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A Simple, General Diastereoselective Synthesis of 5-Hydroxyalkylbutan-4-olides

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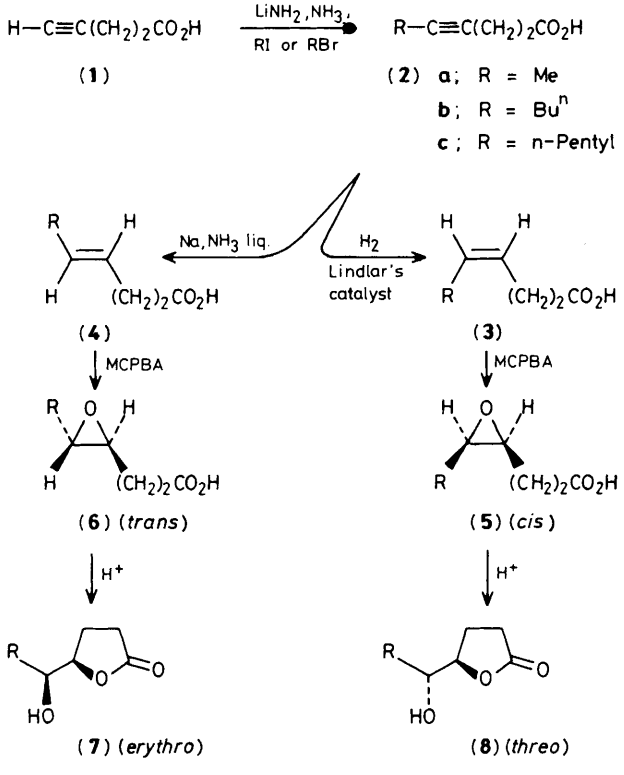
cis- and *trans*-Hex-4-enoic acids and their 6-n-propyl and n-butyl derivatives, when treated with a 1.1 molar excess of *m*-chloroperbenzoic acid and Amberlyst-15 as catalyst in CH_2Cl_2 at 20 °C, gave the corresponding *threo*- and *erythro*-5-hydroxyalkylbutan-4-olides in quantitative yields.

5-Hydroxyalkylbutan-4-olides are widespread in Nature and often show biological activity.[1] Consequently, much attention has been paid to their synthesis[2,3] and exploitation as building blocks for constructing complex natural products.[4] In our quest for new, short ways of preparing these entities[5] we were surprised that the potential of epoxyalkanoic acids, notwithstanding the widely recognized usefulness of epoxides,[6] had not been exploited for preparing γ-lactones with pre-ordained relative configurations at the C-4 and C-5 positions.[7,8] We now describe a simple procedure in which the required diastereoselectivity is determined by the *cis*- or *trans*-geometry of the 4,5-epoxyalkanoic acid chosen as intermediate.



Scheme 1

The treatment of commercially available pent-4-ynoic acid (**1**) with lithium amide in liquid ammonia and an alkyl halide such as methyl iodide, n-butyl or n-pentyl bromide, affords the corresponding alk-4-ynoic acids (**2**) in high yield.[9,10] Subsequent conversion into the *cis*- and *trans*-alk-4-enoic acids (**3**) and (**4**) is smoothly effected either by hydrogenation with Lindlar's catalyst in the presence of quinoline[11] or reduction with sodium in liquid ammonia,[10] respectively. The purity of each isomer is more than 98% as determined by ^1H n.m.r. spectroscopy at 360 MHz. Next, the alkenoic acids are initially treated with *m*-chloroperbenzoic acid (MCPBA) in methylene chloride and then with a catalytic amount of Amberlyst-15. A quantitative yield of the desired 5-hydroxybutan-4-olide is obtained. In this way, isolation of the respective *cis*- and *trans*-epoxides (**5**) and (**6**) is unnecessary. The *cis*-alkenoic acids (**3**) give exclusively the *threo*-diastereoisomer (**8**), whereas the *trans*-acids (**4**) afford solely the *erythro*-isomer (**7**) (see Scheme 1).†

According to the Baldwin rules,[12] cyclization of (**5**) and (**6**) could occur by either an *exo*-5-*tet* or an *endo*-6-*tet* process. However, if the δ-lactone were to form, its tautomerization to the γ-lactone should be rapid under the conditions used.[13]

In order to appreciate these results, they should be

† In a typical experiment, MCPBA (220 mg, 75%) is added to a solution of *cis*-hex-4-enoic acid (100 mg) in CH_2Cl_2 (5 ml) and the mixture is stirred at 20 °C for 5 h. Amberlyst-15 (20 mg) is then added and the mixture stirred for a further 15 h. The reaction mixture is purified twice by column chromatography (silica gel, 230—400 mesh, 10 g; eluant, hexane–EtOAc, 7 : 3). Pure *threo*-lactone (**7a**) is obtained in quantitative yield (102 mg). For the *cis*- and *trans*-acids (**3b**, **c** and **4b**, **c**), a single chromatographic separation suffices for purification, provided the reaction mixture, after dilution with ethyl ether, is washed with 5% aqueous $NaHCO_3$ solution.

The *threo*- and *erythro*-isomers were easily distinguished by the characteristic upfield shift of the C-5 proton of the latter ($\Delta\delta$ ~0.4).[3] It is worth noting that the intermediate *cis*- and *trans*- epoxides (**5**) and (**6**) are stable in the absence of Amberlyst-15, but slowly lactonize on standing.

compared to analogous cases. The only exact precedent was the conversion of *trans*-6-phenylhex-4-enoic acid by hydrogen peroxide and formic acid into *erythro*-5-hydroxy-6-phenylhexan-4-olide in 54% yield.[14] A similar hydroxy-lactonization occurred with the 3-methylsilyl derivatives of *trans*-hex-4-enoic acid, its ethyl ester, and amide.[15] However, *erythro*-diastereoselectivity was only observed for the amide, and was otherwise lost owing to equilibration *via* an intermediate β-silyl carbocation. Other epoxidative lactonizations were not stereoselective[16] or led to δ-lactones[7,17] or mixtures of γ- and δ-lactones,[8,18] often in yields of less than 60%. Consequently, the advantages of the present procedure are simplicity and the exclusive, quantitative formation of γ-lactones in which the desired diastereoselectivity can be preselected by the geometry of the alk-4-enoic acid.

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