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Nucleophilic 1,2 Addition of Bromine by Perbromide Reagents

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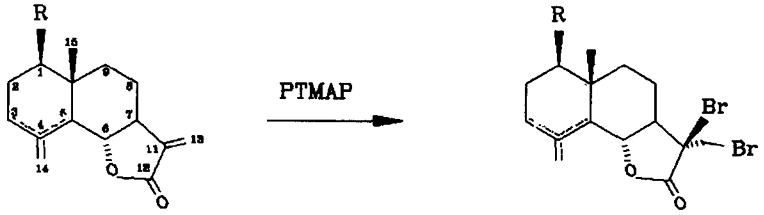
Abstract:*Perbromide compounds have proved to be excellent reagents for achieving nucleophilic 1,2 addition of bromine on to the double bond of α,β-unsaturated compounds. Features of the mechanism are outlined.*

The perbromide reagents, pyridinium perbromide (PPB) and trimethyl(phenyl)ammonium perbromide (TMPAP) are established reagents which have been used for mild and selective bromination, principally on alkenes[1-3] or at the α-position to carbonyl groups[4-6].

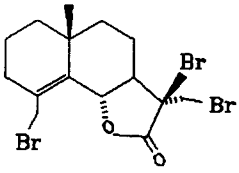
Although TMPAP has been used as a source of bromine for electrophilic addition to double bonds[7], during our work directed toward the synthesis of bioactive sesquiterpene lactones functionalized in the lactone ring, we obtained evidences of nucleophilic bromination[8]. The selectivity, stereospecifity and high yields obtained prompted us to undertake the present study to further evaluate the scope and mechanistic aspects of the reaction.

In a typical experiment the starting material (1-8) was dissolved in dioxane, TMPAP was added in excess (1:1.5) and the reaction mixture was stirred at room temperature until starting material had disappeared. Ether was added to precipitate the reagent and the reaction was then filtered, and the solvent evaporated under reduced pressure to furnish the 11ß,13-dibromo derivatives (9-16). (Scheme 1)

The bromination has been shown to be stereospecific, giving exclusively 11ß,13-dibromocyclocostunolide derivatives in about 75% yield, except for compounds (12-14) which do not possess substituents at C-1 and were obtained in lower yield. From α and ß-cyclocostunolide (4 and 5) were obtained in addition of 11,13-dibromoderivatives the compounds (17-19) which result from bromine addition to C-4/C-14 and C-3/C-4 respectively. The formation of these compounds can be explained by electrophilic addition of bromine, assuming that the Br_3^- species is unstable, which disproportionates to Br_2 and Br^-.[9] Furthermore, it is worth noting that the functionalization on C-1 (R = Br, OH), exerts a protecting effect on double bonds $\Delta^{4,14}$, $\Delta^{3,4}$, $\Delta^{4,5}$, probably due to electronic reasons. The protecting effect on a double bond by the proximity of an electronegative group has been observed by some of us on gibberellic acid and related structures[7].



1	R=βBr	$\Delta^{4,14}$	9	78%
2	R=βBr	$\Delta^{3,4}$	10	71%
3	R=βBr	$\Delta^{4,5}$	11	67%
4	R=H	$\Delta^{4,14}$	12	52%
5	R=H	$\Delta^{3,4}$	13	27%
6	R=H	$\Delta^{4,5}$	14	43%
7	R=βOH	$\Delta^{4,14}$	15	80%
8	R=βOH	$\Delta^{3,4}$	16	75%



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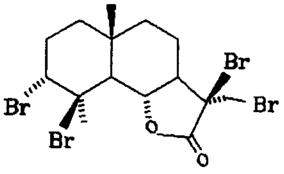

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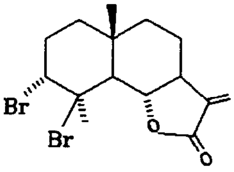

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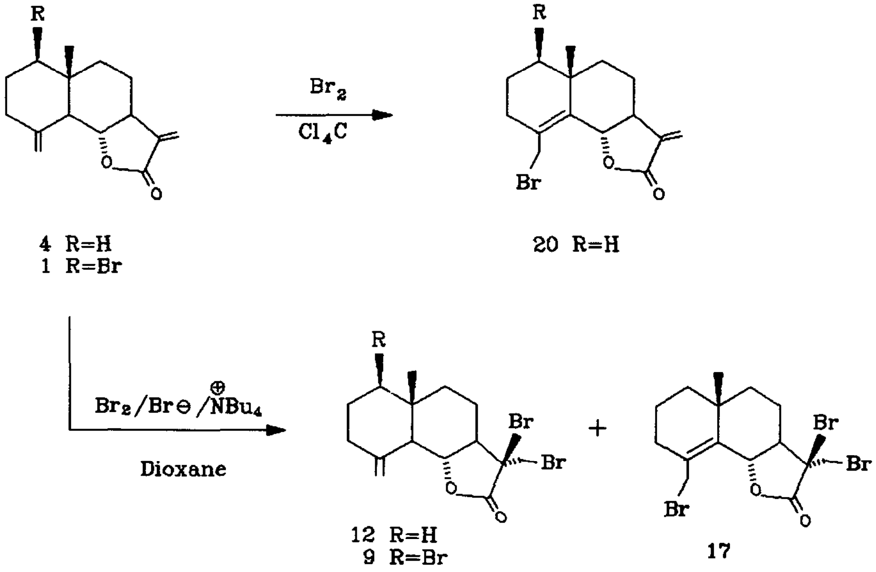
SCHEME 1

To exclude the possibility that Br$_2$ specie could form Br$_3^-$ in situ and give the same reaction as TMPAP, we carried out reaction of compound 1 and 4 (scheme 2) with Br$_2$ / Cl$_4$C and Br$_2$ / dioxane. In these instances, with R = Br, no reaction was observed and starting material was recovered. With R = H we obtained compound 20, the formation of which can be explained by electrophilic bromination followed by dehydrobromination.

Bromide ion is known to be completely transformed into tribromide when an equimolecular amount of Br$_2$ is added to solutions of tetrabutylammonium bromide (TBAB) in 1,2-dichloroethane[10] . In order to confirm that Br$_3^-$ ion is the brominating specie , under the conditions of this reaction, compounds

1 and 4 were treated with this perbromide obtaining (R= Br, 9), (R= H, 12 and 17) in an analogous result to the reaction using TMPAP.

The above results show that reaction of TMPAP with double bonds conjugated to carbonyl group is an intriguing reaction which involves stereospecific addition of bromine to the C-11/C-13 double bond and can be explained as a nucleophilic 1,2 addition of bromine via initial attack of Br_3^- at C-13[9].



SCHEME 2

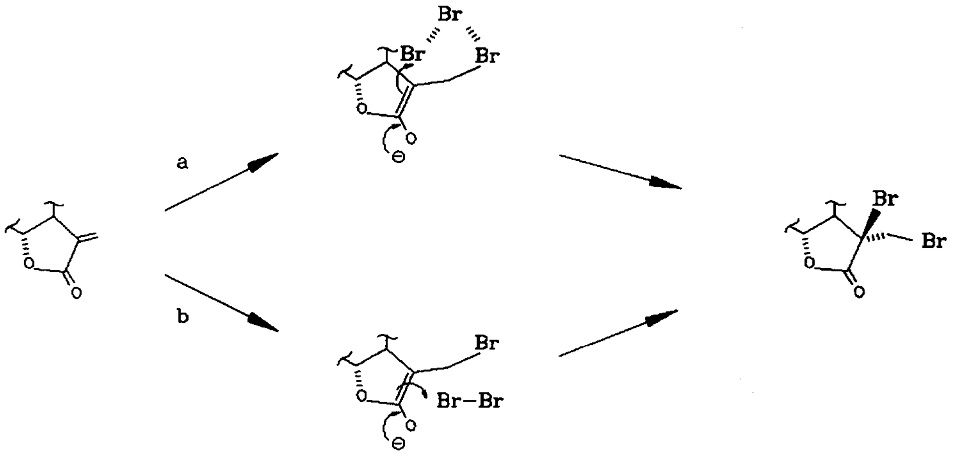
The mechanism is depicted in scheme 3 and two routes may be proposed. Route "a" implies a cyclic intermediate where Br_3^- is located on the ß face of the lactone ring.

Route "b" involves nucleophilic attack of Br_3^- to the $\Delta^{11,13}$ double bond. The resulting bromoenolate can be captured by bromine to give the corresponding dibromide derivative.

In order to obtain information which would permit us to decide between these possibilities, the mixed perhalide $(IBr_2)^-$ $(NBu_4)^+$ was prepared[11]. If we assume that the trihalide ion XY_2^- has a structure in which the halogen with higher atomic number is the central atom[11], then the reaction of this perhalide with a α-methylene-γ-lactone might decide between the two proposed routes.

When compound 1 was treated with $(IBr_2)^-$ $(NBu)_4^+$ in either dioxane or bromoethane compound 9 (60%) together with recovered starting material was obtained. Attempts to obtain derivatives with substituent, different to Br , on C-11 were unsuccessful.

All experimental facts, above mentioned can be accommodated by the mechanism shown in scheme 3, route"a" which involves a nucleophilic 1,2 addition of bromine, via a cyclic intermediate in which the chemoselectivity is induced by Br_3^- situated on the β face of the lactone ring.



SCHEME 3

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