Convergent Formal Synthesis of (±)-Heliannuols A, K, and L from a Common Intermediate

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Dedicated to Jacques Salaün on the occasion of his retirement

Abstract: The intramolecular titanium-mediated cyclopropanation reaction of an oxa-ester bearing a terminal double bond followed by appropriate oxidation and dehydrohalogenation allows easy access to an aryl-fused oxacyclooctenone, an effective precursor of (±)-heliannuols A, K and L.

Key words: bicyclic compounds, cyclization, enones, heterocycles, organometallic reagents, radical reactions, titanium

Isolated from *Helianthus annus*, heliannuols A–L constitute a new class of sesquiterpenes possessing allelopathic activity.[1] Heliannuols A, K and L (**1**, **2** and **3**, respectively) contain the same basic skeleton of an aromatic ring fused to an eight-membered oxacycle (Figure 1).

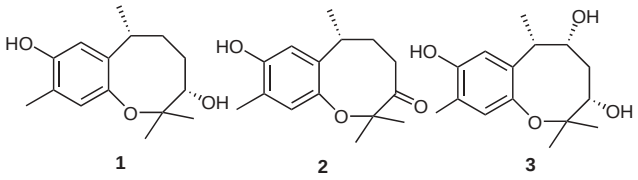


Figure 1

We recently reported[2] a general procedure for the construction of benzo-fused cyclic ethers from oxa-ω-alkenoic esters, which allows the benzoxocinone **5** to be obtained from the acetate **4** (Figure 2).

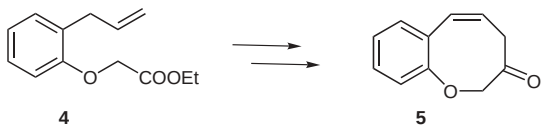
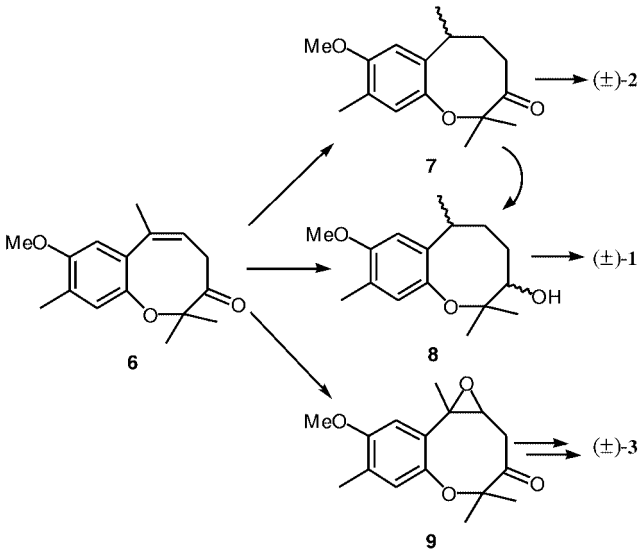


Figure 2

In order to widen the scope of this approach towards biologically important compounds, we reasoned that the oxacyclooctenone **6** could constitute a particularly efficient intermediate in the total synthesis of the various heliannuols. Demethylation of the methoxy moieties has been previously reported to provide the natural products Heliannuol A[3a,b] and Heliannuol D.[3c–e]

Indeed, simple reduction of the double bond of the heterocycle **6** should lead to the oxacycloctanone **7**; double reduction of the double bond and the ketone function should furnish the oxacyclooctanol **8**; oxidation of the double bond would give the epoxide **9**, which, by regioselective ring opening, would provide the benzoxocinone **10**. Deprotection of the methoxy group on the aryl moiety would then lead directly to the heliannuols K (**2**), A (**1**) and L (**3**), respectively. The direct reduction of the ketone **7** leads to the oxacyclooctanol **8** and has been previously reported[3b] (Scheme 1).



Scheme 1

Thus, the formylation-oxidation of 2-methylanisole **11** led after base hydrolysis[4] to 4-methoxy-3-methylphenol **12**, which was then alkylated with 1-chloro-2-butene to yield the allylic ether **13** (Scheme 2).

Refluxing in *N*,*N*-dimethylaniline for 72 hours achieved Claisen rearrangement of **13** to give 4-methoxy-5-methyl-2-(1-methyl-2-propen-1-yl)phenyl (**14**, 75%) and a small amount (3%) of the regioisomeric 3-methyl product. Alkylation of the chromatographically purified major product **14** with ethyl 2-bromo-2,2-methypropanoate

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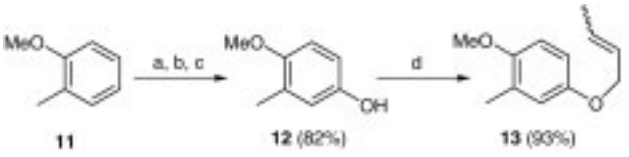
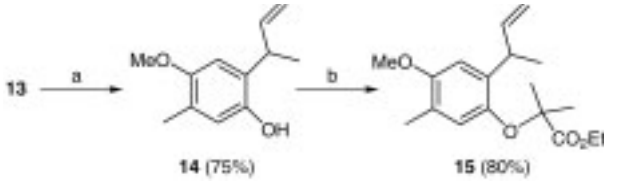


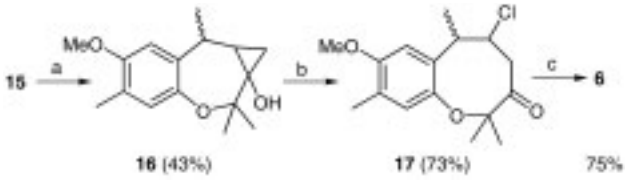
Scheme 2 *Reagents and conditions*: a) $TiCl_4$, Cl_2CHOMe, CH_2Cl_2, r.t.; b) *m*-CPBA, CH_2Cl_2, reflux; c) NH_4OH, CH_3OH, r.t.; d) 1-chloro-2-butene, K_2CO_3, acetone, reflux.

furnished in high yield the ω-alkenoic ester **15**, suitable for the intramolecular Kulinkovich reaction[5] (Scheme 3).

Thus, cyclopropanation was carried out using a titanium tetraisopropoxide–cyclohexylmagnesium halide couple[6] to produce a diastereomeric mixture (1:1) of cyclopropanols **16**. For structural characterization the mixture was separated by column chromatography. Ring opening on cyclopropanols **16** was achieved using the Saegusa procedure[7] to produce a diastereomeric mixture (77:23) of β-chloroketones **17** also separable by chromatography. Subsequent base dehydrohalogenation effected on either or both chlorides **17** delivered the expected oxocinone **6**[8] (Scheme 4).



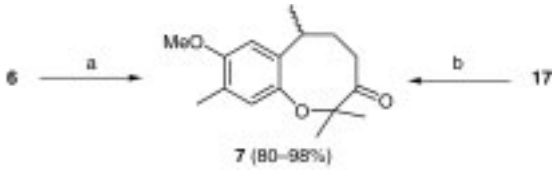
Scheme 3 *Reagents and conditions*: a) Dimethylaniline, reflux; b) NaH, DMPU, $(CH_3)_2CBrCO_2Et$, toluene, reflux.



Scheme 4 *Reagents and conditions*: a) $C_6H_{11}MgCl$ (4 equiv), $Ti(O\textit{i}\text{-}Pr)_4$ (1 equiv), Et_2O–THF, r.t., 4 h; b) $FeCl_3$, DMF, pyridine, 0 °C; c) DBU, Et_2O, 0 °C to r.t.

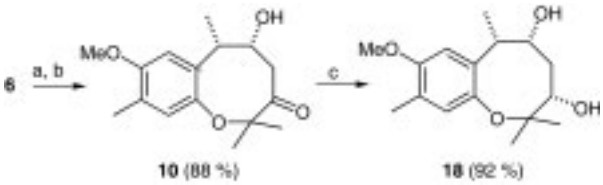
Subsequent staightforward hydrogenation of the double bond of the enone **6** gave quantitatively the oxacyclooctanone **7**[9] as the methoxy parent of (±)-heliannuol K (**2**). Alternatively, while tris(trimethylsilyl)silane is known as a hydrosilylating agent for dialkylketones,[10] application of the radical chain process on the β-chlorooctanone **17** entailed only the reduction of the halide group to produce the required oxacyclooctanone **7** with 80% yield (Scheme 5).

As suggested in Scheme 1, the direct transformation of enone **6** into the benzoxocinol **8**[11] was performed successfully (Raney nickel, H_2O, THF, Na_2CO_3, H_2, 94% yield)[12] and the product was isolated as a diastereomeric mixture (82:18) in which the major compound was the *cis*-isomer.



Scheme 5 *Reagents and conditions*: a) H_2, Pd/C, EtOAc, r.t., 72 h; b) $(Me_3Si)_3SiH$, AIBN, toluene, 80 °C, 2 h.

Likewise, epoxidation of enone **6** allowed the oxirenone **9**[13] to be obtained in 89% yield, and this was then submitted to ring opening hydrogenation[14] to produce the oxacyclooctanone **10** as a single *cis*-diastereomer. Subsequent stereocontrolled reduction of the ketone function[15] furnished the expected diol **18** as a 9:1 mixture of *syn*- and *anti*-isomers (Scheme 6).



Scheme 6 *Reagents and conditions*: a) *m*-CPBA, CH_2Cl_2, 0 °C; b) H_2, Pd/C, MeOH, EtOAc, r.t., 48 h; c) DIBALH, THF, 0 °C.

In conclusion, we describe herein access to an intermediate for the efficient preparation of (±)-heliannuols A, K, and L. The extension of this pathway to enantioselective synthesis of these allelopathic agents is under current investigation.

Acknowledgment

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(8) **8-Methoxy-2,2,6,9-tetramethyl-2*H*-1-benzoxocin-3 (4*H*)-one (6).**
Mp: 66 °C.^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.88 (s, 1 H), 6.64 (s, 1 H), 5.75 (t, *J* = 7.5 Hz, 1 H), 3.83 (s, 3 H), 2.98 (d, *J* = 7.5 Hz, 2 H), 2.21 (s, 3 H), 2.06 (s, 3 H), 1.47 (s, 6 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 208.65, 154.52, 145.04, 137.10, 132.82, 127.48, 126.38, 119.31, 108.46, 81.63, 55.50, 40.95, 24.59, 23.77, 16.13. IR (neat): 2984, 2938, 1713, 1504, 1464, 1395, 1205, 1152, 1022 cm^{-1}. MS (EI): *m/z* (%) = 260 (72.4)[M$^+$], 217 (15.2), 191 (35.5), 190 (49.1), 189 (100), 176 (34.3), 175 (43.8), 159 (8.6), 115 (8.3). HRMS: found 260.1414; $C_{16}H_{20}O_3$ requires 260.1412.

(9) We noted several omissions in the reported data of this compound.[3]
8-Methoxy-2,2,6,9-tetramethyl-5,6-dihydro-2*H*-1-benzoxocin-3 (4*H*)-one (7).
Mp: 71 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.74 (s, 1 H), 6.58 (s, 1 H), 3.80 (s, 3 H), 3.20–3.02 (m, 1 H), 2.61–2.39 (m, 2 H), 2.15 (s, 3 H), 2.07–1.90 (m, 1 H), 1.79–1.61 (m, 1 H), 1.49 (s, 3 H), 1.45 (s, 3 H), 1.34 (d, *J* = 7.1 Hz, 3 H). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 212.98, 154.86, 145.96, 136.90, 127.46, 124.37, 108.71, 85.91, 55.45, 36.03, 34.65, 34.46, 24.36, 23.45, 20.43, 15.78. IR (neat): 3038, 2939, 2854, 1713, 1504, 1464, 1397, 1380, 1203, 1144, 1019 cm^{-1}. MS (EI): *m/z* (%) = 262 (21.9) [M$^+$], 178 (19.3), 165 (100), 163 (4.4), 91 (4.3). HRMS: found 262.1557; $C_{16}H_{22}O_3$ requires 262.1568.

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(11) We noted omissions in the reported data of this compound.[3]
8-Methoxy-2,2,6,9-tetramethyl-3,4,5,6-tetrahydro-2*H*-1-benzoxocin-3-ol (8).
^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.76 (s, 1 H, *cis*), 6.72 (s, 1 H, *trans*), 6.62 (s, 1 H, *cis*), 6.58 (s, 1 H, *trans*), 3.81 (s, 6 H), 3.43 (d, *J* = 9.1 Hz, 2 H), 3.30–3.11 (m, 2 H), 2.16 (s, 6 H), 2.15–1.94 (m, 8 H), 1.62 (br s, 2 H), 1.44 (s, 6 H), 1.38 (s, 6 H), 1.29 (d, *J* = 7.1 Hz, 6 H). MS (EI, *trans* isomer): *m/z* (%) = 264 (26.4) [M$^+$], 246 (8.7), 178 (16.0), 166 (21.6), 165 (100). MS (EI, *cis* isomer): *m/z* (%) = 264 (17.2) [M$^+$], 246 (5.8), 178 (13.1), 166 (17.6), 165 (100). HRMS (*trans* isomer): found 264.1735; $C_{16}H_{24}O_3$ requires 264.1725. HRMS (*cis* isomer): found 264.1716; $C_{16}H_{24}O_3$ requires 264.1725.

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(13) **8-Methoxy-4,4,7,9b-tetramethyl-1a,9b-dihydro-2*H*-oxireno[*e*][1]benzoxocin-3 (4*H*)-one (9).**
Mp: 89 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.86 (s, 1 H), 6.79 (s, 1 H), 3.85 (s, 3 H), 3.24 (dd, *J* = 9.6, 4.0 Hz, 1 H), 2.89 (dd, *J* = 12.4, 4.0 Hz, 1 H), 2.19 (s, 3 H), 2.18–2.11 (m, 1 H), 1.58 (s, 3 H), 1.56 (s, 3 H), 1.37 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 207.96, 155.26, 144.27, 131.50, 126.82, 126.53, 109.82, 87.09, 61.25, 59.14, 55.60, 42.50, 25.64, 24.17, 23.62, 16.21. IR (neat): 2984, 2936, 1714, 1505, 1464, 1398, 1378, 1205, 1148, 1020 cm^{-1}. MS (EI): *m/z* (%) = 276 (94.5) [M$^+$], 247 (25.0), 219 (77.1), 205 (78.0), 192 (28.7), 189 (100), 178 (15.9), 177 (16.7), 176 (28.0), 175 (50.3), 165 (87.6), 164 (39.9), 163 (39.9), 162 (41.9), 149 (32.4), 91 (26.6), 69 (22.9). HRMS: found 276.1352; $C_{16}H_{22}O_3$ requires 276.1361.

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