Tetrahedron Letters No.34, pp. 2917-2919, 1969. Pergamon Press. Printed in Great Britain.

A FACILE AND STEREOSPECIFIC CYCLIZATION OF COSTUNOLIDE

Tikam C. Jain and John Edmund McCloskey

Department of Chemistry, University of Victoria
Victoria, British Columbia, Canada

(Received in USA 19 May 1969; received in UK for publication 20 June 1969)

The intermediacy of a ten-membered carbocycle in the biogenesis of bicyclic sesquiterpenes originally suggested by Barton and de Mayo[1] has been brilliantly extended by Hendrickson[2]. Acid catalyzed cyclization of the naturally occurring monocyclic sesquiterpenoid lactone costunolide (I) of germacrane type[3] should yield cyclocostunolides (II and III), and consequently one anticipates their occurrence in the plants. However, so far there has been no such report on the isolation of these lactones (II and III) with a conjugated α-methylene-γ-lactone moiety. Because of the ease with which costunolide (I) polymerizes, biogenetically patterned cyclization studies of (I) with acid catalysts in our laboratories have met with a limited success. We wish to describe now a simple and efficient method of cyclization of costunolide (I) which proceeds smoothly in a stereospecific manner without any significant polymerization.

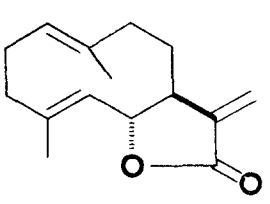
Treatment of costunolide (I) with Amberlite IR-120 cation exchange resin (20-50 mesh) in dioxane at 50° for 140 hours in an atmosphere of dry nitrogen afforded cyclocostunolides (II and III) in 67% yield*. β-Cyclocostunolide (II) [m.p. 66.5-67.0°, $[\alpha]_D^{27}$ + 179° (c,0.94)†; U.V. end absorption: ε_{205} 15130; ν_{max}^{KBr}: 1765 cm^{-1} (γ-lactone), 1674, 1650 and 894 cm^{-1}(>C=CH_2)] analyzed for $C_{15}H_{20}O_2$, further confirmed by high resolution mass measurements (Found: 232.1466. Calcd.: 232.1463). The n.m.r. spectrum of (II) was very instructive and permitted the identification of nearly every proton in the molecule.

---

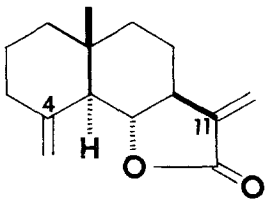
* This yield is based on the total weight of TLC pure crystalline lactones (II and III). Besides these, we have not been able to detect any other cyclization product.

† Unless otherwise stated, specific rotations were determined in $CHCl_3$ solution on a Perkin-Elmer model 141 polarimeter. N.M.R. spectra were obtained with a Varian Associates HA-60 spectrometer using Me_4Si as internal standard.

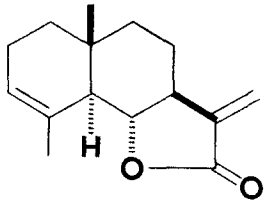
The key features of the n.m.r. spectrum were two sets of sharp doublets at 3.95τ(1H, J = 3.0 Hz), 4.61τ(1H, J = 3.0 Hz) and two broadened singlets (1H each) at 5.07 and 5.20τ assignable to >C = CH_2 units at C-11 and C-4 respectively. The former signal disappeared in the n.m.r. spectrum of dihydro β-cyclocostunolide (IV) [m.p. 137-138°, $[\alpha]_D^{27}$ + 166.7° (c, 0.88] prepared by catalytic hydrogenation (PtO_2 - absolute ethanol) of (II). Furthermore, the spectrum displayed a doublet at 8.79τ(3H, J = 6.5 Hz) ascribed to the newly created secondary methyl group at C-11. Catalytic hydrogenation of (IV) in glacial acetic acid over PtO_2 led to a fully saturated lactone, m.p. 154-155°, proven to be 4:5 αH, 6, 11 βH-eudesman-6, 13-olide (V) (3).



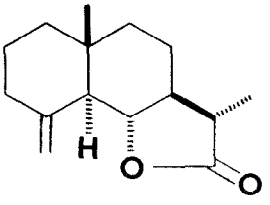
I



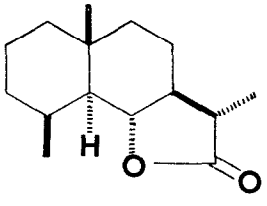
II



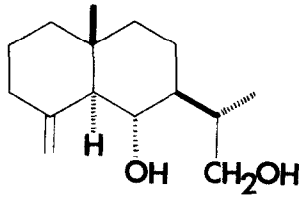
III



IV



V



VI

Reduction of (II) with sodium borohydride in absolute ethanol yielded a crystalline diol (VI) [m.p. 109-111°, $[\alpha]_D^{30}$ + 57.0° (c, 0.78); ν_{max}^{KBr}: 3280 cm^{-1} (hydroxyl), 878, 1647 cm^{-1} (>C = CH_2); N.M.R. spectrum ($CDCl_3$)τ: 5.03, 5.33 (s, 2H, >C = CH_2), 6.14-6.53 (m, 3H, -$\underline{CH}_2$OH and >$\underline{CH}$OH), 7.25 (s, 2H, -OH, disappeared on exchange with D_2O), 9.10 (d, J = 7.0 Hz, secondary methyl at C-11) and 9.27 (s, 3H, angular methyl); mass spectrum m/e (%Σ_{18}): 238 (0.14, M+), 220 (1.18, M - H_2O), 109 (11.66, base peak)].

Finally, a direct comparison of (IV-VI) with the corresponding authentic specimens* (mixed m.p., I.R., N.M.R. and mass spectra) unequivocally established the stereo-structure of β-cyclocostunolide implicit in (II). The same sequence of reactions was essentially employed for the structure elucidation[4] of α-cyclocostunolide (III) [m.p. 83-84°, $[\alpha]_D^{27}$ + 119.70° (c, 1.04)].

We wish to thank the National Research Council of Canada and the UVIC Research Committee for financial support of these studies.

REFERENCES

1. D. H. R. Barton and P. de Mayo, J. Chem. Soc., 150 (1957).

2. J. B. Hendrickson, Tetrahedron, 7, 82 (1959); see also J. H. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes and Acetogenins," W. A. Benjamin, Inc., N.Y., 1964, p. 231.

3. A. S. Rao, G. R. Kelkar and S. C. Bhattacharyya, Tetrahedron, 9, 275 (1960); V. Herout, M. Suchý and F. Šorm, Coll. Czech. Chem. Commun., 26, 2612 (1961).

4. Cf. G. H. Kulkarni, G. R. Kelkar and S. C. Bhattacharyya, Tetrahedron, 20, 2639 (1964). Besides isolating α-cyclocostunolide (III), these authors were not successful in isolating pure β-cyclocostunolide (II). However, they report $[\alpha]_D$ + 59° on an impure liquid specimen.

*Preparative details pertaining to these compounds will be reported in a full paper.