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TRANSFORMATION OF ARTEMISIN INTO ARTAPSHIN AND 8α-HYDROXY-11β,13-DIHYDROBALCHANIN#

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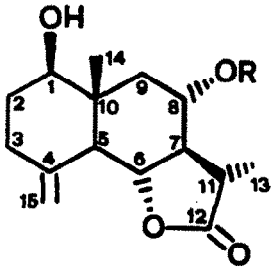
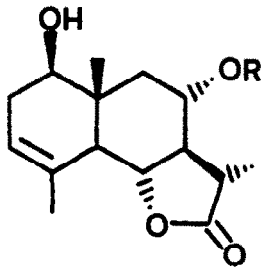
Abstract: Partial syntheses of the sesquiterpene lactones artapshin (1) and 8α-hydroxy-11β,13-dihydrobalchanin (2) from artemisin (3) are described.

The eudesmanolide 8α-hydroxy-11β,13-dihydroreynosin (1) was first isolated from Lasiolaena santosii[1] and more recently, with the name artapshin, from Artemisia fragans[2]. However, the spectroscopic data reported in both papers do not allow a comparison of the two products. The eudesmanolide (2) is the dihydro-derivative of 8α-hydroxybalchanin isolated for the first time from Leucanthemella serotina[3]. In this paper we report the syntheses of eudesmanolides (1) and (2) from artemisin (3). As the total synthesis of artemisin[4] has been accomplished, the syntheses of (1) and (2) reported in this paper are formal total syntheses of these compounds. The known cytotoxic[5] properties of related compounds make this research very interesting[6].





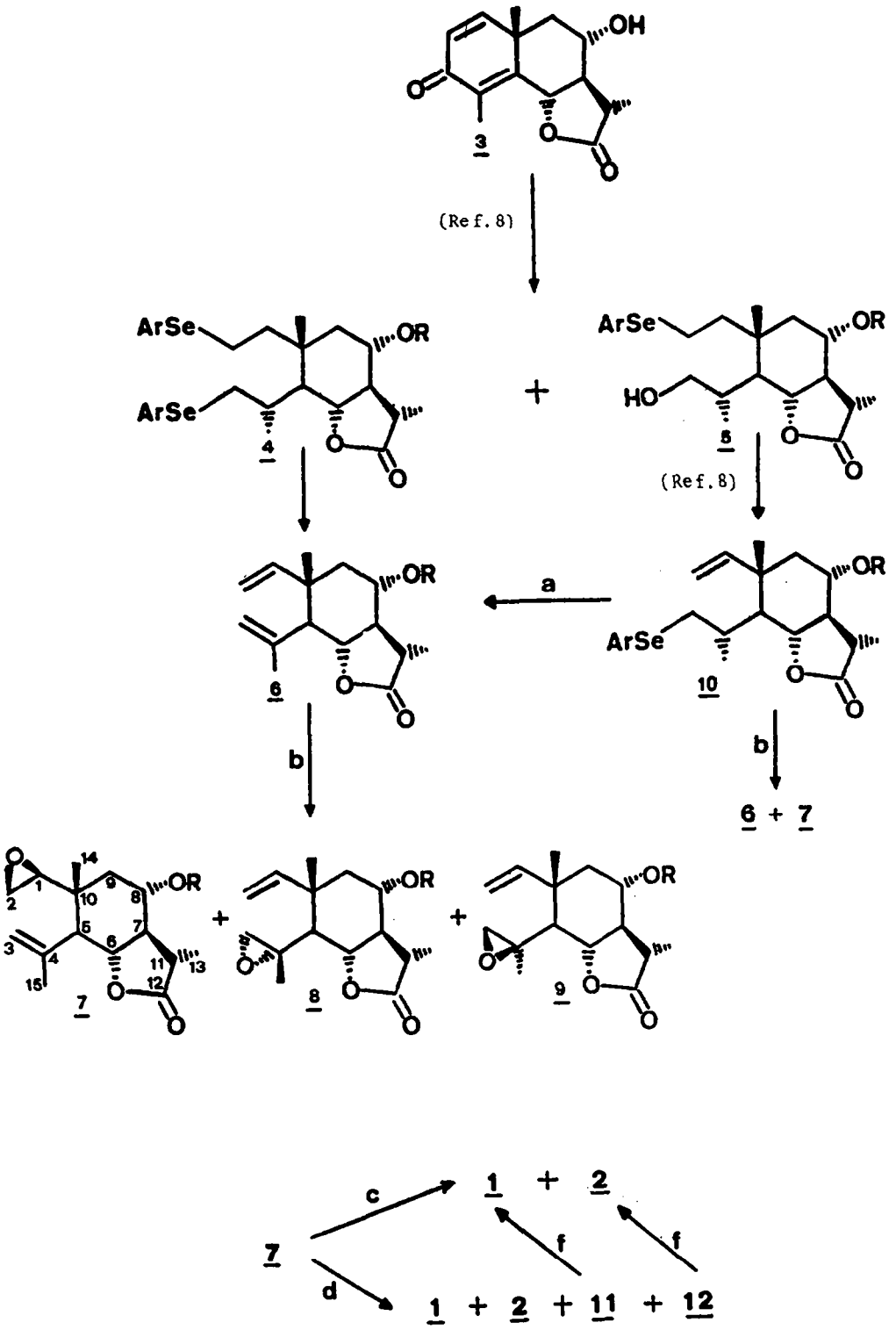
1 R = H
10 R = $SiMe_2Bu^t$

2 R = H
12 R = $SiMe_2Bu^t$

The key product to attain the desired synthesis is the 1,2-epoxide (7) which by acid treatment[7], ought to give the eudesmanolides (1) and (2). The preparation of this epoxide was carried out in two different ways.

In a first way, artemisin (3) was transformed into tert-butyldimethylsilyl ether of temisin (6) through diselenide (4), as is described by us[8]. By direct

#This article is dedicated to the memory of the late Prof. Dr. E. Seoane



Reagents: a, 50% H_2O_2; b, m-CPBA; c, $BF_3.Et_2O$ (1 eq); $BF_3.Et_2O$ (0.25 eq); f, n-Bu_4NF; R = $SiMe_2Bu^t$; Ar = o-$NO_2C_6H_4$-

epoxidation[7] of product (6) with m-chloroperbenzoic acid, a mixture of three epoxides, which were separated by column chromatography, was obtained and 50% of the starting product was recovered. The first eluted epoxide (14%) was identified as the 1,2-epoxide (7), as is shown in the ^{1}H NMR by the double doublet at δ 2.88 (J= 2.9 and 3.8 Hz) for H-1 and the multiplet at δ 2.75-2.55 for H-2. The other eluted epoxides were (8)[9] (5%, ^{1}H NMR : a multiplet at δ 2.54-2.43 for H-3) and (9)[9] (25%, ^{1}H NMR : two doublets at δ 2.75 and 2.52, J = 4.5 Hz for H-3).

In a second way artemisin (3) was transformed into 4-selenide (10) through 3-selenide (5)[10]. Oxidation of (10) with 50% hydrogen peroxide in THF followed by spontaneous elimination of arylselenenic acid, afforded the compound (6)[8]. However, when m-chloroperbenzoic acid is used, instead of hydrogen peroxide, the oxidation of selenide to selenoxide[11] and the epoxidation of the 1,2-double bond are produced simultaneously. As a result, a mixture of divinyl compound (6) (40%) and 1,2-epoxide (7) (55%) was obtained after the elimination of selenoxide at room temperature. It is interesting to note that in the second way the ratio 1,2-epoxide/divinyl compound is more favourable and besides the 3,4-epoxides were not obtained.

When the epoxide (7) was treated with 1 eq. of $BF_3.OEt_2$, it underwent a simultaneous rearrangement to eudesmane and cleavage of the silyl ether giving a mixture of two compounds which were separated by preparative TLC. The less polar compound (48%) was (2), as is shown in the ^{1}H NMR by two broad singlets at δ 5.34 and 1.82 for H-3 and H-15 respectively. The more polar compound (32%) was identified as (1). In its ^{1}H NMR spectrum a pair of broad singlets (δ 4.99 and 4.83) were atributed to the hydrogens of the exocyclic methylene group attached to C-4. The lactonic proton (H-6) appeared as three lines (J= 10.7 Hz) at δ 4.05, the proton at C-8 as a doublet of three lines (J= 4.5 and 10.0 Hz) at δ 3.96 and the proton at C-1 as a double doublet (J= 4.5 and 11.0 Hz) at δ 3.53. These signals, as all the remaining signals of the ^{1}H NMR spectrum, were assigned by spin decoupling. The α-orientation of the11-methyl group was verified from the coupling $J_{7,11}$ observed in the signal of H-11 which appeared as a double quartet at δ 2.57 ($J_{7,11}$ = 12.5 Hz and $J_{11,13}$ = 7.0 Hz).

The ^{1}H NMR spectrum data are consistent with the structure (1) which has been proposed for a natural product isolated from Lasiolaena santosii[1]. However, the ^{1}H NMR spectrum described for this natural product does not coincide with that of the synthetic product, especially in the signals of the protons H-6 and H-8, which appeared crossed (in Cl_3CD, δ 4.05 and 3.96 for the synthetic product and δ 3.99 and 4.01 for the natural product[1] and in C_6D_6 δ 3.38 and 3.13 for the synthetic product and δ 3.36 and 3.43 for the natural product[1]). The same sructure (1) was proposed posteriorly for artapshin, a natural product isolated from Artemisia fragans[2], based on the ^{1}H NMR spectrum of its diacetate (the ^{1}H NMR spectrum of the natural product is not given). For this reason the preparation of the diacetate of the synthetic product was carried out with Ac_2O/4-dimethylaminopyridine in CH_2Cl_2. The ^{1}H NMR spectrum of this diacetate was identical to the one described for the diacetate of the natural product from Artemisia fragans[2], and the expected downfield shift of the protons H-1 {δ 4.73 (dd, J= 5.0 and 11.6 Hz)} and H-8 { δ 5.04 (ddd, J= 4.5 and ~ 11.0 Hz)} was observed in it. The downfield shift for H-8 is consistent with the structure (1) with a C-6 lactone unit, while the natural product of Lasiolaena santosii[1] could be a C-8 lactonized product.

Finally, treatment of the epoxide (7) with 0.25 eq. of $BF_3.OEt_2$ leads to a mixture of (1), (2) and their corresponding silyl ethers (11) and (12). Cleavage of the silyl ether with n-Bu_4NF afforded (1) and (2) respectively, which were identical with the products obtained by simultaneous rearrangement and cleavage with $BF_3.OEt_2$ (1 eq.).

EXPERIMENTAL

Mps were determined in capillary tubes with a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 281 spectrometer. ^{1}H NMR spectra were determined with a Bruker AC-200 (200.13 MHz) spectrometer in $CDCl_3$ solution. Mass spectra were performed at 70 eV on a Varian MAT-311A spectrometer.

1,2β-Epoxy-8α-t- butyldimethylsilyloxy-5,7α H,6,11βH-elem-3-en-6,12-olide (7) from (6). To a suspension of (6) (107 mg, 0.29 mmol) and anhydrous NaOAc (ca. 85 mg) in $CHCl_3$ (6.9 mL), m-choroperbenzoic acid (66 mg, 0.33 mmol peracid) was added and the resulting mixture stirred at room temperature for 65 hours. The reaction mixture was extracted with 5% aq. Na_2CO_3 solution, washed with brine, dried (Na_2SO_4) and concentrated in vacuo . The reaction product was chromatographed on silica gel, from which mixtures of increasing polarity of hexane-ether eluted four products. The first one was unreacted product (6) (54 mg, 50%). The second product was (7) (16 mg, 14%) : m.p. 170-172 °C (hexane-ether); High res. MS : 323.1669 ((M^+-C_4H_9), $C_{17}H_{27}O_4Si$ requires 323.1678) and further peaks at 295, 293, 265, 231, 225, 195, 145 and 75; IR ν_{max} (KBr) 3080, 3060, 1775, 1640, 1080 and 1070 cm^{-1}; ^{1}H NMR δ 5.10 (br. s, H-3), 4.84 (br. s, H-3'), 4.07 (dd, J ~ 11.0 Hz, H-6), 3.87 (ddd, J = 4.5 and ~ 10.5 Hz, H-8), 2.88 (dd, J = 2.9 and 3.8 Hz, H-1), 2.75-2.55 (m, H-2), 2.47 (dq, J = 12.0 and 6.8 Hz, H-11), 2.46 (d, J = 11.0 Hz, H-5), 1.83 (br. s, H-15), 1.75 (ddd, J ~ 11.0 Hz, H-7), 1.66 (dd, J = 4.5 and 13.0 Hz, H-9β), 1.47 (dd, J = 10.5 and 13.0 Hz, H-9α), 1.34 (d, J = 6.8 Hz, H-13), 0.89 (s, H-14 and $SiCMe_3$) and 0.09 (s, $SiMe_2$).

The two other eluted products were the 3,4 α-epoxide (8) (6 mg, 5%) and the 3,4 β-epoxide (9) (52 mg, 25%). Compound (8) : m.p. 173-176 °C (hexane-ether); high res. MS: 323.1671 ((M^+ - C_4H_9), $C_{17}H_{27}O_4Si$ requires 323.1678) and further peaks at 305, 295, 265, 185, 157 and 75 ; IR ν_{max} (KBr) : 3080, 3060, 1775, 1640, 1075, 995, 870, 840 and 780 cm^{-1} ; ^{1}H NMR δ 5.98 (dd, J = 17.0 and 11.0 Hz, H-1), 5.03 (d, J= 11.0 Hz, H-2), 5.02 (d, J = 17.0 Hz, H-2'), 4.03 (dd, J ~ 11.5 Hz, H-6), 3.87 (ddd, J = 10.0 and ~ 7.0 Hz, H-8), 2.54-2.43 (m, H-3 and H-11), 1.75 (ddd, J ~ 11.0 Hz, H-7), 1.55 (d, J = 7.0 Hz, 2 H-9), 1.44 (d, J = 11.5 Hz, H-5), 1.37 (s, H-15), 1.35 (d, J = 7.0 Hz, H-13), 1.31 (s, H-14), 0.89 (s, $SiCMe_3$), 0.09 and 0.08 (two s, $SiMe_2$). Compound (9) : m.p. 167-168 °C (hexane-ether); high res. MS: 323.1668 ((M^+-C_4H_9), $C_{17}H_{27}O_4Si$ requires 323.1678) and further peaks at 305, 295, 265, 185, 157 and 75; IR ν_{max} (KBr): 3080, 3060, 1780, 1640, 1075, 995, 870 and 780 cm^{-1}; ^{1}H NMR δ 5.80 (dd, J = 17.0 and 10.5 Hz, H-1), 5.07 (d, J = 10.5 Hz, H-2), 5.06 (d, J = 17.0 Hz, H-2'), 4.05 (dd, J ~ 11.2Hz, H-6), 3.64 (ddd, J = 10.0, 7.5 and 7.0 Hz, H-8), 2.75 (d, J = 4.5 Hz, H-3), 2.52 (d, J = 4.5 Hz, H-3'), 2.46 (dq, J = 12.0 and 7.0 Hz, H-11), 1.78 (ddd, J ~ 11.0 Hz, H-7), 1.57 (d, J = 11.5 Hz, H-5), 1.55 (d, J ~ 7.0 Hz, 2 H-9), 1.37 (s, H-15), 1.35 (d, J = 7.0 Hz, H-13), 1.21 (s, H-14), 0.89 (s, $SiCMe_3$), 0.08 and 0.07 (two s, $SiMe_2$).

1,2β-Epoxy-8α-t-butyldimethylsilyloxy-5,7α H,6,11β H-elem-3-en-6,12-olide (7) from (10). Compound (10) (25 mg, 0.043 mmol) was dissolved in CH_2Cl_2 (0.3 mL), cooled to 0°C and treated with 85% m-chloroperbenzoic acid (37 mg, 0.18 mmol). The reaction mixture was stirred for 5 days at 0 °C, diluted with CH_2Cl_2 and washed several times with brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo and chromatographed on silica gel. Elution with ethyl acetate gave 6 mg of divinyl compound (6) (40%) and 9 mg of 1,2β-epoxide (7) (55%).

1β,8α-Dihydroxy-5,7α H,6,11β H-eudesm-4(15)-en-6,12-olide (1) and 1β,8α-dihydroxy-5,7α H,6,11β H-eudesm-3-en-6,12-olide (2) from (7). To a solution of compound (7) (12 mg, 0.03 mmol) in benzene (0.4 mL), BF_3.OEt_2 (8μL, 0.03 mmol) was added. The mixture was stirred at room temperature for 30 min, after which it was worked up in the usual way. By preparative TLC (ether, 2 elution) were separated 2.6 mg of (1) (32%) and 3.8 mg of (2) (48%).

Compound (1) : an oil, high res. MS: 266.1509 ((M^+), $C_{15}H_{22}O_4$ requires 266.1512) , and further peaks at 248, 230, 220, 205, 204, 202, 191, 160, 133 and 107; IR ν_{max} (NaCl): 3500-3250, 1750, 1635, 1440, 1370, 1115, 1060, 1030, 970 and 950 cm^{-1} ; ^{1}H NMR δ 4.99 (br. s, H-15), 4.83 (br. s, H-15'), 4.05 (dd, J ~ 10.7 Hz, H-6), 3.96 (ddd, J = 4.5 and ~ 10.0 Hz, H-8), 3.53 (dd, J = 4.5 and 11.0 Hz, H-1), 2.57 (dq, J = 12.5 and 7.0 Hz, H-11), 2.32 (dd, J = 4.5 and 13.0 Hz, H-9β), 2.40-2.00 (m, 2 H-3), 2.07 (d, J = 10.7 Hz, H-5), 1.90-1.40 (m, 2 H-2 and H-7),

1.39 (d, J = 7.0 Hz, H-13), 1.30-1.10 (m, H-9α) and 0.83 (s, H-14).

Compound (2) : an oil ; high res.MS: 266.1511 [(M^+), $C_{15}H_{22}O_4$ requires 266.1512], and further peaks at 249, 225, 209, 191, 161, 135 and 107 ; IR ν_{max} (NaCl): 3500-3200, 1750, 1640, 1440, 1370, 1220, 1170, 1120, 1060, 1030, 970 and 960 cm^{-1} ; ^1H NMR δ 5.34 (br. s, H-3), 4.03 (ddd, J = 4.5 and ~ 10.0 Hz, H-8), 3.97 (dd, J ~ 11.0 Hz, H-6), 3.68 (dd, J = 6.7 and 9.5 Hz, H-1), 2.53 (dq, J = 12.5 and 6.8 Hz, H-11), 2.31 (d, J = 12.0 Hz, H-5), 2.40- 2.15 (m , H-2β), 2.16 (dd, J = 4.5 and 13.0 Hz, H-9β), 2.00-1.80 (m, H-2α), 1.82 (br. s, H-15), 1.73 (ddd, J ~ 11.0 Hz, H-7), 1.39 (d, J = 6.8 Hz, H-13) and 0.86 (s, H-14).

8α-t-Butyldimethylsilyloxy-1β-hydroxy-5,7α H,6,11β H-eudesm-4(15)-en-6,12-olide (11), 8α-t-butyldimethylsilyloxy-1β-hydroxy-5,7α H,6,11β H-eudesm-3-en-6,12-olide (12) and compounds (1) and (2) from (7). The compound (7) (12 mg, 0.03 mmol) dissolved in benzene (0.4 mL) was treated with $BF_3.OEt_2$ (2 μL, 0.0075 mmol) as above, giving a mixture of (11), (12), (1) and (2) which were separated by preparative TLC.

Compound (11) : an oil; high res. MS: 323.1668 [(M^+ - C_4H_9), $C_{17}H_{27}O_4Si$ requires 323.1678] and further peaks at 305, 277, 231, 203, 145, 107 and 75; IR ν_{max} (NaCl) : 3450-3100, 1770, 1640, 1450, 1250, 1145, 1120, 1075, 995, 970, 830 and 770 cm^{-1} ; ^1H NMR δ 4.98 (br. s, H-15), 4.83 (br. s, H-15'), 3.99 (dd, J ~ 11.5 Hz, H-6), 3.89 (ddd, J = 4.5 and ~ 10.0 Hz, H-8), 3.51 (dd, J = 4.5 and 11.5 Hz, H-1), 2.46 (dq, J = 12.0 and 7.0 Hz, H-11), 2.32 (ddd, J = 2.0, 5.5 and 14.0 Hz, H-3β), 2.20 (dd, J = 4.5 and 13.0 Hz, H-9β), 2.05 (d, J = 11.5 Hz, H-5), 1.95-1.70 (m, H-7 and H-2β), 1.65-1.40 (m, H-2α and H-9α), 1.35 (d, J = 7.0 Hz, H-13), 0.90 (s, $SiCMe_3$), 0.83 (s, H-14) and 0.10 (s, $SiMe_2$).

Compound (12) : m.p. 150-152 °C (hexane-ether) : high res. MS: 323.1670 [(M^+-C_4H_9), $C_{17}H_{27}O_4Si$ requires 323.1678] and further peaks at 305, 277, 231, 203, 145, 107 and 75 ; IR ν_{max} (KBr) : 3520-3400, 1740, 1630, 1450, 1395, 1250, 1135, 1115, 1070, 970, 955, 860, 830 and 765 cm^{-1} ; ^1H NMR δ 5.32 (br. s, H-3), 3.95 (dd, J ~ 11.0 Hz, H-6), 3.95 (ddd, J = 4.0 and ~ 11.0 Hz, H-8), 3.66 (dd, J = 7.0 and 9.5 Hz, H-1), 2.50-2.25 (m, H-2 β and H-11), 2.16 (dd, J = 4.0 and 13.0 Hz, H-9 β), 2.35-2.05 (d, overlapped with H-9β, H-5), 2.10-1.80 (m, H-2α), 1.81 (br. s, H-15), 1.73 (ddd, J ~ 11.0 Hz, H-7), 1.35 (d, J = 7.0 Hz, H-13), 0.90 (s, $SiCMe_3$), 0.88 (s, H-14) and 0.10 (s, $SiMe_2$).

1β,5α-Dihydroxy-5,7α H,6,11β H-eudesm-4(15)-en-6,12-olide (1) from (11). Compound (11) (6.5 mg, 0.017 mmol) in THF (0.11 mL) was treated with n-Bu_4NF (0.67 mmol, 21 mg n-$Bu_4NF.3H_2O$ dried overnight in vacuo over P_2O_5), stirring the mixture at room temperature for 1 h. The cleavage product was worked up in the usualway giving (1) (4.2 mg, 94%).

1β,8α-Dihydroxy-5,7α H,6,11β H-eudesm-3-en-6,12-olide (2) from (12). Compound (12) (10 mg, 0.026 mmol) in THF (0.17 mL) was treated with n-Bu_4NF (1.02 mmol, 32 mg n-$Bu_4NF.3H_2O$ dried in vacuo over P_2O_5) as above providing (2) (6.5 mg, 95%).

Acknowledgments

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