Tetrahedron Letters,Vol.23,No.21,pp 2229-2232,1982 0040-4039/82/212229-04$03.00/0
Printed in Great Britain

THE TOTAL SYNTHESIS OF 1-OXYGENATED EUDESMANE SESQUITERPENES : (±) DIHYDROREYNOSIN AND (±) 1-OXOCOSTIC ACID

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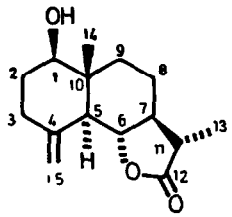
SUMMARY

The total synthesis of (±) dihydroreynosin 1 and of (±) 1-oxocostic acid 2 (R = H) are illustrative examples for a short entry into 1-oxygenated eudesmanes via an easily accessible key intermediate 7.

Many total syntheses of eudesmanes have been accomplished[2]; however the 1-oxygenated numbers comprise an important subclass which has received little attention from a synthetic viewpoint[3]. We want to describe a short highly stereo- and regioselective approach to this subclass with special emphasis on those members which carry a heavily functionalized C-7 "isopropyl group" amenable for lactone ring formation; therefore including also some eudesmanolides as target molecules. Eudesmanolides[4] possess a γ-lactone ring mostly closed in a trans manner toward C-6 and about 45 % of them carry an oxygen function at C-1. Many members contain 3,4-, 4,5-, 4,15, 11,13-double bonds. A characteristic feature of the eudesmane framework is the relative cis configuration of the C-7 side chain and the angular methyl group. The approach is based on previously discussed photocycloaddition reactions of 1,2-bis(trimethylsiloxy)cycloalkenes[5] with 2-cycloalkenones and allows a facile construction of key intermediate 7 (+8). The potentiality of 7 (+8) is illustrated by the synthesis of (±) dihydroreynosin 1[6] and of (±) 1-oxocostic acid 2[7] (R=H).

All, but one, of the carbon atoms of the eudesmane skeleton were assembled during the photocycloaddition of 3 and 4 (350 nm, pentane, N_2, r.t.). The crude product (5; major isomer[8]) was reduced ($NaBH_4$, MeOH, -20°C, 1 h); subsequent hydrolysis and oxidative cleavage ($NaIO_4$, H_2O-MeOH, r.t., 30 min, dark) afforded 6 which upon column chromatography on SiO_2 partially isomerized to the trans fused epimers 7 and 8 (36 % combined overall yield from 4). Stirring an ether solution of 6 in the presence of SiO_2 (r.t., 48 h) cleanly led to an equilibrium mixture (7 + 8 : 6 = 9:1) from which the epimers 7 and 8 were isolated in 87 % yield upon crystallization from ether.
Epimers 7 and 8 will be potential key intermediates if both carbonyl functions can be differentiated. During the study for this differentiation a remarkable observation was made. Starting from the epimers 7 and 8, a complete stereo-

homogeneous TMS ether 9 was formed (98 % yield; TMSCl, Et_3N, DMF, r.t., 2 h) as was proven by the ^1H NMR spectrum (9 : 13-CH_3; δ = 1.10, J = 7 Hz, 1 doublet; 7+8 : 2 doublets at 1.13 and 1.20 ppm (J = 7.25 Hz)). Concommitant equilibration to the most thermodynamically stable C-11 isomer had occurred; this was confirmed by treatment of the mixture 7 and 8 with Et_3N in DMF (2 h at r.t.) which led to pure 7 |m.p. 143°C; ν 1735, 1710 cm^{-1}; δ ($CDCl_3$) 3.93 1H, ddd, 9.50 Hz, 11 Hz and 2.25 Hz), 3.68 (3H, s), 3.35 (OH, 1H, d, 2.25 Hz), 1.13 (3H, d, 7 Hz), 1.03 (3H, s); m/z at 282 (M^+, 3) 195 (100)|.



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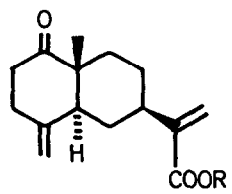

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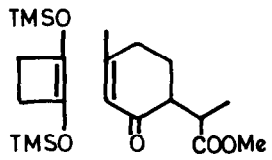

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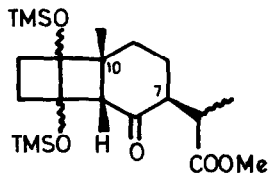

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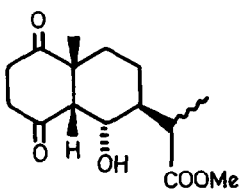

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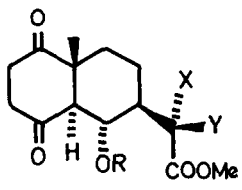
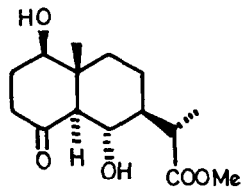


7 R = H, X = Me, Y = H
8 R = H, X = H, Y = Me
9 R = TMS, X = Me, Y = H



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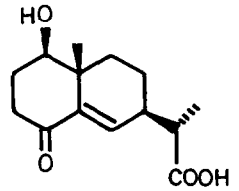

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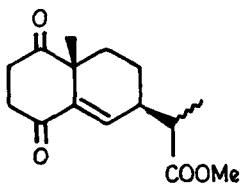

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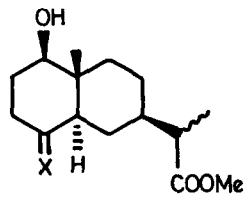
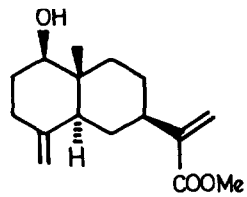


13 X = O
14 X = CH_2



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This result suggests a hydrogen bond between the ester and hydroxyl functions, thereby fixing the side chain in a preferred cyclic conformation. As can be deduced from Dreiding models the most stable configuration should carry an α oriented 13-CH_3 group (vide infra).

Formation of the TMS ether 9 not only provided a highly stereoselective route but also allowed complete regiocontrol[9]. The TMS ether function efficiently blocked the 4-carbonyl group; $NaBH_4$ reduction of 9 in MeOH (-30°C, 10 min) and subsequent acid hydrolysis afforded stereohomogeneous 10 in 95 % yield

after crystallization from ether [10 : m.p. 153-154°C; ν : 3420, 1730, 1710 cm^{-1}, δ ($CDCl_3$) 3.86 (1H, ddd, 9.5, 9, 2.5 Hz), 3.84 (1H, dd, 11.5, 4.5 Hz), 3.68 (3H, s), 3.1 (OH; 1H, d, 2.5 Hz), 2.97 (1H, qd, 7.25 Hz, 4.75 Hz), 2.22 (1H, d, 9.5 Hz), 1.12 (3H, d, 7.25 Hz), 0.8 (3H, s); m/z at 284 (M^+, 1), 41 (100)]. Ketone 10 is a direct precursor for the synthesis of (±) dihydroreynosin 1; formation of 1 proved the assumed configuration at C-11 in 7. Treatment of 10 with an excess methylene triphenylphosphorane (THF, HMPA, 1:3) gave albeit in low yield (21 %) directly (±) dihydroreynosin 1; the major product was keto acid 11 (71 %) occurring from β-elimination. The spectral properties of synthetic 1 [m.p. 108°C; ν : 3360, 1747 cm^{-1}, δ ($CDCl_3$) 4.97 (1H, s), 4.83 (1H, s), 4.05 (1H, dd, 10.5 and 10.5 Hz), 3.5 (1H, dd, 11 and 4.6 Hz), 1.23 (3H, d, 6.75 Hz), 0.83 (3H, s); δ (C_6D_6) 1.00 (3H, d, 6.75 Hz); m/z at 250 (M^+, 47); 206 (100); 149 (90)] were identical to those of natural dihydroreynosin[6,10] (m.p. 120°).

Treatment of 7 and 8 with Burgess reagent[11] ($MeOOC\bar{N}SO_2\overset{+}{N}Et_3$, benzene, 55°C, 3 h) led to enone 12 [m.p. 73°C; ν : 1730, 1710, 1690, 1615 cm^{-1}; δ ($CDCl_3$) 6.87 (1H, dd, 1.3 Hz, 2.2 Hz), 3.69 (3H, s), 1.3 (3H, s), 1.24 (3H, d, 6.75 Hz); m/z at 264 (M^+, 84), 176 (100); UV : 243 nm] in which both carbonyl groups are differentiated because of electronic reasons. Reduction of 12 ($NaBH_4$, MeOH, -30°C, 15 min) followed by catalytic hydrogenation (Pt/C, 5 %, MeOH) and epimerization (DBU, CH_2Cl_2, 3 days, r.t.) afforded 13 in 72 % yield after column chromatography (SiO_2, benzene-acetone 8:2) [13; oil; ν : 3430, 1730, 1710 cm^{-1}, δ ($CDCl_3$) : 3.82 (1H, dd, 4.75 Hz, 11.5 Hz), 3.67 (3H, s), 1.14 (3H, d, 7 Hz), 0.72 (3H, s); m/z at 268 (M^+, 8)]. Wittig reaction of 13 with excess ylid (from $Ø_3PCH_3Br$ and t.AmONa, toluene, r.t. 30 min) yielded 14 (86 %) after column chromatography (SiO_2, ether-hexane 1:1). Formation of the α-phenylselenide (LDA, ØSeSeØ, THF, HMPA, -78° to -40°C, 3 h) followed by oxidative elimination (H_2O_2-HOAc-THF, 0°C, 1 h) led to 15 (82 % yield). Collins oxidation of 15 (CrO_3.2 Py, CH_2Cl_2, N_2, r.t.) and column chromatography (SiO_2:isooctane-ethylacetate 8:2) afforded (±) 1-oxocostic acid methyl ester 2 (R = Me) in 83 % yield. The spectral properties of 2 (R = Me) [m.p. 37°C; ν : 1710 (broad), 1650, 1625 cm^{-1}; δ ($CDCl_3$) : 6.18 (1H, d, 0.5 Hz), 5.58 (1H, t, 1 Hz), 4.99 (1H, d, 1.5 Hz), 4.73 (1H, d, 1.5 Hz), 3.76 (3H, s), 1.01 (3H, s); δ (C_6D_6) : 6.27 (1H, d, 0.5 Hz), 5.35 (1H, t, 12 Hz), 4.84 (1H, d, 1.5 Hz), 4.64 (1H, d, 1.5 Hz), 3.49 (3H, s), 0.87 (3H, s); m/z at 262 (M^+, 8); UV : 212 nm] were identical to those of 2 (R = Me) derived from the natural 1-oxocostic acid[7,12]. Hydrolysis (K_2CO_3, MeOH, H_2O, reflux, 12 h) of 2 (R=Me) gave (±) 1-oxocostic acid 2 (R=H) (83 %), [m.p. 118°C; δ ($CDCl_3$) : 6.34 (1H, br. s), 5.72 (1H, br. s), 5.00 (1H, d, 1.2 Hz), 4.75 (1H, d, 1.2 Hz), 1.03 (3H, s)].

ACKNOWLEDGEMENTS

We thank the NFWO and the "Ministerie voor Wetenschapsbeleid" for financial help to the laboratory.

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8. The relative configuration at C_7 and C_{10} was proven at the stage of product 7. High stereoselectivity for the photoaddition of piperitone with cyclobutenes has already been observed; see ref. 5c and references cited therein. It is worthwhile mentioning that no stereoselectivity was observed when the cyclohexenone carries a C-6 acetic acid methyl ester side chain.
9. We also observed that methylene triphenylphosphorane reacted exclusively (83 % yield) with the 1-carbonyl group in 9.
10. We thank Dr. G. A. Cordell for kindly sending us copies of the spectra of 1.
11. E.M. Burgess, H.R. Penton Jr. and E.A. Taylor; J. Org. Chem., 1973, 38, 26.
12. We thank Prof. F. Bohlmann for kindly sending us copies of the spectra of 2 (R = Me).

(Received in UK 30 March 1982)