A Biomimetic Approach to C-secolimonoids: Synthesis of CDE Ohchinolide and Nimbolidin Model Compounds

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Abstract: A concise and stereoselective synthesis of CDE ohchinolide and nimbolidin model compounds has been accomplished in ten and twelve steps respectively from α-cyclocitral, in 30% overall yield. The key step is a biomimetic type of allylic rearrangement induced by thionyl chloride. A potent insect antifeedant activity was found for two of the model compounds synthesised.

Key words: stereoselective synthesis, allylic rearrangement, C-secolimonoids, ohchinolide, nimbolidin

Ohchinolide and nimbolidin[1] (Figure 1) are insect antifeedants belonging to a large and structurally complex group of biologically active nortriterpenes named C-secolimonoids. Little attention has been devoted to their biogenesis and synthesis,[2] although this type of compounds could be useful in the development of environmentally safe pest control methods for sustainable agriculture.

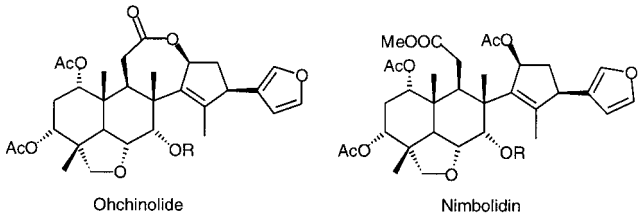


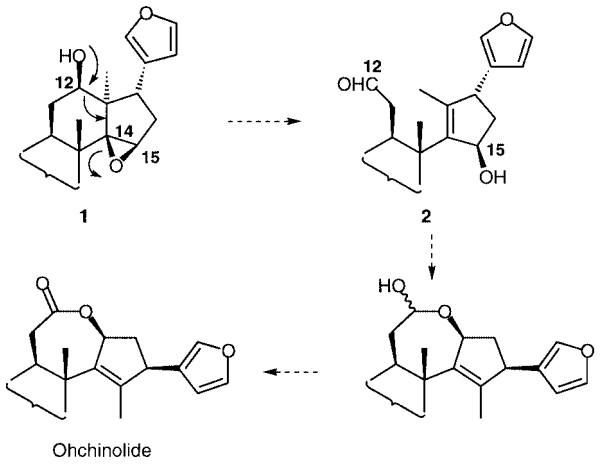
Figure 1

Proposals have been made regarding the hypothetical biogenesis of C-secolimonoids such as ohchinolide, arising from the hydrolytic cleavage of the 12β-hydroxy-14,15β-oxide **1**, which will be opened to give the 12-aldehyde-$\Delta^{13,14}$-15β-ol intermediate **2**, followed by attack of the hydrate aldehyde to the allylic carbon C-15 with inversion and later oxidation to lactone (Scheme 1).[3]

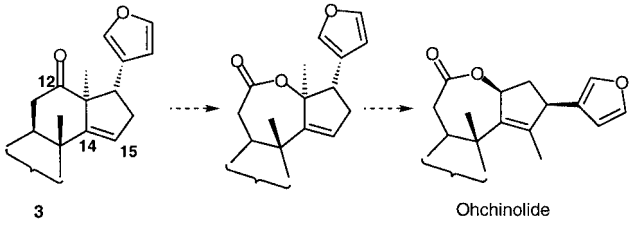
However, an easier alternative biosynthesis could be proposed, starting from the 14,15-en-12-oxo intermediate **3**, which after Baeyer-Villiger reaction and allylic rearrangement will give the same type of lactones (Scheme 2).

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

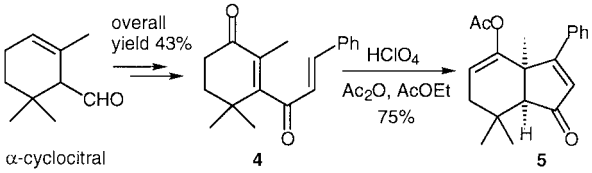
Recently, we published an approach to the synthesis of CDE C-secolimonoid models starting from α-cyclocitral, using as a key step the Nazarov reaction of β-acyl-divinylketone **4** (Scheme 3).[4]



Scheme 1

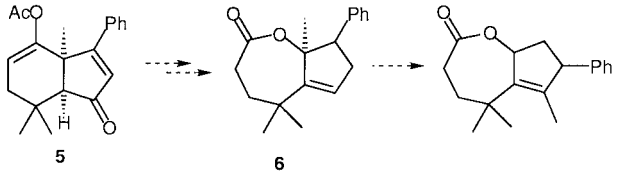


Scheme 2



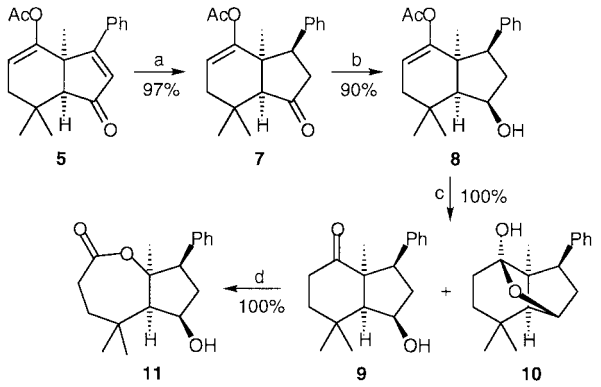
Scheme 3

Here we report a solution to the synthesis of ohchinolide model compounds, that utilises the electrocyclization product from the Nazarov reaction **5** as starting material, and the potential allylic rearrangement of the unsaturated lactone **6** as the key step (Scheme 4).[9]



Scheme 4

Taking advantage of the one-keto group protected as an enol acetate and the differences between the C-C double bonds in **5**, a catalytic hydrogenation was undertaken to obtain the keto acetate **7** in a chemo- and stereoselective manner. The reduction of compound **7** carried out with $NaBH_4$ gave only the hydroxy acetate **8** in a totally stereoselective way. Further hydrolysis of the acetate afforded the expected hydroxy ketone **9** and the isomeric hemiketal **10** in equal amounts, as an inseparable mixture. However, treatment of the mixture with *m*-chloroperoxybenzoic acid gave only one compound, the hydroxy lactone **11**, in excellent yield (Scheme 5).[10]

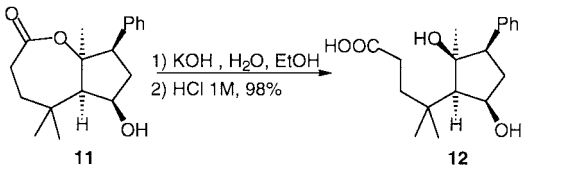


Scheme 5 (a) H_2 1 atm, Pd/C, AcOEt. (b) $NaBH_4$, MeOH, 0 ºC. (c) KOH (aq) 5 M, EtOH. (d) *m*-CPBA, CH_2Cl_2.

The relative stereochemistry of **11** (and indeed of **8** and **9**) was established by X-ray diffraction analysis of its hydrolysis product, the diol acid **12** (Figure 2).[5,11]

The reaction of **11** with thionyl chloride and pyridine, which must lead to the unsaturated lactone **6**, subject of the allylic rearrangement that we considered as the cornerstone of the synthesis, was completely unexpected because it afforded directly the target CDE ohchinolide model compound **13** in good yield (72%),[12] together with the unsaturated isomer lactone **14** (10%). The transformation of **11** by an absolutely stereoselective allylic rearrangement to give **13**, could be explained by the proximity of the orbitals through the space of the lactone oxygen and the carbocation formed after dissociation of the chlorosulfite intermediate (Scheme 6).[6]

Our next target, the CDE nimbolidin model compound **15**, was obtained from ohchinolide model **13** in two simple steps: transesterification and acetylation (Scheme 7).



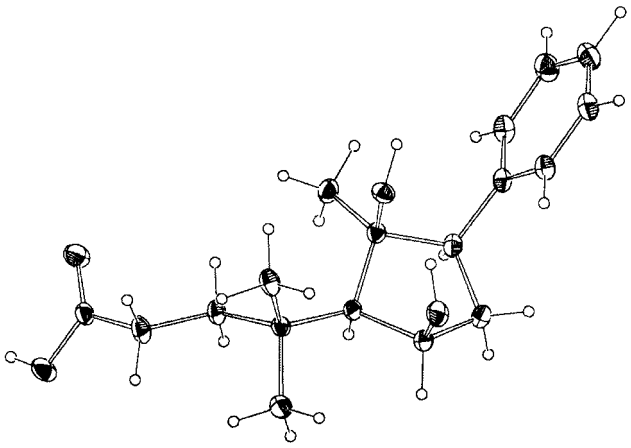
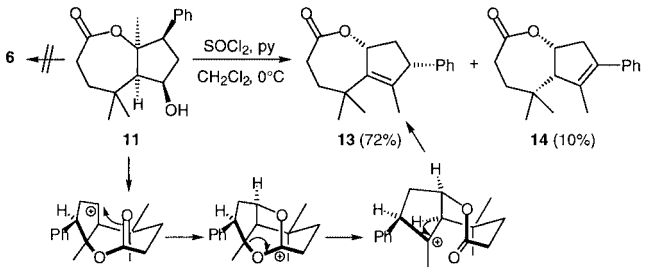
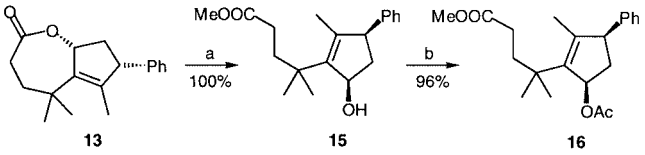


Figure 2 Formation and X-ray structure of **12**.



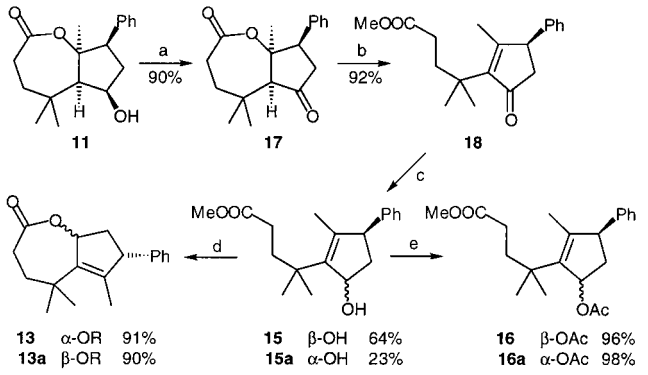
Scheme 6



Scheme 7 (a) MeONa, MeOH. (b) Ac_2O, py, DMAP.

Another less biomimetic way to obtain the ohchinolide and nimbolidin model compounds was carried out from the hydroxy lactone **11** through the sequence described in Scheme 8, which consists of the oxidation of **11** to give the keto lactone **17**, followed by elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene and esterification with diazomethane to the keto ester **18**. The reduction of **18** with diborane gave a diastereomeric 3:1 mixture of hydroxy esters **15** and **15a**. Acetylation of the major isomer **15** afforded the CDE nimbolidin model compound **16**. Hydrolysis of the hydroxy ester **15**, followed by the Corey-Nicolau[7] lactonization of the hydroxy acid intermedi-

ate, gave the CDE ohchinolide model compound **13**. Following the methods described above, the minor hydroxy ester **15a** was transformed into the diastereomers of the CDE nimbolidin and ohchinolide model compounds **13a** and **16a**. The latter two compounds exhibit very potent insect antifeedant activity against *Spodoptera littoralis* larvae.[8]



Scheme 8 (a) PCC, CH_2Cl_2. (b) i) DBU, toluene, 80 ºC; ii) CH_2N_2, diethyl ether. (c) $BH_3{\cdot}SMe_2$, THF, 0 ºC. (d) i) KOH (aq) 5M, EtOH; ii) HCl (aq) 1M, pH = 5; iii) $(pyS)_2$, PPh_3, xilene. (e) Ac_2O, py, DMAP.

The relative stereochemistry of compounds **13** and **16** was established by nOe experiments (Figure 3).

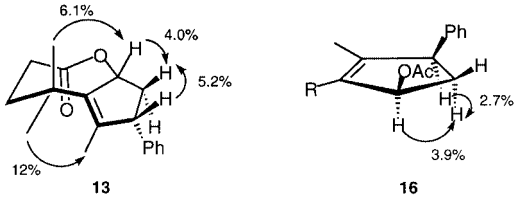


Figure 3

Acknowledgement

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References and Notes

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(5) Crystallographic data (excluding structure factors) for the structure **12** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 159677. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: 44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
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(8) Assays of insect antifeedant activity of all compounds described in this work will be published in due course.
(9) All compounds synthesised are racemic although, only one enantiomer is depicted.
(10) **(5a*RS*,6*RS*,8*RS*,8a*SR*)-6-Hydroxy-5,5,8a-trimethyl-8-phenyl-octahydro-cyclopenta[*b*]oxepin-2-one (11).** White solid (CH_2Cl_2/hexane) mp 148-150 °C. IR (film, ν): 3582, 3547, 2955, 1730, 735 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 1.21 (3H, s), 1.30 (3H, s), 1.31 (3H, s), 1.70-1.85 (3H, m), 2.35 (1H, m), 2.50 (1H, m), 2.65 (1H, m), 2.85 (1H, m), 2.97 (1H, t, *J* = 9.5 Hz), 5.04 (1H, t, *J* = 7.5 Hz), 7.25-7.50 (5H, m) ppm. ^{13}C NMR ($CDCl_3$, δ): 26.4, 27.4, 31.1, 33.2, 35.1, 36.3, 36.7, 55.8, 60.4, 80.8, 81.1, 127.1, 128.3 (2C), 129.6 (2C), 138.0, 174.2 ppm. MS (EI, m/z): 288 (M^+, 15), 173 (100), 117 (100), 91 (20). HRMS (FAB): exp. 289.1771 (M+1, $C_{18}H_{24}O_3$), calc. 289.1804. Anal. Calcd for $C_{18}H_{24}O_3$: C 74.97, H 8.39; Found: C 75.09, H 8.48.
(11) **(1*RS*,2*SR*,3*RS*,5*RS*)-4-(2,5-Dihydroxy-2-methyl-3-phenyl-cyclopentyl)-4-methyl-pentanoic acid (12).** Colorless solid (EtOH) mp 179-182 °C. IR (film, ν): 3374, 2971, 1709, 760, 708 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 1.17 (3H, s), 1.19 (3H, s). 1.23 (3H, s), 1.40 (1H, br s), 1.85-2.05 (3H, m), 2.20-240 (2H, m), 2.50 (1H, m), 2.84 (1H, dd, J_1 = 8.5, J_2 = 11 Hz), 4.40 (1H, m), 7.20-7.35 (5H, m) ppm. ^{13}C NMR ($CDCl_3$, δ): 25.5, 26.9, 27.5, 29.4, 35.3, 37.1, 40.2, 56.2, 59.9, 74.7, 82.6, 126.8, 128.0 (2C), 129.0 (2C), 139.1, 177.2 ppm. HRMS (FAB): exp. 307.1914 (M+1, $C_{18}H_{26}O_4$), calc. 307.1909.
Crystal data: $C_{18}H_{26}O_4$; Mr = 306.39; monoclinic; space group P21/c; unit cell dimensions a = 10.0017 (5) Å, b = 10.35.89 (4) Å; c = 16.4097 (9) Å, α = 90 º, β = 104.824 (5) º, γ = 90 º; volume 1643.6 (1) $Å^3$; Z = 4, Dx = 1.238 gcm^{-3}; absorption coefficient 0.694 mm^{-1}; crystal size 0.48 × 0.24 × 0.24 mm; θ range for data collection 4.57 to 65.00 º; limiting indices -11<h<11, 0<k<12, 0<l<18; R = 0.0350; Rw = 0.0793.
(12) **(7*RS*,8a*RS*)-5,5,6-Trimethyl-7-phenyl-3,4,5,7,8,8a-hexahydro-cyclopenta[*b*]oxepin-2-one (13).** White solid (*t*-BuOMe/hexane) mp 88-90 °C. IR (film, ν): 2961, 1732, 764, 702 cm^{-1}. ^1H NMR (C_6D_6, δ): 0.82 (3H, s), 1.05 (3H, s), 1.20 (1H, m), 1.35 (1H, m), 1.49 (3H, s), 2.01 (1H, d, *J* = 16 Hz), 2.19 (1H, m), 2.45 (2H, m), 3.22 (1H, d, *J* = 9.6 Hz), 4.77 (1H, d, *J* = 7.3 Hz), 7.10 (1H, m), 7.23 (2H, m), 7.41 (2H, m) ppm. ^{13}C NMR (C_6D_6, δ): 14.9, 27.5, 28.8, 31.2, 35.8, 37.5, 37.7, 57.1, 83.6, 126.6, 128.6 (2C), 128.3 (2C), 139.0, 142.0, 143.6, 172.7 ppm. MS (EI, m/z): 270 (M^+, 11), 211 (15), 156 (30), 91 (100), 77 (61). HRMS (IE): exp. 270.1631 (M^+, $C_{18}H_{22}O_2$), calc. 270.1620. Anal. Calcd for $C_{18}H_{22}O_2$: C 79.96, H 8.20; Found: C 79.89, H 8.32.
(7*RS*,8a*SR*)-5,5,6-Trimethyl-7-phenyl-3,4,5,7,8,8a-hexahydro-cyclopenta[*b*]oxepin-2-one (13a). White solid (*t*-BuOMe/hexane) mp 74-76 °C. IR (film, ν): 2961, 2859, 1728, 762, 706 cm^{-1}. ^1H NMR (C_6D_6, δ): 0.87 (3H, s), 1.08 (3H, s), 1.20 (1H, m), 1.40 (1H, m), 1.42 (3H, s), 1.70 (1H, m), 2.45 (3H, m), 3.83 (1H, t, *J* = 7.3 Hz), 4.83 (1H, d, *J* = 6.4 Hz), 6.94 (2H, m), 7.12 (1H, m), 7.20 (2H, m) ppm. ^{13}C NMR

(C_6D_6, δ): 14.7, 27.6, 28.9, 31.2, 36.2, 37.5, 41.5, 55.8, 82.2, 126.5, 127.9 (2C), 128.6 (2C), 140.5, 141.8, 144.2, 172.8 ppm. MS (EI, m/z): 270 (M^+, 2), 220 (7), 153 (75), 107 (83), 84 (100), 67 (100). HRMS (IE): 270.1652 (M^+, $C_{18}H_{22}O_2$), calc. 270.1620.

(3*RS*,5*RS*)-4-(5-Acetoxy-2-methyl-3-phenyl-cyclopent-1-enyl)-4-methyl-pentanoic acid methyl ester (16). White solid (*t*-BuOMe/hexane) mp 58-60 °C. IR (film, ν): 2961, 2888, 1738, 1728, 764, 702 cm^{-1}. ^1H NMR (C_6D_6, δ): 1.10 (3H, s), 1.15 (3H, s), 1.54 (3H, s), 1.73 (3H, m), 1.75 (1H, m), 1.85-2.10 (2H, m), 2.35 (2H, m), 2.57 (1H, ddd, J_1 = 7.4, J_2 = 9.3, J_3 = 14 Hz), 3.24 (1H, d, J = 9.3 Hz), 3.42 (3H, s), 5.90 (1H, d, J = 7.4 Hz), 7.10-7.30 (5H, m) ppm. ^{13}C NMR (C_6D_6, δ): 15.2, 20.7, 27.6, 28.2, 30.2, 35.6, 37.3, 39.1, 50.7, 56.8, 81.1, 126.3, 127.9 (2C), 128.5 (2C), 139.1, 143.4, 144.9, 169.4, 173.5 ppm. MS (EI, m/z): 284 (M^+-60, 20), 269 (2), 197 (100), 129 (50), 97 (45), 69 (45). Anal. Calcd for $C_{21}H_{28}O_4$: C 73.23, H 8.19; Found: C 73.33, H 8.23.

(3*RS*,5*SR*)-4-(5-Acetoxy-2-methyl-3-phenyl-cyclopent-1-enyl)-4-methyl-pentanoic acid methyl ester (16a). Colorless oil. IR (film, ν): 2963, 2874, 1734, 766, 702 cm^{-1}. ^1H NMR (C_6D_6, δ): 1.08 (3H, s), 1.15 (3H, s), 1.49 (3H, s), 1.81 (3H, s), 1.90-2.10 (3H, m), 2.25 (1H, m), 2.35 (2H, m), 3.42 (3H, s), 3.75 (1H, t, J = 7.4 Hz), 6.00 (1H, d, J = 6.4 Hz), 6.96 (2H, m), 7.10 (1H, m), 7.18 (2H, m) ppm. ^{13}C NMR (C_6D_6, δ): 15.0, 20.6, 27.7, 28.0, 30.2, 35.7, 37.1, 41.2, 50.6, 56.1, 81.5, 126.3, 127.6 (2C), 128.5 (2C), 140.0, 144.1, 144.3, 169.5, 173.4 ppm. MS (EI, m/z): 284 (M^+-60, 16), 269 (3), 253 (6), 197 (100), 129 (62), 97 (45), 69 (52), 59 (58).

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