (1H, m), 4.99 (1H, dddd, *J*= 12.9, 4.4, 2.5, 0.9 Hz), 4.91 (1H, m), 2.22 (1H, m), 2.12 (1H, m), 2.03 (1H, dd, *J*= 13.5, 6.6 Hz), 1.75 (1H, m), 1.53 (1H, dd, *J*= 8.6, 4.3 Hz), 1.48 (1H, dd, *J*= 6.6, 4.3 Hz), 1.38 (1H, m); ^{13}C NMR δ 178.8, 134.2, 113.2, 70.2, 24.3, 23.5, 19.1, 19.0, 18.0; HRMS (FAB): for $C_9H_{11}O_2$ calcd 151.0759 $[M+H]^+$; found 151.0757.

5-Methoxytetrahydro-1a*H*-cyclopropa[*d*]oxireno[*h*][2]benzofuran (13). A 1.2 M solution of DIBAL-H (3.3 ml) in toluene was added very slowly to a solution of **12** (0.59 g, 3.93 mmol) in toluene (10 ml) at –78°C. A saturated aqueous solution of potassium sodium tartrate (5 ml) was added to the reaction at –78°C after 3 h. The mixture was allowed to warm to room temperature and then extracted with EtOAc. The combined extracts were dried, filtered and concentrated to afford the crude lactol, which was used directly without further purification. To a solution of the lactol in pentane/MeOH (9:1, 50 ml) was added a catalytic amount of *p*-TsOH. A saturated aqueous solution of $NaHCO_3$ was added after 10 min and the organic phase was separated. The aqueous phase was extracted with Et_2O. The combined organic extracts were dried with Na_2SO_4 and concentrated to afford an epimeric mixture (10:7) of crude methyl-acetal, which was used

directly without further purification. To a solution of the crude acetal in acetone (10 ml) was added a solution of dimethyldioxirane (3.9 mmol, 65 ml, ~0.06M in acetone) at 0°C. The solvent was removed after 1 h and the residue was re-dissolved in Et_2O, dried with Na_2SO_4, concentrated and chromatographed on Al_2O_3 (neutral, activity II-III) to give an epimeric mixture (10:7) of **13** (0.13 g, mmol, 18%): ^{1}H NMR (500 MHz, C_6D_6) δ major 4.67 (1H, s), 4.14 (1H, d, *J*= 11.9 Hz), 4.12 (1H, d, *J*= 11.9 Hz), 3.25 (3H, s), 2.78 (1H, t, *J*= 2.9 Hz), 1.59 (1H, m), 1.57 (1H, m), 1.39 (1H, m), 1.23 (1H, m), 1.11 (1H, m), 0.75 (1H, m), 0.64 (1H, dd, *J*= 8.6, 4.6 Hz); minor 4.65 (1H, s), 4.33 (1H, d, *J*= 9.5 Hz), 3.83 (1H, d, *J*= 9.5 Hz), 3.32 (3H, s), 2.66 (1H, dd, *J*= 5.4, 2.8 Hz), 1.47 (1H, m), 1.38 (1H, m), 1.29 (1H, m), 1.12 (1H, m), 0.90 (1H, m), 0.84 (1H, m), 0.76 (1H, m); ^{13}C NMR δ major 108.8, 68.6, 62.9, 53.9, 52.9, 26.5, 22.1, 18.9, 12.8, 9.1; minor 108.6, 67.9, 62.2, 53.9, 52.3, 26.7, 20.7, 18.9, 13.7, 8.0; HRMS (ESI): for $C_{10}H_{14}O_3$ calcd 182.0943 $[M]^+$; found 182.0942.

3-Methoxy-4a,5,6,7-tetrahydro-4*H*-cyclopropa[1,6]benzo[1,2-*c*]furan-7-ol (4). *n*-BuLi (0.61 ml, 1.51 mmol, 2.5 M in hexane) was added to a solution of diisopropyl amine (0.21 ml, 1.51 mmol) in THF (10 ml) at –78°C. After 0.5 h **13** (0.13 g, 0.72 mmol) in THF (5 ml) was added drop wise to the solution at -78°C. The reaction mixture was allowed to equilibrate to room temperature. A saturated aqueous solution of $NaHCO_3$ (5 ml) was added after 4 h. The organic layer was separated and the aqueous layer was extracted with Et_2O (10 ml). The combined organic fractions were dried with Na_2SO_4, concentrated and chromatographed on Al_2O_3 (neutral, activity II-III) to give **4** as an epimeric mixture (10:7) (0.08 g, 0.43 mmol, 60%): ^{1}H NMR (500 MHz, C_6D_6) δ 5.07 (1H, s), 6.40 (1H, s), 4.24 (1H, t, *J*= 5.1 Hz), 3.25 (3H, s), 1.74 (2H, m), 1.71 (1H, m), 1.48 (1H, d, *J*= 5.7 Hz), 1.46 (1H, d, *J*= 5.7 Hz), 1.12 (1H, t, *J*= 4.4 Hz), 0.72 (1H, dd, *J*= 8.7, 4.4 Hz); ^{13}C NMR δ 140.2, 118.0, 110.7, 62.8, 54.3, 31.4, 30.6, 20.9, 20.5, 14.2; HRMS (FAB): for $C_{10}H_{14}O_3$ calcd 182.0943 $[M]^+$; found 182.0939.

Ethyl 2-oxooctahydrocyclopropa[*e*]indene-1a(1*H*)-carboxylate (15) was prepared according to the procedure described for **11** using α,β–unsaturated β-keto ester **14** (prepared according to reference 7) as starting material. Chromatography afforded **15** (2.4 g, 10.8 mmol, 69%): ^{1}H NMR (300 MHz) δ 4.18 (2H, q, *J*=7.1 Hz), 2.37 (1H, q, *J*= 7.4 Hz), 2.25 (1H, dd, *J*= 15.1, 4.6 Hz), 2.15 (1H, m), 2.08 (1H, m), 2.02 (1H, m), 1.87 (2H, brs), 1.75 (2H, m), 1.65 (2H, m), 1.40 (1H, m), 1.25 (3H, t, *J*= 7.1 Hz), 1.18 (1H, brs); ^{13}C NMR δ 204.4, 170.7, 61.8, 40.4, 37.7, 36.3, 35.4, 31.8, 31.4, 31.2, 22.5, 20.3, 14.5; HRMS (FAB): for $C_{13}H_{19}O_3$ calcd 223.1334 $[M+H]^+$; found 223.1336.

Ethyl 2-methyleneoctahydrocyclopropa[*e*]indene-1a(1*H*)-carboxylate (16) was prepared and purified according to the procedure described for **11** using β-keto ester **15** as starting material. The reaction afforded **16** (1.52 g, 6.90 mmol, 69%): ^{1}H NMR (400 MHz) δ 5.09 (2H, m), 4.12 (2H, m), 4.10 (2H, m), 2.19 (1H, m), 1.91 (2H, m), 1.89 (1H, m), 1.72 (1H, m), 1.71 (1H, dd, *J*= 9.6, 4.1 Hz), 1.70 (1H, m), 1.52 (4H, m), 1.40 (1H, m), 1.23 (3H, t, *J*= 7.1 Hz), 0.72 (1H, dd, *J*= 7.0, 4.1 Hz); ^{13}C NMR δ 174.1, 143.7, 114.4, 60.6, 37.8, 36.9, 35.3, 31.6, 31.4, 28.0, 27.7, 22.6, 22.4, 14.2; HRMS (FAB): for $C_{14}H_{21}O_2$ calcd 221.1542 $[M+H]^+$; found 221.1543.

1,4,5a,6,7,8,8a,8b-octahydrocyclopropa[4,5]indeno[5,6-*c*]furan-2-one (17). To a solution of alkene **16** (1.10 g, 5.00 mmol) in acetone (10 ml) was added a solution of dimethyldioxirane (55 ml, ~0.10 M in acetone) at 0°C. The solvent was removed after 1 h and the residue was re-dissolved in Et_2O, dried with Na_2SO_4 and concentrated to afford the crude epoxide, which was used directly without further purification. The epoxide was refluxed in $CHCl_3$ (50 ml) with a catalytic amount *p*-TsOH for 3 h. After cooling, the mixture was washed twice with water, dried, concentrated and chromatographed to give **17** (0.75 g, 3.9 mmol, 79%) and unreacted **16** (0.08 g, 0.38 mmol, 8%) was recovered: ^{1}H NMR (400 MHz) δ 5.00 (1H, m), 4.96 (1H, m), 4.91 (1H, dt, *J*= 12.4, 2.2 Hz), 2.44 (1H, m), 2.39 (1H, m), 2.18 (1H, dd, *J*= 8.4, 7.0 Hz), 1.84 (1H, m), 1.77 (1H, m), 1.60 (1H, m), 1.58 (2H, m), 1.57 (1H, m), 1.33 (1H, dd, *J*= 6.7, 3.9 Hz), 1.19 (1H, m); ^{13}C NMR δ 178.8, 133.3, 118.0, 70.1, 36.7, 36.1, 32.4, 29.7, 26.5, 23.9, 23.1, 23.0; HRMS (ESI): for $C_{12}H_{14}O_2$ calcd 190.0994 $[M]^+$; found 190.0991.

2-Methoxy-1,4,5a,6,7,8,8a,8b-octahydrocyclopropa[4,5]indeno[5,6-*c*]furan (18). A 1.2 M solution of DIBAL-H (3.4 ml) in toluene was added very slowly to a solution of **17** (0.74 g, 3.91 mmol) in toluene (25 ml) at –78°C. A saturated aqueous solution of potassium sodium tartrate (5 ml) was added to the reaction, at –78°C, after 3 h. The mixture was allowed to warm to room temperature and was then extracted with EtOAc. The combined extracts were dried and concentrated to afford the crude lactol, as a mixture of lactol/aldehyde-alcohol and lactol epimers, which was used directly without further purification. A catalytic amount of *p*-TsOH was added to a solution of the lactol in pentane/MeOH (9:1, 50 ml). A saturated aqueous solution of $NaHCO_3$ was added after 10 min and the organic phase was separated. The aqueous phase was extracted with Et_2O. The combined organic extracts were dried with Na_2SO_4, concentrated and chromatographed to give **18** (0.43 g, 2.10 mmol, 53%) as an epimeric mixture (3:1): ^{1}H NMR (400 MHz, C_6D_6) δ major 4.66 (1H, s), 4.57 (1H, m), 4.26 (1H, m), 3.24 (3H, s), 2.18 (2H, m), 1.65 (2H, m), 1.63 (1H, m), 1.60 (2H, m), 1.59 (1H, m), 1.49 (1H, m), 1.36 (1H, m), 0.85 (1H, dd, *J*= 8.5, 4.1 Hz), 0.73 (1H, dd, *J*= 5.8, 4.1 Hz); ^{13}C NMR δ major 141.2, 115.3, 109.8, 70.2, 54.7, 38.3, 38.0, 33.8, 30.8, 24.2, 22.7, 20.6, 19.7; HRMS (FAB): for $C_{13}H_{19}O_2$ calcd 207.1385 $[M+H]^+$; found 207.1383.

2-Methoxy-1,5,5a,6,7,8,8a,8b-octahydrocyclopropa[4,5]indeno[5,6-*c*]furan-5-ol (5). To a solution of acetal **18** (0.43 g, 2.06 mmol) in acetone (10 ml) was added a solution of dimethyldioxirane (2.4 mmol, 48 ml, ~0.05M in acetone) at 0°C. The solvent was removed after 1 h and the residue was re-dissolved in Et_2O, dried with Na_2SO_4 and concentrated to afford the crude epoxide, which was used directly without further purification. *t*-BuLi (1.56 ml, 2.34 mmol, 1.5 M in pentane) was added to a solution of diisopropyl amine (0.26 ml, 1.82 mmol) in THF (5 ml) at –78°C. The crude epoxide (0.25 g) dissolved in THF (1 ml) was added dropwise to the solution during 0.5 h at -78°C. The reaction mixture was allowed to reach room temperature. A saturated aqueous solution of $NaHCO_{3\ (sat)}$ (5 ml) was added after 2 h. The organic layer was separated and the aqueous layer was extracted with Et_2O (10 ml). All organic fraction were dried with Na_2SO_4, concentrated and chromatographed on Al_2O_3 (neutral, activity II-III) to give **5** as an epimeric mixture (3:1) (0.17 g, 0.74 mmol, 63%): ^{1}H NMR (500 MHz, C_6D_6) δ 6.29 (1H, s),

4.96 (1H, s), 4.00 (1H, d, *J*= 3.0 Hz), 3.19 (3H, s), 2.37 (1H, dt, *J*= 6.5, 3.0 Hz), 2.05 (1H, m), 1.78 (1H, m), 1.71 (1H, m), 1.61 (1H, m), 1.46 (1H, m), 1.45 (1H, m), 1.27 (1H, m), 1.26 (1H, m), 1.23 (1H, m), 0.71 (1H, dd, *J*= 11.4, 6.1 Hz); ^{13}C NMR δ 140.4, 115.2, 111.1, 65.8, 55.4, 46.6, 36.8, 36.4, 32.3, 28.8, 24.2, 20.8, 19.9; HRMS (FAB): for $C_{13}H_{18}O_3$ calcd 222.1256 $[M]^+$; found 222.1252.

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