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TOTAL SYNTHESES OF ROTHIN-A AND ROTHIN-B

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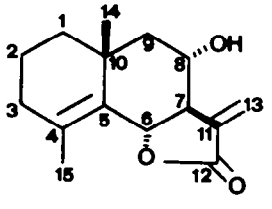
Abstract- The eudesmanolides rothin-A 1 and rothin-B 2 have been synthesized from (-)-artemisin in 7 and 9 steps, respectively.

The two eudesmanolides rothin-A 1 and rothin-B 2 were isolated 14 years ago[1] by Irwin and Geissman from *Artemisia rothrockii*. To the best of our knowledge, no other report of these two compounds has appeared in the literature. In prosecution of our current synthetic program[2,3,4] related to natural sesquiterpene lactones, we now report the successful transformation of (-)-artemisin 3 into the two above mentioned lactones, which amounts to a total synthesis of both products, since artemisin has already been arrived at by total synthesis[5]. The observed cytotoxic and antitumoral properties of α-methylene-γ-lactones[6] has stimulated much effort toward their synthesis, as evidenced by numerous reviews in this field[7,8].



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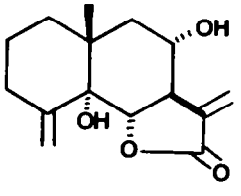

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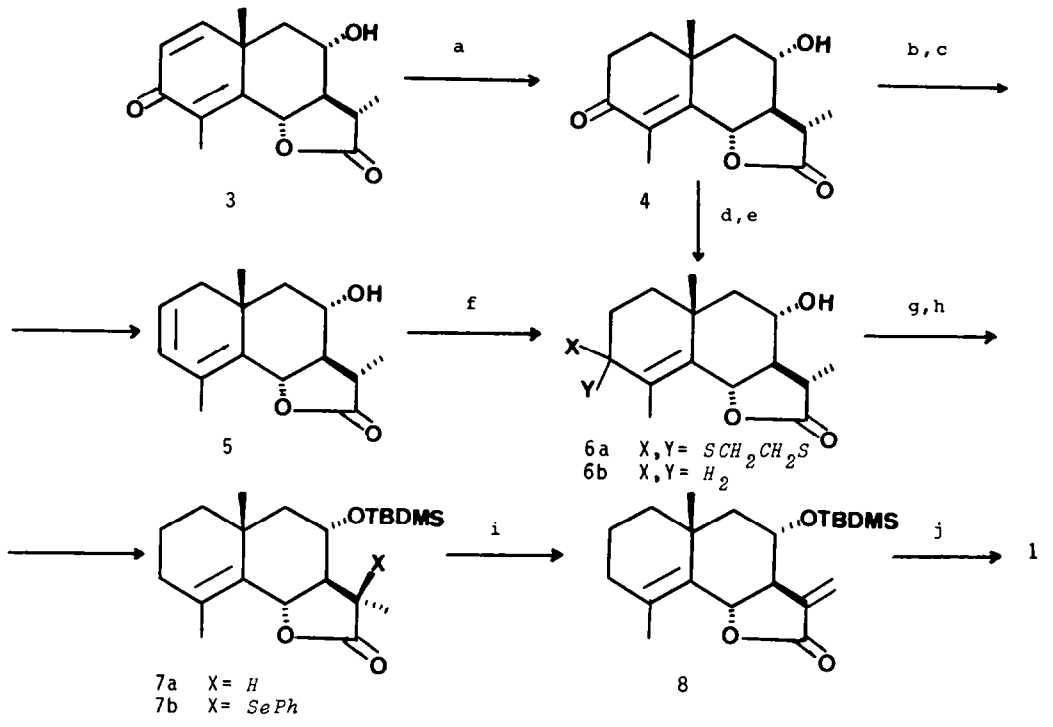
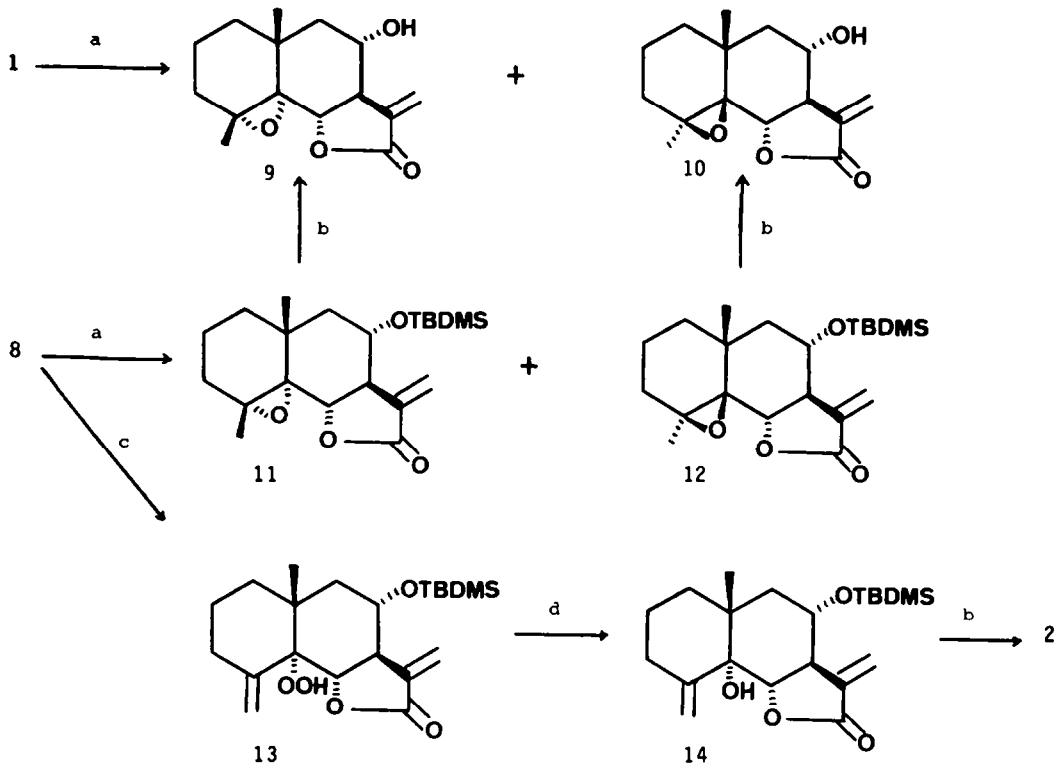
The first step of the synthesis (Scheme 1) is the selective reduction of the Δ^1 double bond of artemisin. This was achieved in almost quantitative yield, as already reported for α-santonin[9], by hydrogenation in the presence of Wilkinson catalyst. The obtained 1,2-dihydroartemisin 4 could be transformed into the desired 11,13-dihydrorothin-A 6b by Shapiro reaction[10], affording diene 5, and subsequent partial hydrogenation. Remarkably, 5 was inert to hydrogenation with Wilkinson catalyst and the more active Pd on charcoal had to be utilized instead. However, better overall yields were obtained by thioketalization of 4 followed by desulfurization with Raney nickel. For the purpose of transforming 6b into 1, the phenylselenylation-oxydation procedure[11] was selected. Since 6b could not be phenylselenylated in any of the reaction conditions tried (only recovery of



Scheme 1. a) H_2, Wilkinson cat.; b) $TsNHNH_2$; c) LDA, -78°; d) $(CH_2SH)_2$; e) W-2 Raney Ni; f) H_2, Pd/C; g) TBDMSiCl; h) LDA, PhSeCl; i) 30% H_2O_2; j) nBu_4NF.

unreacted compound was observed), we decided to protect the free hydroxyl group at C-8. The tetrahydropyranyl derivative of 6b proved suitable as it could be phenylselenylated and oxidized to 8-O-tetrahydropyranylrothin-A (8, THP instead of TBDMS), but the yields were only moderate[12] and the oily intermediates, being mixtures of diastereomers, did not give well-resolved NMR spectra. Much higher yields and crystalline products could be obtained using the t-butyldimethylsilyl (TBDMS) protective group. The compound 6b was silylated[13] and the protected lactone 7a was sequentially phenylselenylated[11] and oxidized to 8 in 60-65% overall yield from 6b. By desilylation, 8 gave rothin-A 1, mp 133-134°, identical in all physical properties (mp, α_D, IR, MS, ^1H NMR) with natural rothin-A[1].

For the synthesis of rothin-B 2 (Scheme 2) we first tried the acid-catalyzed ring opening of the 4,5α-epoxyde 9, easily obtained from 1 by reaction with m-chloroperbenzoic acid (m-CPBA), together with small amounts of the diastereomeric 4,5β-epoxide 10. Unfortunately, treatment of 9 with p-TsOH in acetic acid, as described by Geissman[1] for a closely related case, gave only traces of the desired 2. We also tried other ring opening methods such as reaction of 9 with TMSiOTf/DBU[14] or treatment with H_2SO_4-saturated CH_2Cl_2[15], without any success. Furthermore, the reaction of 11 with lithium diethylamide in refluxing ether[16] took place with complete decomposition of the starting product. Success was eventually met via a photochemical reaction: by bubbling O_2 through an irradiated ethanolic solution of 8[17], the hydroperoxyde 13 was obtained in ca. 60% yield. A good diagnostic of the stereochemistry of the hydroperoxyde group is the signal of H-7, a double doublet of triplets at δ 3.51.



Scheme 2. a) m-CPBA; b) nBu$_4$NF; c) hν/O$_2$; d) Ph$_3$P.

The marked downfield shift experienced by H-7 and also by other protons (H-3α, H-9α) in 1,3-transdiaxial relationship to the 5-OOH is evidently originated in the steric compression effect of this group. 13 was deoxygenated with triphenylphosphine[17] to 8-O-t-butyldimethylsilylrothin-B 14, which by desilylation afforded rothin-B 2, mp 256-258°, in 65% overall yield from 13. The obtained product had identical mp, α_D, and spectral properties (IR, MS, ^{1}H NMR) as natural rothin-B[1].

Acknowledgements- The authors are indebted to Prof.Dr. D.H.R. Barton for a generous gift of artemisin.

EXPERIMENTAL

Mps were determined in open capillary tubes and are not corrected. IR spectra were measured as KBr pellets on a Perkin-Elmer 281 spectrophotometer. UV spectra were registered in EtOH solution. ^{1}H NMR spectra were measured at 200.13 MHz (Bruker AC-200 model) in $CDCl_3$ solution, unless otherwise stated. Mass spectra were run by electron impact (70 eV) on a Varian MAT-311A spectrometer. Optical rotations were measured in $CHCl_3$ solution, unless otherwise stated, at a concentration of about 0.2 gr/100 mL.

3-Oxo-8α-hydroxy-6,11β,7αH-eudesm-4-en-6,12-olide (4). 100 mg (0.11 mMol) of freshly prepared Wilkinson catalyst were suspended in 5 mL of dry C_6H_6 and stirred under H_2 atmosphere until complete dissolution (30 min.). A solution of artemisin 3 (800 mg, 3.05 mMol) in 20 mL of dry C_6H_6/EtOH 1:2 was then added via syringe. After stirring for 12 h. at room temperature, the hydrogenation mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel. Elution with hexane-ethyl acetate 1:1 gave 780 mg (97%) of 1,2-dihydroartemisin 4 as colorless cubes, mp 204-205°(ethyl acetate), $[\alpha]_D^{25}$ +95°; high resolution MS: m/z 264.1361 (M^+) and further peaks at m/z 249, 246, 236, 231, 221, 218, 208 and 203.

$C_{15}H_{20}O_4$ requires M=264.1361, IR, ν_{max} (KBr): 3470 (OH), 1775 (γ-lactone), 1640, 1610 (α,β-unsat. ketone) cm^{-1}. UV, λ_{max} nm (ε_{max}): 242 (17000). ^1H NMR: δ 4.70 (*dq*, J=12, 1.6 Hz, H-6), 4.09 (*ddd*, J=11.1, 10, 4.4 Hz, H-8), 2.61 (*dq*, J=11.8, 6.9 Hz, H-11), 2.60-2.45 (*m*, 2H, overlapped by H-11, H-2α and 2β), 2.02 (*dd*, J=12.9, 4.4 Hz, H-9β), 2.01 (*d*, 3H, J=1.6 Hz, H-15), 1.99 (*td*, J=12, 10 Hz, H-7), 2.00-1.80 (*m*, 2H, overlapped by H-7 and H-15, H-1α and 1β), 1.53 (*dd*, J=12.9, 11.1 Hz, H-9α), 1.42 (*d*, 3H, J=6.9 Hz, H-13), 1.35 (*s*, 3H, H-14).

8α-Hydroxy-6,11β,7αH-eudesma-2,4-dien-6,12-olide (5). 250 mg (0.95 mMol) of 4 and 215 mg (1.16 mMol) of p-toluenesulfonylhydrazine were dissolved in 4 mL of dry C_6H_6/MeOH 3:1. A drop of $BF_3.OEt_2$ was added and the mixture was stirred 4 h. at room temperature. The reaction mixture was then diluted with CH_2Cl_2, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The foamy residue was dried overnight in an evacuated dessicator containing P_2O_5 and directly utilized, without further purification, in the next reaction.

3.6 mL (5.7 mMol) of a *n*BuLi solution (ca. 1.6M in hexane) were added at room temperature under Ar atmosphere via syringe to a solution of diisopropylamine (0.8 mL, 5.7 mMol) in dry THF (1 mL). After stirring for 15 min., the mixture was cooled to -78° (dry ice-acetone bath). The p-tosylhydrazone obtained in the previous step was dissolved in 9 mL of dry THF and added dropwise in 10 min. to the cooled reaction mixture. The reaction was stirred 6 h. at -78°, the temperature raised to 0° and the mixture further stirred for 1 h. at this temperature. After quenching with saturated aqueous NH_4Cl, extraction with ethyl acetate and usual work-up, an oily residue was obtained and chromatographed on silica gel. Hexane-ethyl acetate 6:4 eluted 66 mg (28%) of diene 5 as a white powder, mp 195° (dec.) (hexane-CH_2Cl_2), $[\alpha]_D^{25}$ +126.5°; high resolution MS: m/z 248.1423 (M^+) and further peaks at m/z 233, 230, 215, 204, 202, 187, 169, 159, 135 and 107. $C_{15}H_{20}O_3$ requires M=248.1412. IR, ν_{max} (KBr): 3475 (OH), 1753 (γ-lactone), 690, 655 (C=C-H def.) cm^{-1}. UV, λ_{max} (ε_{max}): 264 (9900). ^1H NMR: δ 5.80-5.65 (*m*, 2H, H-2 and H-3), 4.53 (*dq*, J=11.7, 2 Hz, H-6), 3.93 (*ddd*, J=10.9, 10.2, 4.4 Hz, H-8), 2.54 (*dq*, J=11.7, 7 Hz, H-11), 2.23 (br *d*, J=16.5 Hz, H-1α or 1β), 2.04 (*dd*, J=12.9, 4.4 Hz, H-9β), 1.98 (*d*, 3H, J=2 Hz, H-15), 1.87 (*td*, J=11.7, 10.2 Hz, H-7), 1.41 (*d*, J=7 Hz, 3H, H-13), 1.02 (*s*, 3H, H-14).

Further elution with hexane-ethyl acetate 4:6 led to the recovery of 123 mg (30%) of unreacted p-tosylhydrazone. The yield of diene 5 thus amounts to 40%, based on consumed p-tosylhydrazone, though it could not be improved by variation of the reaction conditions.

3,3-Ethanedithio-8α-hydroxy-6,11β,7αH-eudesm-4-en-6,12-olide (6a). A solution of 450 mg (1.7 mMol) of 4, 1.08 mL (12.84 mMol) of ethanedithiol and 0.09 mL of $BF_3.OEt_2$ in 5 mL of glacial acetic acid was stirred 5 h. at room temperature. The reaction mixture was then diluted with CH_2Cl_2 and washed several times with saturated aqueous $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and chromatographed on silica gel. Hexane-ethyl acetate 1:1 eluted 520 mg (90%) of the thioketal 6a as white needles, mp 197-198° (hexane-ethyl acetate), $[\alpha]_D^{25}$ +72°; high resolution MS: m/z 340.1156 (M^+) and further peaks at m/z 322, 312, 294, 284, 280, 262 and 252. $C_{17}H_{24}O_3S_2$ requires M=340.1167. IR, ν_{max} (KBr): 3480 (OH), 1750 (γ-lactone) cm^{-1}. ^1H NMR: δ 4.55 (*dq*, J=11.6, 1.3 Hz, H-6), 3.98 (*ddd*, J=11, 10, 4.5 Hz, H-8), 3.50-3.20 (*m*, 4H, thioketal group), 2.53 (*dq*, J=11.7, 6.9 Hz, H-11), 2.35-2.15 (*m*, 2H, H-2α and 2β), 2.10 (*d*, 3H, J=1.3 Hz, H-15), 1.90 (*dd*, J=12.7, 4.5 Hz, H-9β), 1.85 (*m*, 1H, overlapped by H-9β, H-7), 1.80-1.60 (*m*, 2H, H-1α and 1β), 1.39 (*d*, 3H, J=6.9 Hz, H-13), 1.37 (*dd*, J=12.7, 11 Hz, partly overlapped by H-13, H-9α), 1.18 (*s*, 3H, H-14).

8α-Hydroxy-6,11β,7α H-eudesm-4-en-6,12-olide (6b). A) By hydrogenation of diene 5: A solution of 100 mg (0.4 mMol) of 5 in 4 mL of ethyl acetate/methanol 2:1 was stirred 30 min. at room temperature under H_2 atmosphere (1 atm) in the presence of 15 mg of 5% Pd/C. The hydrogenation mixture was diluted with ethyl acetate (30 mL), filtered through a pad of silica gel, concentrated *in vacuo* and chromatographed on silica gel. Elution with hexane-ethyl acetate 7:3 gave 96 mg (95%) of 6b as white needles, mp 187-188°(hexane-ether), $[\alpha]_D^{25}$ +61°; high resolution MS: m/z 250.1583 (M^+) and further peaks at m/z 235, 232, 217, 207 and 189. $C_{15}H_{22}O_3$ requires M=250.1569. IR, ν_{max} (KBr): 3490 (OH), 1756 (γ-lactone) cm^{-1}. ^1H NMR: δ 4.55 (*dq*, J=11.6, 1.4 Hz, H-6), 3.97 (*ddd*, J=11, 10, 4.4 Hz, H-8), 2.52 (*dq*, J=11.7, 6.9 Hz, H-11), 1.85 (*dd*, J=12.8, 4.4 Hz, H-9β), 1.84 (*d*, 3H, J=1.4 Hz, partly overlaps H-9β, H-15), 1.76 (*td*, J=11.7, 10 Hz, H-7), 1.39 (*d*, 3H, J=6.9 Hz, H-13), 1.13 (*s*, 3H, H-14).

B) By desulfurization of 6a: 11.5 g W-2 Raney nickel were added at once to a solution of 6a (500 mg, 1.47 mMol) in 10 mL MeOH. The reaction mixture was stirred 3 h. at room temperature and then filtered through a short silica gel column (elution with ethyl acetate). Elimination of the solvent *in vacuo* gave 305 mg (83%) of a white solid, identical in all its properties with the product 6b obtained by hydrogenation of 5.

8α-t-Butyldimethylsilyloxy-6,11β,7αH-eudesm-4-en-6,12-olide (7a). A solution of 6b (200 mg, 0.8 mMol), t-butyldimethylsilylchloride (433 mg, 2.88 mMol) and imidazole (544 mg, 8 mMol) in 8 mL dry DMF was stirred for 6 h. at 40° with exclusion of moisture. The reaction mixture was diluted with ethyl acetate (30 mL)

and washed several times with water. The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and chromatographed on silica gel. Elution with hexane-ethyl acetate 8:2 gave 262 mg (90%) of **7a** as colorless needles, mp 129-130° (hexane-ethyl acetate); high resolution MS: m/z 364.2442 (M^+) and further peaks at m/z 349 and 307. $C_{21}H_{36}O_3Si$ requires M=364.2433. IR, ν_{max} (KBr): 1785 (γ-lactone), 863, 840, 774 (silyl group) cm^{-1}. ^1H NMR: δ 4.52 (*dq*, J=11.6, 1.4 Hz, H-6), 3.90 (*ddd*, J=10.8, 10, 4.4 Hz, H-8), 2.39 (*dq*, J=11.7, 6.9 Hz, H-11), 1.82 (br *s*, 3H, H-15), 1.73 (*dd*, J=13, 4.4 Hz, partly overlapped by H-15, H-9β), 1.33 (*d*, 3H, J=6.9 Hz, H-13), 1.10 (*s*, 3H, H-14), 0.88 (*s*, 9H, Me_3CSi), 0.08 (*s*, 6H, Me_2Si).

8α-t-Butyldimethylsilyloxy-11β-phenylseleno-6β,7αH-eudesm-4-en-6,12-olide (**7b**). 1 mL (1.6 mMol) of a *n*BuLi solution (ca. 1.6M in hexane) was added at room temperature under Ar atmosphere via syringe to a solution of diisopropylamine (0.24 mL, 1.68 mMol) in dry THF (4 mL). After stirring for 15 min., the mixture was cooled to -78° (dry ice-acetone bath). 278 mg (0.76 mMol) of **7a** were dissolved in 15 mL of dry THF and added dropwise (15 min.) to the cooled reaction mixture. After stirring for 1 h. at -78°, a solution of PhSeCl (321 mg, 1.68 mMol) and HMPT (0.2 mL) in 10 mL of dry THF was added dropwise via syringe. The reaction mixture was stirred for 45 min. at -78°, then further 45 min. at -40° and quenched at this temperature with 0.5N HCl (6 mL). After extraction with ethyl acetate, washing the organic layer several times with water and evaporation of the solvent *in vacuo*, a yellow oily residue was obtained and chromatographed on silica gel. Elution with hexane-ethyl acetate 19:1 gave unreacted PhSeCl and elution with hexane-ethyl acetate 9:1 gave 323 mg (82%) of **7b** as almost colorless needles, mp 143-144°(hexane). IR, ν_{max} (KBr): 1778 (γ-lactone), 3025, 739, 690 (aromatic ring), 855, 833, 774 (silyl group) cm^{-1}. ^1H NMR: δ 7.70-7.30 (*m*, 5H, aromatic protons), 4.86 (*dq*, J=13.5, 1 Hz, H-6), 4.26 (*ddd*, J=10.8, 10, 4.5 Hz, H-8), 2.10-1.90 (*m*, 1H, partly overlapping H-7, H-3α or H-3β), 1.99 (*dd*, J=13.5, 10 Hz, H-7), 1.82 (br *s*, 3H, H-15), 1.79 (*dd*, J=12.5, 4.5 Hz, partly overlapped by H-15, H-9β), 1.70-1.30 (*m*, 4H, partly overlapped by H-13, H-1α/β and H-2α/β), 1.64 (*s*, 3H, H-13), 1.34 (*dd*, J=12.5, 10.8 Hz, H-9α), 1.10 (*s*, 3H, H-14), 0.92 (*s*, 9H, Me_3CSi), 0.26, 0.15 (two *s*, Me_2Si).

8α-t-Butyldimethylsilyloxy-6β,7αH-eudesma-4,11(13)-dien-6,12-olide (**8**). 0.65 mL 30% H_2O_2 (5.8 mMol) were added at 0° to a solution of **7b** (301 mg, 0.58 mMol) and AcOH (0.1 mL) in 7 mL THF. After stirring for 15 min. at 0° and further 90 min. at room temperature, the reaction mixture was poured into 5% aqueous $NaHCO_3$ (20 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layer was washed several times with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and chromatographed on silica gel. Hexane-ethyl acetate 19:1 eluted 172 mg (82%) of silylated rothin-A **8** as white needles, mp 89-90° (hexane); high resolution MS: m/z 362.2280 (M^+) and further peaks at m/z 347, 319 and 305. $C_{21}H_{34}O_3Si$ requires M= 362.2277. IR, ν_{max} (KBr): 1777 (γ-lactone), 855, 835, 775 (silyl group) cm^{-1}. ^1H NMR: δ 6.19 (*dd*, J= 3.3, 1.2 Hz, H-13'), 5.93 (*dd*, J= 3, 1.2 Hz, H-13), 4.51 (*dq*, J= 11.7, 1 Hz, H-6), 4.08 (*ddd*, J= 10.3, 9.8, 4.4 Hz, H-8), 2.66 (*ddt*, J= 11.7, 9.8, 3.1 Hz, H-7), 1.84 (br *s*, 3H, H-15), 1.80 (*dd*, J= 13, 4.4 Hz, partly overlapped by H-15, H-9β), 1.36 (*dd*, J= 13, 10.8 Hz, H-9α), 1.10 (*s*, 3H, H-14), 0.89 (*s*, 9H, Me_3CSi), 0.11, 0.10 (two *s*, 6H, Me_2Si).

Rothin-A (**1**). 150 mg (0.41 mMol) of compound **8** were dissolved in dry THF (5 mL) and treated with 662 mg (2.1 mMol) of $nBu_4NF.3H_2O$ (previously dried in a dessicator *in vacuo* in the presence of P_2O_5). After stirring for 1 h. at room temperature, the reaction mixture was diluted with ethyl acetate (30 mL) and washed several times with brine. The organic layer was dried over anhydrous $MgSO_4$, concentrated *in vacuo* and chromatographed on silica gel. Elution with hexane-ethyl acetate 6:4 gave 88 mg (87%) of rothin-A **1** as white needles, mp 133-134°(hexane-ethyl acetate), $[\alpha]_D^{25}$ +119°, high resolution MS: m/z 248.1423 (M^+) and further peaks at m/z 233, 230, 215 and 187. $C_{15}H_{20}O_3$ requires M= 248.1412. IR, ν_{max} (KBr): 3520 (OH), 1750 (γ-lactone), 1664 (C=C) cm^{-1}. ^1H NMR: δ 6.23 (*dd*, J= 3.2, 1 Hz, H-13'), 6.05 (*dd*, J= 3, 1 Hz, H-13), 4.53 (*dq*, J= 11.7, 1.3 Hz, H-6), 4.10 (*ddd*, J= 10.9, 10, 4.5 Hz, H-8), 2.61 (*ddt*, J= 11.7, 10, 3.1 Hz, H-7), 1.92 (*dd*, J= 12.6, 4.5 Hz, H-9β), 1.87 (br *s*, 3H, H-15), 1.38 (*dd*, J= 12.6, 10.9 Hz, H-9α), 1.13 (*s*, 3H, H-14).

8α-Hydroxy-4,5α-epoxy-6β,7α H-eudesm-11(13)-en-6,12-olide (**9**). Rothin-A (50 mg, 0.2 mMol) was dissolved in $CHCl_3$ (5 mL), cooled to 0° and treated with 85% m-CPBA (61 mg, 0.30 mMol). The reaction mixture was stirred for 4 h. at 0°, diluted with CH_2Cl_2 (15 mL) and washed several times with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and chromatographed on silica gel. Elution with hexane-ethyl acetate 1:1 gave 41 mg (78%) of a white product, which was shown by NMR to be a 19:1 mixture of **9** and **10**. Repeated crystallizations from hexane-ether gave pure **9** as needles, mp 215-216°, $[\alpha]_D^{25}$ +136°; high resolution MS: m/z 264.1360 (M^+) and further peaks at m/z 249, 246, 231, 221, 203, 188 and 161. $C_{15}H_{20}O_4$ requires M= 264.1361. IR, ν_{max} (KBr): 3480 (OH), 1751 (γ-lactone) cm^{-1}. ^1H NMR: δ 6.20 (*dd*, J= 3.2,

0.8 Hz, H-13'), 6.06 (*dd*, J= 3.1, 0.8 Hz, H-13) 4.33 (*d*, J= 11.4 Hz, H-6), 4.17 (*ddd*, J= 10.9, 10.3, 4.6 Hz, H-8), 3.01 (*ddt*, J= 11.4, 10.3, 3.1 Hz, H-7), 1.85 (*dd*, J= 12.9, 4.6 Hz, H-9β), 1.56 (*s*, 3H, H-15), 1.16 (*s*, 3H, H-14).

8α-t-Butyldimethylsilyloxy-4,5α-epoxy-6β,7αH-eudesm-11(13)-en-6,12-olide (11), *8α-t-Butyldimethylsilyloxy-4,5β-epoxy-6β,7αH-eudesm-11(13)-en-6,12-olide* (12), and *8α-hidroxy-4,5β-epoxy-6β,7αH-eudesm-11(13)-en-6,12-olide* (10) from 8. 56 mg (0.154 mMol) of compound 8 were dissolved in 2 mL $CHCl_3$ and treated as above with 33 mg (0.162 mMol) 85% mCPBA. After stirring for 8 h. at 0°, the reaction mixture was worked-up as above and chromatographed on silica gel. Elution with hexane-ethyl acetate 19:1 gave first 11 (32 mg, 55%), mp 146-147°(hexane-ether); high resolution MS: m/z 378.2238 (M^+) and further peaks at m/z 321 and 303. $C_{21}H_{34}O_4Si$ requires M= 378.2226. IR, ν_{max} (KBr): 1773 (γ-lactone), 850, 830, 769 (silyl group) cm^{-1}. ^1H NMR: δ 6.15 (*dd*, J= 3.3, 1 Hz, H-13'), 5.92 (*dd*, J= 3.1, 1 Hz, H-13), 4.29 (*d*, J= 11.4 Hz, H-6), 4.16 (*ddd*, J= 10.6, 10, 4.7 Hz, H-8), 3.04 (*ddt*, J= 11.4, 10, 3.1 Hz, H-7), 1.70 (*dd*, J= 13.1, 4.7 Hz, H-9β), 1.53 (*s*, 3H, H-15), 1.13 (*s*, 3H, H-14), 0.90 (*s*, 9H, Me_3CSi), 0.12, 0.10 (two *s*, 6H, Me_2Si).

Further elution gave 12 (19 mg, 33%), mp 117-118° (hexane-ether); high resolution MS: m/z 378.2238 (M^+) and further peaks at m/z 321 and 303. $C_{21}H_{34}O_4Si$ requires M= 378.2226. IR, ν_{max} (KBr): 1780 (γ-lactone), 855, 835, 774 (silyl group) cm^{-1}. ^1H NMR: δ 6.20 (*dd*, J= 3.3, 1 Hz, H-13'), 5.96 (*dd*, J= 3, 1 Hz, H-13), 4.43 (*d*, J= 11.9 Hz, H-6), 4.15 (*td*, J= 9.8, 5.4 Hz, H-8), 2.80 (*ddt*, J= 11.9, 9.8, 3.1 Hz, H-7), 1.85-1.70 (*m*, 2H, H-9α and H-9β), 1.54 (*s*, 3H, H-15), 1.11 (*s*, 3H, H-14), 0.91 (*s*, 9H, Me_3CSi), 0.13, 0.12 (two *s*, 6H, Me_2Si).

By desilylation ($nBu_4NF.3H_2O$) in the same conditions as above, 11 and 12 gave, respectively, 9 and 10. Compound 10 crystallizes from hexane-ether as colorless needles, mp 159-160°; high resolution MS: m/z 264.1371 (M^+) and further peaks at m/z 249, 246, 221, 203, 188 and 161. $C_{15}H_{20}O_4$ requires M= 264.1361. IR, ν_{max} (KBr): 3447 (OH), 1771 (γ-lactone) cm^{-1}. ^1H NMR: δ 6.24 (*dd*, J= 3.2, 0.8 Hz, H-13'), 6.08 (*dd*, J= 3, 0.8 Hz, H-13), 4.45 (*d*, J= 11.9 Hz, H-6), 4.20 (*m*, H-8), 2.77 (*ddt*, J= 11.9, 10.1, 3.1 Hz, H-7), 1.83 (*d*, 2H, J= 7.5 Hz, H-9α and H-9β), 1.56 (*s*, 3H, H-15), 1.14 (*s*, 3H, H-14).

8α-t-Butyldimethylsilyloxy-5α-hydroperoxy-6β,7αH-eudesma-4(15),11(13)-dien-6,12-olide (13). Compound 8 (36 mg, 0.1 mMol) and Methylene Blue (2 mg) were dissolved in 50 mL absolute ethanol. The solution was then photooxygenated[17] for 18 h. with water cooling, in order to maintain a temperature of 20 ± 2°. A medium pressure Applied Photophysics mercury 400 W lamp was utilized and the radiation was filtered through a 2% aqueous $NaNO_2$ solution[18] (width of the filter solution: 1 cm). After the prescribed time, the solution was concentrated *in vacuo* and chromatographed on silica gel. Elution with hexane-ethyl acetate 8:2 gave first 4 mg unreacted 8 (11%) and then 21 mg 13 (53% yield, 60% based on recovered 8) as colorless needles, mp 178-179° (hexane-ether); high resolution MS: m/z 361.2191 (M^+-OOH) and further peaks at m/z 337, 321, 319 and 303. $C_{21}H_{33}O_3Si$ requires M= 361.2199. IR, ν_{max} (KBr): 3278 (OH), 1752 (γ-lactone), 858, 830, 770 (silyl group) cm^{-1}. ^1H NMR: δ 6.20 (*dd*, J= 3.2, 0.9 Hz, H-13'), 5.92 (*dd*, J= 3, 0.9 Hz, H-13), 5.25 (br *s*, H-15'), 5.16 (br *s*, H-15), 4.38 (*d*, J= 11.6 Hz, H-6), 4.17 (*ddd*, J= 10.7, 10, 4.8 Hz, H-8), 3.51 (*ddt*, J= 11.6, 10, 3.1 Hz, H-7), 2.65-2.50 (*m*, H-3α), 2.30-2.20 (*m*, H-3β), 2.10-1.90 (*m*, H-9α), 1.52 (*dd*, J= 13, 4.8 Hz, H-9β), 1.02 (*s*, 3H, H-14), 0.91 (*s*, 9H, Me_3CSi), 0.13, 0.10 (two *s*, 6H, Me_2Si).

8α-t-Butyldimethylsilyloxy-5α-hydroxy-6β,7αH-eudesma-4(15),11(13)-dien-6,12-olide (14). Compound 13 (15 mg, 0.038 mMol) and triphenylphosphine (10.5 mg, 0.040 mMol) were dissolved in 2 mL dry acetone and stirred for 30 min. at room temperature. The reaction mixture was concentrated *in vacuo* and chromatographed on silica gel. Elution with hexane-ethyl acetate 9:1 gave 14 (12.2 mg, 85%) as colorless needles, mp 213-214° (hexane-ethyl acetate); high resolution MS: m/z 378.2219 (M^+) and further peaks at m/z 363, 345, 321 and 303. $C_{21}H_{34}O_4Si$ requires M= 378.2226. IR, ν_{max} (KBr): 3424 (OH), 1766 (γ-lactone), 858, 833, 768 (silyl group) cm^{-1}. ^1H NMR: δ 6.13 (*dd*, J= 3.2, 1 Hz, H-13'), 5.84 (*dd*, J= 3.1, 1 Hz, H-13), 4.99 (br *s*, H-15'), 4.95 (br *s*, H-15), 4.26 (*d*, J= 11.4 Hz, H-6), 4.17 (*ddd*, J= 10.8, 10, 4.5 Hz, H-8), 3.45 (*ddt*, J= 11.4, 10, 3.1 Hz, H-7), 2.70-2.50 (*m*, H-3α), 2.20-1.90 (*m*, 2H, H-3β and H-9α), 1.50 (*dd*, J= 12.8, 4.5 Hz, H-9β), 0.95 (*s*, 3H, H-14), 0.90 (*s*, 9H, Me_3CSi), 0.12, 0.10 (two *s*, 6H, Me_2Si).

Rothin-B (2). Compound 14 (10 mg, 0.026 mMol) was dissolved in dry THF (1 mL) and treated as above with $nBu_4NF.3H_2O$ (41.5 mg, 0.13 mMol). Stirring for 1 h. at room temperature, work-up as above and chromatography on silica gel (elution with hexane-ethyl acetate 1:1) gave 2 (5.5 mg, 80%) as colorless needles, mp 256-258°(ethyl acetate), $[\alpha]_D^{25}$ +249° (MeOH); high resolution MS: m/z 264.1353 (M^+) and further peaks at m/z 249, 246, 231, 228, 217, 202, 175 and 153. $C_{15}H_{20}O_4$ requires M= 264.1361, IR, ν_{max} (KBr): 3474, 3372 (OH), 1751 (γ-lactone), 790 ($C=CH_2$) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.17 (*dd*, J= 3.2, 0.8 Hz, H-13'), 5.97 (*dd*, J= 3.1, 0.8 Hz, H-13), 5.02 (br *s*, H-15'), 4.98 (br *s*, H-15), 4.28 (*d*, J= 11.3 Hz,

H-6), 4.16 (*m*, partly overlapped by H-6, H-8), 3.41 (*ddt*, J= 11.3, 10.2, 3.1 Hz, H-7), 2.65-2.50 (*m*, H-3α), 2.20-1.95 (*m*, 2H, H-3β and H-9α), 1.65 (*dd*, J= 12.6, 4.5 Hz, H-9β), 0.98 (*s*, 3H, H-14). ^{1}H NMR (C_5D_5N): δ 6.30 (*m*, 2H, H-13 and H-13'), 5.11 (br *s*, H-15'), 5.00 (br *s*, H-15), 4.55 (*d*, J= 11.1 Hz, H-6), 4.45 (*ddd*, J= 10.9, 10.1, 4.5 Hz, H-8), 4.06 (*ddt*, J= 11.1, 10.1, 3.1 Hz, H-7), 2.90-2.75 (*m*, H-3α), 2.50-2.20 (*m*, 2H, H-3β and H-9α), 1.86 (*dd*, 12.5, 4.5 Hz, H-9β), 1.00 (*s*, 3H, H-14).

Satisfactory microanalytical data were obtained for all new compounds[19].

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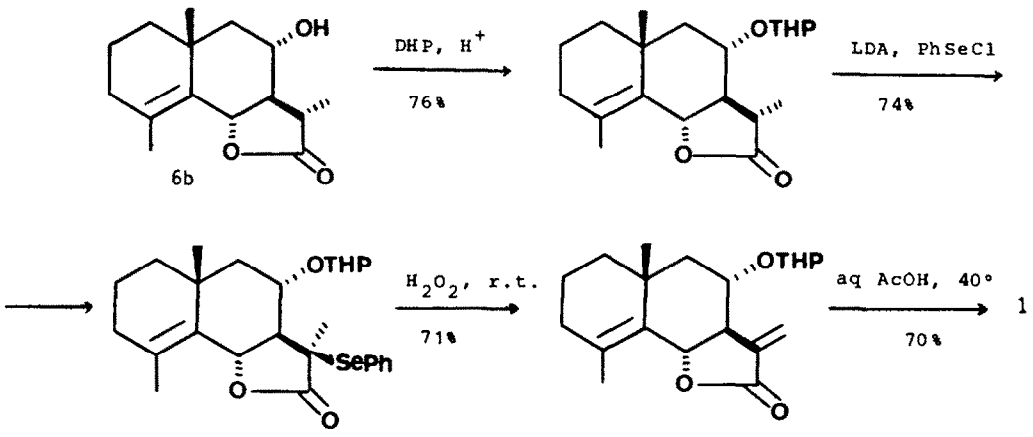

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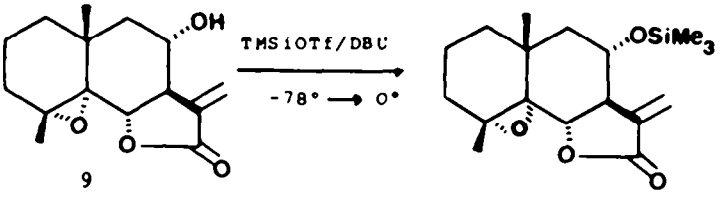

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19. 4: Found: C, 68.30; H, 7.71. Calc. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.62. 5: Found: C, 72.69; H, 8.05. Calc. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. 6a: Found: C, 60.02; H, 7.21; S, 18.74. Calc. for $C_{17}H_{24}O_3S_2$: C, 59.96; H, 7.10; S, 18.83. 6b: Found: C, 71.88; H, 8.94. Calc. for $C_{15}H_{22}O_3$: C, 71.96; H, 8.86. 7a: Found: C, 69.15; H, 9.98. Calc. for $C_{21}H_{36}O_3Si$: C, 69.17; H, 9.95. 7b: Found: C, 62.28; H, 7.70; Se, 15.31. Calc. for $C_{27}H_{40}O_3SiSe$: C, 62.40; H, 7.76; Se, 15.19. 8: Found: C, 69.68; H, 9.31. Calc. for $C_{21}H_{34}O_3Si$: C, 69.56; H, 9.45. 9: C, 68.03; H, 7.57. Calc. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.62. 10: Found: C, 68.00; H, 7.59. Calc. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.62. 11: Found: C, 66.73; H, 9.15. Calc. for $C_{21}H_{34}O_4Si$: C, 66.62; H, 9.05. 12: Found: C, 66.70; H, 9.13. Calc. for $C_{21}H_{34}O_4Si$: C, 66.62; H, 9.05. 13: Found: C, 63.98; H, 8.60. Calc. for $C_{21}H_{34}O_5Si$: C, 63.92; H, 8.68. 14: Found: C, 66.59; H, 9.13. Calc. for $C_{21}H_{34}O_4Si$: C, 66.62; H, 9.05.