Tetrahedron. Vol. 31, pp. 2211 to 2214. Pergamon Press 1975. Printed in Great Britain

CARBOCYCLIZATION IN NATURAL PRODUCTS—I

AMBERLITE IR-120 CATION EXCHANGE RESIN CATALYZED CYCLIZATION OF COSTUNOLIDE. STRUCTURE OF β-CYCLOCOSTUNOLIDE[†,‡]

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(*Received in the USA* 14 *March* 1975; *Received in the UK for publication* 23 *April* 1975)

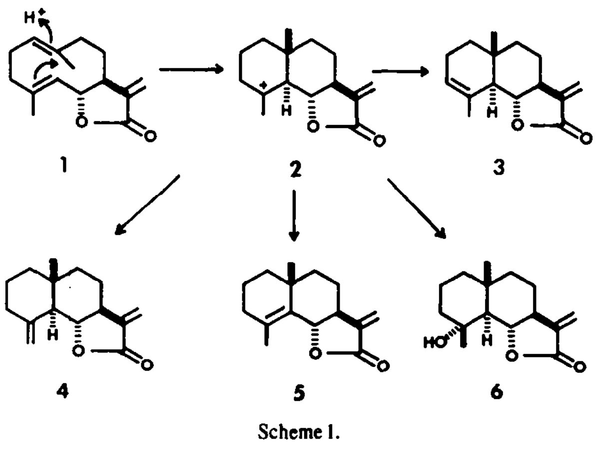
Abstract—A simple and efficient method of cyclization of costunolide leading to the isolation of pure β-cyclocostunolide is described. Evidence leading to the assignment of absolute stereostructure 4 to β-cyclocostunolide is presented.

The *trans,trans* - cyclodeca - 1,5 - diene system in a germacranolide readily undergoes transannular cyclization under the influence of acid catalysts. Costunolide 1,[1] undergoing similar carbocyclization by a stepwise process would proceed *via* the tertiary carbocationic intermediate 2 yielding, theoretically without further rearrangement the three possible unsaturated isomers 3, 4 and 5, as well as the alcohol 6 (Scheme 1). It is also conceivable that a similar reaction could be catalyzed in natural systems by means of suitable enzymes. Consequently it might be expected that the isomers 3, 4 and 5 and the alcohol 6 would occur as natural products.[¶] Successful chemical transformation of costunolide 1 to these potential natural products was a prime objective of the present investigation. In this paper we report the full details pertaining to the conversion of costunolide 1 to cyclocostunolides 3 and 4.[2]

Earlier studies[6] had shown that costunolide 1 when treated with a mixture of perchloric and acetic acids in ether at 0° for 72 hr, yields a mixture of olefins from which the unsaturated lactone 3 was isolated in low yield. A liquid sample with $[\alpha]_D + 59°$ was assigned structure 4. A careful examination of the experimental details coupled with certain anomalous features in the published spectra of the products led us to suspect the purity of β-cyclocostunolide 4. Consequently we undertook to reexamine this reaction under comparatively milder conditions.

Costunolide 1 has a great tendency to polymerize and consequently in attempting a cyclization it was decided that mild experimental conditions, patterned along the lines of natural systems, were highly desirable. As a result of preliminary experiments, Amberlite IR-120 cation exchange resin (H^+ form) was chosen to provide a suitable template where the acidic sites should initiate the carbocyclization.[7]

Treatment of costunolide 1 with Amberlite IR-120 in dioxan at 50° for 140 hr yielded a viscous liquid. The crude reaction mixture showed a strong tendency to polymerize; on standing at room temperature for a few hours a sample hardened into a polymeric mass, insoluble in organic solvents. However, this could be largely prevented by storage of the reaction product at −20° under nitrogen. TLC analysis of the reaction product with different sol-



Scheme 1.

[†] Abstracted, in part, from the Ph.D. Dissertation (University of Victoria, 1971) of J. E. McCloskey.

[‡] For a preliminary communication see Ref. 2.

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[¶] α-Cyclocostunolide 3 and C-11 dihydroderivative of β-cyclocostunolide 4 have recently been isolated as natural products from the Brazilian plant *Mochina vellutina*.[3] This lends further support to the intermediacy of a ten-membered carbocycle in the biogenesis of bicyclic sesquiterpenes originally suggested by Barton and de Mayo,[4] and later extended by Hendrickson.[5]

vent systems indicated the presence of two principal components in the crude mixture. The NMR spectrum (3·95, 4·61 and 8·15 τ) confirmed the presence of the α- and β-isomers 3 and 4. Our previous experience in resolving such closely related structural isomers suggested the use of silver complexing as an effective means of separating this mixture. Thus, chromatography of the crude product over a 50-fold column of silica gel impregnated with silver nitrate (4:1) was carried out. Elution with light petroleum/benzene (1:1) [Table 1, Experimental] led to the isolation of α-cyclocostunolide 3,[6] while elution with benzene afforded β-cyclocostunolide 4; the overall yield of TLC pure crystalline fractions was 67%.

Structure of β-cyclocostunolide 4. Crystallization of fractions 19–25 (Table 1, Experimental) from ether gave β-cyclocostunolide 4, m.p. 66·5–67°, in 36% yield. Combustion analysis of the lactone gave the molecular formula of $C_{15}H_{20}O_2$, confirmed by high resolution mass measurement of the molecular ion peak (obs: 232·1466; cal: 232·1463). The presence of the α,β-unsaturated γ-lactone unit was indicated by bands at 1765 and 1145 cm^{-1} in the IR spectrum (Fig. 1) as well as by its UV maximum at 205 nm (ε, 15130). The NMR spectrum given in Fig. 2 was particularly instructive and permitted the identification of nearly every proton in the molecule. The key features of the NMR spectrum were two sets of sharp doublets at 3·95 and 4·61 τ (1H each, J = 3·0 Hz), and two broadened singlets at 5·07 and 5·20 τ (1H each) assignable to the *exo*-methylene groups at C_{11} and C_4 respectively. A one-proton triplet at 6·03 τ (J = 10·5 Hz) is attributed to the C_6 methine hydrogen; the coupling constant confirming the axial–axial–axial arrangement of the protons at C_5, C_6 and C_7.[8] Finally, the C_{10} quaternary Me group resonates as a sharp 3-proton singlet at 9·16 τ. The structure and stereochemistry were proven by its catalytic hydrogenation to the known compounds 4,*exo*-santenolide 7 and santanolide 'a' 8. These compounds were shown to be identical with authentic specimens by mixed m.p. and through spectral comparison.

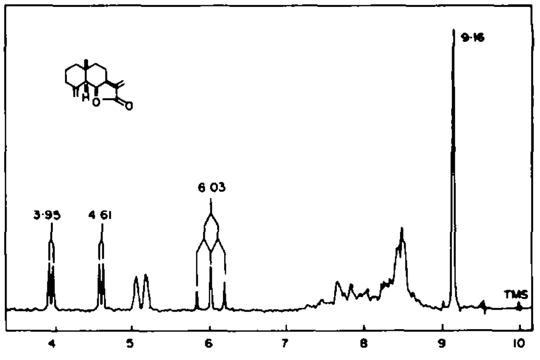
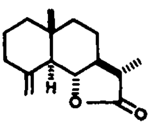


Fig. 2. NMR spectrum of β-cyclocostunolide.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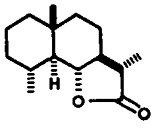
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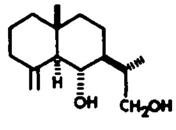

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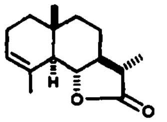
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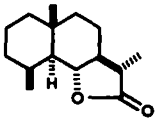
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Initial attempts to selectively reduce the unsaturated lactone 4 to its dihydroderivative 7 involved the use of sodiumborohydride.[9] Contrary to expectation, however, treatment of β-cyclocostunolide 4 with $NaBH_4$ in ethanol solution yielded a diol, m.p. 109–111°, subsequently shown to have structure 9. The IR spectrum of the reduction product displayed bands due to OH and exocyclic methylene moieties (3280, 1647 and 878 cm^{-1}); the absence of a band in the region of 1770 cm^{-1} indicated the cleavage of the lactone ring. The presence of OH groups was further confirmed by deuterium exchange whereupon a 2-proton singlet at 7·25 τ in the NMR spectrum, disappeared. A multiplet between 6·14 and 6·53 τ integrating for three hydrogens was attributed to protons *alpha* to OH groups. Finally, two broadened singlets at 5·03 and 5·33 τ (1H each) confirmed the presence of the C_4 *exo*-methylene grouping. Final proof of the structure and stereochemistry was provided by a rigorous comparison with an authentic sample.

EXPERIMENTAL

M.ps were determined on a Kofler hot-stage microscope and are uncorrected. IR spectra were recorded in KBr pellets on a Perkin-Elmer model 337 grating spectrophotometer calibrated with polystyrene film at 1601·4 and 1028·0 cm^{-1}; model 700 was used for routine scans. UV spectra were obtained in abs EtOH with Unicam models S.P. 700 and S.P. 800 spectrophotometers. Mass spectra were measured with A.E.I. MS-9 double focusing mass spectrometer, chamber voltage being 70 eV; all mass spectra are reported in terms of total ionization current (%Σ). Specific rotations were determined in chloroform with a Perkin-Elmer model 141 polarimeter. NMR spectra were obtained in $CDCl_3$ with Varian Associates HA-60 spectrometer, the chemical shift data

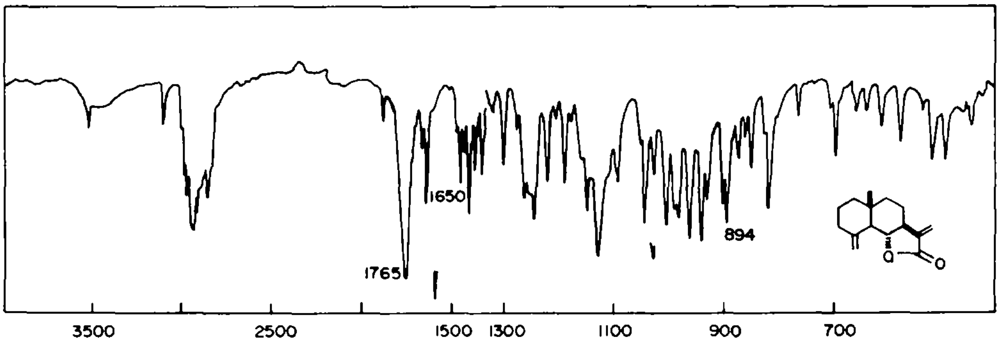

Fig. 1. IR spectrum of β-cyclocostunolide.

are given in ppm (τ) from TMS. The removal of solvent under reduced pressure was accomplished with a Büchi flash evaporator at ~25 mm of Hg. Thin layer chromatography (TLC) plates were prepared, 25 μ thick, from Camag silica gel and alumina. All chromatographic solvent mixtures are v/v, and were freshly distilled. Visualization of the thin layer plates was affected by exposure to iodine vapour. Microanalyses were performed by Scandinavian Microanalytical Laboratories, Herlev, Denmark and by Swartzkopf Microanalytical Laboratory, New York. The authentic samples used in this investigation were prepared by modifying the literature procedures. For complete details including their spectra (see Ref. 10).

Acid catalyzed carbocyclization of costunolide 1. Amberlite IR-120 cation exchange resin (10 g; 20–50 mesh)† was added to a soln of 1 (1·0 g) dissolved in dioxan (50 ml). The mixture was stirred magnetically in an atmosphere of dry N_2 at 50° (bath temp) for 140 hr. On cooling the resin was filtered off and the solvent removed *in vacuo*. The gummy residue was taken up in benzene (25 ml), washed with water (5 × 25 ml), dried over Na_2SO_4 and evaporated under reduced pressure to give a viscous liquid (1·1 g) which showed two spots on a silica gel/$AgNO_3$ TLC plate. The product (5·3 g) obtained from several runs was chromatographed over silica gel/$AgNO_3$‡ (200 g). In all 25 fractions were collected and combined as shown in Table 1 on the basis of TLC and spectral analysis.

Table 1.

Fraction	Solvent	Volume	Weight	ν_{max}
1-4	Pet. ether	2.0 ℓ	trace	--
5-8	Pet. ether-Benzene (3:1)	2.0 ℓ	trace	--
9-13	Pet. ether-Benzene (1:1)	2.5 ℓ	1.51 g	1672 cm^{-1}
14-16	Pet. ether-Benzene (1:1)	1.5 ℓ	trace	--
17-18	Pet. ether-Benzene (1:3)	0.5 ℓ	trace	--
19-25	Benzene	3.5 ℓ	1.81 g	1650 cm^{-1}

α-Cyclocostunolide 3. Crystallization of fraction 9–13 (Table 1) from ether yielded 3 (31%), m.p. 83–84°; $[\alpha]_D^{29}$ +119·7° (*c*, 1·04); UV spectrum: λ_{max} 205 nm (ϵ, 12004); IR spectrum: 1765, 1141 cm^{-1} (γ-lactone), 1672, 866 cm^{-1} (double bonds); Mass spectrum *m/e* ($\%\Sigma_{18}$): 232 (4·70, M^+); NMR spectrum (τ): 3·95 (d, 1H, J = 3·0 Hz, >C=CH_2), 4·61 (d, 2H, J = 3·0 Hz, >C=CH_2 and –C=CH), 6·12 (q, 1H, ABX pattern with J_{AX} = 11·0 Hz, J_{BX} = 10·7 Hz, HC–O–C=O), 8·15 (t, 3H, J = 1·5 Hz, –C=C–CH_3), 9·09 (s, 3H, –C–CH_3). (Found: C, 77·39; H, 8·61. $C_{15}H_{20}O_2$ requires: C, 77·55; H, 8·68%).

α-Cyclodihydrocostunolide **10**. α-Cyclocostunolide 3 (37 mg) was dissolved in abs EtOH (10 ml) and PtO_2 (1·0 mg) was added to the soln. The mixture was stirred in an atmosphere of H_2 for 17·5 hr. Filtration of the catalyst and removal of the solvent under reduced pressure yielded a solid material crystallized from pet ether–ether and then from EtOH to give crystals of **10**, m.p. 139–140° (undepressed on admixture with an authentic sample). The IR and mass spectra of this product were identical with those of an authentic specimen.

Santanolide 'c' **11**. PtO_2 (1·0 mg) was added to a soln of 3 (110 mg) in abs EtOH (15 ml), and the mixture was stirred under H_2 for 15·5 hr. The catalyst was filtered and the solvent removed *in vacuo*, yielding a crude product which was analyzed by NMR spectroscopy to ascertain the extent of the reaction. This material was then dissolved in glacial AcOH (10 ml) and stirred in the presence of PtO_2 (25 mg) in an atmosphere of H_2 for 23 hr. The catalyst was removed by filtration, solvent distilled off under reduced pressure to yield crude **11**, crystallized from EtOH to give pure **11**, m.p. 154–155° (undepressed on admixture with an authentic sample); $[\alpha]_D^{31}$ +58·7° (*c*, 0·79); Found: C, 76·22; H, 10·66. $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%).

The IR, NMR and mass spectra of this product were identical with those of the authentic specimen.

β-Cyclocostunolide 4. Crystallization of fraction 19–25 (Table 1) from ether gave 4 (36% yield), m.p. 66·5–67·0°; $[\alpha]_D^{27}$ +179·0° (*c*, 0·94); UV spectrum: λ_{max} 205 nm (ϵ, 15130); IR spectrum (Fig. 1): 1765, 1147 cm^{-1} (γ-lactone), 1674, 1650, 894 cm^{-1} (unsaturated linkages); Mass spectrum *m/e* ($\%\Sigma_{18}$): 232 (7·28, M^+); (Found: C, 77·58; H, 8·65. $C_{15}H_{20}O_2$ requires: C, 77·55; H, 8·68%).

β-Cyclodihydrocostunolide 7. β-Cyclocostunolide 4 (40 mg) dissolved in abs EtOH (10 ml) was hydrogenated in the presence of PtO_2 (1·0 mg) for 2·25 hr. Filtration followed by removal of solvent yielded crude product (40 mg). Crystallization from EtOH yielded cubic crystals which melted at 137–138° (undepressed on admixture with an authentic sample of 7); $[\alpha]_D^{27}$ + 166·7° (*c*, 0·88); (Found: C, 76·84; H, 9·56. $C_{15}H_{22}O_2$ requires: C, 76·88;, H, 9·46%).

The IR, NMR and mass spectra of this compound were identical with those of the authentic sample.

Catalytic hydrogenation of β-cyclocostunolide 4. β-Cyclocostunolide (30 mg), dissolved in EtOH (10 ml) was hydrogenated (3 hr) in the presence of PtO_2 (1·0 mg). Catalyst and solvent were removed, the product analyzed by NMR and then returned for further hydrogenation (22 hr) in glacial AcOH (10 ml) over PtO_2 (20 mg). Upon completion of the reaction the catalyst was filtered off, and the solvent removed *in vacuo*. The crude product was crystallized twice from EtOH to give pure **8**,§ m.p. 153–154°, and was shown by IR and NMR spectroscopy to be identical with an authentic sample.

Sodium borohydride reduction of β-cyclocostunolide 4. β-Cyclocostunolide 4 (200 mg) dissolved in abs EtOH (20 ml) was treated with $NaBH_4$ (162 mg; 5 eq) at room temp. for 22 hr. 5% NaOH aq (1 ml) was added to decompose the complex, the resulting solution was filtered through celite, and the solvent removed *in vacuo*. The residue taken up in ether was washed with brine, the organic layer dried over Na_2SO_4 and concentrated *in vacuo* to give a gummy material. Crystallization from ether yielded needles, m.p. 109–111°; $[\alpha]_D^{30}$ +57·0° (*c*, 0·78). (Found: C, 75·50; H, 11·03. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%).

Diol 9 from β-cyclodihydrocostunolide 7. Sodium borohydride (27 mg; 5 eq) was added to a soln of 7 (35 mg) in abs EtOH (10 ml). The mixture was stirred for 24 hr at room temp and was worked up as described above to give a viscous liquid which upon crystallization from ether furnished diol 9, m.p. 111·0–112·5°; $[\alpha]_D^{27}$ +50·0° (*c*, 0·74); IR spectrum: 3281 cm^{-1} (OH), 1645, 877 cm^{-1} (exocyclic methylene); Mass spectrum *m/e* ($\%\Sigma_{18}$): 238 (0·14, M^+); NMR spectrum (τ): 5·03, 5·34 (s, 1H each, >C=CH_2), 6·15–6·53 (m, 3H, >C$\underline{H}$OH and >C$\underline{H}_2$OH), 7·41 (s, 2H, OH groups, disappeared on exchange with D_2O), 9·10 (d, 3H, J = 7·0 Hz, HC–C$\underline{H}_3$) and 9·27 (s, 3H, –C=C–CH_3). (Found: C, 76·21; H, 11·23. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%).

The IR, NMR and mass spectra of the diol 9 were identical with the corresponding spectra of the product obtained by $NaBH_4$ reduction of 4 described above. Furthermore, the mixed melting point of the two products remained constant.

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

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†Strongly acidic sulfonated polystyrene type of medium porosity; supplied by Mallinckrodt Chemical Works, Montreal.

‡Silver nitrate impregnated silica gel has been extensively used in our laboratory with remarkable success in resolving various closely related structural isomers. For this purpose, we have standardized its preparation and the experimental details are as follows: Silica gel (500 g) was added with vigorous stirring to a boiling solution of $AgNO_3$ (125 g) dissolved in water (1·0 l). Stirring and heating was maintained for 30 min. The mixture was then filtered by suction for 1 hr, and baked overnight at 115°. All operations were shielded from light.

§This was inadvertently reported as santanolide 'c' in Ref. 2.

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