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BROMINATIVE LACTONIZATION IN EUDESMANES.

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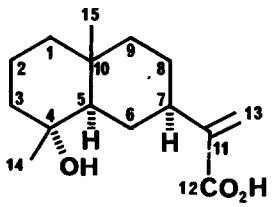
Summary: The interaction of ilicic acid 1 with bromine affords directly the bromolactone 3.

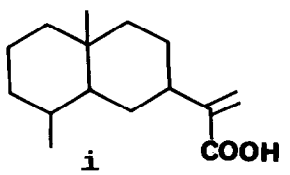
Ilicic acid 1, one of the typical eudesmane sesquiterpenes, was first isolated from Ambrosia Ilicifolia by Herz and co-workers in 1965[1] and recently detected widely in several other Compositae.[2]

The relative abundance of this compound made it possible to start a program of chemical modifications of 1 as an alternative route to the synthetic approach for the preparation of biologically active derivatives.

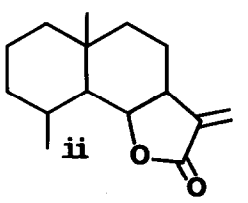


1

The work outlined in this paper is concerned with the conversion of the eudesmanes into the corresponding eudesmanolides (i → ii).



i

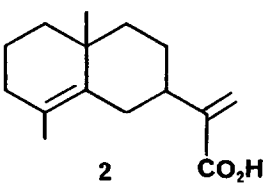


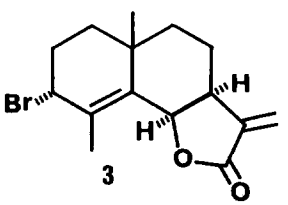
ii

Ilicic acid 1 as well as many of the naturally occurring eudesmanes, incorporates an acrylate unit at C-7, therefore its transformation into a eudesmanolide derivative requires the oxidation of an unactivated carbon.

In connection with our synthetic plain we needed to transform 1 into 2, which possesses suitable functionality for subsequent oxidation at C(6). The olefine 2 was previously obtained by dehydratation of 1 with phosphorus oxychloride-pyridine, but the reaction produced an inseparable mixture of three isomeres (Δ^3, Δ^4 and $\Delta^{4,14}$).[1] Indeed, a series of experiments on the dehydratation of 1 was carried out, including reaction with halogens.[3]

While treatment of 1 with iodine generated selectively the olefine 2, much to our surprise, treatment with bromine provided a mixture of compounds from which the bromolactone 3 was easily isolated in 20% yield.[4]





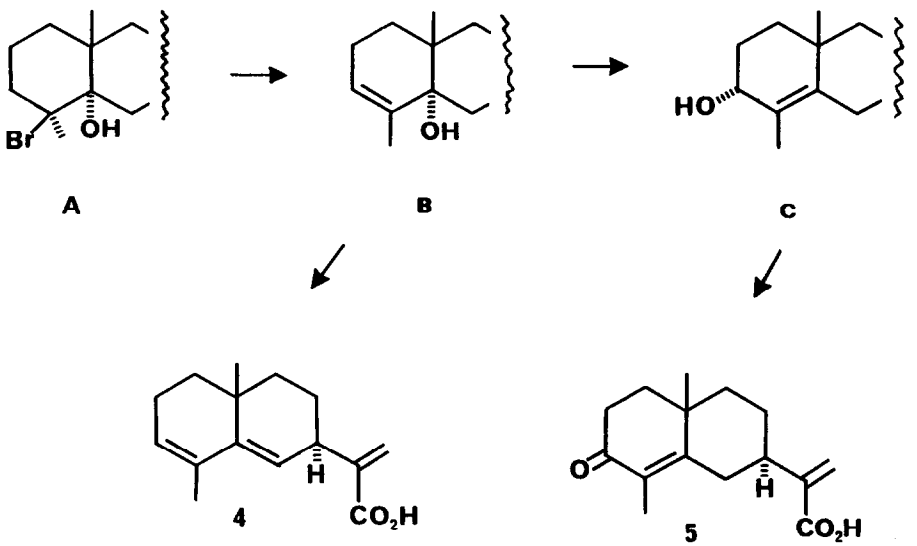
3 is clearly an α-methylene-γ-lactone as evidenced by infrared band at 1775 cm^{-1}. In addition, the presence in the ^1H NMR spectrum of a doublet (J = 6 Hz) centered at δ 5.10, coupled with C-7 proton, is diagnostic for the 6,7-cis lactoning ring closure. Data confirming C-skeleton as the configuration at C-3 and C-6 of 3 came from ^{13}C NMR spectral analysis. The chemical shift assignment (vide infra) has been facilitated by an earlier designation of the δ values of some eudesmanolides[5] and eudesmanes[6]. The deshielding of C-10 methyl group in 3 vs. 2 is a reflection of δ effect exerted by the interaction of the C-6 β-oriented substituent which, in turn, shields the C-8. A further comparison of shift values of the bromolactone 3 and acid 2 indicates that the C-1 in the former is shielded. The shift alteration can be ascribed to the presence of the C-3 bromine α-oriented, this relationship places the substituent in a quasi-axial conformation thus exerting γ-effect on C-1.

The transformation of ilicic acid 1 into the bromolactone 3 requires a multistep process.

A reaction pathway that is consistent with the formation of 3 presumably involves the initial dehydratation of 1 into 2. It must be mentioned that efforts to transform 2 into 3 by treatment with bromine have not afforded the expected result, addition products being recovered.

The interaction of a tertiary alcohol and bromine produces an olefine and hypobromous acid,[3] thus 2 was treated with an excess of hypobromous acid, generated in situ by decomposition of NBS with sulphuric acid.[7] Under these conditions, the olefine 2 was transformed into the diene 4 and enone 5 as major products. This compounds appear to be produced <u>via</u> intermediates A, B and C (Scheme):[6] while diene 4 is clearly formed from A by two β-elimination processes,[8] 5 comes from allylic alcohol C by oxidation with hypobromous acid.[9]

SCHEME



Under conditions used to effect lactonization of 1, the diene 4 is transformed into the expected bromolactone 3. The formation of the <u>cis</u>-fused lactone is a consequence of the known reluctance of <u>trans</u>-lactones to form under mild conditions.[10]

Characterization of some main products, 2, 3, 4 and 5 is as follows (NMR and IR spectra were recorded in $CDCl_3$ solution):

2: Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.99; H, 9.33. ^1H NMR δ 1.06 (s, 3H, 10-Me), 1.62 (s, 3H, 4-Me), 5.65, 6.26 (each bs, 2H, H_2-13), ^{13}C NMR, 19.0 (C-2), 19.2 (C-14), 24.6 (C-15), 28.0 (C-8), 31.4 (C-6), 33.1 (C-3), 34.4 (C-10), 40.2 (C-1), 40.3 (C-7), 42.1 (C-9), 124.7 (C-13), 125.2 (C-5), 134.2 (C-4), 145.2 (C-11), 173.0 (C-12).

3: Anal. Calcd. $C_{15}H_{19}BrO_2$: C, 57.88; H, 6.15. Found: C, 57.94; H, 6.09. m.p. 86-87°C (hexane), IR ν_{max} 1775 cm^{-1}, ^1H NMR δ 1.06 (s, 3H, 10-Me), 1.92 (s, 3H, 4-Me), 4.65 (m, W =7 Hz, 1H, H-3), 5.10 (d, J=4.5 Hz, 1H, H-6), 5.53, 6.10 (each d, J=1.8 Hz, H_2-13), ^{13}C NMR 18.9 (C-14), 24.8 (C-8), 25.4 (C-15), 28.8 (C-2), 33.3 (C-10), 34.0 (C-1), 37.4 (C-9), 40.9 (C-7), 56.8 (C-3), 75.3 (C-6), 120.8 (C-13), 128.3 (C-5), 133.7 (C-4), 141.4 (C-11), 170.4 (C-12).

4: Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.62; H, 8.59. ^1H NMR δ 1.03 (s, 3H, 10-Me), 176 (bs, 3H, 4-Me), 3.68 (m, 1H, H-7), 5.40 (bs, 1H, H-6), 5.55 (m, 1H, H-3), 5.70, 6.38 (each bs, 2H, H_2-13), ^{13}C NMR 20.1 (C-14), 23.5 (C-15), 22.9 (C-2), 26.4 (C-8), 32.3 (C-10), 37.1 (C-1), 38.2 (C-9), 38.7 (C-7), 121.6 (C-3), 125.0 (C-6), 126.0 (C-13), 131.1 (C-4), 143.3 (C-5), 145.3 (C-11), 172.4 (C-12).

5: Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.61; H, 8.01 ^1H NMR δ 1.25 (s, 3H, 15-Me), 178 (s, 3H, 4-Me), 5.73, 6.40 (each bs, 2H, H_2-13), ^{13}C NMR 10.8 (C-14), 22.2 (C-15), 27.0 (C-8), 33.3 (C-6 or C-2), 33.6 (C-2 or C-6), 35.7 (C-10), 37.2 (C-1), 39.7 (C-7), 41.7 (C-9), 125.2 (C-13), 129.1 (C-4), 143.9 (C-11), 161.5 (C-5), 171.4 (C-12), 199.3 (C-3).

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