Applications of Bromolactones in Synthesis. Stereospecific Syntheses of *cis*-2-Hydroxy-1-methylcyclohex-5-ene-1-carboxylic Acid and Related Compounds

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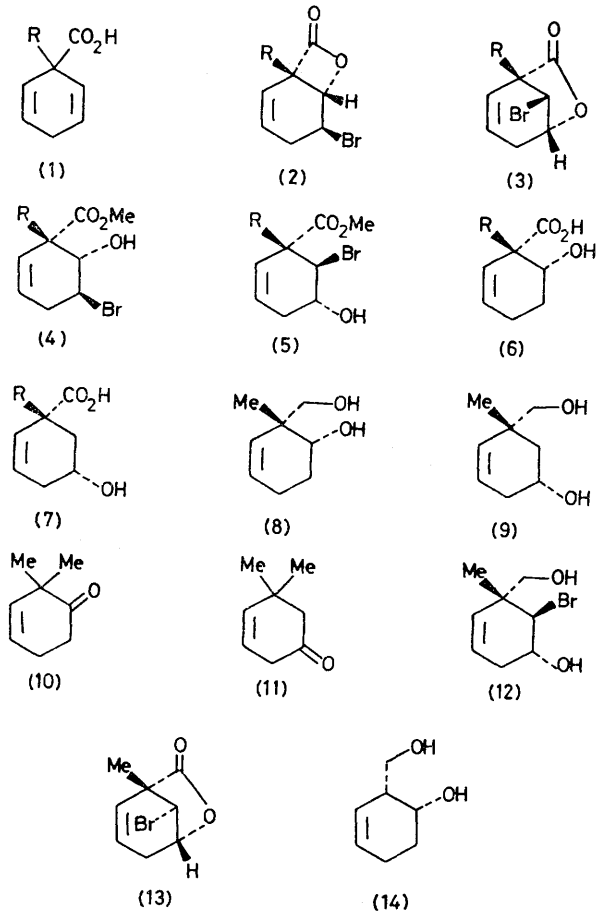
Summary *cis*-2-Hydroxy-1-methylcyclohex-5-ene-1-carboxylic acid (**6**; R = Me) is prepared in over 60% yield from the bromo-β-lactone (**2**; R = Me); attempted hydrolysis of the bromo-β-lactone (**2**; R = Me) gave the γ-isomer (**3**; R = Me), and lithium aluminium hydride reduction of both the bromo-β-lactone (**2**; R = Me) and the bromo-γ-lactone (**3**; R = Me) gave *cis*-2-hydroxymethyl-2-methylcyclohex-3-en-1-ol (**8**).

THE bromolactonization of suitably substituted 1,4-dihydrobenzoic acids (**1**) is known to give bromo-β-lactones (**2**).[1] These bromolactones have recently been used in an elegant approach to benzene oxides and related natural products, and have been shown to isomerize on heating to the related bromo-γ-lactones (**3**).[2] We here demonstrate the use of these β- and γ-lactones in the stereospecific synthesis of substituted cyclohexenes.

Treatment of the bromo-β-lactone (**2**; R = Me) with toluene-*p*-sulphonic acid in refluxing methanol gave a bromohydrin (88%) to which structure (**4**; R = Me) was tentatively assigned, although the isomeric structure (**5**; R = Me) was not excluded by the spectroscopic data.†

† Satisfactory spectroscopic and analytical or accurate mass data were obtained for all new compounds.



Reduction of the bromohydrin with Bu^n_3SnH[3] followed by hydrolysis of the crude product (10% KOH–MeOH) gave a hydroxy-acid (75%) to which structure (**6**; R = Me) was provisionally assigned although the isomeric structure (**7**; R = Me) could not be excluded.

The possibility that the bromohydrin obtained on methanolysis of the bromo-β-lactone (**2**; R = Me) was the rearranged isomer (**5**; R = Me), was suggested by the results obtained on attempted hydrolysis of (**2**; R = Me). Treatment of this bromo-β-lactone with refluxing aqueous acid gave the isomeric γ-lactone (**3**; R = Me) as the only isolable product in good yield.

Moreover reduction of either (**2**; R = Me) or (**3**; R = Me) with excess of $LiAlH_4$ gave the same diol product; the spectroscopic data of this diol were consistent with it being either *cis*-2-hydroxymethyl-2-methylcyclohex-3-en-1-ol (**8**) or its isomer (**9**).

The 1,3-diol structure (**8**) for the reduction product was confirmed by several methods. Firstly, the diol was selectively monotosylated,[4] reduced ($LiAlH_4$), and oxidized to give a dimethylcyclohexenone whose ^1H n.m.r. spectrum was consistent with the 2,2-dimethylcyclohex-3-en-1-one structure (**10**) rather than the isomeric (**11**).[5] Also spin decoupling experiments suggested that the intermediate alcohol was 2,2-dimethyl- and not 5,5-dimethyl-cyclohex-3-en-1-ol. Secondly, reduction of (**3**; R = Me) with less $LiAlH_4$ gave the hydroxybromohydrin (**12**) which gave a new diol, the 1,4-diol (**9**), on reduction with Bu^n_3SnH. This same diol was also prepared, but less efficiently, by reduction with $LiAlH_4$ of the bromo-γ-lactone (**13**).

Therefore reduction with $LiAlH_4$ of both (**2**; R = Me) and (**3**; R = Me) gave the same 1,3-diol, (**8**). Reduction of the methyl ester of the hydroxy acid tentatively identified as (**6**) also gave (**8**) so confirming the structure of this hydroxy acid.

Since the methanolysis–reduction and reduction with $LiAlH_4$ of (**2**; R = Me) provided easy access to the *cis*-hydroxy-acid (**6**) and the *cis*-1,3-diol (**8**), the generality of these reactions was briefly explored. Acid catalysed methanolysis followed by reduction with Bu^n_3SnH of (**2**; R = H) gave the methyl ester of *cis*-2-hydroxycyclohex-5-ene-1-carboxylic acid (**6**; R = H),‡ and reduction with $LiAlH_4$ gave a diol tentatively identified as the *cis*-1,3-diol (**14**).

We thank the S.R.C. (for support to T.M.) and the Malaysian Government (for support to H.M.S.).

(*Received*, 16*th August* 1978; *Com.* 903.)

‡ Structure confirmed by hydrogenation to the known methyl *cis*-2-hydroxycyclohexane-1-carboxylate, (E. E. Smissman and R. A. Mode, *J. Amer. Chem. Soc.*, 1957, **79**, 3447; J. Castells and J. Palau, *J. Chem. Soc.*, 1964, 4938; H. Baumann, N. C. Franklin, and H. Möhrle, *Tetrahedron*, 1967, **23**, 4331).

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