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CARBOCYCLIZATION IN NATURAL PRODUCTS—II[a]

BROMINATIVE CYCLIZATION OF DIHYDROCOSTUNOLIDE[b,c]

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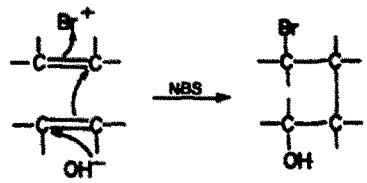
Abstract—Treatment of dihydrocostunolide 1 with NBS in aqueous acetone at room temperature furnished bromolactones 3, 4 and 5. Structural evidence for these bromolactones rests upon spectral data and chemical correlations with santanolide "c" 10. Mass spectral fragmentation patterns for the bromolactones, with special reference to 4, have been also discussed.

The organic chemist has been faced with the problem of imitating Nature's process of cyclizing acyclic olefins since 1953, when the elaborate biogenetic pathway of the conversion of squalene to cholesterol was elucidated.[3] These biogenetic cyclizations are enzyme controlled. However in 1955 Stork[4] and Eschenmoser[5] independently set forth the concept that the configuration of the acyclic olefin was of paramount importance in the cyclization process. Thus the problem for non-enzymic cyclizations has been to obtain suitable olefinic substrates which could adopt the correct orientation of double bonds for facile cyclization.

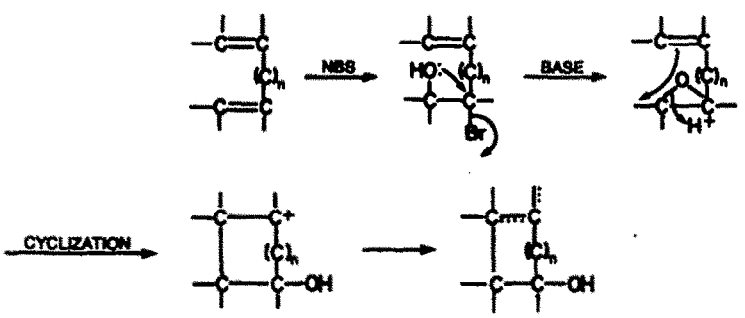
N-Bromosuccinimide (NBS) has been elegantly applied by van Tamelen *et al.* to various acyclic polyisoprenoids which under controlled conditions invariably yielded terminal bromohydrins,[6] which were ideal precursors for the corresponding epoxides. The epoxide group in an olefinic system provided an excellent site for initiating the cyclization step in a given molecule (Scheme 1). It has been demonstrated that the course of carbocyclization largely depends, among other factors, on the steric and conformational characteristics of the olefinic substrate which are controlled by the polarity of the solvent employed. If in a given substrate two olefinic systems are oriented in an overlapping manner, then the oxidative attack of NBS with concurrent cyclization would yield the bromohydrin (Scheme 2). The significant features of this reaction are formation of a new C–C bond and the introduction of two functional groups in a stereospecific manner. This prompted us to undertake a detailed study of this reaction on costunolide 2 and its derivatives where the conformation of the ring would play a major role. This study would provide us with precursors functionalized at C-1 and C-4, suitable for the syntheses of certain bicyclic natural products.

The cyclic substrates previously investigated were germacratriene[7] and humulene.[8,9] As it will become evident from the following account our results differed markedly from those obtained by Sutherland. The conformational characteristics of these cyclic substrates were largely responsible for the variation.

Dihydrocostunolide as a substrate for brominative cyclization. Due to several considerations dihydrocostunolide 1.[10] rather than the parent lactone costunolide 2, was chosen for our initial brominative cyclization stu-



Scheme 2.



Scheme 1.

[a] For Part I in this series see Ref. 1.
[b] For a preliminary communication on this work see Ref. 2.
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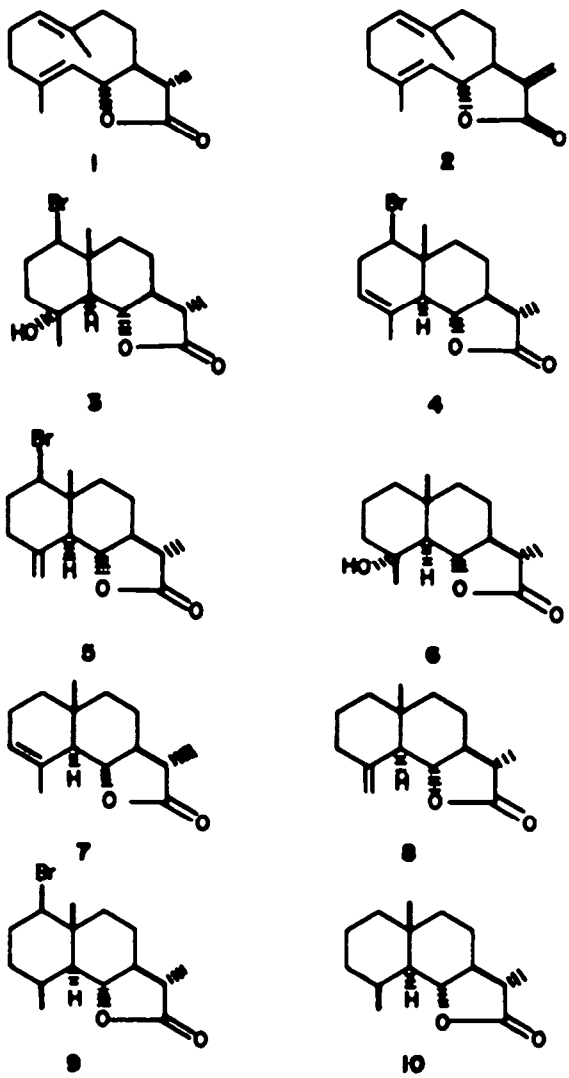
dies. Dihydrocostunolide was dissolved in 5% water/acetone to which a molar quantity of NBS was added. After stirring for 19 hr at room temperature the reaction was worked up to yield a crude gum which displayed three distinct spots in several solvent systems on a silica gel tlc plate. Careful chromatography over a silica gel column separated the gum into three crystalline compounds described in the sequel as the bromohydrin 3, and the bromolactones 4 and 5.

Structure of bromohydrin 3. The crystalline material obtained from fractions 21 to 24 (Experimental) constituting about 55% of the product was thermally unstable, indicated by its wide range of m.p. Nevertheless, a reproducible range of 160.0–166.5° was obtained by placing the crystals on a preheated block at 150°. Combustion analysis gave the molecular formula of $C_{15}H_{23}O_3Br$ supported by high resolution mass measurements of the fragment ions given in Table 1. Of the three O atoms in the bromohydrin 3, one was present in the form of a tertiary OH group evident by its IR bands at 3685 and 3583 cm^{-1}. The remaining two O atoms could be accommodated in a γ-lactone moiety which was responsible for the characteristic bands at 1794 and 1168 cm^{-1}[a] (Fig. 1).

That a transannular cyclization had occurred was revealed by the NMR spectrum of the bromohydrin 3 which showed that the diagnostic vinylic methyl signals of the *trans, trans* - 1,5 - cyclodecadiene system[12] in costunolide at τ8.31 and 8.57 had shifted upfield to τ8.63 and 8.87 due to HO–C–Me and –C–Me groups respectively. This assumption was confirmed by the complete absence of any olefinic resonances. A broad two-proton multiplet centered at τ5.92 was attributed to the methine hydrogens *a* to a Br atom and *a* to the ethereal O of a γ-lactone ring.

The key experiment in the structure determination was catalytic dehalogenation of the bromohydrin 3 (10% Pd/C, H_2) in the presence of a trace of triethylamine[13] whereupon the hydroxylactone 6 was obtained. The NMR spectrum displayed a one-proton triplet with finer splittings centered at τ5.96 (HC–O–C=O) which indicated creation of a new methylene group from the former methine position *a* to the bromine. The C-10 Me (τ9.00) was diamagnetically shifted by τ0.12 units in the spectrum of the hydroxylactone 6 due to removal of the adjacent bromine at C-1. The above data were confirmed by elemental analysis and mass spectrometry which supported the formula $C_{15}H_{24}O_3$ (M^+ *m/e* 252).



Scheme 3.

[a]The bromohydrin exhibited a sharp intense CO band at 1783 cm^{-1} in $CHCl_3$ solution. Steroidal saturated γ-lactones generally absorb between 1782 and 1772 cm^{-1} in the same solvent.[11]

Table 1. Accurate mass measurements and composition of ions

Lactone	Obs. Mass	Calc. Mass	Composition	Fragment
3	315.0593	315.0596	$C_{14}H_{20}O_2{}^{79}Br$	$M^+ - CH_3$
	250.1567	250.1569	$C_{15}H_{22}O_2$	$M^+ - HBr$
4	312.0724	312.0720	$C_{15}H_{21}O_2{}^{79}Br$	M^+
	297.0493	297.0492	$C_{14}H_{18}O_2{}^{79}Br$	$M^+ - CH_3$
	233.1540	233.1542	$C_{15}H_{21}O_2$	$M^+ - Br$
5	312.0724	312.0720	$C_{15}H_{21}O_2{}^{79}Br$	M^+
	233.1540	233.1542	$C_{15}H_{21}O_2$	$M^+ - Br$
9	314.0882	314.0880	$C_{15}H_{23}O_2{}^{79}Br$	M^+
	235.1696	235.1698	$C_{15}H_{23}O_2$	$M^+ - Br$

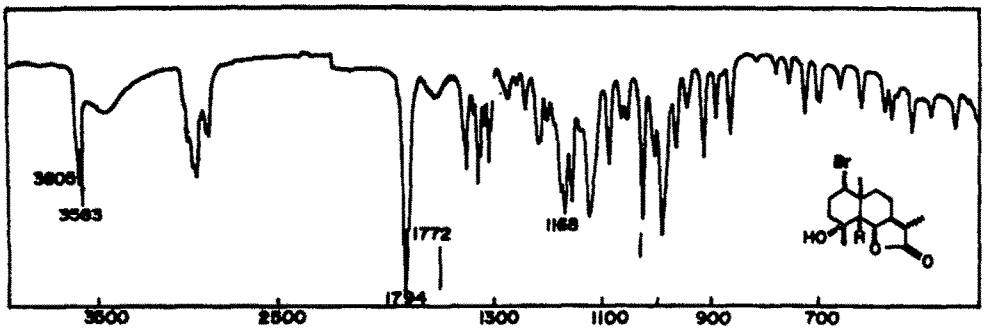


Fig. 1.

Location of hydroxyl group. In order to ascertain chemically the position of the OH group, the hydroxylactone 6 was subjected to various dehydration procedures. The method that provided the most useful information was the reaction of 6 with pyridine-treated alumina (2%) at high temperature.[14] The product displayed two distinct spots on a silica gel-$AgNO_3$ tlc plate; also the presence of two compounds was detected by the NMR spectrum of the crude material which showed signals characteristic of endocyclic and exocyclic double bonds. Column chromatography of the dehydration product over silica gel impregnated with $AgNO_3$ resolved it into the minor *endo*-isomer 7 (30%) and the major *exo*-isomer 8 (70%).

The NMR spectrum of the *endo*-isomer 7, m.p. 137–139.5°, revealed a broad one-proton multiplet at τ4.63 (–C=C–H) and a poorly resolved triplet at τ8.18 ascribed to the C-4 Me. The *endo*-isomer 7 was found identical with an authentic sample [IR, NMR, MS and mixed m.p.].[15] The *exo*-isomer 8, m.p. 137–140°, in its NMR spectrum exhibited two one-proton singlets characteristic of an exocyclic double bond (τ5.08, 5.24) which was further supported by its IR absorptions at 1655 and 887 cm^{-1}. Again, the identity of lactone 8 was established by its comparison with an authentic specimen [IR, NMR, MS and mixed m.p.].[15] Thus, the chemical correlation between the bromohydrin 3 and the isomers 7 and 8 confirmed the occurrence of the transannular oxidative cyclization of dihydrocostunolide 1 deduced initially on the basis of the NMR spectral features of the product (*vide supra*).

Stereochemical arguments. Having proven the identity of the dehydration products with compounds of known structure and absolute configuration the stereochemical assignment of the ring juncture in 6 was established as *trans*. The OH group in lactone 6 placed at C-4 was assigned an α-equatorial configuration due to the predominance of the exocyclic isomer 8 during the dehydration experiments.[16] These data indirectly established the presence of a *trans* ring juncture and the equatorial α-configuration of C-4 OH group in the parent bromohydrin 3.

The chemical transformation carried out accounted for the configurations at all asymmetric centers of the bromohydrin 3 except at C-1 which was accomplished in the following manner. The course of transannular cyclization together with the above stereochemical arguments suggested the β-configuration of the Br atom at C-1 in the bromohydrin 3. Further evidence was provided by the failure to replace the Br atom with nucleophiles even under rigorous conditions (Experimental). An attempt was made to dehydrohalogenate the bromohydrin 3 using $LiBr/Li_2CO_3$ in refluxing dimethyl sulfoxide;[17] after 75 min the bromohydrin was recovered unchanged. No elimination product was detected by NMR or mass spectrometry. These negative experiments suggested the β-equatorial placement of the bromine confirming the assignment based upon the mechanism of the transannular cyclization. Finally, additional proof was secured by a detailed analysis of the splitting pattern of the resonances arising from the hydrogen at C-1 in the NMR spectrum of bromolactone 4 described in the sequel.

Bromolactones 4 and 5. Crystallization of fractions 12 to 17 (Experimental) from ethyl acetate led to the isolation of bromolactone 4, m.p. 136–137°, which analyzed for $C_{15}H_{21}O_2Br$ confirmed by high resolution mass spectrometry (Table 1). The trisubstituted nature of the olefinic linkage was demonstrated by its IR spectrum (853 and 793 cm^{-1}). The NMR spectrum exhibited the broad multiplet at τ4.73 and (–C=C–H) and the vinylic methyl signal at τ8.19 as a triplet (J = 1.5 Hz). The lone proton at C-1 gave the X part of an ABX splitting pattern[18] as a quartet centered at τ5.74 (J_{AX} = 9.5 Hz, J_{BX} = 7.5 Hz).[8,19] These splittings were consistent with axial–axial and axial–equatorial interactions respectively and hence Hx at C-1 must be axial. This in turn established the equatorial and β character of the C–1-Br linkage in the bromolactone 4.

Fractions 19–24 (Experimental) yielded the *exo*-isomer 5,[15] m.p. 169–170°, the exocyclic nature of which was revealed by its spectral features: ν_{max} 1655 and 893 cm^{-1}; NMR (τ5.02 and 5.14, s, 2 H, –C=CH_2). High resolution mass measurement as well as elemental analysis revealed its composition as $C_{15}H_{21}O_2Br$ (Table 1).

Unlike the NMR spectrum of bromolactone 4, the NMR spectra of 3 and 5 were not very informative from the stereochemical viewpoint in analyzing the X part of an ABX splitting pattern since the multiplet due to C-6 hydrogen overlapped that of the C-1 hydrogen. However, from a mechanistic viewpoint the genesis of the other two products 3 and 5 was presumed to be the same as that of 4 and therefore their configuration must be identical at C-1. This deduction was strengthened by the identical assignment of the Br atom in the bromohydrin derived from germacratriene by Sutherland *et al.*[6]

Structure elucidation of bromolactones 4 and 5. The approach taken in elucidating the structures of the isomeric bromolactones 4 and 5 was conversion of these compounds to a derivative of known structure. The lactones were hydrogenated in glacial acetic acid which surprisingly yielded the same compound, 1-β-bromo-

santanolide "c" 9, m.p. 199–200°.[A] The NMR and IR spectra were devoid of olefinic signals and frequencies respectively. Catalytic debromination of 9 by the previously described method produced a known compound which was found to be identical with an authentic specimen of santanolide "c" 10[12] [IR, NMR, mixed m.p.]. The *trans*-ring configuration of bromolactones 4 and 5 followed from this identity, since for santanolide "c" 10 the stereochemistry portrayed in formula 10 has been rigorously proven.[15,20]

Mass spectral fragmentation. The bromolactones 3, 4, 5 and 9 revealed many of the mass spectral fragmentation patterns common to the derivatives of santonin.[21] Scheme 4 depicts the patterns of bromolactone 4; the presence of metastable peaks [m*] suggested the course of the fragmentations.

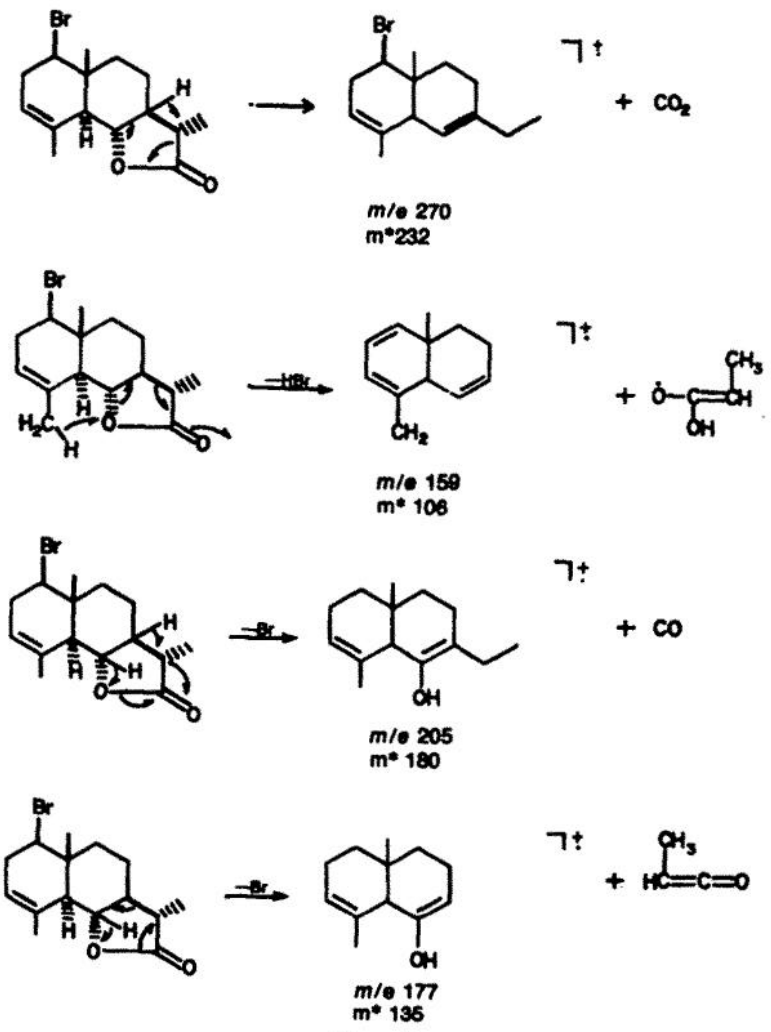
Mechanism of NBS-induced cyclization. The mechanism of the NBS-induced transannular cyclization of dihydrocostunolide 1 differs from that of the corresponding reaction of germacratriene in terms of yield as well as products. Careful examination of the Dreiding models of dihydrocostunolide 1 and germacratriene indicates that the major structural difference between these two substrates lies in the conformational mobility of the *trans,trans* - 1,5 - cyclodecadiene ring. In the case of germacratriene the ring is free to adopt any number of conformations, although, since the advent of NOE and X-ray studies, the ground state would appear to be comprised of a conformation with the C-10 and C-4 methyl groups *syn*. Inasmuch as all the germacranolides studied so far adopt the aforementioned conformation, it would appear that in the ground state dihydrocostunolide 1 has the structure shown in Scheme 5.

It was shown by van Tamelen that NBS reacts quite differently than hypobromous acid in the cyclization studies carried out by his group and thus NBS is not a source of HOBr.[22] Therefore, the actual attacking electrophile must be NBS itself which would have its N–Br bond cleaved in the manner given below (Scheme 5).[1] Thus the reaction should be catalyzed by acids and this has been demonstrated.[22] However, in the NBS-induced cyclization of dihydrocostunolide acids cannot be employed due to the ease of acid catalyzed cyclization of the ring.

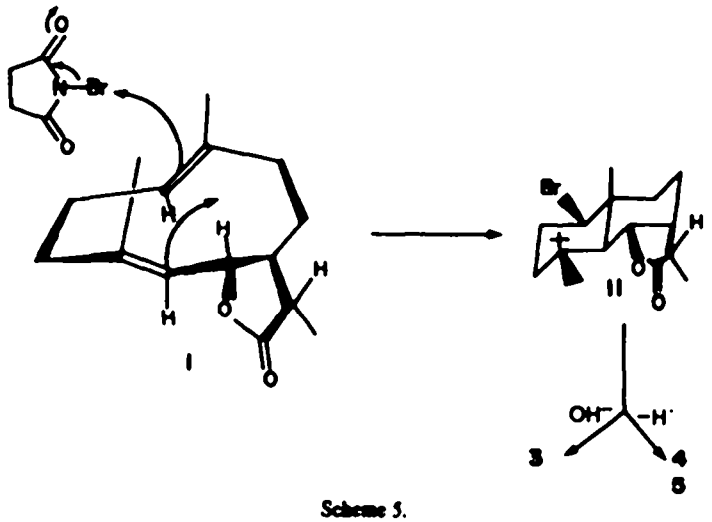
The overall reaction is initial attack by NBS on the more nucleophilic double bond between C-1 and C-10

[A] This unusual behavior of 4 and 5 towards catalytic hydrogenation is difficult to understand.

[1] Although in the oxidation of alcohols with NBS in polar media it is generally accepted that the attacking species is "positive" halogen.[23]



Scheme 4.



Scheme 5.

with concomitant cyclization to yield the possible intermediate 11. The fate of the carbonium ion 11 is decided by elimination of a proton from either C-3 and C-14 to give bromolactones 4 and 5 or by nucleophilic attack of hydroxide ion (or water) to produce the bromohydrin 3. The overall process leading to the formation of 3, 4 and 5 could be either a concerted or a multi-step process or both.

It may be argued that the unsaturated bromolactones 4 and 5 could have been formed from the bromohydrin 3 during the reaction or workup procedures. However, due to the extremely mild conditions this is highly unlikely since tertiary OH groups generally require an acid catalyst or high temperatures for dehydration.

The NBS-induced transannular cyclization of dihydrocostunolide 1 affords an excellent preparative method of transforming germacranolides into eudesmanolides in a stereospecific manner functionalizing positions 1 and 4. A parallel reaction on the substrate costunolide 2 should provide entry into the syntheses of bicyclic seaquiterpenes with a methylene group at C-11 common to natural products. This synthetic potentiality coupled with our knowledge of the reaction of dihydrocostunolide prompted us to study the brominative cyclization of costunolide,[24] a full account of which will be reported in due course.

EXPERIMENTAL[1]

NBS-Induced cyclization of dihydrocostunolide 1. Dihydrocostunolide 1 (2.36 g) dissolved in 5% H_2O/acetone (400 ml) was stirred magnetically overnight with N-bromosuccinimide (1.78 g). Removal of solvent *in vacuo* resulted in a viscous gum which was taken up in ether and extracted with H_2O (3 × 10 ml) to remove succinimide. The aqueous layer was back extracted and the combined ethereal soln was dried over Na_2SO_4 and the solvent was removed under reduced pressure yielding a semi-crystalline mass (3.365 g). Tlc (silica gel) in the following solvent systems—benzene, 5% methanol/benzene and chloroform revealed the presence of three compounds. The semi-crystalline mass was chromatographed over a thirtyfold silica gel column. There were 24 fractions collected and each fraction of 180 ml was concentrated, examined by spectral data, and combined together as shown in Table 2.

[1]For general experimental details see Ref. 25.

Table 2.

Fraction	Solvent	Volume	Weight	ν_{max}
1–4	Benzene	720 ml	trace	-
5–13	Benzene	1620 ml	1.32 g	1650 cm^{-1}
14–20	Benzene/$CHCl_3$ (1:1)	1260 ml	trace	-
21–24	$CHCl_3$	720 ml	1.93 g	3400 cm^{-1}

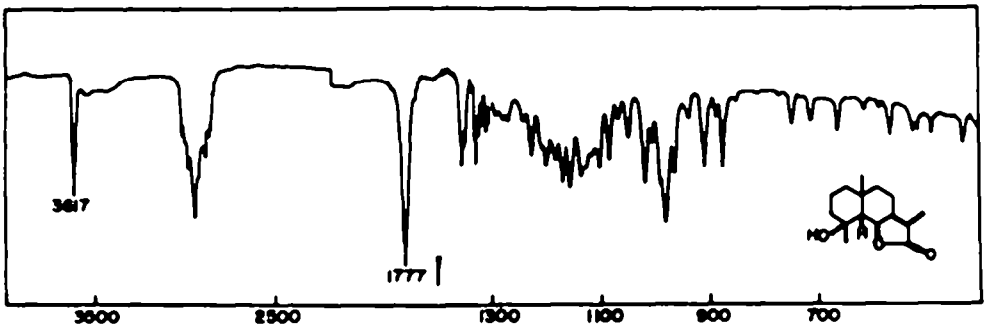


Fig. 2.

Bromohydrin 3. The combined fractions (21–24, Table 2) were crystallized from EtOAc to yield cubic crystals of 3, m.p. 160.0–166.5° (block preheated to 150°). $[\alpha]_{589}$ – 15.0°, $[\alpha]_{578}$ – 15.6°, $[\alpha]_{546}$ – 17.6°, $[\alpha]_{436}$ – 28.2°, $[\alpha]_{365}$ – 40.6° (*c*, 1.45 at 29°). IR: Fig. 1; NMR: τ 5.92 (m, 2 H, HC–Br, HC–O–C=O), 8.63 (s, 3 H, HO–C–CH_3), 8.78 (d, *J* = 6.5 Hz, 3 H, HC–CH_3), 8.87 (s, 3 H, –C–CH_3); MS: *m/e* 330 (M^+, $\%\Sigma_{10}$ 0.05). (Found: C, 54.17, 54.20, 54.85; H, 6.98, 6.79, 7.47; Br, 24.60, 28.92, 26.86. Calc. for $C_{15}H_{23}O_3Br$: C, 54.39; H, 7.00; Br 24.12%). An accurate analysis for bromine was difficult to obtain, presumably due to the unstable nature of 3.

Hydroxylactone 6. Compound 3 (50 mg) in EtOH (10 ml) was hydrogenated (66 hr) in the presence of a trace of Et_3N and 10% Pd/C (100 mg) at ambient temp. and pressure. The catalyst was removed by filtration and the solvent was evaporated at reduced pressure. The crystalline residue was taken up in ether and washed with dil. HCl (3 × 10 ml), followed by water (3 × 10 ml). The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. Crystallization from petroleum ether afforded shiny flakes of 6, m.p. 109–110°. $[\alpha]_{589}$ + 11.9°, $[\alpha]_{578}$ + 12.4°, $[\alpha]_{546}$ + 14.5°, $[\alpha]_{436}$ + 27.9°, $[\alpha]_{365}$ + 52.5° (*c*, 1.24 at 25°). IR: 3617 cm^{-1} (tertiary OH) and 1777 cm^{-1} (γ-lactone) (Fig. 2). NMR: τ 5.96 (m, 1 H, HC–O–C=O), 8.67 (s, 3 H, HO–C–CH_3), 8.77 (d, *J* = 7.0 Hz, 3 H, HC–CH_3), 9.00 (s, 3 H, –C–CH_3). MS: *m/e* 252 (M^+, $\%_{\Sigma 10}$ 0.40). (Found: C, 71.29; H, 9.57. Calc. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.58%).

Santonolides 7 *and* 8. Compound 6 (75 mg) mixed intimately with alumina (150 mg, impregnated with 2% pyridine)[14] was heated to 220° for 4 hr under N_2. After completion of the reaction, the alumina was washed free of organic material with boiling chloroform to yield after evaporation white crystals (67 mg). Chromatography over fiftyfold silica gel–$AgNO_3$ and elution with petroleum ether–benzene mixtures afforded two crystalline double bond isomers 7 (15 mg, 30% yield) and 8 (35 mg, 70% yield).

Isomer 7. 3-Endocyclosantonolide 7 was crystallized from EtOH to yield flakes, m.p. 137–139.5° (undepressed upon admixture with an authentic sample).[13] $[\alpha]_{589}$ + 78.7°, $[\alpha]_{578}$ + 81.6°, $[\alpha]_{546}$ + 92.9°, $[\alpha]_{436}$ + 162.7°, $[\alpha]_{365}$ + 264.1° (*c*, 0.74 at 29°). IR: 1770 cm^{-1} (γ-lactone), 854 and 794 cm^{-1} (trisubstituted double bond), the spectrum was superimposable with that of an authentic sample. NMR: τ 4.63 (s, broad, 1 H, –C=CH), 8.18 (t, *J* = 1.5 Hz, 3 H, HC=C–CH_3), 8.78 (d, *J* = 6.5 Hz, 3 H, HC–CH_3), 9.08 (s, 3 H, –C–CH_3).

Isomer 8. Crystallization, again from EtOH, afforded 4-exocyclosantonolide 8, m.p. 137–140° (undepressed upon admixture with an authentic sample).[13] $[\alpha]_{589}$ + 150.2°, $[\alpha]_{578}$ + 156.4°, $[\alpha]_{546}$ + 178.2°, $[\alpha]_{436}$ + 308.2°, $[\alpha]_{365}$ + 497.7° (*c*, 0.9 at 35°). IR: 1766 cm^{-1} (γ-lactone), 1655 and 887 cm^{-1} (exocyclic methylene), the spectrum was superimposable with that of an authentic sample. NMR: τ 5.08, 5.24 (s, 2 H, –C=CH_2), 6.01 (m, broad, 1 H, HC–O–C=O), 8.77 (d, *J* = 6.5 Hz, 3 H, HC–CH_3), 9.14 (s, 3 H, –C–CH_3). (Found: C, 77.00; H, 9.82. Calc. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46%).

Attempted elimination studies on bromohydrin 3. Compound 3 (50 mg) was dissolved in dimethylformamide (5 ml) to which LiBr (30 mg) and Li_2CO_3 (40 mg) was added; the mixture was refluxed for 75 min. The contents of the flask were poured into AcOH (5 ml) and extracted with CH_2Cl_2 (4 × 5 ml). The organic layer was washed with water (3 × 5 ml), dried over Na_2SO_4 and was concentrated *in vacuo*. An NMR spectrum showed that the bromohydrin was recovered unchanged. Similar results were obtained when the refluxing was carried out for 3.5 hr.

Attempted displacement studies on bromohydrin 3. Compound 3 (30 mg) dissolved in 60% acetone/water was stirred at 75° with a suspension of freshly prepared Ag_2O (300 mg) for 24 hr. After filtration and removal of solvent the residue was taken up with ether and washed with water (3 × 5 ml). The organic layer was dried over Na_2SO_4 and the ether was removed *in vacuo*. The NMR spectrum of the product showed it to be unchanged bromohydrin.

Attempted KOAc displacement studies on bromohydrin 3. Compound 3 (20 mg) was stirred for 4 hr in the presence of KOAc (35 mg) dissolved in glacial AcOH (3 ml). The mixture was diluted with ice water (20 ml) and extracted with ether (8 × 5 ml); followed by washings with Na_2CO_3 (2 × 5 ml) and water (3 × 5 ml). The ethereal layer was dried over Na_2SO_4 and concentrated *in vacuo*. The product on the basis of its NMR spectrum was identified as the starting material.

Isolation of bromolactones 4 *and* 5. The combined fractions (5–13, Table 2) were rechromatographed over a thirtyfold silica gel column. There were 24 fractions collected and each fraction of 80 ml was concentrated examined by spectral data, and combined together as shown in Table 3.

Crystallization of fractions 12–17 (Table 3) from EtOAc yielded 4 (400 mg, 14%), m.p. 136–137°. $[\alpha]_{589}$ – 2.8°, $[\alpha]_{578}$ – 2.8°, $[\alpha]_{546}$ – 2.8°, $[\alpha]_{436}$ – 5.4°, $[\alpha]_{365}$ – 7.8° (*c*, 1.4 at 29°). IR: 1766 and 1176 cm^{-1} (γ-lactone), 853 and 793 cm^{-1} (trisubstituted double bond); NMR: τ 4.73 (s, broad, 1 H, –C–C–H), 5.74 (quartet, ABX, J_{AX} = 9.5 Hz, J_{BX} = 7.5 Hz, 1 H, HC–Br), 8.19 (t, *J* = 1.5 Hz, 3 H, HC=C–CH_3), 8.78 (d, *J* = 6.5 Hz, 3 H, HC–CH_3), 9.00 (s, 3 H, –C–CH_3); MS: *m/e* 312 (M^+, $\%\Sigma_{10}$ 1.17). (Found: C, 57.64; H, 7.02; Br, 24.79. Calc. for $C_{15}H_{23}O_2Br$: C, 57.51; H, 6.75; Br, 25.51%).

Crystallization of fractions 19–24 (Table 3) from EtOAc gave needles of 5 (730 mg, 25%), m.p. 169–170°. $[\alpha]_{589}$ + 79.1°, $[\alpha]_{578}$ + 82.6°, $[\alpha]_{546}$ + 94.2°, $[\alpha]_{436}$ + 162.6°, $[\alpha]_{365}$ + 262.1° (*c*, 1.46 at 29°). IR: 1770 and 1173 cm^{-1} (γ-lactone), 1655 and 893 cm^{-1} (exocyclic methylene). NMR: τ 5.02, 5.14 (s, 2 H, –C=CH_2), 5.97 (m, 2 H, HC–Br and HC–O–C=O), 8.79 (d, *J* = 7.0 Hz, 3 H, HC–CH_3), 9.03 (s, 3 H, –C–CH_3). MS: *m/e* 312 (M^+, $\%\Sigma_{10}$ 1.24). (Found: C, 56.76; H, 6.67. Calc. for $C_{15}H_{23}O_2Br$: C, 57.51; H, 6.79%).

1-*Bromoeuantanolide "c"* 9. (a) Bromolactone 4 (50 mg) dissolved in AcOH (5 ml) was hydrogenated (9 hr) in the presence of PtO_2 (25 mg). Filtration followed by removal of solvent yielded crude 9 (40 mg). Crystallization from EtOH gave shiny needles of 9, m.p. 199–200°. $[\alpha]_{589}$ + 11.9°, $[\alpha]_{578}$ + 12.7°, $[\alpha]_{546}$ + 14.6°, $[\alpha]_{436}$ + 25.8°, $[\alpha]_{365}$ + 40.8° (*c*, 0.69 at 29°). IR: 1761 cm^{-1} (γ-lactone). NMR: τ 6.01 (m, 2 H, HC–Br and HC–O–C=O), 8.73, 8.83 (d, 6 H, HC–CH_3, partially superimposed on singlet due to C-10 Me), 8.96 (d, *J* = 7.0 Hz, 3 H, HC–CH_3). MS: *m/e* 314 (M^+, $\%\Sigma_{10}$ 0.36). (Found: C, 57.20; H, 7.33. Calc. for $C_{15}H_{23}O_2Br$: C, 57.14; H, 7.35%).

(B) Bromolactone 5 (45 mg) dissolved in AcOH (5 ml) was hydrogenated (23 hr) in the presence of PtO_2 (25 mg). Filtration followed by removal of solvent afforded crude 9 (47 mg). Crystallization from EtOAc gave shiny needles of 9. The m.p. was undepressed upon admixture with the sample of 9 prepared from 4, furthermore their IR and NMR spectra were identical.

Santanolide "c" 10. Compound 9 (20 mg) dissolved in EtOH

Table 3.

Fraction	Solvent	Volume	Weight	ν_{max}
1–6	Petroleum Ether	480 ml	trace	-
7–11	Pet. Ether/Benzene (3:1)	400 ml	trace	-
12–17	Pet. Ether/Benzene (1:1)	480 ml	400 mg	-
18	Pet. Ether/Benzene (1:1)	80 ml	186 mg	1650 cm^{-1}
19–24	Pet. Ether/Benzene (1:3)	480 ml	730 mg	1650 cm^{-1}

(10 ml) containing a trace of Et_3N was hydrogenated (60 hr) in the presence of 10% Pd/C (50 mg). The catalyst was filtered off and solvent was removed *in vacuo*; the crystalline residue was taken up in ether washed with dil. HCl (3 × 10 ml) and then with water (3 × 10 ml). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Chromatography over silica gel and elution with benzene gave a fraction, crystallization of which from EtOH afforded shiny flakes of **10**, m.p. 155–156° (undepressed upon admixture with an authentic sample).[15] IR: 1772 cm^{-1} (γ-lactone), the spectrum was superimposable with that of an authentic compound.

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