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A SHORT SYNTHESIS OF (+)-COLARTIN AND (+)-ARBUSCULIN A FROM (−)-SANTONIN

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ABSTRACT.—Colartin [**8**] and arbusculin A [**9**] have been synthesized from α-santonin [**1**] in 18.2% (8 steps) and 12.9% (10 steps) overall yields, respectively.

Sesquiterpene lactones make up a group of natural compounds, widely present in plants (1), which exhibit a broad spectrum of biological activities (2). Colartin [**8**] and its 11,13-dehydroderivative, arbusculin A [**9**], are two members of the eudesmane class of sesquiterpene lactones, which show significant cell growth inhibitory activity against murine lymphocytic leukemia and plant growth regulating activity (3).

Two syntheses of both natural products **8** and **9** starting from α-santonin [**1**] have been reported (3,4); however, these syntheses are rather lengthy. Therefore, we have developed a shorter synthetic pathway for **8** and **9** from **1**, involving the epoxide **3** as a key intermediate.

RESULTS AND DISCUSSION

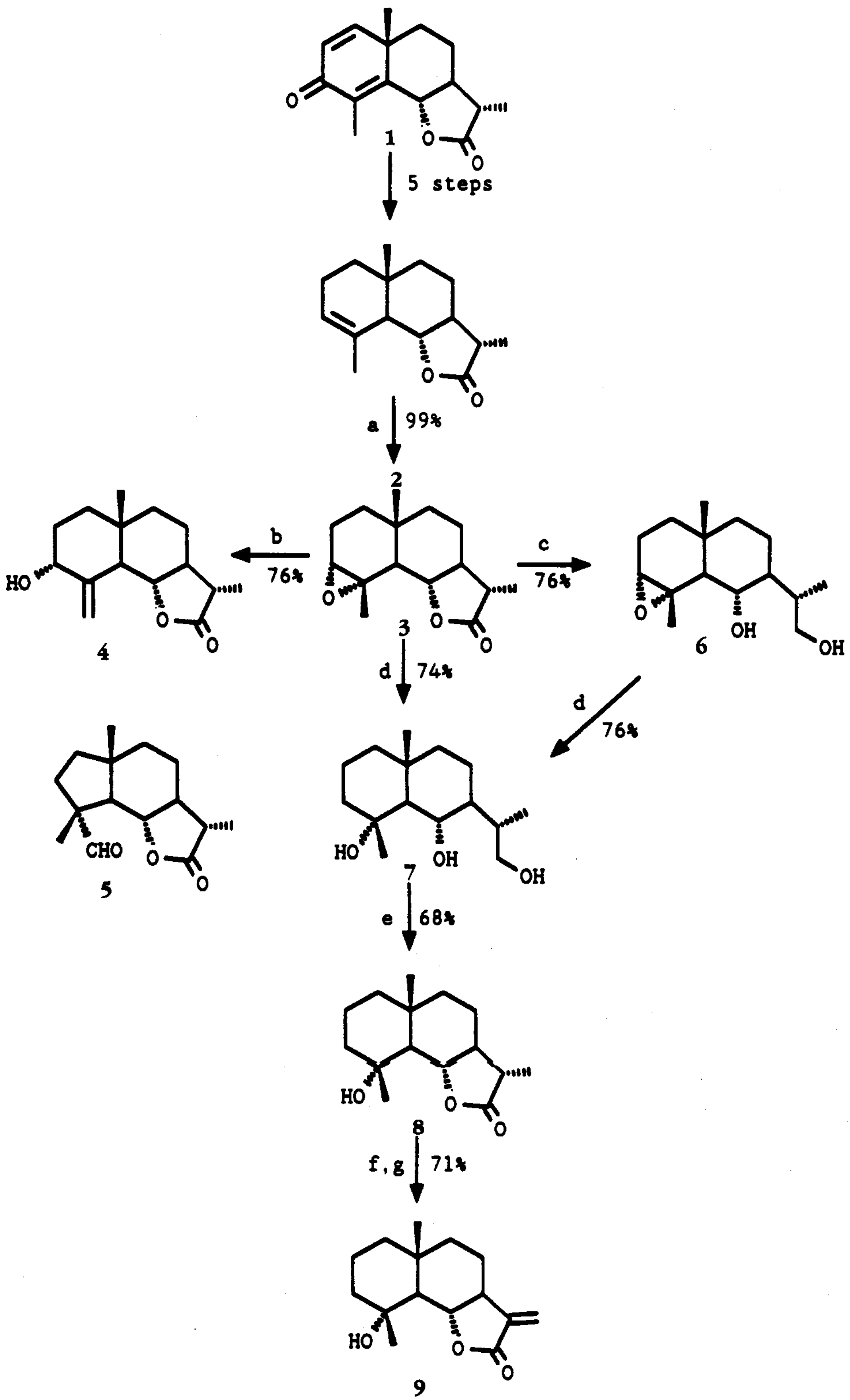
The starting material **1** was converted into alkene **2** in a five-step sequence described earlier (5). In a preliminary approach we attempted a direct Markownikoff hydration of the 3,4 double bond (6). However, all experimental results were unsuccessful, and we then proceeded to introduce the desired functionality at C-4 by indirect hydration through the 3,4-epoxide **3** by opening of the oxirane ring with a selenide anion followed by deselenization with Raney nickel (7). This epoxide **3** was prepared by reaction of alkene **2** with *m*-CPBA or with in situ generated dimethyldioxirane (8) in 90% and 99% yield, respectively. However, experiments to open the oxirane ring with PhSeNa/Ti(iPrO)$_4$/DMF (9) and other similar reagents (10) were unsuccessful, as they gave primarily unreacted starting material along with a poor yield of allylic alcohol **4**.

Other attempts to open the oxirane ring with a variety of reagents, to give a 4-hydroxyfunctionalized product, were also unsuccessful. Thus, for example, with I_2/Ph_3P (11) or CCl_4/Ph_3P (12), the allylic alcohol **4** was obtained in 76% yield, while with PhSH/$LiClO_4$/MeCN (13) or ZnI_2/Et_2O (14) mixtures with variable ratios of starting material **3**, allylic alcohol **4**, and rearranged aldehyde **5** were obtained. The 11,13-dehydroderivative of **5** has recently been described as a natural product (15).

Attempts were also made to open the oxirane ring by selective reduction with $NaBH_4$/*t*-BuOH/MeOH (16) or DIBALH/toluene (17). In both cases the reactivity of the lactone was higher than that of the epoxy group, so that with the former reagent the epoxy-diol **6** was obtained in 76% yield. This product afforded the triol **7** (76% yield) upon reduction with $LiAlH_4$. In a last approach we carried out the simultaneous reduction of both functional groups with $LiAlH_4$/THF to give triol **7** (74%) (18), which was reoxidized with CrO_3-H_2SO_4/Me_2CO (19) to give colartin [**8**] in 71% yield. Phenylselenylation of **8** by Grieco's method (20) followed by oxidative elimination then gave arbusculin A [**9**] in 71% yield (Scheme 1).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All melting points are uncorrected. Tlc was carried out on Merck 0.25 mm Si gel HF 254 analytical aluminum plates. Cc separations were performed on Merck Si gel



SCHEME 1. (a) Dimethyldioxirane; (b) I_2/Ph_3P, CH_2Cl_2; (c) $NaBH_4$, *t*-BuOH/MeOH; (d) $LiAlH_4$, THF; (e) CrO_3-H_2SO_4, Me_2CO; (f) LDA, PhSeCl, THF; (g) H_2O_2, THF.

60 (230–400 mesh). Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Ir spectra were recorded on a Perkin-Elmer 281 spectrometer. Nmr spectra were run on a Bruker AC-200 instrument (200.1 MHz for ^{1}H nmr and 50.3 MHz for ^{13}C nmr), using $CDCl_3$ solutions. Mass spectra (eims) were recorded at 70 eV on a Hewlett-Packard 5988A spectrometer.

5αH,7αH,6βH,11βH-Eudesm-3-en-6,12-olide [**2**].—The starting material **2** was prepared from α-santonin (Sigma) by the reported method (5).

3α,4α-Epoxy-5αH,7αH,6βH,11βH-eudesman-6,12-olide [**3**].—(a) With *m*-CPBA. To a suspension of 5αH,7αH,6βH,11βH-eudesm-3-en-6,12-olide [**2**] (190 mg, 0.812 mmol) and NaOAc (420 mg, 5.1 mmol) in $CHCl_3$ (18 ml), 85% *m*-CPBA (335 mg, 1.95 mmol) was added at room temperature. The resulting mixture was stirred for 3.5 h, diluted with EtOAc, washed with saturated aqueous Na_2CO_3 and brine, and dried over Na_2SO_4. After filtration and solvent removal, cc eluting with EtOAc-hexane (3:7) gave **3** (184 mg, 90%): mp 130–131° (EtOAc/hexane); $[\alpha]^{24}$D +71 (c=0.79); ir (KBr) 1770 cm^{-1}; ^{1}H nmr δ 0.91 (3H, s, H-14), 1.21 (3H, d, J=6.8, H-13), 1.45 (3H, broad s, H-15), 1.79 (1H, d, J=11.6, H-5), 1.93 (1H, dddd, J=2.8, 7.6, 12.0, 16.0, H-2β), 2.06 (1H, dd, J=6.0, 16.0, H-2α), 2.28 (1H, qd, J=6.8, 11.1, H-11), 2.94 (1H, d, J=2.8, H-3), 3.85 (1H, dd, J=9.6, 11.6, H-6); eims *m/z* (rel. int.) [M]$^+$ 250 (6), 235 (50), 207 (6), 43 (100); ^{13}C nmr see Table 1.

(b) With Oxone. To a solution of **2** (52 mg, 0.216 mmol) in CH_2Cl_2 (3 ml) were added Me_2CO (3 ml), H_2O (3 ml), 18-Crown-6 (5 mg), and $NaHCO_3$ (300 mg, 3.57 mmol). The mixture was vigorously stirred, and 1 ml of 0.29 M Oxone (0.58 mmol of $KHSO_5$) in H_2O was added dropwise at 0°. Stirring was continued for 1 h, after which time saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, and then dried. After evaporation of the solvent under reduced pressure, the residue was chromatographed to give **3** (55.2 mg, 99%) with the above-described features.

3α-Hydroxy-5αH,7αH,6βH,11βH-eudesm-4(15)-en-6,12-olide [**4**].—To a solution of iodine (23 mg, 0.088 mmol) in anhydrous CH_2Cl_2 (2.6 ml), triphenylphosphine (24 mg, 0.088 mmol) was added in one portion. The brown solution turned immediately to a pale yellow. Epoxylactone **3** (20.0 mg, 0.08 mmol) was then added. After 15 min the reaction mixture was poured into aqueous $NaHCO_3$ and worked up in the usual way. Chromatography of the crude material eluting with EtOAc-hexane (4:6) afforded compound **4** (15.3 mg, 76%): mp 161–162° (hexane/CH_2Cl_2); $[\alpha]^{20}$D +99 (c=1.6); ir (KBr) 3520, 1760, 1010, 900 cm^{-1}; ^{1}H nmr δ 0.82 (3H, s, H-14), 1.20 (3H, d, J=6.7, H-13), 2.31 (1H, qd, J=6.7, 12.0, H-11), 2.68 (1H, broad d, J=10.5, H-5), 3.94 (1H, t, J=10.5, H-6), 4.28 (1H, t, J=1.9, H-3), 4.88 (1H, d, J=1.2, H-15), 5.09 (1H, s, H-15); eims *m/z* (rel. int.) [M]$^+$ 250 (51), 235 (46), 217 (2), 177 (28), 55 (100); ^{13}C nmr see Table 1.

3α-Hydroxy-5αH,7αH,6βH,11βH-eudesm-4(15)-en-6,12-olide [**4**] *and aldehyde* **5**.—To a solution of epoxylactone **3** (40 mg, 0.16 mmol) in Et_2O (2 ml), ZnI_2 (77 mg, 0.24 mmol) was added at room temperature, and the mixture was stirred for 1 h. The reaction was then diluted in EtOAc, washed with aqueous $NaHCO_3$, Na_2SO_3, and brine, and dried over Na_2SO_4. After filtration and solvent removal, chromatography of the residue eluting with EtOAc-hexane (7:3) gave aldehyde **5** (13.8 mg, 35%), epoxylactone **3** (11 mg, 27%), and compound **4** (12.5, 31%). Compound **5**: mp 126–128° (CH_2Cl_2/hexane); $[\alpha]^{20}$D +34 (c=2.5); ir (KBr) 2680, 1765, 1725 cm^{-1}; ^{1}H nmr δ 1.05 (3H, s, H-14), 1.19 (3H, d, J=7.1, H-15), 1.32 (3H, s, H-15), 1.92 (1H, d, J=11.5, H-5), 2.31 (1H, qd, J=7.1, 12.2, H-11), 3.93 (1H, dd, J=9.4, 11.5, H-6), 9.46 (1H, s, H-3); eims *m/z* (rel. int.) [M]$^+$ 250 (0.2), 221 (9), 207 (43), 175 (9), 149 (71), 55 (99), 45 (100); ^{13}C nmr see Table 1.

3α,4α-Epoxy-5αH,7αH,11βH-eudesman-6α,12-diol [**6**].—MeOH (0.4 ml) was added over a period of 30 min to the refluxing mixture of $NaBH_4$ (82 mg, 2.2 mmol) and epoxylactone **3** (98 mg, 0.392 mmol) in *t*-BuOH (2.4 ml) under argon. The reaction mixture was refluxed for 15 min, quenched with NH_4Cl, and extracted with EtOAc. Usual workup and chromatography of the residue eluting with EtOAc gave epoxydiol **6** (75 mg, 76%): mp 99–100° (Et_2O/hexane); $[\alpha]^{20}$D +26 (c=4.1); ir (KBr) 3500–3020, 1020 cm^{-1}; ^{1}H nmr δ 0.77 (3H, s, H-14), 0.84 (3H, d, J=6.8, H-13), 1.32 (1H, d, J=10.8, H-5), 1.52 (3H, s, H-15), 1.88 (1H, dddd, J=2.4, 3.0, 8.4, 16.0, H-2β), 2.00 (1H, td, J=4.0, 16.0, H-2α), 2.23 (1H, m, H-11); 2.90 (1H, d, J=2.6, H-3), 3.3–3.6 (3H, m, H-6 and H-12); eims *m/z* (rel. int.) [M]$^+$ 254 (0.13), 239 (3), 237 (1.4), 221 (14), 193 (8), 43 (100); ^{13}C nmr see Table 1.

5αH,7αH,11βH-Eudesman-4α,6α,12-triol [**7**] *from epoxydiol* **6**.—A solution of epoxydiol **6** (30 mg, 0.118 mmol) in THF (2 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (43 mg, 1.1 mmol) in THF (1 ml) under argon at room temperature. The resulting mixture was heated at 45° for 20 h. After this time, the mixture was cooled and the reaction quenched by slowly adding 2 ml of a mixture of THF-iPrOH-H_2O (4:1:1). The resulting suspension was diluted with EtOAc and dried (Na_2SO_4). Usual workup and chromatography with EtOAc yielded triol **7** (23.5 mg, 76%): colorless oil; $[\alpha]^{20}$D −29 (c=1.2); ir (NaCl)

TABLE 1. ^{13}C-nmr Data for Compounds **3**–**9** (δ, 50.3 MHz, $CDCl_3$).

Carbon	Compound						
	3	**4**	**5**	**6**[a]	**7**	**8**	**9**
C-1	34.6	39.5	39.4[b]	35.6	43.2[b]	43.1[b]	42.8[b]
C-2	23.0[b]	28.9[b]	33.2[b]	20.9	21.0[c]	23.5[c]	21.9[c]
C-3	60.1	72.7	203.7	61.1	41.3[b]	40.9[b]	40.9[b]
C-4	57.5	146.3	52.1	59.5	74.5	71.5	71.6
C-5	53.6[c]	48.2	55.0[c]	56.2	57.9	57.2	57.8
C-6	80.9	79.3	79.5	69.3	71.2	81.3	81.5
C-7	52.6[c]	52.6	54.2[c]	46.8	47.4	53.4	50.7
C-8	21.1[b]	23.1[b]	23.5	19.3	19.6[c]	19.3[c]	19.3[c]
C-9	38.8	35.7	40.6[b]	38.8	43.5[b]	40.0[b]	40.0[b]
C-10	34.8	38.4	46.5	33.8	35.9[e]	37.4	37.6
C-11	40.8	41.1	40.9	34.6	35.9[e]	40.6	138.4
C-12	179.3	179.5	179.2	66.1	66.7	178.6	169.8
C-13	12.4	12.4	12.8	11.7	12.8	12.4	117.7
C-14	17.8	17.3	18.6[d]	16.8	19.7	19.7	19.7
C-15	21.8	111.6	20.5[d]	21.9	23.3	24.1	24.2

[a]Assignment by heteronuclear ^{1}H-^{13}C correlation.
[b–d]The signals with these superscripts may be interchanged within the corresponding spectrum.
[e]Overlapped signals.

3550–3020, 1020 cm^{-1}; ^{1}H-nmr δ 0.84 (3H, s, H-14), 0.89 (3H, d, J=7.1, H-13), 1.31 (3H, s, H-15), 2.02 (1H, m, H-11), 3.4–3.6 (2H, m, H-12), 3.83 (1H, t, J=10.1, H-6); eims *m/z* (rel. int.) [M−Me]$^+$ 241 (1.5), 223 (18), 220 (18), 190 (46), 43 (100); ^{13}C nmr see Table 1.

5αH,7αH,11βH-Eudesman-4α,6α,12-triol [**7**] *from epoxylactone* **3**.—Epoxylactone **3** (46 mg, 0.18 mmol) was treated with $LiAlH_4$ (60 mg, 1.5 mmol) in THF (3 ml) as described above and yielded triol **7** (34.6 mg, 74%).

4α-Hydroxy-5αH,7αH,6βH,11βH-eudesman-6,12-olide or colartin [**8**].—A solution of CrO_3 (70 mg, 0.7 mmol) in aqueous 1.5 M H_2SO_4 (0.8 ml) was added dropwise to a solution of triol **7** (30 mg, 0.137 mmol) in Me_2CO at 0° for 4 min. The resulting mixture was stirred at room temperature for 2.5 h. After this time, usual workup and chromatography eluting with EtOAc-hexane (3:7) yielded colartin [**8**] (20.0 mg, 68%): mp 109–110° (Et_2O/hexane) [lit. (3) 109–110° (Et_2O/hexane)]; [α]^{20}D +12 (c=2.0) [lit. (3) +11.4 (c=0.97)]; ir (KBr) 3590, 1775 cm^{-1}; ^{1}H nmr δ 0.97 (3H, s, H-14), 1.21 (3H, d, J=6.9, H-13), 1.31 (3H, s, H-15), 1.70 (1H, d, J=11.4, H-5), 2.27 (1H, qd, J=6.9, 11.9, H-11), 3.04 (1H, s, OH), 4.03 (1H, dd, J=10.3, 11.4, H-6); eims *m/z* (rel. int.) [M]$^+$ 252 (2), 237 (60), 219 (10), 206 (20), 191 (31), 43 (100); ^{13}C nmr see Table 1.

4α-Hydroxy-5αH,7αH,6βH-eudesm-11(13)-en-6,12-olide or arbusculin A [**9**].—To a THF solution of LDA (0.54 mmol) [prepared from diisopropylamine (0.076 ml), 1.6 M butyllithium (0.33 ml), and THF (0.5 ml) at −80°] compound **8** (40 mg, 0.158 mmol) in THF (0.5 ml) was added dropwise over a period of 10 min. After the solution was stirred at −80° for 1 h, phenylselenyl chloride (113 mg, 0.591 mmol) in THF (1.5 ml) containing HMPA (91 μl) was added dropwise over a period of 10 min. The reaction mixture was stirred at −80° for 1 h and then warmed to −40°, where stirring was continued for an additional 40 min. The reaction was quenched by adding 0.5 M aqueous HCl and extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give a yellow oil, which, after chromatography eluting with EtOAc-hexane (2:8), afforded the corresponding phenylselenolactone (48.9 mg, 80%): mp 162–166° (Et_2O/hexane); ir (KBr) 3560, 1770 cm^{-1}; ^{1}H nmr δ 0.96 (3H, s, H-14), 1.24 (3H, s, H-13), 1.53 (3H, s, H-15), 1.66 (1H, d, J=11.5, H-5), 2.99 (1H, s, -OH), 4.37 (1H, dd, J=9.9, 11.5, H-6), 7.2–7.5 (3H, m, aromatic), 7.64 (2H, dd, J=1.3, 8.0, aromatic).

A solution of this phenylselenolactone (48 mg, 0.118 mmol) in THF (0.75 ml) containing HOAc (17 μl) was treated at 0° with 30% H_2O_2 (0.1 ml) for 1 h. The reaction mixture was diluted in EtOAc, washed with 10% aqueous $Na_2S_2O_3$ and saturated aqueous NaCl, and dried ($MgSO_4$). Usual workup and chromatography eluting with EtOAc-hexane (3:7) yielded arbusculin A [**9**] (26.3 mg, 89%): mp 75–77° (Et_2O/hexane) [lit. (3) 73° (Et_2O/hexane)]; [α]^{20}D +25 (c=1.0) [lit. (3) 25.8 (c=1.33)]; ir (KBr) 3580, 1760, 1660 cm^{-1}; ^{1}H nmr δ 0.95 (3H, s, H-14), 1.30 (3H, s, H-15), 1.80 (1H, d, *J*=11.0, H-5), 1.99 (1H, qd, *J*=3.1, 12.6, H-8α), 2.57 (1H, qt, *J*=3.1, 11.0, H-7), 3.00 (1H, s, -OH), 4.00 (1H, t, *J*=11.0, H-6), 5.40 (1H, d, *J*=3.1, H-13), 6.07 (1H, d, *J*=3.1, H-13′); eims (rel. int.) $[M-Me]^{+}$ 235 (19), 217 (36), 189 (31), 165 (40), 147 (70), 119 (100); ^{13}C nmr see Table 1.

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