Tetrahedron Letters, Vol.30, No.7, pp 859-862, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

REGIO- AND STEREOSELECTIVE PHOTO-OXYGENATION OF (+)-11,12-DIACETOXYDRIM-8-ENE; AN EFFICIENT SYNTHESIS OF A KEY INTERMEDIATE FOR DRIMANE-RELATED SESQUITERPENES

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Abstract: *Photo-oxygenation of the title compound exclusively yielded (+)-(E)-11,12-diacetoxy-9α-hydroxydrim-8(12)-ene, a useful intermediate for the partial synthesis of some naturally occurring drimanes of biological interest.*

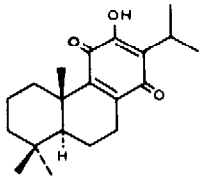
Several sesquiterpenes of the drimane class have recently attracted interest because of their important biological activity including insect antifeedant, plant growth regulation, cytotoxic, antimicrobial, molluscicidal, and anticomplemental properties.[1] Among the numerous syntheses that have appeared within the last ten years,[2] very few led to optically active compounds,[2a,3] and only in the case of both the enantiomers of polygodial an enantioselective total synthesis has been achieved.[3a] In all the other cases[2a,3b-e] the starting material for obtaining optically active drimanes is a natural product possessing the suitable absolute configuration.

We have found that royleanone (**1**), an abietane diterpenoid[4] easily available as a main constituent of the root of several *Salvia* species,[5] is a good chiral synthon for the preparation of sesquiterpenoids belonging to the drimane hydrocarbon skeleton, since oxidative degradation[6] of the 12-*O*-methyl derivative[4] of compound **1** gave (+)-drim-8-ene-11,12-dioic acid[7] (**2**) in two steps and 72% overall yield. Further easy transformations[6] of the diacid **2** provided the derivatives **3**,[7] **4**,[8] and **5**,[8] some of which have already been used as intermediates in the synthesis of some naturally occurring drimanes of biological interest.[2a,3b,d,8a]

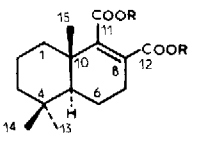
A key step in the synthesis of warburganal and related drimanes possessing a 9α-hydroxyl group is the introduction of this substituent. The problem has been solved by a variety of methods,[2,3b,d,e] obtaining 9α-hydroxydrimane derivatives in 65-85 per cent yields. For this purpose photo-oxygenation of compound **3** seemed to be a method of choice, since the regioselectivity of the reaction of singlet oxygen with α,β-unsaturated esters is well known[9] and consequently, we expected dimethyl 9-hydroxydrim-7-ene-11,12-dioate as the product of this reaction. However, compound **3** was found to be very resistant to this oxygenation, and it was recovered unchanged after 72 hours of reaction.[10]

On the contrary, when compound **5** was subjected to this reaction[10] only the derivative **6** was obtained[7] in 76% yield, besides minor quantities of the starting material (21%). The presence of a 9α-hydroxyl group in compound **6** was established by comparison of its ^{13}C NMR spectrum[7] with those of closely related substances possessing the same substituted *trans*-decalin moiety but lacking the C-9α alcohol function.[11] The observed strong diamagnetic shift in the γ-gauche carbons, *i.e.* those of C-1, C-5 and C-7 (Δδ -6.9, -11.5 and -12.0 ppm, respectively), together with the almost identical

resonance of the C-15 carbon (γ-trans, Δδ +1.4) firmly supported this conclusion. Moreover, the existence in compound **6** of a C-8,C-12 enol acetate group was in agreement with the observed allylic coupling (J = 1.8 Hz) between the H-12 and H-7α protons (δ 6.90 *d* and δ 2.11 *tdd*, see note[7]). The *E*-configuration of this enol acetate was established by nOe experiments, since irradiation at δ 6.90 (H-12 proton) caused an nOe enhancement (7 %) in the signal of one of the C-11 protons (δ 4.30).

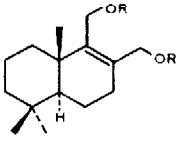


1



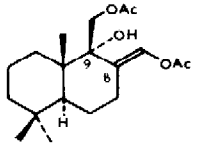
2 R = H

3 R = Me



4 R = H

5 R = Ac



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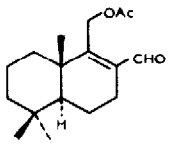

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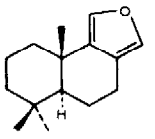

8

The stereoselectivity of this photo-oxidation is consistent[12] with a preferential attack of singlet oxygen from the more accessible α side of compound **5**, whereas its regioselectivity could be explained through a stepwise mechanism of the ene-reaction involving an 8α,9α-perepoxide intermediate,[12] which collapses into a 9α-hydroperoxide by removal of one of the less hindered allylic protons, namely one of those of C-12. Reduction[10] of this hydroperoxide give the derivative **6**.

Treatment of compound **6** with *p*-TsOH/silica gel[13] quantitatively yielded the derivative **7**,[7] which after hydrolysis (LiOH/THF) and treatment with acid (5 % HCl) was transformed into a substance [thick oil, $[\alpha]_D^{20}$ +17.3° ($CHCl_3$, c 0.87); 90 % yield] identical in all respects[7] which (+)-euryfuran **8**, a naturally occurring drimane.[2c,3d,14]

Although euryfuran (**8**) has been synthesised in both racemic and optically active forms by a variety of effective strategies,[2a,c] including a one step synthesis from the diol **4**,[3d] this easy and highly efficient preparation of compounds such as **6** and **7** provides an alternative choice for the synthesis of drimane-related sesquiterpenoids.

Acknowledgment

This work was supported in part by the 'Comisión Interministerial de Ciencia y Tecnología', Grant SEUI No. PB0418.

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6. The 12-*O*-methyl derivative of royleanone was prepared from this diterpenoid (**1**) as previously described.[4]

   Ozone treatment of 12-*O*-methylroyleanone in CH_2Cl_2 solution at -78°C for 3 h., followed by reaction with a cooled (0°C) mixture of aqueous NaOH (10%, w/v) and H_2O_2 (30%) (4:1, respectively) for 12 h. gave a crude of reaction (90% yield) which, without characterization, was treated with an excess of $Pb(OAc)_4$ in C_6H_6-MeOH (1:1) solution for 1.5 h. at 0°C producing compound **2** in 80% yield. Methylation of **2** with diazomethane in the usual manner quantitatively yielded the diester **3**.[7]

   Reduction of compound **3** ($LiAlH_4$, Et_2O solution, 0°C) gave the diol **4** (90% yield), mp 118-120°C (*n*-hexane); $[\alpha]_D^{20}$ +175.0° ($CHCl_3$, c 0.116). Treatment of compound **4** with Ac_2O-pyridine for 48 h. at room temperature quantitatively yielded the diacetate **5**, a colourless thick oil, $[\alpha]_D^{20}$ + 81.9° ($CHCl_3$, c 1.009). Compounds **4** and **5** were identical in all respects (IR, ^1H NMR, MS) with the previously described substances.[8]
7. All the new compounds were characterised by spectroscopic methods, mass and microanalysis. **3**: a colourless oil; $[\alpha]_D^{18}$ +66.1° ($CHCl_3$, c 0.281); IR ν_{max} (NaCl): 1750, 1730, 1640 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 3.75 and 3.67 (3H each, *s*, COOMe), C-Me at 1.22, 0.90 and 0.85 (3H each, *s*). **6**: mp 96-98°C (*n*-hexane); $[\alpha]_D^{20}$ +106.8° ($CHCl_3$, c 0.44); IR ν_{max} (KBr): 3565, 3450, 3120, 1760, 1745, 1680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.90 (1H, *d*, $J_{12,7\alpha}$ = 1.8 Hz, H-12), 4.36 and 4.30 (AB system, J = 11.9 Hz, 2H-11), 2.79 (1H, *ddd*, $J_{7\beta,7\alpha}$ = 13.5 Hz, $J_{7\beta,6\beta}$ = 4.8 Hz,

$J_{7\beta,6\alpha}$ = 2.4 Hz, H-7β), 2.16 and 2.11 (3H each, *s*, OAc), 2.11 (1H, *tdd*, $J_{7\alpha,7\beta} = J_{7\alpha,6\beta}$ = 13.5 Hz, $J_{7\alpha,6\alpha}$ = 5.3 Hz, $J_{7\alpha,12}$ = 1.8 Hz, H-7α), C-Me at 0.92, 0.89 and 0.84 (3H each, *s*); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 171.1 *s* (11-OAc), 168.3 *s* (12-OAc), 130.7 *d* (C-12), 124.6 *s* (C-8), 76.8 *s* (C-9), 64.5 *t* (C-11), 44.9 *d* (C-5), 42.5 *s* (C-10), 41.3 *t* (C-3), 33.8 *q* (C-13), 33.4 *s* (C-4), 32.1 *t* (C-1), 22.6 *t* (C-7), 22.0 *q* + *t* (C-14 and C-6), 21.0 and 20.8 (*q* each, OAc), 18.9 *t* (C-2), 16.7 *q* (C-15). **7**: thick oil, IR ν_{max} (NaCl): 1745, 1675, 1625 cm^{-1}; UV λ_{max} (EtOH): 244 nm (log ε 3.92); ^{1}H NMR (90 MHz, $CDCl_3$): δ 10.03 (1H, *s*, H-12), 5.00 and 4.87 (AB system, *J* = 13 Hz, 2H-11), 2.03 (3H, *s*, OAc), C-Me at 1.07, 0.91 and 0.87 (3H each, *s*). For the IR, ^{1}H NMR, and MS data of **8** see refs [2c,3d,14].

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10. Photo-oxidations were carried out at room temperature in pyridine solution with rose Bengal (10^{-3} M) as sensitizer. After 72 h. the solvent was removed and the residue treated with an aqueous solution of Na_2SO_3 (10 %, w/v) during 30 min. under stirring. Extraction with $CHCl_3$ and work-up in the usual manner yielded the crude products, which were purified by column chromatography.
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(Received in UK 30 December 1988)