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THE TOTAL SYNTHESIS OF 1-OXYGENATED EUDESMANOLIDES

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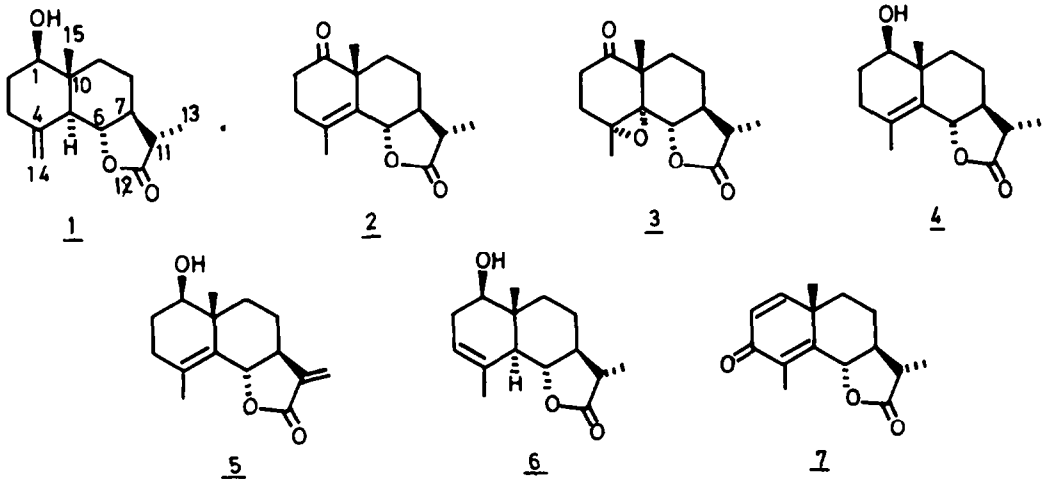
Abstract - A route towards 1-oxygenated eudesmanolides, via a (2+2)photocycloaddition reaction for constructing the decalin framework is described. The following natural substances have been synthesized. (±)-dihydroreynosin (1), (±)-1-oxo-dihydromagnolialide (2), (±)-maritimin (3), (±)-dihydromagnolialide (4), (±)-magnolialide (5), (±)-dihydrosantamarine (6). Also a synthesis of (±)-α-santonin (7) is presented.

INTRODUCTION

Eudesmanolides[2] are a group of sesquiterpene lactones based on the angularly methylated decalin nucleus. A characteristic structural feature is the relative cis configuration of the angular methyl group and the C-7 substituent. In the largest subgroup, the γ-lactone ring is trans fused between C-6 and C-7 and about 45 % of these naturally occurring 6,12-olides carry an oxygen function at C-1. Further diversification in this subgroup arises from the presence of double bonds and/or additional oxygen functions.



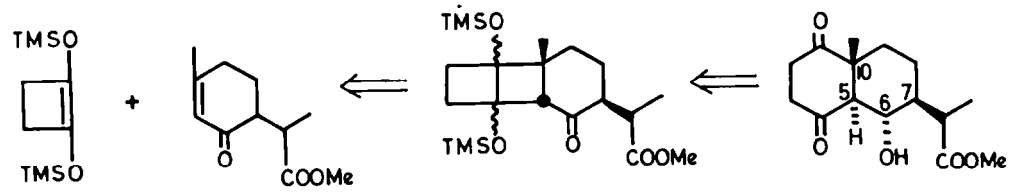
Scheme 1

Although eudesmanes have traditionally been attractive target molecules for synthetic chemists, it is only more recently that progress in the total synthesis of eu-

desmanolides has been observed[3,4]. This is mainly due to the more functionalized nature of the C-7 three-carbon side chain and to the lack of direct annelation procedures leading to adequately functionalized decalin intermediates. Indeed relatively few annelation methods allow simultaneous incorporation of a functionalized C-7 side chain. Interesting solutions for assembling the eudesmane framework have recently been described by Yoshikoski[5], Schultz[6] and Takahashi[7].

However no progress has yet been made with respect to the total synthesis of the 1-oxygenated eudesmanolides such as substances 1 to 6 (scheme 1). To the best of our knowledge, the only described approach is based on relay synthesis via (-)α-santonin (7)[8]. We presently want to describe an efficient and versatile route to the title compounds.

As obviously a C-1 hydroxyl group serves as a latent 1,2-double bond, eudesmanolides such as 7 are also likely targets. Transformations along that line are shortly addressed and are illustrated with the synthesis of (±)α-santonin (7).



9 10 11 8

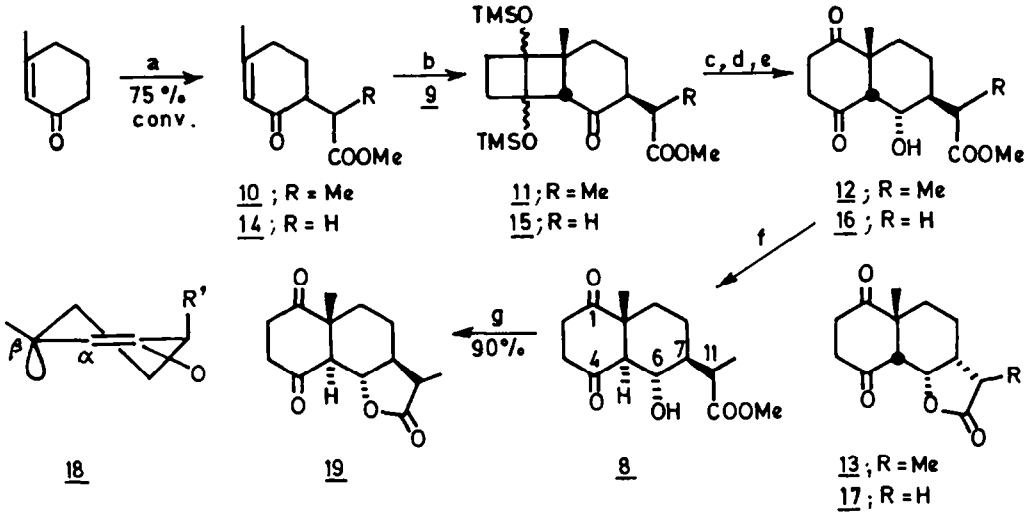
Scheme 2

Our synthetic plan centers around the dione 8 (scheme 2) which is available via an annelation procedure previously developed in our laboratory. The method is based on the photocycloaddition reaction of 1,2-bis(trimethylsiloxy)cycloalkenes with 2-cycloalkenones and subsequent oxidative α-diol cleavage[9]. It allows facile construction of bicarbocyclic compounds, functionalized at three positions adjacent to the ring fusion. The intermediate 8 seems ideally suited for further transformation into eudesmanolides, as it features the correct relative stereochemistry at the centers indicated. The crucial C-7,C-10 cis-configuration in 11, obtained during the photocycloaddition step, is in accord with Wiesners' rule[10] and is precedented in the literature[11]. Success of the plan largely depends upon selective manipulation of the 4-keto function, which must serve as a handle for the introduction of the remaining C-14 carbon atom[9d,12].

RESULTS

The starting cyclohexenone 10 was obtained upon trapping the kinetic enolate of 3-methyl-2-cyclohexenone with methyl α-iodo-propionate (scheme 3). Irradiation of 10 and 1,2-bis(trimethylsiloxy)-cyclobutene (9)[13] afforded crude adduct 11; subsequent selective reduction of the keto function to the endo-alcohol, hydrolysis and oxidative α-diol cleavage led to 12. None of the tricyclic intermediates has been purified or characterized. The cis-fused decalin 12 was obtained in 36 % isolated overall yield from 10 and was accompanied by the cis γ-lactone 13 (5 %), thus indicated good stereoselectivity (9:1 ratio) of the photocycloaddition step. During the chromatographic separation on silicagel, 12 isomerized already partially to 8. Confident with regard to the stereoselectivity of the (2+2)cycloaddition, we had originally planned to utilize 16 as a key-intermediate. Starting from 14 (as described for 10 → 11 → 12) the dione 16 was obtained in 28 % yield next to γ-lactone 17 (12 %) in a 7:3 ratio. The increased stereoselectivity of the photocycloaddition of 10 versus 14 can be rationalized according to Wiesner's rule[10]. It has been proposed that the excited state of an enone is best visualized with the α-atom

trigonal and the β-atom pyramidal and in its most stable configuration. Thus, due to the $A^{1,2}$-strain[14,15], the excited state represented by 18 becomes of increasing importance when the 6-substituent (R') is a more space demanding group. As initial reaction occurs at the lobe of the β-carbon atom, cycloaddition anti to R' is the preferred pathway.



(a) LDA, THF, HMPA, -78°C then $CH_3CHICOOMe$, -10°C; (b) hν, hexane, rt; (c) $NaBH_4$, MeOH, -30°C; (d) H^+, MeOH, rt; (e) $NaIO_4$, H_2O-MeOH, rt; (f) DBU, CH_2Cl_2, rt; (g) Me_2Zn, DMF, rt.

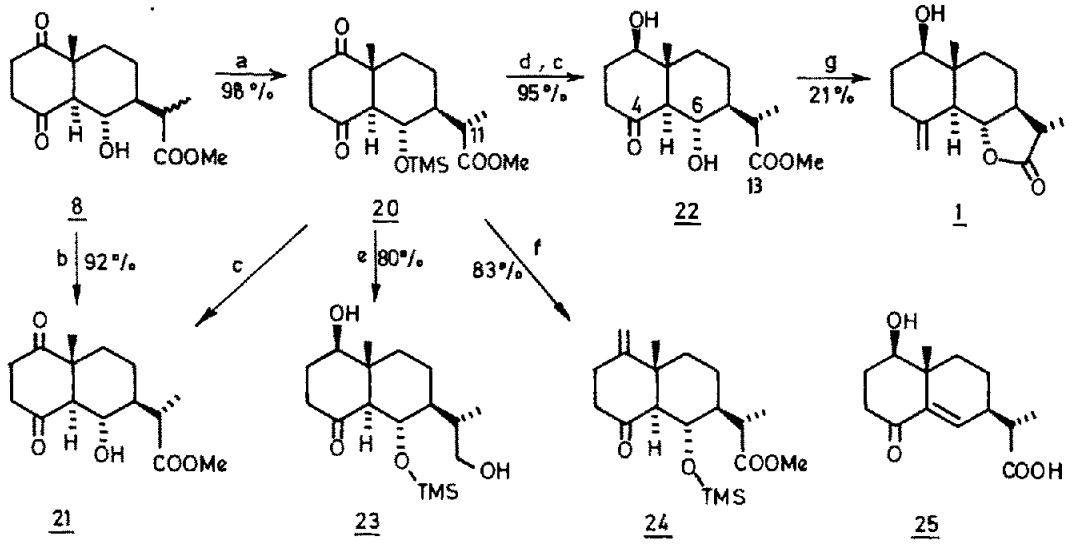
Scheme 3

Compared to 16[16], the dione 12 is thus a superior intermediate; it is formed with a higher stereoselectivity and carries already the C-13 atom of the sesquiterpene framework. The problem of working with a C-11 diastereoisomeric mixture was circumvented by the fortuitous observation of a facile epimerization at that center (vide infra). The isomerization of 12 to the trans fused decalin 8 was easily achieved and led to a 1:9 equilibrium mixture from which 8 was isolated by crystallization. Recycling of the mother liquor and column chromatography gave 8 in a combined yield of ca. 95 %. The structures 8 and 12 are fully confirmed by ^1H NMR spectral data; the α values of the angular methyl protons[17] are respectively 1.03 and 1.23 ppm. The coupling pattern for H-6 establish the relative configuration at C-5, C-6 and C-7 (8 = 10 and 10 Hz; for 12, 10 and 4 Hz).

With the formation of the key-intermediate 8 secured, we turned our attention to the problem for differentiating both carbonyl functions. A complete lack of selectivity was observed for a number of reactions (ketalization, hydride reduction, Wittig reagents). This suggests that the 6-hydroxyl group exerts an inhibiting effect on the 4-keto group comparable to the neopentyl effect on the 1-keto group[18]. In order to obtain selective nucleophilic attack on C-4, via initial bonding of the reagent on the 6-hydroxyl group, reaction of 8 with dimethyl zinc was explored. This however resulted in the formation of lactone 19; which also showed no selectivity.

We then investigated differentiation of both carbonyl function after derivatising the 6-hydroxyl group (scheme 4). During this study a remarkable observation was made. Treatment of the epimeric mixture 8 with chlorotrimethylsilane and triethylamine in DMF for 2 h led exclusively to homogeneous 20. The C-11 epimerization to the sole α-isomer 21 also occurred under the same conditions but without chlorotrimethylsilane. It should be noted that the use of dimethylformamide as solvent is essential for this isomerization. This result can be rationalized by assuming hindered rotation of the side chain due to hydrogen bonding and thereby populating the rotamer related to the γ-lactones in scheme 1. In these lactones, the α-orien-

tation of the C-13 methyl group corresponds to the more stable equatorial position.



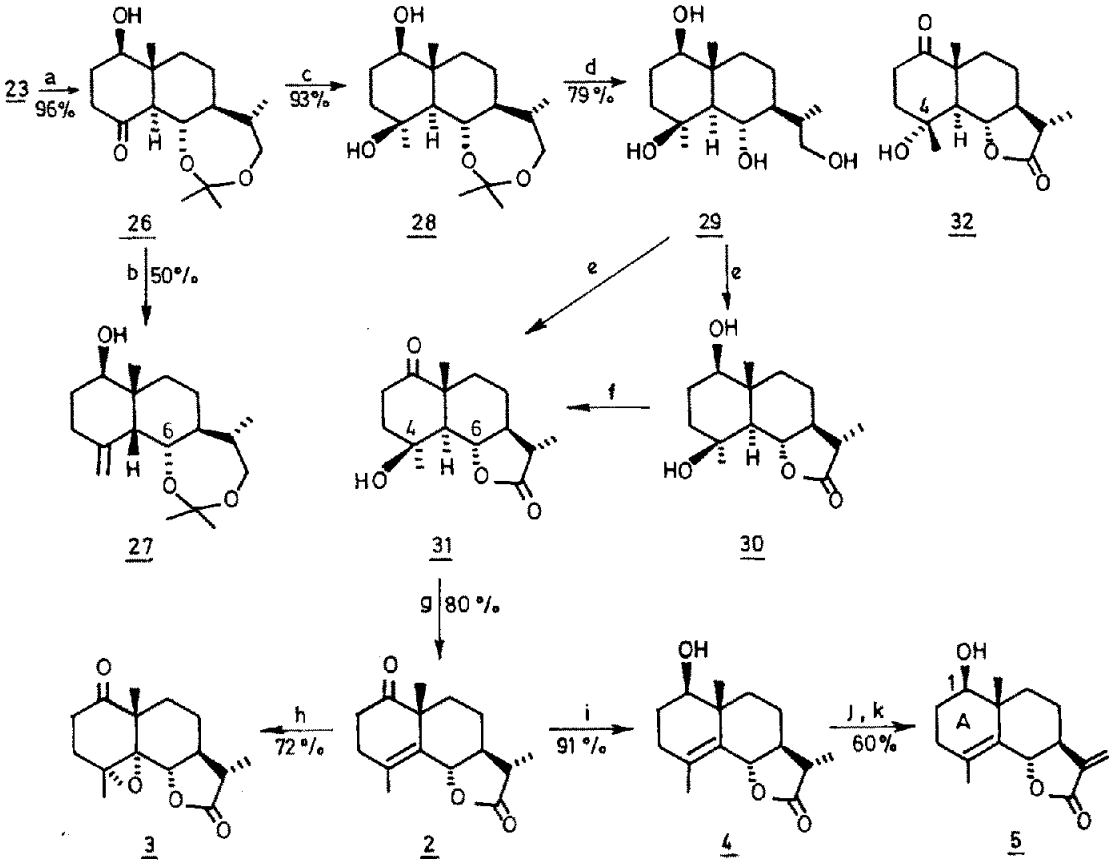
(a) Et_3N, TMSCl, DMF, rt; (b) Et_3N, DMF, rt; (c) MeOH, HCl; (d) $NaBH_4$, MeOH, 0°C; (e) $LiEt_3BH$, THF; (f) $Ph_3P{=}CH_2$, THF, rt; (g) $Ph_3P{=}CH_2$, HMPA, THF, rt.

Scheme 4

Furthermore, the sole formation of 20 indicates that silylation occurs faster on 21 than on its C-11 β-epimer. The structural relationship between 20 and 21 was confirmed by the hydrolysis of the silylether. The C-11 configuration in 20 was subsequently proven by its transformation into the eudesmanolides shown in scheme 1.

Next to this interesting result, the intermediacy of 20 also provided a solution for the problem of regiocontrol; the silylether renders the 4-carbonyl group completely inert towards hydride reducing agents and ylids, as is shown by the transformation of 20 into 22, 23 and 24 (scheme 4). Ketone 22 is a direct precursor for (±)-dihydroreynosin (1). However, a number of experiments for the formation of the required methylene unit led to rather disappointing results. The eudesmanolide 1 was obtained directly, albeit in low yield, upon treatment of 22 with excess methylene triphenylphosphorane in THF-HMPA (1:3) solution. The major product was keto acid 25 (71 % yield) most presumably formed upon β-elimination of the lactone intermediate[12]. The spectral data of (±)-dihydroreynosin[19a] were identical with those of natural 1 kindly provided by Dr. Cordell[19b].

As shown by the properties of compounds 20 and 22 it is obvious that the presence of either a protected or a free 6-hydroxyl function, in combination with the C-13 ester group, is responsible for the poor reactivity at C-4. We therefore decided to remove temporarily the ester function, using the opportunity of the facile formation of diol 23. The corresponding acetonide 26 (scheme 5) then took a central position in our further planning. Again, a Wittig reaction was unsuccessful; while at room temperature no reaction occurred, slow transformation was observed in refluxing toluene[20]. The product proved to be the cis decalin 27 (H-6; J = 10.75 and 5.0 Hz); it is of interest to note that during the epimerization no β-elimination occurred. On the other hand, treatment of 26 with methyllithium allowed efficient introduction of the remaining carbon atom; the configuration of 28 was proven at the stage of lactone 31. After hydrolysis of the acetonide, oxidation of the 6,12-diol 29 to a γ-lactone was studied. Despite literature precedents, pyridinium chlorochromate[21] showed to be unselective in this case. Catalytic oxidation on platinum[22], during 24 h, led to a mixture of 30, its corresponding lactol and 31.



(a) pTsOH, Me_2CO, rt; (b) $Ph_3\overset{+}{P}$-Me.Br^-, t.AmONa, Δ, toluene; (c) MeLi, ether, 0°C; (d) Amerlite IR 120, MeOH; (e) Pt, O_2, 55°C; (f) PCC, CH_2Cl_2, rt; (g) $SOCl_2$, Py, THF, 0°C; (h) mCPBA, $CHCl_3$, rt; (i) $NaBH_4$, MeOH, 0°C; (j) LDA, THF, HMPA, Ph_2Se_2, -78°C → -40°C; (k) H_2O_2, THF, HOAc.

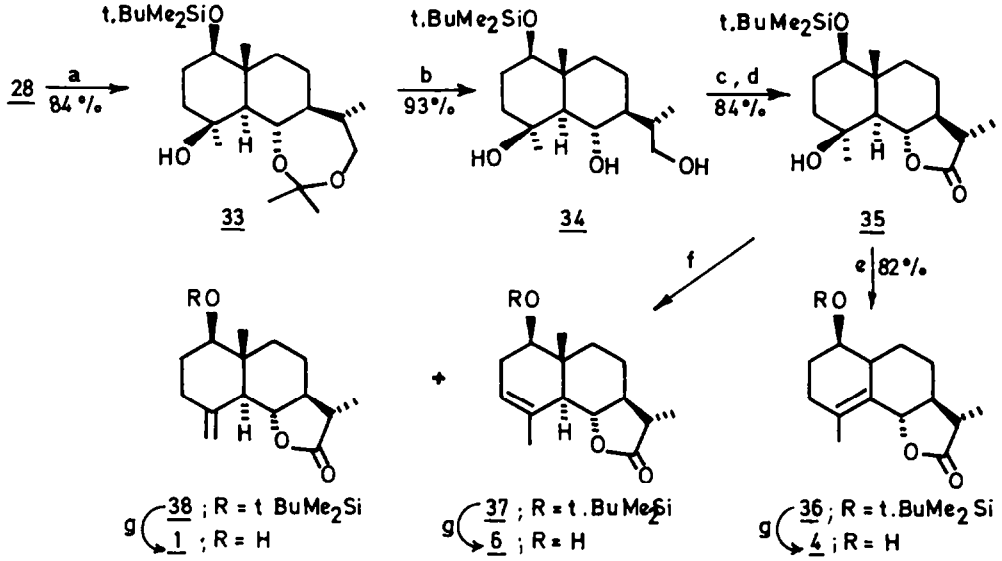
Scheme 5

Subsequent treatment of this crude mixture with pyridinium chlorochromate produced 31 in 84 % overall yield from 29. Prolonged catalytic oxidation during 6 days also converted 29 into 31 (ca. 80 %). Assignment of the C-4 configuration in 31 was possible upon comparison of the ^{1}H NMR data with those of the epimer 32, previously synthesized by Ando et al[8]. For 31 a downfield shift of the protons of the angular methyl group and of the axial H-6 signal clearly indicated the β-orientation of the 4-hydroxyl group (31; 15-H, δ = 1.38 ppm and 6-H, δ = 4.29 ppm; for 32 respective values of 1.18 and 4.12 ppm are reported). Dehydration[23] of 31 produced with high regioselectivity (±)-1-oxo-dihydromagnolialide[24] (2). Epoxidation of 2 led in 72 % yield to (±)-maritimin[24] (3) next to 18 % of the β-epoxide. Reduction of 2 gave (±)-dihydromagnolialide[25] (4). Finally phenylselenylation of 4, followed by oxidative elimination[26] gave (±)-magnolialide[27] (5). The four natural products described in scheme 5 showed identical spectral properties as the naturally occurring compounds[28,29].

It is worth noting that the apparent coupling pattern of H-1 in the ^{1}H NMR spectra of 4 and 5 changes from an almost triplet (ABS system; J = 6.6 and 8.8 Hz) at 60 MHz to a doublet of doublets (AMX system; J = 11.1 and 4.7 Hz) at 360 MHz. This observation led us to the conclude that the proposed conformational distorsion of the A-ring in 5, due to the double bond, as suggested by El-Feraly[27], might be incorrect. Indeed, conformational calculations[30] indicated a -64° torsion angle around the 1,2 bond. These results fit completely with the coupling con-

stants for the axial C-1 proton in 5 (and 4) observed at 360 MHz.

In the above described sequence, the oxidation step destroyed the already controlled configuration at C-1; therefore an alternative route was investigated (scheme 6). After protection of the secondary hydroxyl group in 28 as a t.butyldimethylsilyl ether[31] and methanolysis of the acetonide triol, 34 was obtained in 76 % combined yield. Catalytic oxidation of 34, as described for 29 proved less successful. The lactone 35 was efficiently obtained upon treatment of 34 with tris(triphenylphosphonium)ruthenium dichloride[32], followed by oxidation of the intermediate lactol with pyridinium chlorochromate. An oxidation mechanism involving formation of a ruthenium alkoxide followed by elimination has been proposed for the lactol formation step. However we observed that oxidation only occurred under atmospheric condition. In the absence of oxygen no reaction took place, thereby suggesting the existence of a catalytic oxidation process. While thionylchloride-pyridine mediated dehydration converted 35 almost exclusively into 36, Burgess reagent[33] gave 37 and 38 in 70 % and 19 % yield respectively, after HPLC separation. Removal of the protective group afforded (±)dihydromagnolialide (4), (±)-dihydrosantamarine[8,34] (6) and (±)-dihydroreynosin (1) in 80-90 % yield.



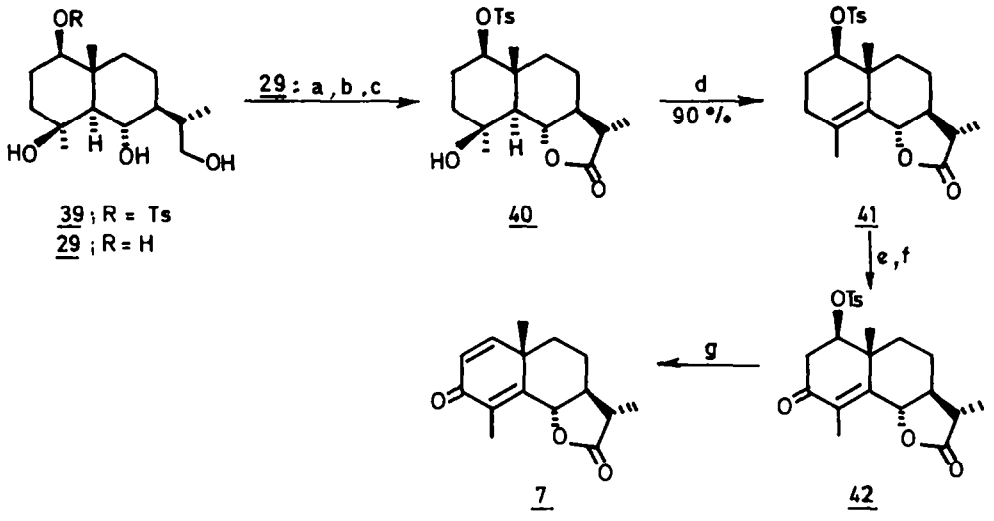
(a) t.BuMe$_2$SiCl, imidazole, DMF, rt; (b) MeOH, PPTs, rt; (c) $(Ph_3P)_3RuCl_2$, benz.; (d) PCC, CH_2Cl_2; (e) $SOCl_2$, Py, THF, 0°C; (f) $MeOOCNSO_3^+.NEt_3$, benz. 60°C; (g) $Bu_4N^+F^-$, THF, rt.

Scheme 6

The spectral data of 6 are identical with those reported by Ando et al.[8].

α-Santonin (7)[35] is a representative of the eudesmanolide subgroup having a 1,2-double bond. This structural unit can be obtained upon elimination of the C-1 oxy function subsequent to introduction of the required C-3 carbonyl group in a suitable intermediate. We therefore decided to convert 28 into its monotosylate and to carry this molecule through the 4-step sequence described for the transformation of silylether 33 into 36. Tosylation of 28 followed by acidic methanolysis of the acetonide gave 39 in 76 % combined yield. Unfortunately, both the catalytic oxidation (e.g. scheme 5) and the tris(triphenylphosphonium)ruthenium dichloride mediated oxidation (e.g. scheme 6) of the primary alcohol function in 39, gave lactone 40 in rather low yields (ca. 50 %).

We therefore adopted an alternative route (scheme 7); as already mentioned (scheme 5, reaction e) catalytic oxidation of 29 provided a mixture of 30 and 31.



(a) Pt, O_2, 55°C; (b) $NaBH_4$, MeOH, 0°C; (c) TsCl, Py, rt; (d) $SOCl_2$, Py, THF, 0°C; (e) NBS, AIBN, CCl_4, Δ; (f) $(Bu_4N)_2Cr_2O_7$, $CHCl_3$, Δ; (g) DBU, CH_2Cl_2, rt.

Scheme 7

Reduction of this crude mixture with sodium borohydride gave the alcohol 30 in 80 % combined yield. Tosylation led to the desired intermediate 40; which upon dehydration finally afforded 41. We now faced introduction of the 3-keto group. Allylic oxidation with Collins[86] reagent or with chromium trioxide dimethylpyrazole complex[37] met with complete failure. Allylic bromination of 41 gave rise to a mixture of bromides, which were directly oxidized to enone 42 using the Rolla-Landini procedure[38]. TLC analysis indicated already the presence of 7. After completion of the facile β-elimination, (±)-α-santonin (7) was isolated in 33 % combined yield from 41. Synthetic 7 was found identical, except for rotation with a sample of (-)-α-santonin[40].

EXPERIMENTAL SECTION

The melting points are uncorrected. IR spectra were recorded on a Perkin Elmer 337 spectrophotometer, mass spectra on a AEI MS-50 spectrometer. The ^1H NMR spectra were recorded at 360 MHz (WH-Brucker) in $CDCl_3$ unless otherwise stated with TMS as internal standard. Chemical shifts (δ) are expressed in ppm. Rf values are quoted for Merck silica gel 60 GF_{254} TLC plates of thickness 0.25 mm.

Reaction products were isolated by the addition of water and extraction with diethylether. The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed from the filtered solution on a rotary evaporator. Column chromatographic purifications were performed on silica gel. HPLC purifications (silica gel) were carried out with the Waters Ass. Prep. LC/System 500 apparatus.

6-(1'-Methoxycarbonyl-ethyl)-3-methyl-2-cyclohexenone (10).

A soln of 3-methyl-2-cyclohexenone (56 ml, 0.5 mol) in THF (200 ml) was added dropwise to a soln of LDA (0.55 mol) in THF (300 ml) at -78°C under nitrogen. After addition of HMPA (269 ml, 1.5 mol) the mixture was warmed to -20°C, and methyl-α-iodopropionate (160.5 g, 0.75 mol) was added in one portion. After 2 h the mixture was allowed to warm to rt and the reaction was quenched with sat NH_4Cl aq (1.000 ml). Work-up and distillation (110°C, 0.1 mm Hg) afforded, next to starting material (10.5 g, 19 %), 10 (60 g, 61 %). Rf (ether) 0.50; IR (film) 2970, 1745, 1680, 1630 cm^{-1}; ^1H NMR, 5.87 (1H, s), 3.65 and 3.7 (3H, s), 3.00 and 3.06 (1H, qd, J = 7.5, 5.0 Hz), 2.57 and 2.74 (1H, ddd, J = 5.0, 5.0, 12.5 Hz), 1.95 (3H, s), 1.10 and 1.19 (3H, d, J = 7.5 Hz); MS m/z 196 ($M^{+\cdot}$, 1), 109 (80), 82 (100); UV (MeOH), λ_{max} = 245 nm.

2-(1,2,3,4,4a,5,6,7,8,8aα-Decahydro-1α-hydroxy-4aβ-methyl-5,8-dioxo-naphthalen-2β-yl)propionic acid methyl ester (8)

A soln of 10 (27.05 g, 0.138 mol) and 9 (63.5 g, 0.276 mol) in hexane (550 ml) was irradiated at 350 nm under nitrogen at rt for 21 days. After removal of the excess 9 (30-40°C, 0.04 mm Hg), the crude residue was dissolved in MeOH (260 ml) and $NaBH_4$ (9.9 g, 0.26 mol) was added at -20°C. After 1 h, the reaction was quenched with sat NH_4Cl aq (550 ml). After work-up, the residue was dissolved in MeOH (200 ml) and HCl aq (37 %, 20 µl) was added. After 1 h, $NaIO_4$ aq (0.1 M, 2000 ml, 0.2 mol) was added and the reaction mixture was, protected from light, stirred at 25°C for 30 min. Continuous extraction with ether and column chromatography (ether/CH_2Cl_2/hexane : 1/1/1) afforded 12 and 8 (14.0 g, 36 %) and 13 (2.0 g, 5 %). A soln of 12 and 8 (14 g, 49.6 mmole) and DBU (1.7 ml) in CH_2Cl_2 (496 ml) was stirred during 3 days. Quenching with sat NH_4Cl aq, work-up, crystallization from ether, recycling of the mother liquor and column chromatography (ether/hexane : 7/3) yielded 8 (11.76 g, 84 %).
13 : mp (ether) 110-111°C; Rf (ether) 0.18; IR (KBr) 2940, 1770, 1710 cm^{-1}; ^1H NMR 4.81 (1H, t, J = 4 Hz), 2.55 (1H, d, J = 4.0 Hz), 2.33 (1H, q, J = 7.75 Hz), 1.27 (3H, d, J = 7.75 Hz), 1.23 (3H, s); MS m/z 250 ($M^{+\cdot}$, 92), 93 (100).
8 : mp (ether) 110-115°C; Rf (ether) 0.18; IR (KBr) 3425, 2950, 1735, 1710 cm^{-1}; ^1H NMR 3.93 and 4.13 (1H, td, J = 10.0, 2.25 Hz), 3.68 and 3.69 (3H, s), 3.32 and 3.35 (1H, d, -O-H, J = 2.25 Hz), 1.13 and 1.20 (3H, d, J = 7.25 Hz), 1.02 and 1.03 (3H, s). MS m/z 282 ($M^{+\cdot}$, 3), 264 (42), 195 (100).

Lactone 19

To a soln of 8 (56.4 mg, 0.2 mmol) in THF (3 ml) was added, at rt, a soln of Me_2Zn in DHF (2 M, 0.3 ml, 0.3 mmol) under nitrogen. After 2 h the reaction was quenched with sat NH_4Cl aq. Work-up and recrystallization (ether/hexane) afforded 19 (45 mg, 90 %, mp (ether) 142°-143°C). Rf (ether) 0.16; IR (KBr) 2970, 1765, 1710 cm^{-1}; ^1H NMR 4.19 (1H, t, J = 10.4 Hz), 2.99 (1H, d, J = 10.4 Hz), 2.34 (1H, qd, J = 6.75, 12.25 Hz), 1.23 (3H, d, J = 6.75 Hz), 1.12 (3H, s); MS m/z 250 ($M^{+\cdot}$, 47), 206 (100), 93 (96) 91, 91 (100).

Silylether 20

A soln of 8 (141 mg, 0.5 mmol), NEt_5 (0.35 ml, 2.5 mmol) and TMSCl (0.158 ml, 1.25 mmol) in DMF (2.5 ml) was stirred for 2 h at rt under nitrogen. The mixture was poured into water (10 ml); work-up afforded pure 20 (174 mg), 98 %, mp (ether/hexane) 125°C). Rf (ether/hexane : 50/50) 0.22; IR (KBr) 2950, 1730, 1710 cm^{-1}; ^1H NMR 3.95 (1H, dd, J = 9.0, 10.25 Hz), 3.69 (3H, s), 2.84 (1H, d, J = 9.0 Hz), 1.1 (3H, d, J = 7.0 Hz), 0.96 (3H, s), 0.15 (9H, s); MS m/z 339 (100), 89 (43), 73 (69).

Epimerization of 8; formation of 21

A soln of 8 (141 mg, 0.5 mmol) and NEt_3 (0.35 ml, 2.5 mmol) in DMF (2.5 ml) was stirred for 2 h at rt under nitrogen. Work-up and crystallization (ether/hexane) afforded 21 (130 mg, 92 %, mp (ether) 143°C). Rf (ether) 0.18; ^1H NMR 3.93 (1H, td, J = 10.0, 2.25 Hz), 3.68 (3H, s), 3.35 (1H, d, -O-H, J = 2.25 Hz), 1.13 (3H, d, J = 7.25 Hz), 1.03 (3H, s); Anal. calc. for $C_{15}H_{22}O_5$ C, 63.81; H, 7.85. Found C, 63.70; H, 7.60.

2S-(1,2,3,4,4a,5,6,7,8,8aα-Decahydro-1α,5β-dihydroxy-4aβ-methyl-8-oxo-naphthalen-2β-yl)propionic acid methyl ester (22)

To a soln of 20 (177 mg, 0.5 mmol) in MeOH (5 ml) was added $NaBH_4$ (9.5 ml, 0.25 mmol) at -30°C. After 10 min the reaction mixture was poured into sat NH_4Cl aq (15 ml). Work-up afforded the silylether which was dissolved in MeOH (2 ml). HCl aq (37 %, 2 µl) was added; after stirring for 1 h at rt, the reaction mixture was poured into sat $NaHCO_3$ aq (10 ml). Work-up and crystallization (ether) yielded 22 (135 mg, 95 %, mp (ether) 153-154°C). Rf (ether) 0.13; IR (KBr) 3420, 2940, 1730, 1710, 1700 cm^{-1}; ^1H NMR 3.86 (1H, ddd, J = 9.5, 9, 2.5 Hz), 3.84 (1H, dd, J = 11.5, 4.5 Hz), 3.68 (3H, s), 3.1 (1H, d, O-H, J = 2.5 Hz), 2.97 (1H, qd, J = 7.25, 4.75 Hz), 2.22 (1H, d, J = 9.5 Hz), 1.12 (3H, d, J = 7.25 Hz), 0.8 (3H, s); MS m/z 284 ($M^{+\cdot}$, < 1), 55 (85), 41 (100).
Anal. calc. for $C_{15}H_{24}O_5$ C, 63.36; H, 8.51. Found C, 63.60; H, 8.40.

(±)-Dihydroreynosin (1)

To a suspension of methylene triphenylphosphorane [from methyltriphenylphosphonium bromide (1.07 g, 3 mmol) and n.BuLi (1.87 ml, 1.7 M in hexane, 3 mmol)] in THF (5 ml) and HMPA (10 ml) was added a soln of 22 (142 mg, 0.5 mmol) in HMPA (5 ml) at rt under argon. After 2 h the reaction mixture was quenched with sat NH_4Cl aq (30 ml). Work-up and column chromatography (ether/hexane : 50/50) afforded (±)-dihydroreynosin (1) (130 mg, 21 % with mp (hexane) 108°C (lit.[19a] 129°C). Rf (ether) 0.36; IR (KBr) 3360, 2960, 1750 cm^{-1}; ^1H NMR 4.97 (1H, s), 4.83 (1H, s), 4.05 (1H, t, J = 10.5 Hz), 3.50 (1H, dd, J = 11.0, 4.5 Hz), 1.23 (3H, d, J = 6.75 Hz), 0.83 (3H, s); MS ($M^{+\cdot}$, 3) 232 (79), 165 (93), 55 (97), 41 (100).

2S-(1,2,3,4,4a,5,6,7,8,8aα-Decahydro-5β-hydroxy-4aβ-methyl-1α-trimethylsilyloxy-8-oxo-naphthalen-2β-yl)-propanol (23)

To a soln of 20 (630 mg, 1.77 mmol) in THF (10 ml) was added a soln of $LiEt_3BH$ in THF (7.1 ml, 1 M in THF, 7.08 mmol) at rt under nitrogen. After 15 min the reaction mixture was poured into sat NH_4Cl aq (30 ml). After the work-up the Et_3B was removed under vacuum (0.01 mm Hg). Column chromatographic purification (EtOAc) afforded 23 (465 mg, 80 %, mp (ether) 142-144°C). Rf (EtOAc) 0.22; IR (KBr) 3340, 2950, 1720 cm^{-1}; ^1H NMR 3.89 (1H, t, J = 9.5 Hz), 3.80 (1H, dd, J = 11.5, 4.5 Hz), 3.51 (2H, m), 2.34 (1H, d, J = 9.5 Hz), 0.83 (3H, d, J = 7.0 Hz), 0.72 (3H, 5), 0.11 (9H, s); MS m/z 313 (11), 75 (90), 43 (100).

The acetonide 26

A soln of 23 (435 mg, 138 mmol) and TsOH (5 mg) in acetone (27 ml) was stirred for 24 h at rt. After addition of K_2CO_3 (20 mg) the mixture was stirred for 30 min and the salts were filtered. Column chromatography (EtOAc/hexane : 50/50) yielded 26 (392 mg, 96 %, mp (hexane) 95°C). Rf (ether/hexane : 80/20) 0.18; IR (KBr) 3440, 2930, 1720 cm^{-1}; ^1H NMR 3.96 (1H, t, J = 10.0 Hz), 3.79 (1H, dd, J = 11.25, 4.5 Hz), 3.54 (1H, dd, J = 12.25, 10.75 Hz), 3.40 (1H, dd, J = 3.5, 12.25 Hz), 2.43 (1H, d, J = 10.0 Hz), 1.47 (3H, s), 1.25 (3H, s), 0.83 (3H, d, J = 6.5 Hz), 0.75 (3H, s); MS m/z 296 ($M^{+\cdot}$, < 1), 281 (38), 43 (92), 41 (100). Anal. calc. for $C_{17}H_{28}O_4$ C, 68.70; H, 9.60. Found C, 68.40; H, 9.53.

2S-(1,2,3,4,4a,5,6,7,8,8aα-Decahydro-1α,5β,8β-trihydroxy-4aβ,8α-dimethyl-naphthalen-2β-yl)-propanol (29)

To a soln of 26 (870 mg, 2.94 mmol) in THF at 0°C (30 ml) was added a solution of MeLi in ether (10 ml, 10 mmol) under nitrogen. After 30 min the reaction mixture was quenched with sat NH_4Cl aq (50 ml). Work-up and crystallization (hexane) yielded 28 (853 mg; 93 %, mp (ether) 128-130°C). Rf (ether/hexane : 80/20); IR (KBr) 3430, 3360, 2940 cm^{-1}; ^1H NMR 4.06 (1H, t, J = 10.0 Hz), 3.62 (1H, dd, J = 12.25, 10.75 Hz), 3.35 (1H, dd, J = 12.25, 3.5 Hz), 3.21 (1H, dd, J = 12.0, 3.75 Hz), 1.46 (3H, s), 1.39 (3H, s), 1.33 (3H, s), 1.20 (1H, d, J = 10.0 Hz), 1.04 (3H, s), 0.84 (3H, d, J = 6.6 Hz); MS m/z 312 ($M^{+\cdot}$, < 1), 43 (100).
A mixture of 28 (210 mg, 0.673 mmol) and Amberlite IR 120 (200 mg) in MeOH (10 ml) was stirred for 24 h at room temperature. Filtration and evaporation yielded 29 (179 mg; 97 %, mp (toluene) 158°C). Rf (acetone/hexane : 2/1) 0.18; IR (KBr) 3310, 2920; ^1H NMR (CD_3OD) 3.89 (1H, t, J = 10.1 Hz), 3.44 (2H, m), 3.14 (1H, dd, J = 11.5, 4.0 Hz), 1.42 (3H, s), 1.05 (1H, d, J = 10.1 Hz), 0.98 (3H, s), 0.88 (3H, d, J = 7.0 Hz); MS m/z 247 (11), 107 (58), 101 (92), 43 (100). Anal. calc. for $C_{15}H_{28}O_4$ C, 66.14; H, 10.36. Found C, 66.20; H, 10.50.

4β-Hydroxy-1-oxo-5αH,6,11βH-eudesman-6,13-olide (31)

A suspension of 29 (179 mg, 0.66 mmol) and Pt [from hydrogenation of PtO_2 (100 mg) in H_2O for 2 h at 50°C] in H_2O (15 ml) was stirred at 50°C under oxygen for 24 h. The catalyst was filtered and the water layer was extracted with ether. After the work-up, the residue was dissolved in CH_2Cl_2 (2 ml) and PCC (430 mg, 2 mmol) was added. After 2 h stirring at rt the reaction mixture was filtered through silica gel (ether). Column chromatography (EtOAc/hexane : 50/50) gave 31 (147 mg, 84 %, mp (ether/hexane) 162-163°C). IR (KBr) 3460, 2930, 1760, 1705 cm^{-1}; ^1H NMR 4.29 (1H, t, J = 10.5 Hz), 2.78 (1H, ddd, J = 4.0, 8.5, 15.0 Hz), 2.31 (1H, qd, J = 7.0, 12.5 Hz), 1.76 (1H, d, J = 10.5 Hz), 1.52 (3H, s), 1.38 (3H, s), 1.23 (3H, d, J = 7.0 Hz); MS m/z 266 ($M^{+\cdot}$, 2), 99 (81), 43 (100).

(±)-1-Oxo-dihydromagnolialide (2)

To a soln of 31 (52 mg, 0.195 mmol) in THF (1 ml) at 0°C was added a soln of pyridine (0.26 ml) and $SOCl_2$ (0.20 ml) in THF (0.2 ml) under nitrogen. After 30 minutes the reaction mixture was poured into ice water. The water layer was extracted with ether. The combined organic layers were washed with sat $NaHCO_3$ aq and brine. Work-up and HPLC purification (ether/hexane : 50/50) afforded (±)-1-oxo-dihydromagnolialide (2, 39 mg, 80 %) with mp (hexane) 112°C (lit[24] for (-)-2; 116-118°C). Rf (ether/hexane : 50/50) 0.19; IR (KBr) 2960, 1765, 1710 cm^{-1}; ^1H NMR 4.6 (1H, br d, J = 11.0 Hz), 2.30 (1H, qd, J = 7.0, 12.0 Hz), 1.96 (3H, br s), 1.33 (3H, s), 1.24 (3H, d, J = 7.0 Hz); MS m/z 248 ($M^{+\cdot}$, 14), 165 (80), 55 (90), 41 (100). Anal. calc. for $C_{15}H_{20}O_3$ C, 72.55; H, 8.12. Found C, 72.60; H, 7.90.

(±)-Maritimin (3) and (±)-4,5-epi-maritimin

A soln of 2 (14 mg, 0.056 mol) and MCPBA (34.4 mg, 0.2 mmol) in $CHCl_3$ was stirred for 2 h at rt. The reaction was quenched with sat $NaHCO_3$ aq. After worked-up, HPLC separation afforded (±)-maritimin (3, 12 mg, 72 %) with mp (ether/hexane) 165-166°C (lit[24] for (-)-3, 176-178°C) and β-epoxide (2.6 mg, 18 %) with mp (ether/hexane) 92-93°C).
(3) Rf (ether 0.32; IR (KBr) 2930, 1775, 1700 cm^{-1}; ^1H NMR 4.30 (1H, d, J = 10.75 Hz), 1.70 (3H, s), 1.28 (3H, s), 1.26 (3H, d, J = 6.75 Hz); MS m/z 264 ($M^{+\cdot}$, 1), 165 (100), 43 (92).

β-epoxide : Rf (ether) 0.39; IR (KBr) 2940, 1770, 1700 cm^{-1}; ^1H NMR 4.33 (1H, d, J = 11.25 Hz), 2.37 (1H, qd, J = 6.9, 12.0 Hz), 1.67 (3H, s), 1.33 (3H, s), 1.27 (3H, d, J = 6.9 Hz); MS m/z 264 ($M^{+\cdot}$, 1), 165 (59), 55 (100).

(±)-Dihydromagnolialide (4)

To a soln of 2 (100 mg, 0.4 mmol) in MeOH (2 ml) at 0°C was added $NaBH_4$ (15 mg, 0.4 mmol). After stirring for 30 min, the reaction mixture was poured into sat NH_4Cl aq (10 ml). Work-up and crystallization (hexane) afforded (±)-dihydromagnolialide (4) (26,91 mg, 91 %) with mp (ether/hexane) 182-183°C (lit[25] for (+)-4; 172-174°C. Rf (EtOAc/hexane : 50/50) 0.28; IR (KBr) 3260, 2950, 1770 cm^{-1}; ^1H NMR 4.59 (1H, br d, J = 11.0 Hz), 3.52 (1H, dd, J = 11.0, 4.73 Hz), 2.27 (1H, qd, J = 7.0, 12.0 Hz), 1.85 (3H, br s), 1.23 (3H, d, J = 7.0 Hz), 1.11 (3H, s); MS m/z 250 ($M^{+\cdot}$, 1), 232 (2), 56 (100).

(±)-Magnolialide (5)

A soln of 4 (27 mg, 0.108 mmol) in THF (1 ml) was added dropwise to a soln of LDA (0.36 mmol) in THF (2 ml) at -78°C under argon. After 1 h a soln of $Ø_2Se_2$ (111 mg, 0.36 mmol) and HMPA (60 µl) in THF (1 ml) was added. After 15 min the mixture was allowed to warm to -40°C and poured after 90 min into sat NH_4Cl aq (10 ml). The residue, obtained after the work-up, was dissolved in THF (1 ml) and H_2O_2 aq (30 %, 0.055 ml, 0.63 mmol) and acetic acid (0.012 ml) were added. After 1 h the reaction was quenched with sat $NaHCO_3$ aq. Work-up and column chromatography (EtOAc/hexane : 30/70) yielded (±)-magnolialide (5) (16 mg, 60 %) with mp (ether/hexane) 106-107°C (lit for (+)-5; 152-153°C. Rf (EtOAc/hexane : 50/50) 0.28; IR (KBr) 3500, 2950, 1775 cm^{-1}; ^1H NMR 6.16 (1H, d, J = 3.2 Hz), 5.47 (1H, d, J = 3.2 Hz), 4.56 (1H, br d, J = 11.5 Hz, 3.55 (1H, dd, J = 4.0 Hz), 11.0 Hz), 5.28 (1H, q t, J = 3.2, 11.5 Hz), 1.88 (3H, br s), 1.10 (3H, s); MS m/z 248 ($M^{+\cdot}$, 17), 230 (41), 91 (81), 53 (88), 41 (100); UV (MeOH), λ_{max} 213 nm.

Silylether 33

A soln of 28 (261 mg, 0.84 mmol), imidazole (286 mg, 4.2 mmol) and TBDMSCl (316 mg, 2.1 mmol) in DMF (8.4 ml) was stirred 30 h at rt under nitrogen. The reaction mixture was poured into sat NH_4Cl aq (30 ml). The combined organic layers, from the extraction, were washed with 5 % HCl aq, sat $NaHCO_3$ and brine. Purification with EPLC (hexane/acetone : 95/5) afforded 33 (300 mg, 84 %, mp (ether/hexane) : 131-133°C). Rf (hexane/acetone : 95/5) 0.23; IR (KBr) 3420, 2920 cm^{-1}; ^1H NMR 4.05 (1H, t, J = 10.0 Hz), 3.62 (1H, dd, J = 11.0, 12.0 Hz), 3.34 (1H, dd, J = 12.0, 3.6 Hz), 3.15 (1H, dd, J = 11.5, 4.0 Hz), 1.46 (3H, s), 1.38 (3H, s), 1.33 (3H, s), 1.19 (1H, d, J = 10.0 Hz), 1.02 (3H, s), 0.88 (9H, s), 0.84 (3H, d, J = 6.7 Hz), 0.03 (3H, s), 0.02 (3H, s); MS m/z 426 ($M^{+\cdot}$, < 1), 75 (100).

2S-(1,2,3,4,4a,5,6,7,8,8aα-Decahydro-5β-t.butyldimethylsilyloxy-1α,8β-dihydroxy-4aβ,8α-dimethylnaphtalen-2β-yl)-propanol (34)

A soln of 33 (274 mg, 0.643 mmol) and pyridinium-p.toluene sulfonic acid (40 mg) in MeOH (10 ml) was stirred for 3 h at rt. The reaction mixture was poured into 20 % NaCl aq and worked-up. Crystallization (EtOAc) and column chromatography (EtOAc) yielded 34 (231 mg, 93 %, mp (EtOAc) 132-133°C). Rf (EtOAc) 0.15; IR (KBr) 3290, 2940 cm^{-1}; ^1H NMR 3.94 (1H, t, J = 10.0 Hz), 3.56 (2H, m), 3.18 (1H, dd, J = 4.3, 11.0 Hz), 1.47 (3H, s), 1.08 (1H, d, J = 10.0 Hz), 1.00 (3H, s), 0.91 (3H, d, J = 7.0 Hz), 0.88 (9H, s), 0.03 (3H, s), 0.02 (3H, s); MS m/z 219 (20), 159 (39), 75 (100).

1β-t.Butyldimethylsilyloxy-4β-hydroxy-5αH,6,11βH-eudesman-6,12-olide (35)

A soln of 34 (186 mg, 0.482 mmol) and $(Ø_3P)_3RuCl_2$ (323 mg, 0.337 mmol) in benzene (5 ml) was stirred at rt without exclusion of oxygen. After 5 h, CH_2Cl_2 (5 ml) and PCC (259 mg, 1.205 mmol) were added and the suspension was stirred for 16 h. The reaction mixture was filtered through silica gel (ether) and chromatography of the residue gave 41 (147 mg, 84 %, mp (diisopropylether/hexane) 145-146°C. Rf (EtOAc/hexane : 30/70) 0.29; IR (KBr) 3450, 2920, 1750 cm^{-1}; ^1H NMR 4.25 (1H, t, J = 10.5 Hz), 3.26 (1H, dd, J = 11.3, 4.0 Hz), 2.27 (1H, qd, J = 6.7, 12.2 Hz), 1.41 (3H, s), 1.33 (1H, d, J = 10.5 Hz), 1.21 (3H, d, J = 6.7 Hz), 1.14 (3H, s), 0.89 (9H, s), 0.05 (3H, s), 0.03 (3H, s); MS m/z 233 (37), 159 (65), 75 (100).

1β-t.Butyldimethylsilyloxy-6,11βH-eudesm-4(5)-en-6,12-olide (36)

To a soln of 35 (150 mg, 0.393 mg) in THF (3 ml), at 0°C, was added under nitrogen a soln of pyridine (0.5 ml) and $SOCl_2$ (0.37 ml) in THF (1 ml). After 30 min the reaction mixture was poured into water. The ether extracts were washed with sat $NaHCO_3$ aq and brine. Purification by HPLC yielded 36 (117 mg, 82 %). IR (KBr) 2960, 1760 cm^{-1}; ^1H NMR 4.58 (1H, br d, J = 11.0 Hz), 3.48 (1H, dd, J = 11.7, 3.6 Hz), 2.25 (1H, qd, J = 6.9, 12.0 Hz), 1.83 (3H, br s), 1.22 (3H, d, J = 6.9 Hz), 0.89 (9H, s), 0.06 (3H, s), 0.04 (3H, s); MS m/z 306 (29), 159 (45), 75 (100).

1β-t.Butyldimethylsilyloxy-5αH,6,11βH-eudesm-3-en-6,12-olide (37) and exo-isomer 38

To a soln of 35 (123 mg, 0.322 mmol) in benzene (3 ml) at 60°C was added in small portions (2 h) Burgess reagent (250 mg, 1.05 mmol). After stirring for an additional 4 h the reaction mixture was poured into water. Work-up and HPLC purification

(EtOAc/hexane : 5/95) afforded 37 (82 mg, 70 %) and 38 (22 mg, 19 %).
37 : Rf (EtOAc/hexane : 10/90) 0.35; IR (KBr) 2950, 1785, 1650 cm^{-1}; ^1H NMR 5.31 (1H, m), 3.95 (1H, dd, J = 11.0, 9.5 Hz), 3.58 (1H, dd, J = 6.5, 9.5 Hz), 2.26 (1H, qd, J = 6.8, 12.0 Hz), 1.80 (3H, br s), 1.22 (3H, d, J = 6.8 Hz), 0.89 (9H, s), 0.87 (3H, s), 0.04 (6H, s); MS m/z 364 ($M^+\cdot$, < 1), 159 (32), 75 (100).
38 : Rf (EtOAc/hexane : 10/90) : 0.29; IR (KBr) 2950, 1785 cm^{-1}; ^1H NMR 4.94 (1H, d, J = 1.4 Hz), 4.79 (1H, d, J = 1.4 Hz), 4.04 (1H, t, J = 10.6 Hz), 3.43 (1H, dd, J = 4.7, 11.2 Hz), 2.33 (1H, qd, J = 6.7, 12.5 Hz), 2.06 (1H, d, J = 10.6 Hz), 1.22 (3H, d, J = 6.7 Hz), 0.88 (9H, s), 0.81 (3H, s), 0.05 (6H, s); MS m/z 364 ($M^+\cdot$, < 1), 159 (43), 75 (100).

(±)-Dihydrosantamarine (6)

A soln of 37 (20 mg, 0.0655 mmol) and n.Bu_4NF (0.275 ml of a 1 M soln in THF, 0.275 mmol) in THF (0.8 ml) was stirred for 48 h at room temperature. After diluting the reaction mixture with ether (15 ml), the organic layer was washed with brine. Work-up and chromatography (ether/hexane : 50/50) afforded (±)-dihydrosantamarine (6) with mp (ether/hexane) 131-133°C (lit[8] for (+)-6; 134°-136°C in 84 % yield. Rf (EtOAc/hexane : 50/50) 0.27; IR (KBr) 3520, 2950, 1765, 1660; ^1H NMR 5.33 (1H, br m), 3.96 (1H, dd, J = 10.0, 11.0 Hz), 3.65 (1H, dd, J = 9.7, 6.8 Hz), 2.29 (1H, qd, J = 6.8, 12.0 Hz), 1.82 (3H, br s), 1.23 (3H, d, J = 6.8 Hz), 0.90 (3H, s); MS m/z 250 ($M^+\cdot$, 86), 232 (19), 81 (94), 41 (100).

1β,4β-Dihydroxy-5αH,6,11βH-eudesman-6,12-olide (30)

A suspension of 29 (1 g, 3.67 mmol) and Pt (from hydrogenation of PtO_2 (500 mg) in water was stirred at 60°C under oxygen for 3 days. Filtration and extractive work-up afforded an oily residue, which was taken up in MeOH (10 ml). At 0°C, $NaBH_4$ (38 mg, 1 mmol) was added; the reaction mixture was stirred for 30 min and was then poured into sat NH_4Cl aq. Work-up with ether/CH_2Cl_2 : 2/1 and crystallization (ether) afforded 30 (800 mg, 80 %, mp (EtOAc/hexane) 182-184°C). Rf (ether) 0.14; IR (KBr) 3500, 2960, 1760 cm^{-1}; ^1H NMR 4.26 (1H, t, J = 10.6 Hz), 3.32 (1H, dd, J = 11.3, 3.7 Hz), 2.28 (1H, qd, J = 7.0, 12.5 Hz), 1.42 (3H, s), 1.35 (1H, d, J = 10.6 Hz), 1.22 (3H, d, J = 7.0 Hz), 1.16 (3H, s); MS m/" 105 (8), 73 (100).

The tosylate 40

A soln of 30 (500 mg, 1.87 mmol) and tosyl chloride (1.069 g, 5.61 mmol) in pyridine (10 ml) was stirred for 5 days at rt. The reaction mixture was poured into water, extracted and the combined organic layers were washed with 10 % HCl aq, sat $NaHCO_3$ aq and brine. Work-up and chromatography (EtOAc/hexane : 40/60) afforded 40 (643 mg, 82 %, mp (ether/hexane) 166-167°C). Rf (EtOAc/hexane : 50/50) 0.25; IR (KBr) 3490, 2930, 1765, 1595 cm^{-1}; ^1H NMR 7.79 (2H, d, J = 8.0 Hz), 7.35 (2H, d, J = 8.0 Hz), 4.30 (1H, dd, J = 11.7, 3.7 Hz), 4.19 (1H, t, J = 10.5 Hz), 2.47 (3H, s), 2.26 (1H, qd, J = 6.8, 12.2 Hz), 1.40 (3H, s), 1.21 (3H, d, J = 6.8 Hz), 1.20 (3H, s); MS m/z 232 (51), 159 (98), 91 (100), 77 (95).

1β-Tosyloxy-6,11βH-eudesm-4(5)en-6,12-olide (41)

To a soln of 40 (64 mg, 0.152 mmol) in THF (2 ml) at 0°C was added a mixture of pyridine (0.18 ml), $SOCl_2$ (0.14 ml) and THF (0.4 ml). After stirring for 1 h the mixture was poured into ice water and extracted with ether. The combined organic layers were washed with sat $NaHCO_3$ aq and brine. Work-up and crystallization (hexane) afforded pure 41 (57 mg, 94 %, mp (hexane) 129°-130°C). Rf (EtOAc/hexane : 30/70) 0.27; IR (KBr) 2920, 1775, 1660, 1595 cm^{-1}; ^1H NMR 7.80 (2H, d, J = 7.0 Hz), 7.35 (2H, d, J = 8.0 Hz), 4.51 (1H, br d, J = 9.5 Hz), 4.48 (1H, dd, J = 12.0, 3.7 Hz), 2.46 (3H, s), 2.24 (1H, qd, J = 6.8, 12.0 Hz), 1.82 (3H, br s), 1.22 (3H, d, J = 6.8 Hz), 1.14 (3H, s); MS m/z 232 (63), 159 (52), 91 (100).

(±)-α-Santonin (7)

A soln of 41 (20 mg, 0.049 mmol), NBS (26.4 mg, 0.148 mmol) and AIBN (2 mg) in CCl_4 (1 ml) was refluxed for 20 min. The reaction mixture was cooled and filtered through celite. The residue after evaporation of the solvent was dissolved in $CHCl_3$ (2 ml), $(Bu_4N)_2Cr_2O_7$ (100 mg, 0.142 mmol) was added and reflux was continued for 2 h. After cooling the soln was filtered through silica gel (ether), and the solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 (2 ml) and DBU (0.02 ml) was added. After stirring for 2 h at room temperature the reaction mixture was poured into sat NH_4Cl aq. Work-up and purification by HPLC (EtOAc/hexane : 50/50) afforded (±)-α-santonin (2, 4 mg, 33 %, mp (ether/hexane) 178-180°C, lit[40] 181°C). Rf (EtOAc/hexane : 50/50) 0.18; IR (KBr) 2930, 1770, 1640, 1620 cm^{-1}; ^1H NMR 6.69 (1H, d, J = 9.7 Hz), 6.26 (1H, d, J = 9.7 Hz), 4.80 (1H, dq, J = 11.0, 1.3 Hz), 2.43 (1H, qd, J = 6.8, 12.0 Hz), 2.14 (3H, d, J = 1.3 Hz), 1.34 (3H, s), 1.29 (3H, d, J = 6.8 Hz); MS m/z 246 ($M^+\cdot$, 17), 41 (100); UV (MeOH) λ_{max} 242 nm.

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