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FACILE BIOMIMETIC SYNTHESIS OF COSTUNOLIDE-1,10-EPOXIDE, SANTAMARIN AND REYNOSIN[*]

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Key Word Index—Sesquiterpene lactone; costunolide-1,10-epoxide; santamarin; reynosin; synthesis.

Abstract—Reaction of costunolide with peracids yields costunolide-1,10-epoxide which undergoes ready cyclization to santamarin and reynosin.

It has been suggested that epoxidation of cyclodecadienolides followed by acid catalysed transformations of the resulting oxides is the most likely biogenetic route to bicyclic sesquiterpene lactones [1]. Indicative evidence supporting the oxidative elaboration of eudesmanolides and guainolides from germacranolide epoxides has been found in the isomerization of pyrethrosin (**1**) [2] to cyclopyrethrosins **2** and **3** [2, 3] and the formation of the guaianolides **4a** and **4b** from dihydroparthenolide (**5a**) [4] and lanuginolide (**5b**) [5] respectively.

Even though several biogenetically relevant cyclizations of costunolide (**6**) have been performed [6, 7†], it is surprising to note that costunolide-1,10-epoxide (**7**) has remained unknown [1, 7]. When **6** was allowed to react with peracetic acid or *m*-chloroperbenzoic acid in $CHCl_3$ containing NaOAc, at room temperature, for 10 min, a *ca* 98% yield of the heretofore unreported epoxide **7** could be isolated by direct crystallization from the reaction mixture. In the MS the M^+ at *m/e* 248 was in agreement with the addition of an O atom to **6**. Epoxidation was indicated by the IR spectrum which showed the appearance of new absorption bands at 1248, 926 and 833 cm^{-1}. The location of the epoxide function was easily determined by inspection of the PMR spectrum obtained with a freshly prepared $CDCl_3$ solution (*vide infra*). A double doublet centered at δ 2.72 ($J = 2$ and 11 Hz) could be assigned to H-1 whereas a sharp 3-proton singlet at δ 1.15 was attributed to the C-10 Me. As expected, H-5 was coupled ($J =$ 10 Hz) with H-6 and long ranged coupled ($J = 2$ Hz) with the C-4 Me (doublet at δ 1.84) appearing as a double doublet centred at δ 5.29. The lactonic methine proton appeared as a triplet ($J = 10$ Hz) centred at δ 4.61.[‡]

Epoxide **7** is not stable and undergoes isomerization to a mixture of santamarin (**8**, *ca* 65%) [8] and reynosin (**9**, *ca* 35%) [9] under a variety of conditions which include: standing at room temperature in $CHCl_3$ solution ($t_{1/2}$, *ca* 7 days), chromatography over silica gel (*ca* 1 hr in contact with the gel) and reaction with $BF_3 \cdot Et_2O$ in benzene at room temperature for 30 min. The relative instability of **7** may explain why it has never been isolated from any reaction [7] or plant material and also casts some doubts on the very existence of **8** and **9**. Obviously, **7** could have never survived the procedures used for the isolation of the latter two compounds [8, 9].

The facile transformation of **7** into **8** and **9** may be regarded as strong indication of the stereochemistry of the epoxide function in **7** as depicted, it being identical with that found for **1** and for heliangin (**10**) [10] (for a revised formula of **10** see [11]; a closely related structure, 1,10-epoxynobilin, in which the C-8 O bond is α-orientated has recently been described [12]) and a further indication that 1,10-epoxi-germacranolides are indeed very probable intermediates in the biogenesis of eudesmanolides.

EXPERIMENTAL

General procedures have already been recorded [13].

Costunolide (**6**). Obtained from the oil of *Vanillosmopsis erythropappa* as previously described [14].

Costunolide-1,10-epoxide (**7**). Costunolide (100 mg, 0.43 mmol) was dissolved in $CHCl_3$ (10 ml) and NaOAc (*ca* 100 mg) added. *m*-Chloroperbenzoic acid (97 mg, 0.43 mmol peracid) was added and the resulting mixture stirred at room temp. for 10 min. The $CHCl_3$ soln was extracted with 5% aq. Na_2CO_3 soln (2 × 50 ml), washed with H_2O (3 × 50 ml), dried (Na_2SO_4), filtered through a small charcoal bed (*ca* 1 g) and concd *in vacuo* to give pure **7** (105 mg, *ca* 98%); mp 97–99° (TLC after mp determination showed the presence of **7**, **8** and **9**); found M^+ 248.1468, calcd. M^+ 248.1412; ν_{max}(KBr) 1739 (*s*), 1667 (*w*), 1248 (*m*), 926 (*m*), 833 (*w*) cm^{-1}; MS (*m/e*): 248 (M^+, 28), 229 (32), 163 (20), 109 (28), 107 (33), 105 (22), 95 (30), 81 (75), 43 (100); PMR ($CDCl_3$, 100 MHz) δ 6.26 and 5.52 (1 each, *d*, $J = 3.5$ Hz, C-11 CH_2), 5.29 (1, *dd*, $J = 2$, 10 Hz, H-5), 4.61 (1, *t*, $J = 10$ Hz, H-6), 2.72 (1, *dd*, $J = 2$, 11 Hz, H-1), 1.84 (3, *d*, $J =$ *ca* 2 Hz, C-4Me), 1.15 (3, *s*, C-10 Me). Similar results were obtained using peracetic acid in place of *m*-chloroperbenzoic acid.

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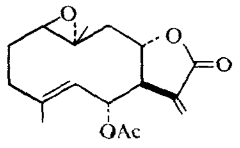
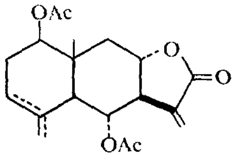
[*] Part 5 in the series 'Chemical Transformations of Abundant Natural Products'. For Part 4 see ref. [15].

[†] The reaction of **6** with perbenzoic acid at 0° for 60 hr was reported to give a mixture of **8** and **9** (undetermined distribution). In this case the proposed intermediate **7** could not be detected.

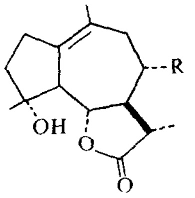
[‡] In compound **5b** the signals corresponding to H-5, H-1 and H-6 appeared at δ 2.63 (*d*, $J = 9$ Hz), δ 5.25 (*m*) and δ 3.94 (*t*, $J = 9$ Hz) respectively [5].



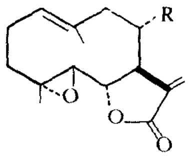
(1)



(2) and (3)



R = H, (4a)
R = OAc, (4b)



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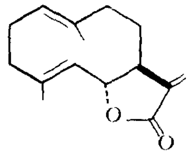
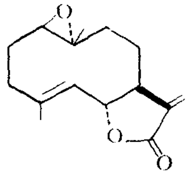
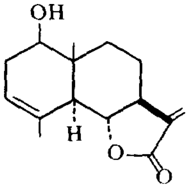
R = OAc, (5b)



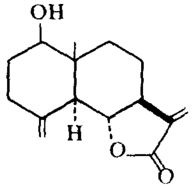
(6)



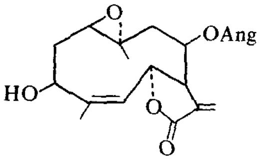
(7)



(8)



(9)



(10)

Santamarin (**8**) *and reynosin* (**9**). Costunolide-1,10-epoxide (100 mg, 0.404 mmol) was dissolved in C_6H_6 (5 ml) and $BF_3 . Et_2O$ (10 µl, *ca* 0.041 mmol) added and the resulting mixture allowed to stand at room temp. for 30 min. EtOAc (25 ml) was added and the mixture extracted with 5 % aq. $NaHCO_3$ (2 × 50 ml), washed with H_2O (2 × 50 ml), dried ($MgSO_4$) and evapd *in vacuo* to give 90 mg of a mixture of **8** (*ca* 65 %) and **9** (*ca* 35 %) as determined by PMR, measuring the relative intensities of the signals corresponding to the angular Me groups. The mixture could be resolved by prep-TLC over $AgNO_3$-impregnated Si gel G [9]. Compounds **8** and **9** gave mps and spectral data in complete agreement with those recorded for santamarin (**8**) [8] and reynosin (**9**) [9].

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