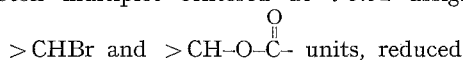


The Direct Brominative Cyclization of Dihydrocostunolide

The outstanding oxidative brominating ability of N-bromosuccinimide (NBS) has been elegantly applied to various acyclic isoprenoids which under controlled conditions yield terminal bromohydrins¹. In this communication, we wish to report on a similar oxidation of dihydrocostunolide² **1** with concurrent cyclization in a stereospecific manner. Treatment of **1** with NBS in aqueous acetone at room temperature furnished a viscous gum (3 spots on thin layer chromatogram plate in several solvent systems); careful fractionation of this gum over silica gel column resulted in a crystalline bromohydrin **2** (55%)³, bromolactones **3** and **4** (14% and 25% resp)³. The bromohydrin⁴ **2** [mp 160.0–166.5°, $[\alpha]_D^{25}$ –15.03° (c 1.45); no characteristic absorption in the UV-spectrum; ν max (cm⁻¹) 3605, 3583 (m) (t – OH), 1794 (s) and 1772 (w, shoulder) (>C = O stretching vibrations of a γ -lactone)⁵, 1168 (C – O stretching vibrations)] analyzed for C₁₅H₂₃O₃Br (Found: C, 54.17; H, 6.90; Br, 24.60), further confirmed by its high resolution mass spectrum which revealed significant peaks due to M-CH₃ (C₁₄H₂₀O₃⁷⁹Br; observed mass 315.0593, calculated mass 315.0596) and M-HBr (C₁₅H₂₂O₃; observed mass 250.1567, calculated mass 250.1569). The NMR-spectrum of **2** exhibited a two-proton multiplet centered at τ 5.92 assigned to



to a one-proton triplet (with finer splittings) centered at τ 5.96 in the debromo compound **5**. Furthermore, the spectrum revealed the presence of 3 C-methyl groups: one secondary (d, 3H, τ 8.78, J = 6.5 Hz) and one tertiary (s, 3H, τ 8.63). In addition, the signal at τ 8.87 attributed to the third methyl group at C-10 is paramagnetically displaced by 0.13 ppm relative to C-10 methyl of the debromo compound **5** (τ 9.00)⁶.

Catalytic hydrogenation⁷ of **2** in ethanol over Pd-C (10%) containing a trace of Et₃N furnished a key compound **5**, C₁₅H₂₄O₃ [mp 108.5–110.0°, $[\alpha]_D^{25}$ +11.9° (c 1.24); ν max (cm⁻¹) 3617 (t – OH) and 1777 (lactonic carbonyl); mass spectrum, m/e (% Σ_{18}): 252 (0.48, M⁺), 234 (0.60, M-H₂O), 219 (0.97, M-H₂O-CH₃), 161 (0.83) and 43 (6.69, base peak)]. The NMR-spectrum was consistent with the assigned structure **5**.

In order to probe chemically for the position of hydroxyl group, the compound **5** on heating with pyridine-treated alumina⁸ afforded the major *exo*-isomer **6** (mp 137–140°, $[\alpha]_D^{25}$ +150.2° (c 0.9); ν max (cm⁻¹) 1766 (lactone), 1655 and 887 (>C = CH₂); mass spectrum, m/e (% Σ_{18}): 234 (7.06, M⁺ as well as base peak), 219 (4.77, M-CH₃), 161 (1.31, M-73)⁹; NMR (τ) 5.08, 5.24 (s, 2H, >C = CH₂), 6.01 (t, broad, 1H, >CH-O-C-), 8.77 (d, 3H, J = 6.5 Hz, C-11 methyl), 9.14 (s, 3H, C-10 methyl); yield¹⁰ 70%). The minor *endo*-isomer **7** (mp 137.0–139.5°, $[\alpha]_D^{25}$ +78.7° (c 0.74); ν max (cm⁻¹) 1770 (carbonyl), 854 and 794 (trisubstituted double bond)); NMR (τ) 4.63 (s, broad, 1H, -CH = C-), 8.18 (t, 3H, J = 1.3 Hz, C-4 Me), 8.78 (d, 3H, J = 6.5 Hz, C-11 Me), 9.08 (s, 3H, C-10 Me); mass spectrum, m/e (% Σ_{18}): 234 (7.02, M⁺), 219 (11.42, M-CH₃, base peak, cf. mass spectrum of **6**), 161 (3.21, M-73)⁹; yield¹⁰ 30%). Because of the predominance of **6**, the hydroxyl group at C-4 in **5** and hence in **2** must be equatorial and α ¹¹. Finally, the identity of **6** and **7** was unambiguously confirmed by their rigorous comparison with authentic specimens of the corresponding santenolides¹² (mixed mp, IR-, NMR- and mass spectra).

The bromolactone **3** [mp 136–137°, $[\alpha]_D^{25}$ –2.78° (c 1.4); ν max (cm⁻¹) 1766, 1176 (saturated γ -lactone), 853 and 793 (trisubstituted double bond)] analyzed for C₁₅H₂₁O₂Br which was supported by high resolution mass measurements: M⁺ (C₁₅H₂₁O₂⁷⁹Br; observed mass 312.0724, calculated mass 312.0726), M-CH₃ (C₁₄H₁₈O₂⁷⁹Br; observed mass 297.0495, calculated mass 297.0492), M-Br (C₁₅H₂₁O₂; observed mass 233.1540, calculated mass 233.1542). The NMR-spectrum showed the following methyl resonances: τ 9.00 (s, 3H, angular methyl), τ 8.78 (d, 3H, J = 6.5 Hz, C-11 Me), τ 8.19 (t, 3H, J = 1.5 Hz, C-4 Me). The lone proton at C-1 exhibited X part of an ABX splitting pattern¹³ in the NMR-spectrum as a quartet centered at τ 5.74 (J_{AX} = 9.5 Hz, J_{BX} = 7.5 Hz)¹⁴. These splittings are consistent with axial-axial and axial-equatorial interactions respectively and hence H_X at C-1 must be axial. This in turn establishes the equatorial and β character of C-1-Br linkage¹⁵ in bromolactone **3**.

¹ For an excellent review article see E. E. VAN TAMELEN, *Accounts, Chem. Res.* **1**, 111 (1968).

² 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).

³ Based on the weight of TLC pure fractions isolated by column chromatography.

⁴ The compound **2** is thermally unstable which accounts for a wide range in its melting point, largely dependent upon the rate with which the block is heated. Satisfactory determinations in this range were repeatedly carried out by placing the crystals on a preheated block (150°C).

⁵ The bromohydrin **2** exhibited sharp intense carbonyl band at 1783 cm⁻¹ in CHCl₃ solution. Steroidal saturated γ -lactones generally absorb between 1782 and 1772 cm⁻¹ in the same solvent; see R. N. JONES and B. S. GALLAGHER, *J. Am. chem. Soc.* **81**, 5242 (1959).

⁶ NMR-spectra were obtained in CDCl₃ solution with a Varian Associates HA-60 spectrometer operated by Mrs. C. GREENWOOD, IR-spectra were recorded in KBr pellets on a Perkin-Elmer model 337 grating spectrophotometer calibrated with polystyrene film, model 700 was used for routine spectral check up; mass spectra were recorded on A.E.I. MS-9 and Hitachi-Perkin-Elmer RMU-6E mass spectrometers. All melting points were determined on a Kofler hot-stage microscope and are uncorrected. Unless otherwise indicated, specific rotations were determined in CHCl₃ solution on a Perkin-Elmer model 141 polarimeter.

⁷ P. N. RYLANDER, *Catalytic Hydrogenation over Platinum Metals* (Academic Press, New York 1967), chapter 24.

⁸ E. VON RUDLOFF, *Can. J. Chem.* **39**, 1860 (1961).

⁹ The significance of this peak will be elaborated in our full paper.

¹⁰ Percentage yields are based on the NMR-analysis of the reaction product.

¹¹ D. H. R. BARTON, A. DA S. CAMPOS-NEVES and R. C. COOKSON, *J. chem. Soc.* **3500** (1956).

¹² W. COCKER and T. B. H. McMURRY, *J. chem. Soc.* **4549** (1956). – A. M. SHALIGRAM, A. S. RAO and S. C. BHATTACHARYYA, *Tetrahedron* **18**, 969 (1962).

¹³ N. S. BHACCA and D. H. WILLIAMS, *Applications of NMR-Spectroscopy in Organic Chemistry* (Holden-Day, Inc., San Francisco 1964), chapter 6.

¹⁴ Cf. E. E. VAN TAMELEN and E. J. HESSLER, *Chem. Commun.* **411** (1966). – E. D. BROWN, M. D. SOLOMON, J. K. SUTHERLAND and A. TORRE, *Chem. Commun.* **111** (1967).

¹⁵ The NMR-spectra of **2** and **4** were not very informative in this context since the triplet due to C-6 proton partly overlapped the quartet due to C-1 proton. However, we base our configurational assignment at C-1 in **2** and **4** on the assumption that the initial electrophilic attack on the most reactive double bond between C-1 and C-10 in **1** follows a pathway common to the formation of **2**, **3** and **4** which could be rationalized in terms of a concerted (nonstop) or a multi-step process or both.

The *exo*-isomer¹⁶ **4** [mp 169–170°, $[\alpha]_D^{29} + 79.1^\circ$ (c 1.46); ν max (cm⁻¹) 1770, 1173 (saturated γ -lactone), 1655 and 893 (exocyclic methylene); NMR (τ) 5.02, 5.14 (s, 2H, $>C=CH_2$), 5.97 (m, 2H, $>CHBr$ and $>CH-O-C(=O)$ -units), 8.79 (d, 3H, $J = 7.0$ Hz, C-11 Me), 9.03 (s, 3H, angular methyl)] gave analysis for C₁₅H₂₁O₂Br, further corroborated by high resolution mass measurements: M⁺ (C₁₅H₂₁O₂⁷⁹Br; observed mass 312.0724, calculated mass 312.0726), M-Br (C₁₅H₂₁O₂; observed mass 233.1540, calculated mass 233.1542). Catalytic hydrogenation of *endo*- as well as *exo*-isomers **3** and **4** in glacial acetic acid over PtO₂ led to a fully saturated bromolactone **9** [mp 199–200°, $[\alpha]_D^{29} + 11.9^\circ$ (c 0.69); NMR (τ) 6.01

(m, 2H, $>CHBr$ and $>CH-O-C(=O)$ -units), 8.73 and 8.83 (6H, doublet due to C-11 methyl partly superimposed on the singlet due to C-10 methyl), 8.96 (d, 3H, $J = 7.0$ Hz, C-4 methyl); ν max 1761 cm⁻¹ (γ -lactone); M⁺ peak at

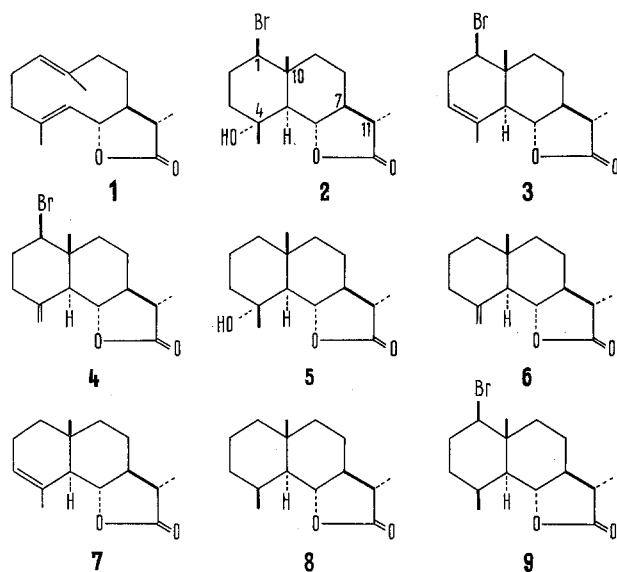
m/e 314 (C₁₅H₂₃O₂⁷⁹Br; observed mass 314.0882, calculated mass 314.0880)] which on catalytic debromination in EtOH (10% Pd-C, H₂, trace of Et₃N) furnished a crystalline compound **8**, mp 155–156°, which showed no depression in its melting point when admixed with an authentic specimen of 4:5 α H, 6, 11 β H-eudesman 6,13-olide (santanolide 'c')¹⁷. Furthermore, their IR- and mass spectra were comparable.

Thus, these chemical correlations with santanolides (**6**, **7**) and santanolide 'c' (**8**), compounds with well-proven stereostructure^{12,17}, establish unequivocally the presence of *trans*-ring juncture in **2**, **3** and **4** produced by NBS-induced cyclization of dihydrocostunolide **1**. It may be relevant to point out that the bromolactones described in this communication are potential intermediates in the syntheses of some of the natural products currently under way in our laboratories^{18,21}.

Zusammenfassung. N-Bromosuccinimid-induzierte trans-annulare Zyklisation von Dihydrocostunolid wird beschrieben.

T. C. JAIN, C. M. BANKS¹⁹
and J. E. McCLOSKEY²⁰

Department of Chemistry, University of Victoria,
Victoria (British Columbia, Canada), 10 June 1969.



¹⁶ The failure to prepare **3** and **4** from bromohydrin **2** under various experimental conditions clearly rules out any possibility of their derivation from **2** during NBS reaction carried out under mild conditions.

¹⁷ E. J. COREY and A. G. HORTMANN, J. Am. Chem. Soc. 87, 5736 (1965) and references cited therein.

¹⁸ Support of this work by the National Research Council of Canada and the UVIC Research Committee is gratefully acknowledged. We wish to thank Professor A. FISCHER for helpful discussions and his interest in this work.

¹⁹ N.R.C. Postgraduate Scholar, 1968 until present.

²⁰ U.VIC Graduate Teaching Assistant, 1968 until present.

²¹ Note added in proof: This reaction has now been successfully applied to costunolide and the results will be published in our full paper.

Phthalate Esters of *Oenanthe stolonifera* DC. (Umbelliferae)¹

In a previous communication², we reported that the isolation and identification of several di-alkyl phthalates from *Cryptotaenia canadensis* DC. var. *japonica* Makino (Umbelliferae). On further investigation, three optically inactive phthalate esters, di-ethyl, *n*-butyl-2-ethylbutyl and di-2-ethylbutyl phthalate, have been found from benzene extract of whole plant of *Oenanthe stolonifera* DC. (Umbelliferae). It is the first case where di-2-ethylbutyl and *n*-butyl-2-ethylbutyl phthalate are isolated in nature.

The benzene extract was chromatographed on silica-gel column, eluted with *n*-hexane and then with *n*-hexane-ethyl acetate. The fraction eluted by *n*-hexane-ethyl acetate (1:1 v/v) gave a yellow oily material, which showed 9 peaks on the gas chromatogram and the characteristic IR- and UV-spectra due to di-alkyl phthalate esters.

n-Butyl-2-ethylbutyl phthalate. The constituent isolated through repeated column chromatography showed UV-maxima at λ_{max}^{EtOH} nm (log ϵ) 225.7 (3.89), 277.5 (3.13) and 283 (3.11) due to benzene ring, IR-bands at 1733 cm⁻¹, 1285, 1130 (aromatic ester), 1605, 1586, 1075, 1043 and 747 (*ortho* substituted benzene ring) and mass spectrum having distinctive fragment ions at m/e 43 (C₄H₉⁺), 85 (C₆H₁₃⁺), 149 (base peak), 205, 223, 233 and 251 as represented below (Diagram). The NMR-spectrum (60 MHz, in CDCl₃) indicated *ortho* substituted benzene

¹ Japanese name is Seri.

² S. HAYASHI, Y. ASAKAWA, T. ISHIDA and T. MATSUURA, Tetrahedron Letters 50, 5061 (1967).