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TRIMETHYL(PHENYL)AMMONIUM PERBROMIDE, AN EFFICIENT REAGENT FOR THE PARTIAL SYNTHESIS OF FUNCTIONALIZED SESQUITERPENE LACTONES

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Abstract:
Brominative carbocyclization of costunolide 2 by trimethyl(phenyl)ammonium perbromide in pyridine leads to the eudesmanolides 6, 7 and 8. Regio and stereospecific addition of bromine to the 11, 13-double bond also occurs providing a useful route to C-7, C-11 and C-13 functionalized sesquiterpene lactones. Dehydrobromination of 1-β-bromocyclocostunolide 6 occurs via epimerization at C-1.

In the course of our research programme directed towards the partial synthesis of biologically active sesquiterpene lactones we required C-1 functionalized eudesmanolides. Bromo-cyclization of the readily available costunolide 2 was selected for this purpose. The cyclization of medium ring 1,5-dienes has been widely investigated[1-8]. N-Bromosuccinimide was employed by Jain et al. [9, 10] in bromo-cyclization studies on dihydro-costunolide 1. However compound 6, in which we were particularly interested, was only obtained in low yield. This prompted us to search for other bromo-cyclization reagents with the aim of obtaining better yields of the desired compound.

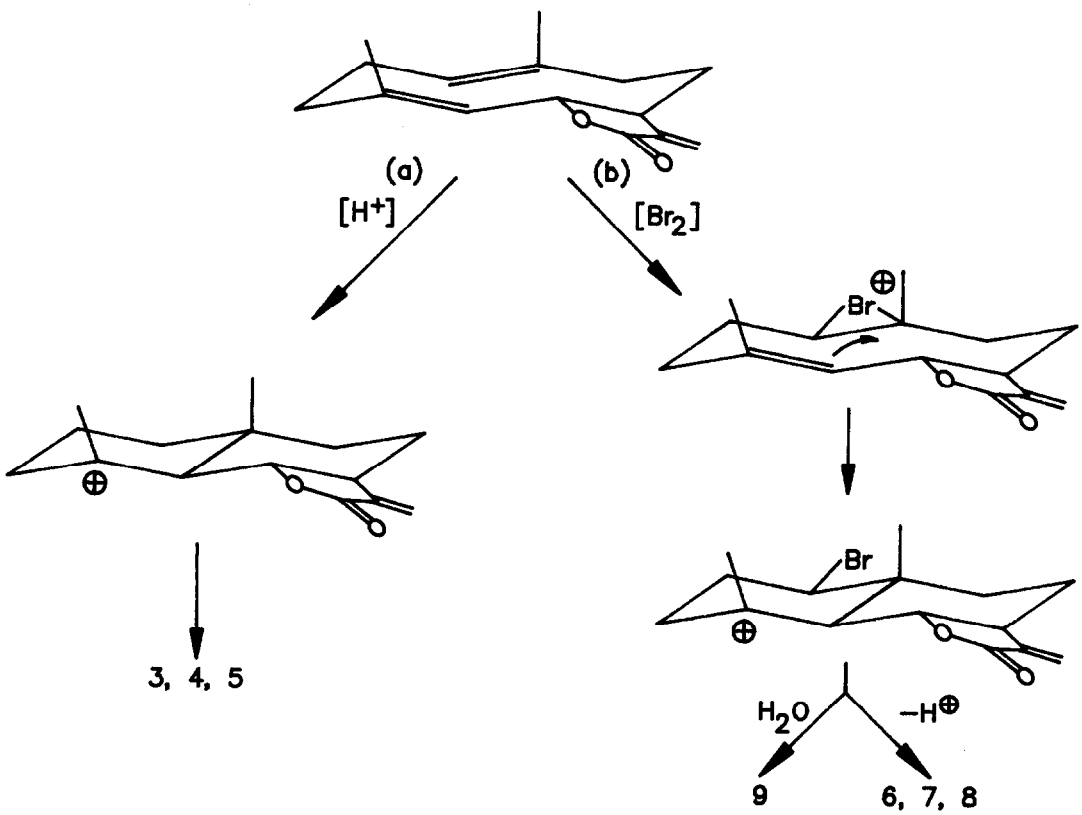
Reaction of 2 with bromine under different conditions gave a very complex mixture of cyclocostunolides, 1-bromo-cyclocostunolides and other polybrominated compounds.

When trimethyl(phenyl)ammonium perbromide[11],[12](TMPAP) in dioxan was used a viscous product was obtained showing seven spots on TLC in several solvent systems. A careful combination of column chromatography and preparative TLC resolved the crude mixture into the cyclocostunolides 3, 4 and 5, 1-bromo-cyclocostunolides 6, 7 and 8, and 1,11,13-tribromo-8-cyclocostunolide 10.

The formation of 3, 4 and 5 can be explained if we assume that this reagent leads to acidic conditions which catalyze the electrophilic transannular cyclization [Scheme 1 path (a)][13]. The 1-bromo-cyclocostunolides can be derived from a bromonium ion produced from bromine arising in the disproportionation

$Br_3^- \rightleftharpoons Br_2 + Br^-$ [Scheme 1, path (b)]

In order to minimize the formation of compounds (3-5), the cyclization was carried out in the presence of a few drops of pyridine. Under these conditions only three clear spots were obtained on TLC. Chromatography afforded the bromo-



lactones 6 (70%)[14], 7 (20%)[14] and 8 (5%)*. The latter, $C_{15}H_{19}O_2Br$, mp. 131-132, $[\alpha]_D^{25}$ + 57° (c, 1.46 at 25°) has not been described previously. It possessed signals in the ^{1}HNMR spectrum (δ 4.45, d, J=10.2 Hz, H-6; 4.15, m, H-1; 1.81, s, C-4-CH_3; 1.20, s, C-10-CH_3) which were consistent with the structure 8. To our knowledge this is the first time that a $\Delta^{4,5}$-alkene has been detected in a transannular cyclization of costunolide 2.

Compound 9 [14] was obtained in 18% yield if the reaction was carried out in the presence of a few drops of water.

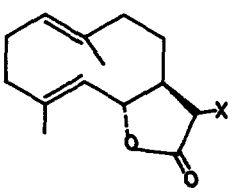
Compounds 13 and 14 were obtained from 6 and 7 by refluxing them in DMF for 3 h. with LiBr/Li_2CO_3. The elimination of bromine from 7 was shown to occur with prior epimerization at C-1 to give 12 ** (^{1}HNMR spectrum: δ 4.03, br.d, H-1; 2.85, d, J=10.8, H-5). This behaviour may be due to the fact that the reaction requires an trans relationship between the proton and the bromide leaving group. The boat conformation in which this orientation can be achieved in 6, 7 is very unstable because of the stereoelectronic repulsion between the β-oriented bromine atom and the C-10 methyl group. The structures of compounds 13 and 14 were in accordance with their spectroscopic data* .

The formation of compound 10 in the above reaction was unexpected. The ^{1}HNMR (δ 4.12, dd, J=11,4.2Hz, H-1; 4,37, t, J=10.2Hz, H-6; 4.15, d, J=11 Hz, H-13; 3.83, d, J=11 Hz, H-13') showed that addition of bromine on C-11, C-13 double bond had taken place.

The paramagnetic shift in the signal of H-6 (0.43 ppm) with respect to that the same proton in 6, indicated a β-orientation for the bromine atom at C-11. Accordingly 10 underwent facile dehydrobromination when treated with LiBr, Li_2CO_3 in DMF to yield 11 (^{1}HNMR spectrum: δ 3.98, d, J=10.5 Hz, H-6; 4.07, s, H-13, H-13').

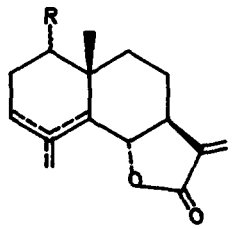
Treatment of compound 6 with excess of TMPAP in dioxan afforded the same compound 10 in 78% yield.

Although TMPAP has been used as a source of bromine for electrophilic addition to double bonds, [15, 16] addition to the C-4:C-14 double bond was not detected. Instead bromine added stereospecifically to the double bond conjugated to the carbonyl group of the γ-lactone. We have obtained the same result with other unsaturated eudesmanolides under these conditions. This interesting reaction probably involves an initial nucleophilic attack of Br_3^- at C-13. It provides a facile way of obtaining sesquiterpene lactones functionalized on the lactone ring [17, 18]. Further work is in progress to investigate the mechanistic aspects and scope of this reaction.



1 X= CH_3

2 X= CH_2



3 R= βH $\Delta^{4,14}$

4 R= βH $\Delta^{3,4}$

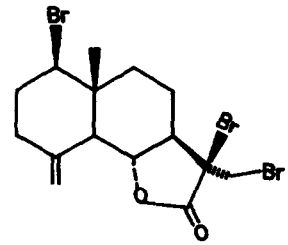
5 R= βH $\Delta^{4,5}$

6 R= βBr $\Delta^{4,14}$

7 R= βBr $\Delta^{3,4}$

8 R= βBr $\Delta^{4,5}$

12 R= αBr $\Delta^{3,4}$



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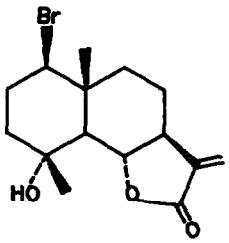

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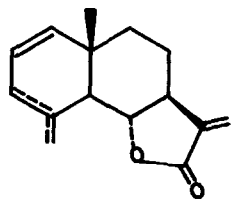
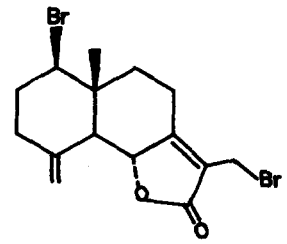


13 $\Delta^{3,4}$

14 $\Delta^{4,14}$



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*.- ^{1}HNMR ($CDCl_3$), 200 MHz. Compound 8. δ , 4.10 (dd,1H,J= 4.12, 10.0 Hz,H-1); 1.9-2.4 (m,2H, H-2, H-3); 4.47 (d(br), 1H, J= 10.2, H-6); 2.53 (ddd, 1H, J= 10.2, 3.2 Hz, H-7); 1.55 (m, 1H, H-8); 1.22 (m, 1H, H-9); 6.10 (d, 1H, J= 3.2 Hz, H-13); 5.42 (d, 1H, J= 3.2 Hz, H-13'); 1.81 (s, 3H, H-14); 1.21 (s, 3H, H-15). Compound 10. 4.12 (dd, 1H, J= 11, 4.2 Hz, H-1); 2.45 (d(br), 1H, J= 10.2 Hz, H-5); 4.37 (t, 1H, J= 10.2 Hz, H-6); 2.18 (ddd, 1H, J= 10.2, 3.5 Hz, H-7); 4.15 (d, 1H, J= 11Hz, H-13); 3.83 (d, 1H, J= 11 Hz, H-13'); 5.03 (s(br), 1H, H-14); 4,86 (s(br), 1H, H-14'); 0.98 (s, 3H, H-15). Compound 11. 3.98 (dd, 1H, J= 11.3, 4.5 Hz, H-1); 2.0-2.5 (m, 2H, H-2, H-3); 1.90 (d(br), 1H, J= 10.5 Hz, H-5); 3.98 (d, 1H, J= 10.5 Hz, H-6), 4.07 (s, 2H, H-13); 5.06 (s(br), 1H, H-14); 4.98 (s, 1H, H-14'); 1.04 (s, 3H, H-15). Compound 12. 4.03 (d, 1H, J= 5 Hz, H-1); 2.85 (d(br), 2H, J= 10.8 Hz, H-5); 3.90 (t, 1H, J= 10.8 Hz, H-6); 2.11 (t(br), 1H, J=10.8 Hz, H-7); 6.06 (d, 1H, J= 3 Hz, H-13); 5.38 (d, 1H, J= 3 Hz, H-13'); 1.89 (s, 3H, H-14); 0.98 (s, 3H, H-15). Compound 13. 5.51 (dd, 1H, J= 10, 0.8 Hz, H-1); 5.78 (dd, 1H, J= 10, 5 Hz, H-2); 5.68 (m, 1H, H-3); 2.65 (d(br), 1H, J= 10.5 Hz, H-5); 3.99 (t, 1H, J= 10.5, H-6); 2.51 (t(br), 1H, J= 10.5, H-7); 6.03 (d, 1H, J= 3 Hz, H-13); 5.38 (d, 1H, J= 3 Hz, H-13'); 1.96 (s, 3H, H-14); 0.88 (s, 3H, H-15). Compound 14. 5.55 (s(br), 2H, H-1, H-2); 2.82 (dd, 1H, H-2); 2.55 (d, 1H, J= 11 Hz, H-5); 4.07 (t, 1H, J= 11 Hz, H-6); 6.09 (d, 1H, J= 3 Hz, H-13); 5.41 (d, 1H, J= 3 Hz, H-13'); 5.06 (s, 1H, H-14); 4.9 (s(br), 1H, H-14'); 0.89 (s, 3H, H-15).

**.- The corresponding epimer of 6 was detected by TLC but could not be isolated in sufficient amounts for characterization.

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