Synthesis of C-*seco* Limonoid Model Insect Antifeedants Related to Ohchinolide and Nimbolidin

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Abstract: A concise and stereoselective synthesis of a CDE-*seco* limonoid related to ohchinolide and nimbolidin was accomplished in eleven and twelve steps, respectively, from α-cyclocitral. Opening of the C ring was first attempted by a retro-Claisen reaction, whereby a very unusual rearrangement occurred. However, the ring-opening was successfully accomplished by a selective Baeyer–Villiger reaction.

Key words: stereoselective synthesis, allylic rearrangement, C-*seco* limonoids, ohchinolide, nimbolidin

Naturally occurring insect antifeedants are the plant chemical defence against insect predators that have pointed the way to environmentally safe methods for avoiding the agricultural damage. Ohchinolide and nimbolidin (Figure 1) are degraded triterpenes of the limonoid family (C-*seco* group) isolated from the well-known plant *Melia azederach Linn*. (Neem tree), which exhibits a very potent antifeedant activity.[1] Only a few synthetic approaches to the group of the C-*seco* limonoids have been made with the exception of the work carried out by Ley et al.[2] to obtain model compounds based on the AB and CD rings of azadirachtin. Part of our own contribution to the synthesis of model compounds related to C-*seco* limonoids, which aims at solving some of the problems arising in this field, has been reported in two preliminary works.[3]

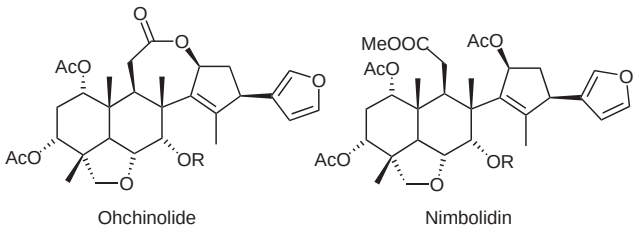
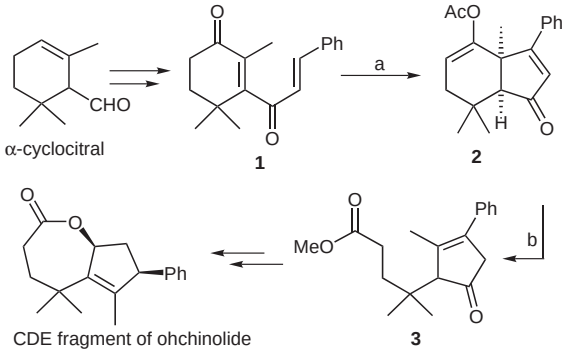


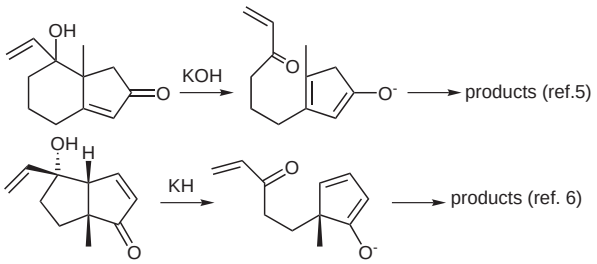
Figure 1 The structures of ohchinolide and nimbolidin.

Our approach to CDE C-*seco* limonoid models is based on the construction of the D ring by an electrocyclic reaction and the opening of the C ring, first attempted by a retro-Claisen reaction and later successfully accomplished by a selective Baeyer–Villiger reaction. The key steps of the first approach depicted in Scheme 1 are the Nazarov reaction of the β-acyl divinylketone **1**, obtained in five steps from α-cyclocitral followed by the retro-Claisen reaction of the keto acetate **2**.[4]



Scheme 1 (a) $HClO_4$, Ac_2O, EtOAc; (b) i. KOH, EtOH, H_2O, ii. aq 2 M HCl, iii. CH_2N_2, Et_2O

Although all the steps related to the formation of the keto ester **2** were correct, from that point onward a rectification was due.[3a] The structure of the product **3** resulting from the retro-Claisen reaction of **2** (step b) was in principle based on the literature background depicted in Scheme 2.[5,6]



Scheme 2

However, an in-depth study of the H-C correlations of compound **3**, together with certain other evidence (explained later), changed our original idea about its structure, and we opted for **6** (Scheme 3).

The main proof of the structure assigned to the product from the retro-Claisen reaction was an X-ray diffraction study of its methyl ester **6** (Figure 2).[7]

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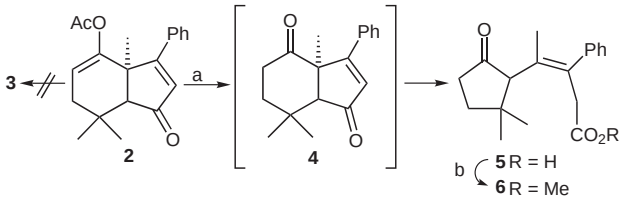


Scheme 3 (a) i. NaOH, MeOH, H_2O, ii. aq 2 M HCl; (b) CH_2N_2, Et_2O

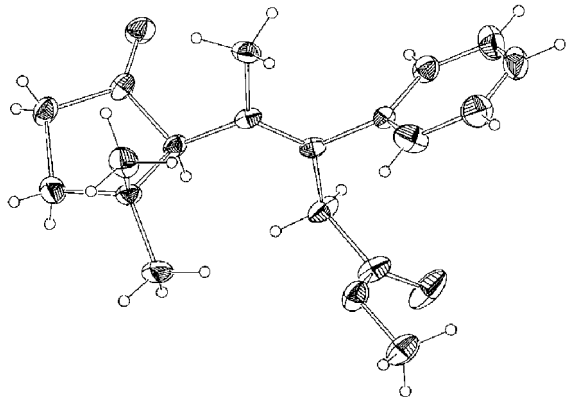
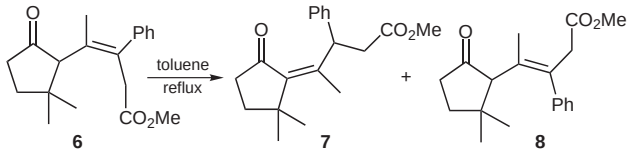


Figure 2 X-ray structure of **6**.

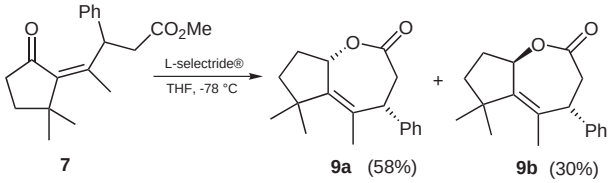
When heated in toluene at reflux, the keto ester **6** was isomerised to the two new compounds **7** and **8**, as shown in Table 1.

Table 1 Thermal Isomerisation of the Keto Ester **6**



Time	Ratio		
	6 (%)	**7** (%)	**8** (%)
1 h 30 min	65	35	-
4 h	52	42	6
59 h	33	45	22

The structures of keto esters **7** and **8** were assigned on the basis of spectroscopic data, and NOE and H-C correlations. Moreover, the reduction of keto ester **7** with L-selectride® afforded a 2:1 mixture of the isomer lactones **9a** and **9b**, respectively (Scheme 4), which were separated by column chromatography. The structure of the major lactone **9a** was established after X-ray diffraction analysis[7] (Figure 3).



Scheme 4

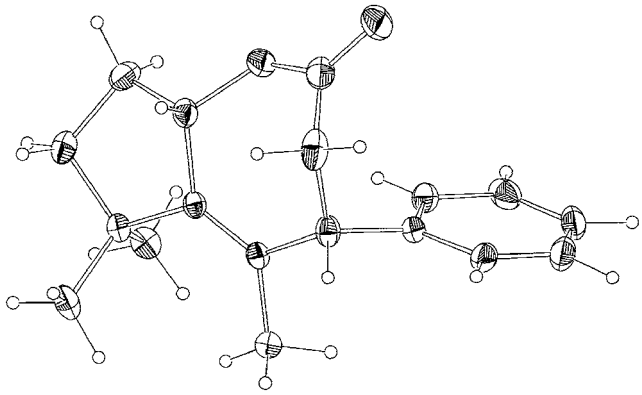
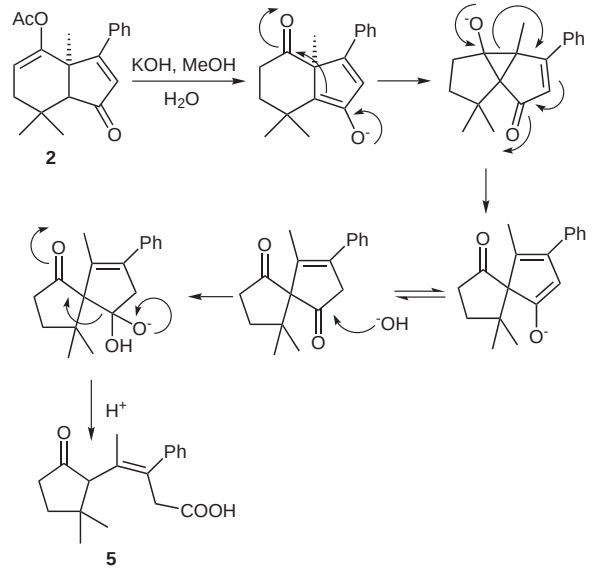


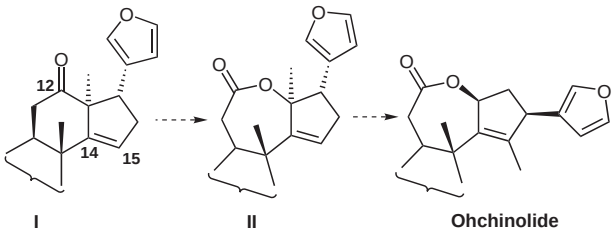
Figure 3 X ray structure of **9a**.

To explain the unusual rearrangement that transforms compound **2** into the keto acid **5** in basic aqueous media, we propose the tentative complex mechanism shown in Scheme 5.



Scheme 5

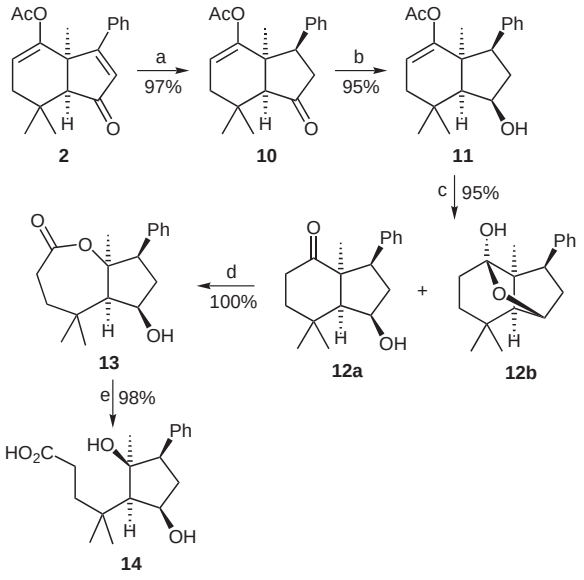
After this frustrated approach, we turned to a biomimetic Baeyer–Villiger reaction. This type of reaction has been invoked to explain the hypothetical biogenesis of the limonoids with the A, B or D ring opened.[1a,8] So why not explain also the biogenesis of limonoid with the ring C opened with the same hypothesis? (Scheme 6).[9]



Scheme 6

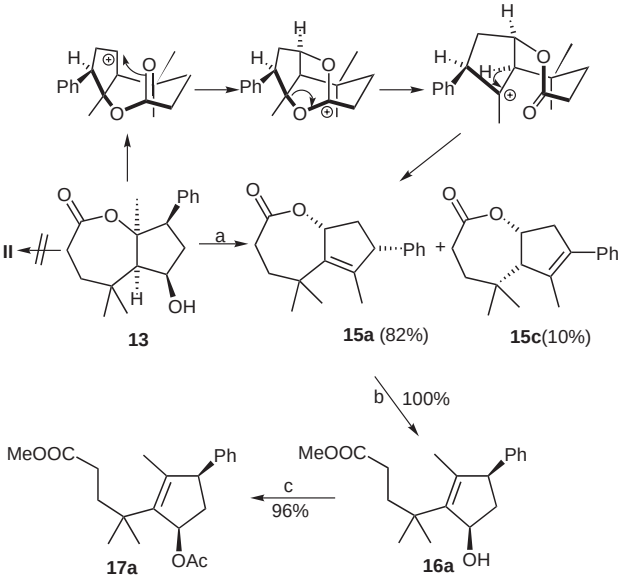
This idea inspired our new contribution to the synthesis of model compounds related to C-*seco* limonoids, which promises to be a general and useful procedure.

Now starting from the keto acetate **2**, obtained as above, and taking advantage of the one keto group protected as an enol acetate and the differences between the C–C double bonds in **2**, a catalytic hydrogenation was undertaken to obtain the keto acetate **10** in a chemo- and stereoselective manner.[10] The reduction of compound **10** carried out with $NaBH_4$ gave only the hydroxy acetate **11** in a totally stereoselective way. Further hydrolysis of the acetate afforded the expected hydroxy ketone **12a** and the isomeric hemiacetal **12b** in equal amounts, as an inseparable mixture. However, treatment of the mixture with *m*-chloroperoxybenzoic acid gave only one compound, the hydroxy lactone **13**, in excellent yield (Scheme 7). The relative stereochemistry of **13** (and indeed of **11** and **12a**) was established by X-ray diffraction analysis of its hydrolysis product, the diol acid **14**.[3b]



Scheme 7 (a) H_2 (1 atm), Pd/C, EtOAc; (b) $NaBH_4$, MeOH, 0 °C; (c) aq 5 M KOH, EtOH; (d) *m*-CPBA, CH_2Cl_2; (e) i. KOH, H_2O, EtOH, ii) aq 1 M HCl

The reaction of **13** with thionyl chloride and pyridine, which must lead to the unsaturated lactone **II**, the subject of the allylic rearrangement that we consider to be the corner-stone of the synthesis, was completely unexpected because it directly afforded the target CDE ohchinolide model compound **15a** in good yield (72%), together with the unsaturated isomer lactone **15c** (10%). The transformation of **13** by an absolutely stereoselective allylic rearrangement to give **15a** could be explained by the proximity of the orbital through the space of the lactone oxygen and the carbocation formed after dissociation of the chlorosulfite intermediate (Scheme 8).[11]

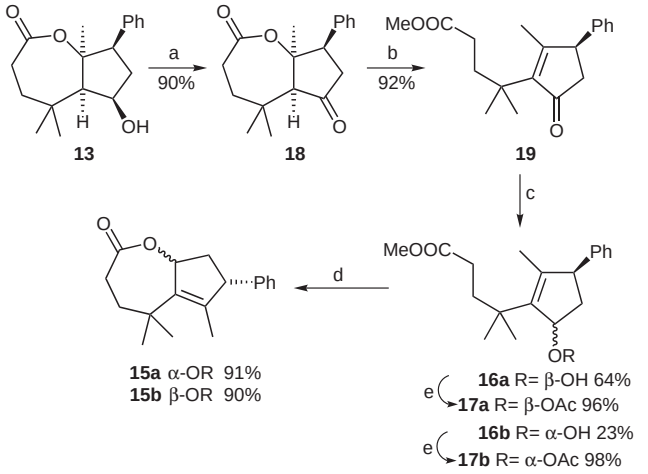


Scheme 8 (a) $SOCl_2$, py, CH_2Cl_2; (b) MeONa, MeOH; (c) Ac_2O, py, DMAP

Our next target, the CDE nimbolidin model compound **17a** was obtained from ohchinolide model **15a** in two simple steps: transesterification and acetylation. Another less biomimetic way to obtain the ohchinolide and nimbolidin model compounds was carried out from the hydroxy lactone **13** through the sequence described in Scheme 9, which consists of the oxidation of **13** to give the keto lactone **18**, followed by elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene and esterification with diazomethane to the keto ester **19**. The reduction of **19** with diborane gave a diastereomeric 3:1 mixture of hydroxy esters **16a** and **16b**. Acetylation of the major isomer **16a** afforded the CDE nimbolidin model compound **17a**. Hydrolysis of the hydroxy ester **16a**, followed by the Corey–Nicolaou lactonization of the hydroxy acid intermediate, gave the CDE ohchinolide model compound **15a**.[12] Following the methods described above, the minor hydroxy ester **16b** was transformed into the diastereomers of the CDE nimbolidin and ohchinolide model compounds **17b** and **15b**. The latter two compounds exhibit very potent insect antifeedant activity against *Spodoptera littoralis* larvae.[13]

The relative stereochemistry of compounds **15a** and **17a** was established by NOE experiments.[3b]

All solvents and reagents were purified, when required, by standard techniques. Reactions were monitored by TLC on Merck silica 60 F_{254}. Organic extracts were dried over Na_2SO_4 and concentrated un-



Scheme 9 (a) PCC, CH_2Cl_2; (b) i. DBU, toluene, 80 °C, ii. CH_2N_2, Et_2O; (c) $BH_3{\cdot}SMe_2$, THF, 0 °C; (d) i. aq 5 M KOH, EtOH, ii. aq 1 M HCl, pH 5, iii. $(pyS)_2$, PPh_3, xylene; (e) Ac_2O, py, DMAP

der reduced pressure with the aid of a rotary evaporator. Column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm). ^1H and ^{13}C NMR spectra were recorded at 200/400 and 50/75 MHz, respectively.

(*E*)-4-(2,2-Dimethyl-5-oxocyclopentyl)-3-phenylpent-3-enoic Acid Methyl Ester (6); Treatment of 2 with Aqueous NaOH/MeOH

To a solution of **2** (700 mg, 2.26 mmol) in MeOH (5.9 mL) was added an aq 6 M solution of NaOH (1 mL). The mixture was stirred at r.t. for 30 min and then concentrated under reduced pressure. To the residue were added H_2O and Et_2O. The organic layer was separated and the aqueous phase was acidified with aq 2 N HCl and extracted with Et_2O. The combined organic extracts were washed with brine and concentrated. The residue was dissolved in Et_2O and then a solution of CH_2N_2 in Et_2O was added dropwise until the release of N_2 had stopped. Removal of the solvent afforded a crude product, which was purified by flash chromatography (hexane–Et_2O, 85:15) to afford (603 mg, 89%) as a white solid; mp 131–133 °C (*t*-BuOMe–hexane).

IR (film): 2955, 1738, 733, 704 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.07 (3 H, s), 1.27 (3 H, s), 1.46 (3 H, s), 1.85 (2 H, m), 2.38 (2 H, m), 3.20 (1 H, s), 3.33 (1 H, d, *J* = 16 Hz), 3.44 (1 H, d, *J* = 16 Hz), 3.55 (3 H, s), 7.1–7.4 (5 H, m).

^{13}C NMR ($CDCl_3$): δ = 19.1, 24.2, 30.0, 36.6, 37.0, 40.5, 42.2, 51.7, 63.7, 126.6, 128.2 (2 C), 128.7 (2 C), 130.9, 134.8, 142.3, 171.4, 219.0.

MS (EI): *m*/*z* (%) = 300 (6, M^+), 285 (6), 171 (100), 115 (24), 91 (33), 77 (29), 55 (34).

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.00; H, 8.10.

Crystal Data for 6

$C_{19}H_{24}O_3$; Mr = 300.38; orthorhombic; space group P212121; unit cell dimensions a = 7.555(5) Å, b = 11.348(1) Å; c = 19.843(2) Å, α = 90°, β = 90°, γ = 90°; volume 1701.3 (3) $Å^3$; Z = 4, Dx = 1.173 gcm^{-3}; absorption coefficient 0.620 mm^{-1}; crystal size 0.48 × 0.16 × 0.08 mm; θ range for data collection 4.46 to 64.98°; limiting indices 0 = h = 8, 0 = k = 13, 0 = l = 23; R = 0.0477; Rw = 0.0825.

Thermal Rearrangement of 6

A solution of **6** (162 mg, 0.54 mmol) in toluene (5 mL) was refluxed for 59 h. Removal of the solvent under reduced pressure afforded a residue, which was purified by flash chromatography (hexane–Et_2O, 90:10). The first fraction was identified as **7**.

(*Z*)-4-(2,2-Dimethyl-5-oxocyclopentylidene)-3-phenyl-3-yl-pentanoic Acid Methyl Ester (7)

Colourless oil; yield: 73 mg (45%).

IR (film): 2955, 1738, 1699, 702 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.23 (3 H, s), 1.29 (3 H, s), 1.68 (3 H, s), 1.70 (2 H, t, *J* = 8 Hz), 2.40 (2 H, t, *J* = 8 Hz), 2.74 (1 H, dd, J_1 = 9, J_2 = 14 Hz), 2.89 (1 H, dd, J_1 = 7, J_2 = 14 Hz), 3.60 (3 H, s), 6.30 (1 H, dd, J_1 = 7, J_2 = 9 Hz), 7.10–7.40 (5 H, m).

^{13}C NMR ($CDCl_3$): δ = 15.6, 27.5, 28.0, 36.3, 37.2, 37.8, 40.1, 41.3, 51.6, 126.4, 127.6 (2C), 128.3 (2C), 141.3, 141.4, 151.3, 172.2, 207.7.

MS (EI): *m*/*z* (%) =: 300 (M^+, 30), 285 (27), 225 (100), 171 (52), 91 (63), 77 (42).

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.00, H, 8.11.

The second fraction was identified as **8**.

(*E*)-4-(2,2-Dimethyl-5-oxocyclopentyl)-3-phenylpent-3-enoic Acid Methyl Ester (8)

Colourless solid; yield: 36 mg (22%); mp 84–86 °C.

IR (film): 2955, 1738, 1161, 706 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.79 (3 H, s), 1.00 (3 H, s), 1.50 (1 H, m), 1.70 (1 H, m), 1.76 (3 H, s), 2.24 (2 H, dd, J_1 = 6, J_2 = 9.5 Hz), 3.08 (1 H, s), 3.28 (1 H, d, *J* = 16 Hz), 3.53 (1 H, d, *J* = 16 Hz), 3.65 (3 H, s), 7.1–7.3 (5 H, m) .

^{13}C NMR ($CDCl_3$): δ = 17.8, 24.3, 29.6, 36.5, 36.6, 40.4, 51.7, 65.5, 126.7, 128.2 (2 C), 128.9 (2 C), 131.2, 135.5, 142.7, 171.6, 219.6.

MS (EI): *m*/*z* (%) = 300 (M^+, 34), 285 (13), 171 (100), 115 (16), 77 (16), 55 (19).

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.01; H, 8.09.

The third fraction was the starting keto ester **6**; recovered yield: 53 mg (33%).

Reaction of 7 with L-Selectride®

To a solution of **7** (30 mg, 0.1 mmol) in THF (2 mL) at –78 °C under argon, was added a 1 M solution of L-selectride® in THF (1.1 mL). The reaction mixture was stirred at –78 °C for 15 min and then acetone was slowly added and concentrated under reduced pressure. The residue was dissolved in H_2O, extracted with Et_2O, and the combined organic extracts were washed with brine. Removal of the solvent afforded a crude solid, which was purified and separated by flash chromatography to give the products **9a** and **9b**.

5,6,6-Trimethyl-4-phenyl-3,4,6,7,8,8a-hexahydrocyclopenta[*b*]oxepin-2-one (9a)

Eluent: hexane–Et_2O, 70:30; colourless solid; yield: 16 mg (58%); mp 165–167 °C (*t*-BuOMe–hexane).

IR (film): 2922, 1730, 752, 702 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.31 (3 H, s), 1.33 (3 H, s), 1.60 (2 H, m), 1.65 (3 H, d, *J* = 2 Hz), 2.10 (2 H, m), 2.60 (1 H, m), 3.56 (1 H, m), 3.60 (1 H, m), 5.35 (1 H, t, *J* = 9 Hz), 7.1–7.4 (5 H, m) .

^{13}C NMR ($CDCl_3$): δ = 19.6, 27.3, 28.7, 30.1, 39.2, 39.9, 42.8, 48.6, 79.9, 127.2, 127.9 (2 C), 128.8 (2 C), 131.1, 141.6, 143.5, 172.4.

MS (EI): *m*/*z* (%) = 270 (M^+, 3), 228 (10), 195 (2), 172 (55), 139 (28), 104 (100), 91 (15), 77 (13).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.01; H, 8.22.

Crystal Data for 9a

$C_{18}H_{22}O_2$; Mr = 270.34; monoclinic; space group $P2_1/c$; unit cell dimensions a = 5.958(3) Å, b = 22.367(1) Å; c = 11.784(7) Å, α = 90°, β = 104.62 (5)°, γ = 90°; volume 1519.6 (1) $Å^3$; Z = 4, Dx = 1.173 gcm^{-3}; absorption coefficient 0.589 mm^{-1}; crystal size 0.48 × 0.40 × 0.24 mm; θ range for data collection 3.95 to 65.00°; limiting indices –7 = h = 7, 0 = k = 26, 0 = l = 13; R = 0.0367; Rw = 0.0959.

5,6,6-Trimethyl-4-phenyl-3,4,6,7,8,8a-hexahydrocyclopenta-[*b*]oxepin-2-one (9b)

Eluent: hexane–Et_2O, 50:50; white solid; yield: 8 mg (30%); mp 98–100 °C.

IR (film): 2924, 1719, 764, 702 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.24 (3 H, s), 1.31 (3 H, s), 1.54 (3 H, d, *J* = 1 Hz), 1.60 (1 H, m), 1,75 (1 H, m), 2.05 (1 H, m), 2.15 (1 H, m), 2.70 (1 H, dd, J_1 = 6, J_2 = 13 Hz), 3.18 (1 H, t, *J* = 13 Hz), 3.64 (1 H, dd, J_1 = 6, J_2 = 13 Hz), 5.61 (1 H, t, *J* = 7 Hz), 7.1–7.4 (5 H, m).

^{13}C NMR ($CDCl_3$): δ = 19.6, 27.0, 28.1, 29.6, 40.2, 41.8, 43.1, 49.6, 80.0, 127.1, 127.3 (2 C), 129.0 (2 C), 132.5, 143.6, 145.1, 173.0.

MS (EI): *m*/*z* (%) = 270 (M^+, 5), 195 (5), 172 (79), 139 (25), 104 (100), 77 (22).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.99; H, 8.23.

Acetic Acid 3a,7,7-Trimethyl-1-oxo-3-phenyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-4-yl Ester (10)

To a solution of **2** (7.0 g, 22.6 mmol) in EtOAc (68 mL) was added 10% Pd/C (1.36 g). The mixture was vigorously stirred at r.t. under H_2 for 10 h. After removal of the catalyst by filtration, the filtrate was concentrated to yield **10** (6.83 g, 97%) as a colourless solid; mp 82–84 °C (*t*-BuOMe–hexane).

IR (film): 2962,1748, 1738, 770, 704 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.17 (3 H, s), 1.31 (3 H, s), 1.35 (3 H, s), 1.44 (3 H, s), 1.82 (1 H, ddd, J_1 = 2, J_2 = 7, J_3 = 17 Hz), 2.01 (1 H, t, *J* = 2 Hz), 2.16 (1 H, dd, J_1 = 2, J_2 = 17 Hz), 2.36 (1 H, m), 2.97 (1 H, m), 3.00 (1 H, s), 5.56 (1 H, dd, J_1 = 2, J_2 = 7 Hz), 7.20–7.40 (5 H, m).

^{13}C NMR ($CDCl_3$): δ = 20.2, 23.8, 28.0, 29.1, 33.5, 35.7, 43.4, 49.5, 52.1, 65.6, 117.2, 126.8, 127.7 (2 C), 128.6 (2 C), 138.0, 146.9, 168.9, 216.1.

MS (EI): *m*/*z* (%) = 312 (4, M^+), 270 (8), 252 (7), 138 (100), 123 (83), 77 (26), 55 (30).

Acetic Acid 1-Hydroxy-3a,7,7-trimethyl-3-phenyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-4-yl Ester (11)

To a solution of **10** (6.70 g, 21.5 mmol) in MeOH (1 L) at 0 °C was added $NaBH_4$ (4.10 g, 108 mmol). The reaction mixture was stirred at 0 °C under argon for 3 h and concentrated after adding acetone. The residue was treated with brine and Et_2O and stirred for 30 min. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined extracts were washed with brine. Removal of the solvent afforded **11** (6.41 g, 95%) as a colourless oil.

^{1}H NMR ($CDCl_3$): δ = 1.00–2.20 (4 H, m), 1.17 (3 H, s), 1.29 (3 H, s), 1.38 (3 H, s), 1.40 (3 H, s), 2.45 (1 H, m), 2.70–2.90 (2 H, m), 4.55 (1 H, m), 5.40 (1 H, m), 7.10–7.40 (5 H, m).

Reaction of 11 with Aqueous KOH/EtOH

To a solution of **11** (6.30 g, 20.1 mmol) in EtOH (50 mL) was added an aq 5 M solution of KOH (9 mL). The mixture was stirred at r.t. for 1 h and then concentrated under reduced pressure. The residue was partitioned between H_2O and Et_2O. The organic layer was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine. Removal of the solvent afforded a 1:1 inseparable mixture of **12a** and **12b** (5.19 g, 95%) as a white solid.

1-Hydroxy-3a,7,7-trimethyl-3-phenyloctahydroinden-4-one (12a)

IR ($CHCl_3$): 3528, 3451, 2953, 2868, 1699, 1071, 737, 700 cm^{-1}.

MS (EI): *m*/*z* (%) = 272 (M^+, 28), 257 (15), 157 (98), 139 (49), 105 (53), 91 (62), 55 (100).

^{1}H NMR ($CDCl_3$): δ = 1.25 (3 H, s), 1.27 (3 H, s), 1.50 (3 H, s), 1.60 (1 H, m), 1.76 (1 H, dd, J_1 = 1.5, J_2 = 2 Hz), 2.15 (2 H, m), 2.50 (2 H, m), 2.55 (1 H, m), 2.84 (1 H, t, *J* = 10 Hz), 4.55 (1 H, dt, J_d = 3, J_t = 6 Hz), 7.15–7.60 (5 H, m).

^{13}C NMR ($CDCl_3$): δ = 28.0, 29.2, 31.4, 32.8, 37.0, 37.8, 40.7, 55.8, 57.3, 74.5, 127.3, 129.2 (2 C), 130.1 (2 C), 140.4, 216.2.

Hemiketal 12b

^{1}H NMR ($CDCl_3$): δ = 1.09 (3 H, s), 1.11 (3 H, s), 1.30–1.45 (2 H, m), 1.33 (3 H, s), 1.60 (1 H, br s), 1.85 (2 H, m), 2.10 (1 H, m), 2.40 (1 H, m), 3.10 (1 H, dd, J_1 = 5.5, J_2 = 12 Hz), 4.43 (1 H, dd, J_1 = 2, J_2 = 3 Hz), 7.15–7.60 (5 H, m).

^{13}C NMR ($CDCl_3$): δ =15.4, 28.0, 31.9, 32.0 (2 C), 34.1, 36.2, 51.3, 52.2, 63.9, 78.0, 109.2, 126.3, 127.3 (2 C), 129.0 (2 C), 141.5.

6-Hydroxy-5,5,8a-trimethyl-8-phenyloctahydrocyclopenta-[*b*]oxepin-2-one (13)

To a stirred solution of the inseparable mixture of **12a**/**12b** (4.00 g, 14.7 mmol) in CH_2Cl_2 (93 mL) was added $NaHCO_3$ (126 mg, 1.5 mmol) and *m*-CPBA (2.79 g, 16.2 mmol). The reaction mixture was stirred under argon at r.t. for 17 h. Then aq 5% Na_2SO_3 (20 mL) was added and the resulting heterogeneous mixture was vigorously stirred for 1 h. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with aq 5% Na_2CO_3 and brine. Removal of the solvent afforded **13** (4.23 g, ~100%) as a white solid; mp 148–150 °C (CH_2Cl_2–hexane).[3b]

4-(2,5-Dihydroxy-2-methyl-3-phenylcyclopentyl)-4-methylpentanoic Acid (14)

To a solution of **13** (25 mg, 0.087 mmol) in EtOH (0.2 mL) was added an aq 6 M solution of KOH (0.036 mL). The mixture was stirred at r.t. for 15 min and then concentrated under reduced pressure. To the residue were added H_2O and Et_2O. The organic layer was separated and the aqueous phase was acidified with aq 2 N HCl (pH 5) and extracted with Et_2O. The combined organic extracts were washed with brine and concentrated. Removal of the solvent afforded **14** (26 mg, 98%) as a colourless solid; mp 179–182 °C (EtOH).[3b]

Reaction of 13 with $SOCl_2$/Pyridine

To a solution of **13** (250 mg, 0.87 mmol) in CH_2Cl_2 (12 mL) at 0 °C under argon, was added gradually pyridine (0.28 mL, 3.48 mmol) and a solution of $SOCl_2$ (0.13 mL, 1.74 mmol) in CH_2Cl_2 (0.87 mL). The reaction mixture was stirred at 0 °C for 5 min and then poured into ice water. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with aq 5% Na_2CO_3 and brine. Removal of the solvent afforded a crude product, which was purified and separated into **15a** (first fraction) and **15c** (second fraction) by flash chromatography (eluent: hexane–Et_2O, 70:30).

5,5,8a-Trimethyl-7-phenyl-3,4,5,7,8,8a-hexahydrocyclopenta-[*b*]oxepin-2-one (15a)
Yield: 193 mg (82%); colourless solid; mp 88–90 °C (*t*-BuOMe–hexane).[3b]

5,5,6-trimethyl-7-phenyl-3,4,5,7,8,8a-hexahydro-cyclopenta-[*b*]oxepin-2-one 15c
Colourless solid; yield: 23 mg (10%); mp 117–120 °C.

IR (film): 2955, 2874, 1738, 1262, 764, 700 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.87 (3 H, s), 1.12 (3 H, s), 1.25 (2 H, m), 1.73 (3 H, s), 2.11 (1 H, d, J = 6 Hz), 2.15 (1 H, m), 2.40 (1 H, m), 2.80 (2 H, br s), 4.41 (1 H, m), 7.10–7.30 (5 H, m).

^{13}C NMR ($CDCl_3$): δ = 16.7, 22.9, 30.5, 33.8, 35.1, 36.3, 43.0, 61.3, 78.6, 126.8, 128.2 (2 C), 128.5 (2 C), 133.3, 136.5, 137.6, 172.4.

MS (EI): *m*/*z* (%) = 270 (M^+, 2), 252 (1), 237 (1), 156 (100), 91 (14), 77 (6), 55 (8).

4-(5-Hydroxy-2-methyl-3-phenylcyclopent-1-enyl)-4-methylpentanoic Acid Methyl Ester (16a)
To a solution of **15a** (50 mg, 0.19 mmol) in MeOH (5.2 mL) was added a 5.5 M solution of MeONa in MeOH (0.16 mL). The reaction mixture was stirred at r.t. under argon for 10 min and then poured into an aq sat. solution of NH_4Cl. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine. Removal of the solvent afforded **16a** (56 mg, ~100%) as a colourless oil.

IR (film): 3511, 2957, 2876, 1738, 764, 702cm^{-1}.

^1H NMR (C_6D_6): δ = 1.25 (3 H, s), 1.31 (3 H, s). 1.57 (3 H, s), 1.61 (1 H, m), 1.88 (1 H, m), 1.96 (1 H, m), 2.15 (1 H, m), 2.41 (3 H, m), 3.31 (1 H, dd, J_1 = 3, J_2 = 9 Hz), 3.42 (3 H, s), 4.60 (1 H, t, J = 6 Hz), 7.12 (1 H, m), 7.25 (2 H, m), 7.37 (2 H, m).

^{13}C NMR (C_6D_6): δ = 15.1, 28.0, 28.5, 30.4, 35.8, 37.4, 42.1, 50.8, 56.6, 78.8, 126.2, 128.2 (2 C), 128.5 (2 C), 139.2, 143.1, 145.7, 174.2.

MS (EI): *m*/*z* (%) = 284 (M^+ – 18, 16), 269 (1), 253 (5), 197 (100), 129 (60), 97 (50), 69 (52).

4-(5-Acetoxy-2-methyl-3-phenylcyclopent-1-enyl)-4-methylpentanoic Acid Methyl Ester (17a)
To a solution of **16a** (200 mg, 0.66 mmol) in pyridine (0.37 mL, 4.62 mmol) was added Ac_2O (0.37 mL, 3.96 mmol) and 4-dimethylaminopyridine (DMAP, 8 mg, 0.07 mmol). The reaction mixture was stirred at r.t. under argon for 30 min, then diluted with Et_2O and poured into ice water. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with aq 5% $NaHCO_3$ and brine. Removal of the solvent afforded **17a** (219 mg, 96%) as a white solid; mp 58–60 °C.[3b]

5,5,8a-Trimethyl-8-phenylhexahydrocyclopenta[*b*]oxepine-2,6-dione (18)
To a stirred solution of PCC (3.36 g, 15.6 mmol) and silica gel (3.36 g) in CH_2Cl_2 (87 mL) was added dropwise a solution of the **13** (3.00 g, 10.4 mmol) in CH_2Cl_2 (22 mL). The reaction mixture was vigorously stirred at r.t. under argon for 7 h. The resulting dark brown slurry was filtered through a short column of silica gel and eluted with CH_2Cl_2. Removal of the solvent afforded **18** (2.68 g, 90%) as a white solid; mp 123–125 °C (CH_2Cl_2–hexane).

IR (Nujol): 2924, 2870, 1728, 1696, 768, 700 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.23 (3 H, s), 1.29 (3 H, s). 1.59 (3 H, s), 1.55 (1 H, m), 1.87 (1 H, m), 2.45 (1 H, s), 2.58 (1 H, dd, J_1 = 8.5, J_2 = 18 Hz), 2.66 (2 H, m), 2.75 (1 H, dd, J_1 = 12, J_2 = 18 Hz), 3.15 (1 H, dd, J_1 = 8.5, J_2 = 12 Hz), 7.20–7.50 (5 H, m).

^{13}C NMR ($CDCl_3$): δ = 23.9, 27.4, 29.0, 32.0, 32.7, 35.3, 42.2, 52.6, 67.5, 87.5, 126.6, 128.1 (2 C), 130.4 (2 C), 135.8, 173.1, 211.7.

MS (EI): *m*/*z* (%) = 286 (M^+, 3), 268 (8), 172 (21), 104 (100), 55 (59).

4-Methyl-4-(2-methyl-5-oxo-3-phenylcyclopent-1-enyl)pentanoic Acid Methyl Ester (19)
To a solution of **18** (2.50 g, 8.74 mmol) in toluene (67 mL) was added DBU (6.5 mL, 43.7 mmol). The reaction mixture was stirred at 80 °C under argon for 10 min. Then, Et_2O and aq 2 M HCl were added, the organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine and concentrated to afford a colourless oil, which was dissolved in Et_2O (10 mL). To the solution was added dropwise a solution of CH_2N_2 in Et_2O until the release of N_2 had stopped. Removal of the solvent afforded **19** (2.41 g, 92%) as a colourless oil.

IR (film): 2953, 1738, 1697, 764, 702 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.33 (3 H, s), 1.35 (3 H, s), 1.97 (3 H, s), 2.12 (2 H, m), 2.20 (2 H, m), 2.29 (1 H, dd, J_1 = 2, J_2 = 19 Hz), 2.80 (1 H, dd, J_1 = 7, J_2 = 19 Hz), 3.65 (3 H,s), 3.70 (1 H, dd, J_1 = 2, J_2 = 7 Hz), 7.05–7.35 (5 H, m).

^{13}C NMR ($CDCl_3$): δ = 18.3, 27.7, 28.0, 30.6, 35.5, 36.7, 45.1, 50.3, 51.5, 127.0, 127.3 (2 C), 128.9 (2 C), 142.3, 143.9, 171.2, 174.3, 208.6.

MS (EI): *m*/*z* (%) = 300 (M^+, 6), 281 (4), 269 (15), 227 (100), 213 (66), 91 (79), 69 (47), 55 (47).

Reaction of 19 with $BH_3{\cdot}SMe_2$
To a solution of **19** (1.80 g, 6.00 mmol) in THF (16 mL) at 0 °C under argon, was added a 2 M solution of $BH_3{\cdot}SMe_2$ in THF (6.0 mL). The reaction mixture was stirred at 0 °C for 6 h and then MeOH (8 mL) was slowly added and the mixture was stirred for 1 h. Removal of the solvent afforded a crude product, which was purified by flash chromatography eluting with hexane–Et_2O, 75:25 to furnish **16a** (1.16 g, 64%) and hexane–Et_2O, 60:40 to afford **16b** (417 mg, 23%) as colourless oils.

4-(5-Hydroxy-2-methyl-3-phenylcyclopent-1-enyl)-4-methylpentanoic Acid methyl Ester (16b)
IR (film): 3443, 2955, 2888, 1738, 754, 702 cm^{-1}.

^1H NMR (C_6D_6): δ = 1.23 (3 H, s), 1.29 (3 H, s), 1.52 (3 H, s), 1.70 (1 H, m), 1.95 (2 H, m), 2.10 (2 H, m), 2.39 (2 H, t, J = 8 Hz), 3.42 (3 H, s), 3.78 (1 H, t, J = 7 Hz), 4.73 (1 H, d, J = 6 Hz), 7.05 (2 H, m), 7.13 (1 H, m), 7.23 (2 H, m).

^{13}C NMR (C_6D_6): δ = 15.1, 28.0, 28.4, 30.4, 35.8, 37.2, 44.6, 50.8, 55.9, 78.5, 126.2, 127.7 (2 C), 128.6 (2 C), 139.7, 144.3, 145.3, 174.3.

MS (EI): *m*/*z* (%) = 284 (M^+ – 18, 18), 269 (1), 253 (6), 197 (100), 129 (47), 97 (42), 69 (43).

5,5,8a-Trimethyl-7-phenyl-3,4,5,7,8,8a-hexahydrocyclopenta-[*b*]oxepin-2-one (15b)
To a solution of **16b** (100 mg, 0.33 mmol) in EtOH (0.87 mL) was added an aq 5 M solution of KOH (0.45 mL). The mixture was stirred at r.t. for 15 min and then concentrated under reduced pressure. To the residue were added H_2O and Et_2O. The organic layer was separated and to the aqueous phase was added aq 2 M HCl (pH 5) and then extracted with Et_2O. The combined organic extracts were washed with brine. Removal of the solvent afforded the crude hydroxy acid, which was suitable for using without further purification. To a solution of the crude hydroxy acid in deoxygenated xylene (4 mL) were added $(pyS)_2$ (110 mg, 0.50 mmol) and Ph_3P (131 mg, 0.50 mmol). The mixture was stirred at r.t. under argon for 20 h and the precipitate formed was filtered. Removal of the solvent af-

forded a crude product, which was purified by flash chromatography (eluent: hexane–Et_2O, 75:25) to furnish **15b** (80 mg, 90%) as a white solid; mp 74–76 °C (*t*-BuOMe–hexane).[3b]

4-(5-Acetoxy-2-methyl-3-phenylcyclopent-1-enyl)-4-methylpentanoic Acid Methyl Ester (17b)

To a solution of **16b** (100 mg, 0.33 mmol) in pyridine (0.18 mL, 2.31 mmol) was added Ac_2O (0.18 mL, 1.98 mmol) and DMAP (4 mg, 0.03 mmol). The reaction mixture was stirred at r.t. under argon for 30 min and then diluted with Et_2O and poured into ice water. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with aq 5% $NaHCO_3$ and brine. Removal of the solvent afforded **17b** (110 mg, 98%) as a colourless oil.[3b]

Acknowledgements

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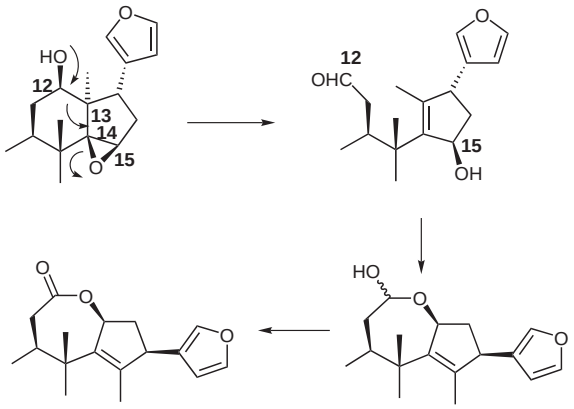

Scheme 10

(10) All compounds synthesised are racemic although, only one enantiomer is depicted.
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