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Functionality Transfer from C_8 to C_9 in Sesquiterpenes. Synthesis of the named Herbolide E from Artemisin.

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Abstract: The key intermediate **6** was obtained in five steps from artemisin (**1**). The spectroscopic characteristics of the synthetic product **7a** reveal that the proposed structure for the natural herbolide E must be revised.

Sesquiterpene lactones constitute a group of natural compounds widely distributed in the vegetal kingdom, which exhibit a broad spectrum of biological activities. In the last years a number of 9-oxyfunctionalized sesquiterpene lactones have been isolated from natural sources.[1] However efficient methodology to functionalize C-9 has not yet been reported.

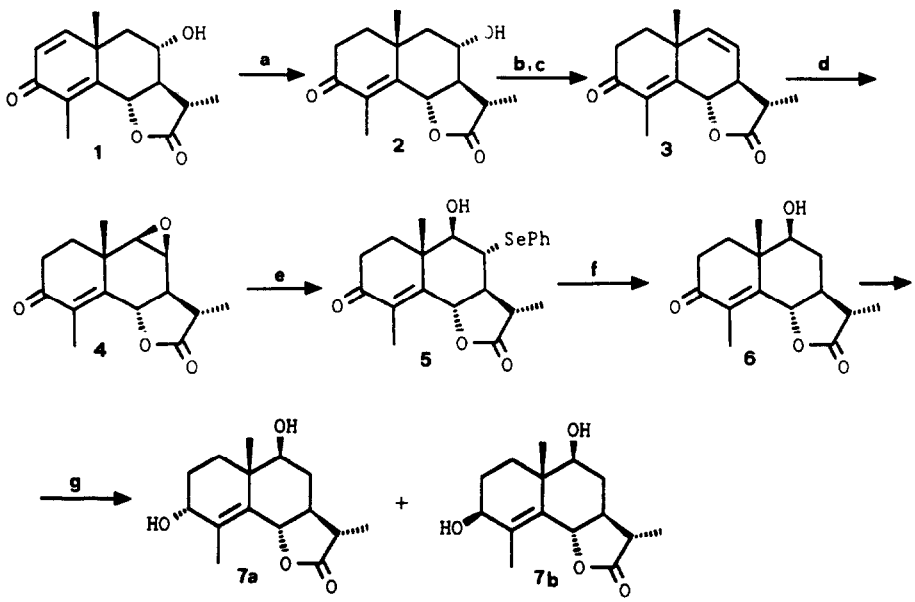
In continuation of our research programme on synthesis of natural sesquiterpene lactones[2] we report in this *Letter* a functionality transfer from C_8 to C_9 in an eudesmane framework obtaining the 9-hydroxy-6,12-eudesmanolide **6** starting from artemisin (**1**). As a first example of the synthetic utility of this functionality transfer we also report in this *Letter*, the transformation of **6** into the named herbolide E (**7a**).

In our approach to the desired 9-oxyfunctionalization we regard the 8,9-epoxide **4** as the key product. So, the starting material **1** was converted, by catalytic hydrogenation over Wilkinson catalyst,[3] into 1,2-dihydroartemisin (**2**), which was dehydrated to alkene **3**. Several attempts of dehydration of hydroxyl at C_8 through the chloride, mesylate and sulfoxide were unsuccessful. However, conversion of **2** into its triflate (triflic anhydride, pyridine/CH_2Cl_2)[4] followed by elimination with Li_2CO_3/ N,N-dimethylacetamide[5] afforded **3** (yield 52%).[6]

Inicial experiments of epoxidation of this alkene with *m*-chloroperbenzoic acid,[7] hexafluoroacetone-H_2O_2[8] or sodium perborate-acetic anhydride[9] were unsuccessful as they gave rise to the recovery of unreacted starting product only. However, treatment of this alkene **3** with dimethyldioxirane[10] provides the epoxide **4**[11] in excellent chemo- and stereoselectivity and yield (99%).

In order to open the oxirane ring, compound **4** was treated with different reagents [PhSH/HNa, PhSH/Ti(*i*-PrO)$_4$].[12] Successful result was obtained with PhSeNa/Ti(*i*-PrO)$_4$/DMF[13] yielding **5** (85%).[14] Once the oxygen function was transferred from C_8 to C_9, the elimination of the phenylselenyl group was carried out by treatment with Raney Ni[15] giving the compound **6** (80%).[16]

This product **6**, with a hydroxyl group at C9, constitute a key intermediate in the synthesis of 9-oxyfunctionalizated sesquiterpenoids with diverse functionalization at the A ring.[17] In this communication we report its $NaBH_4$ reduction, which afforded the epimeric alcohols **7a**[18] and **7b**[19] (1:3 ratio) in good yield (84%).



Reagents and conditions: a) H_2, benzene, Wilkinson Cat., overnight; b) Triflic anhydride (1.5 mmol), pyridine (1.5 mmol), CH_2Cl_2, -15°C, 30 min. c) Li_2CO_3 (8 mmol), N,N-dimethylacetamide, 60°C, 30 min. d) Dimethyl dioxirane (1.2 mmol), acetone, CH_2Cl_2, 0°C, 9 h. e) Ph_2Se_2 (2.5 mmol)-$NaBH_4$ (2.7 mmol), AcOH (1 mmol), Ti(*i*-PrO)4 (1 mmol), DMF, r.t., 25 h. f) Deactivated Raney Ni, MeOH, r.t. 15 min. g) $NaBH_4$ (16 mmol), MeOH, 0°C, 5 min.

The ^1H spectrum of the 3α-alcohol **7a** showed a broad singlet at δ 3.90 for H_3 in equatorial position, a double doublet at δ 3.47, J 11.5 and 4.6 Hz for H_9, indicating the β-equatorial disposition of the hydroxyl group at this carbon and a double doublet at δ 4.51, J 11.0 and 1.2 Hz for the lactonic proton (H_6). These signals, as all the remaining signals of the ^1H NMR spectrum, were assigned by spin decoupling. As in the starting artemisin the C_{11}-methyl group is α. This point was verified from the coupling $J_{7,11}$ observed in the signal of H_{11} which appeared as a double quartet at δ 2.29 ($J_{7,11}$ = 11.5 and $J_{11,13}$ = 6.5 Hz), as well as by the chemical shift (δ 12.4) of the C_{13} in the ^{13}C NMR spectrum.

These data are consistent with the structure **7a**, which has been proposed for herbolide E,[20] a metabolite isolated from *Artemisia herba alba* growing in Israel, and which structure was elucidated by spectroscopic methods in 1984. However the ^1H and ^{13}C NMR spectra described for this natural product do not coincide with those of the synthetic product, especially in the δ values of H_6, H_7 and H_9 which

appear at δ 4.51, 1.70 and 3.47 in the synthetic product and at δ 4.82, 2.27 and 3.82 in the natural product, and in the ^{13}C NMR values for C_{13} at δ 12.4 in the synthetic product and δ 9.9 in the natural product. The downfield shift of H_6 and H_7 signals as well as the δ value for C_{13} in the natural product are in good agreement with a β-methyl group at C_{11} [21,22] and consequently we think that the structure of the natural herbolide E might be the C_{11}-epimer of compound **7a**.

Further synthetic studies on other herbolides are in progress.

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6. Compound (**3**): m.p. 116-117°C (hexane-CH_2Cl_2); $[\alpha]_D$ +41.5 ($CHCl_3$); IR(KBr) 3050, 1780, 1660 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.33 (3H, d, J 6.7 Hz, H_{13}), 1.37 (3H, s, H_{14}), 1.80 (1H, ddd, J 3.0, 5.8, 13.0 Hz, $H_{1\beta}$), 1.98 (3H, d, J 1.3 Hz, H_{15}), 2.42 (1H, dq, J 6.7, 12.5 Hz, H_{11}), 2.67 (1H, dddd, J 1.3, 2.9, 12.4, 10.9 Hz, H_7), 4,73 (1H, dd, J 1.2, 10.9 Hz, H_6), 5.46 (1H, dd, J 2.9, 9.5 Hz, H_8), 5.74 (1H, dd, J 1.3, 9.5 Hz, H_9).
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11. Compound (**4**): m.p. 185-197°C, dec. (Hexane-EtOAc); $[\alpha]_D$ +41.3 ($CHCl_3$); IR(KBr) 3020, 1780, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.38 (3H, d, J 6.7 Hz, H_{13}), 1.44 (3H, s, H_{14}), 1.93 (3H, d, J 1.3 Hz, H_{15}), 2.10 (1H, dt, J 6.0, 13.0 Hz, $H_{1\alpha}$),2.32 (1H, dd, J 11.0, 12.7 Hz, H_7), 2.81(1H, qd, J 6.7, 12.7 Hz, H_{11}), 2.93 (1H, d, J 3.8 Hz, H_9), 3.54 (1H, d, J 3.8 Hz, H_8), 4.86 (1H, dd, J 1.0, 11.0 Hz, H_6).
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14. Compound (**5**): m.p. 167-168°C (Hexane-EtOAc); $[\alpha]_D$ +72.9 ($CHCl_3$); IR(KBr) 3560-3300, 1780, 1670, 1620, 920, 735, 690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.33 (3H, s, H_{14}), 1.61 (3H, d, J 6.8 Hz, H_{13}), 1.94 (3H, d, J 1.0 Hz, H_{15}), 2.03 (1H, t, J 11.0 Hz, H_7), 2.25 (1H, dt, J 4.3, 13.5 Hz, $H_{1\beta}$), 2.57 (1H, qd, J 6.8, 11.0 Hz, H_{11}), 3.15 (1H, d, J 11.0 Hz, H_9), 3.22 (1H, t, J 11.0 Hz, H_8), 4.67 (1H, dd, J 1.0, 11.0 Hz, H_6), 7.4-7.2 (3H, m, Ar), 7.58 (2H, dd, J 2.0, 7.5 Hz, Ar).

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16. Compound (**6**): m.p.167-169°C (Hexane-EtOAc); [α]D +64.1 ($CHCl_3$); IR(KBr) 3560-3200, 1775, 1660, 1620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (3H, d, J 7.3 Hz, H_{13}), 1.30 (3H, s, H_{14}), 1.72 (1H, q, J 11.5 Hz, $H_{8\beta}$), 1.87 (1H, dt, J 3.4, 11.5 Hz, H_7), 2.01 (3H, d, J 1.2 Hz, H_{15}), 2.15 (1H, td, J 4.8, 13.2 Hz, $H_{1\beta}$), 2.22 (1H, ddd, J 3.4, 4.6, 11.5 Hz, $H_{8\alpha}$), 2.39 (1H, qd, J 7.2, 11.5 Hz, H_{11}), 3.60 (1H, dd, J 4.6, 11.5 Hz, H_9), 4.67 (1H, dd, J 1.2, 11.0 Hz, H_6).

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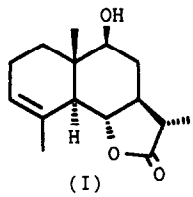

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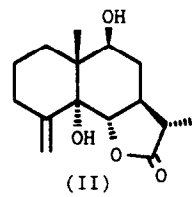

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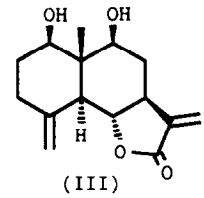

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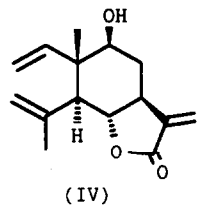

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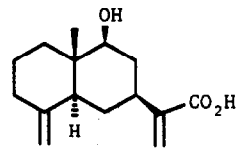

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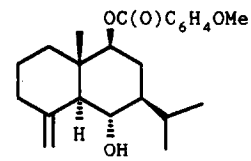

(VI)

18. Compound (**7a**): an oil, [α]D +44.0 ($CHCl_3$); IR(NaCl) 3540-3200, 1780, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.08 (3H, s, H_{14}), 1.22 (3H, d, J 6.9 Hz, H_{13}), 1.58 (1H, q, J 11.5 Hz, $H_{8\beta}$),1.6-1.9 (5H, m, 2 H_1, 2 H_2, H_7), 2.00 (3H, d, J 1.2 Hz, H_{15}), 2.11 (1H, ddd, J 2.5, 4.6, 11.5 Hz, $H_{8\alpha}$), 2.29 (1H, qd, J 6.9, 11.5 Hz, H_{11}), 3.47 (1H, dd, J 4.6, 11.5 Hz, H_9), 3.90 (1H, brs, H_3), 4.51 (1H, dd, J 1.2, 11.0 Hz, H_6).^{13}C RMN (50,3 Mz, $CDCl_3$) δ 178.3 (C_{12}), 132.2 (C_4 or C_5), 129.4 (C_5 or C_4), 81.7 (C_6), 78.6 (C_3), 70.3 (C_9), 48.8 (C_7), 42.3 (C_{10}), 40.8 (C_{11}), 32.4 (C_1 or C_8), 31.2 (C_8 or C_1), 27.1 (C_2), 17.9 (overlapped signals, C_{14} and C_{15}), 12.4 (C_{13}).

19. Compound (**7b**): m.p.177-179°C (Hexane-CH_2Cl_2); [α]D -31.1 ($CHCl_3$); IR(KBr) 3540-3120, 1760, 1640 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.10 (3H, s, H_{14}), 1.22 (3H, d, J 6.9 Hz, H_{13}), 1.93 (3H, d, J 1.2 Hz, H_{15}), 2.11 (ddd, J 2.4, 4.8, 11.5 Hz, $H_{8\alpha}$), 2.27 (1H, qd, J 6.9, 11.7 Hz, H_{11}), 3.45 (1H, dd, J 4.8, 10.7 Hz, H_9), 3.90 (1H, brt, J 5.1, H_3), 4.54 (1H, dd, J 1.2, 10.5 Hz, H_6).

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