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THE FACILE REDUCTION OF METHOXYETHOXYMETHYL ESTERS WITH LITHIUM TRIETHYLBOROHYDRIDE

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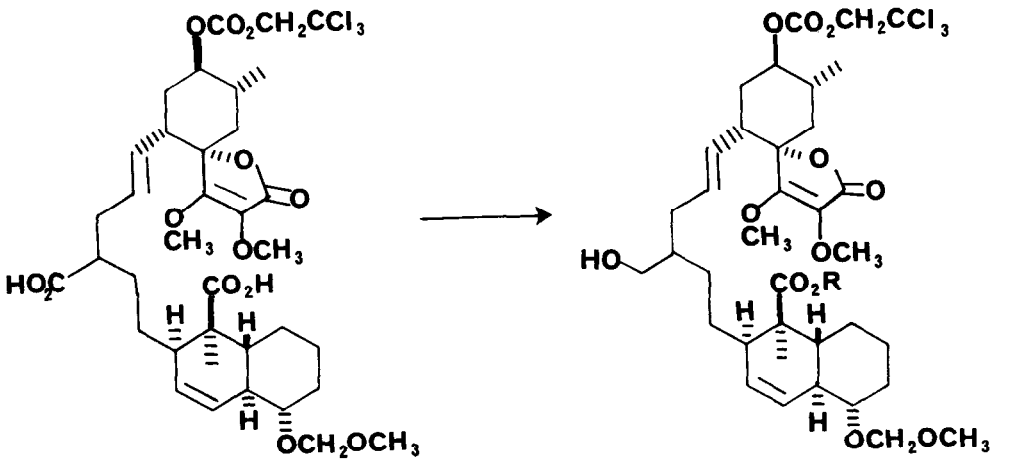
Summary: The use of a methoxyethylmethyl (MEM) ester has been shown to facilitate the selective reduction of that ester function in the presence of other reduceable esters.

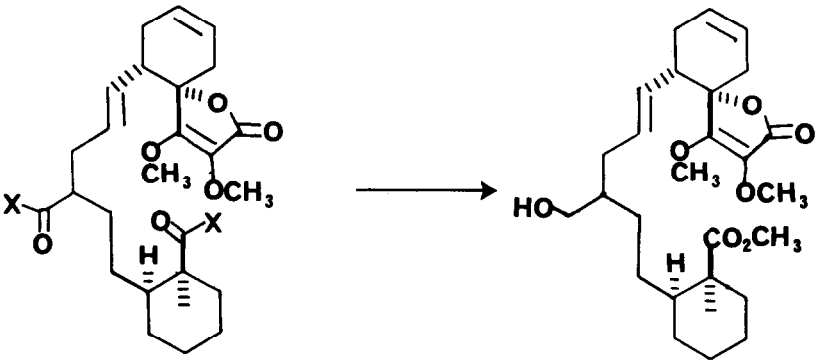
A transformation often encountered in the synthesis of complex organic substrates is the problem of selective reduction of a carboxyl group in the presence of other reduction sensitive functionality. The usual solution to this problem is to increase the reactivity of the carboxyl by introducing a good leaving group (formation of an "active ester"). Some examples of this type of approach are the imidazolide[1], acyl chloride[2], mixed carbonic anhydride[3], acyl azide[4], and trifluoroethyl ester[5].

During a project directed at the total synthesis of the macrolide antibiotic chlorothricolide[6], a selective reduction of a carboxyl group in the presence of other reducible functionality, including a second more hindered carboxyl group (conversion of I to II), was required.



(I) (II)

Attempted reduction of the bis-methyl ester 1 with the usual ester reducing agents (diisobutylaluminum hydride in ether, or lithium triethylborohydride in THF)[8] resulted in only slow reduction of the less hindered carbomethoxy group, and gave low yields (<30%) of the alcohol 2.

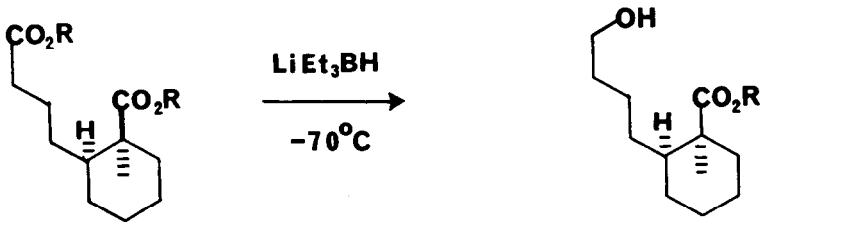


1, X = OCH_3 2

Bis-activation increased the reactivity of the two carboxyls such that selective reduction of the less hindered carboxyl could not be performed (x=Cl, imidazole). Use of lithium triethyl borohydride in the more coordinating solvent dimethoxyethane (DME) produced some of the desired alcohol 2 (~10%), but the major products arose from reduction of the α-methoxy tetronic ring.

A simple yet highly effective solution was then formulated. Attachment of the DME-unit to the ester in the form of a methoxyethoxymethyl ester (MEM-ester)[9] might activate the carboxyl group by chelation of the lithium cation and induce rapid intramolecular delivery of hydride to the ester carbonyl.

The bis-MEM esters 3 and 9 were prepared from the corresponding diacids[6] in high yield (2.5 equiv iPr_2EtN, 2.5 equiv MEMCl, 0.5 M in acid, CH_2Cl_2, 2h, 0°C) after chromatography. These diesters underwent smooth, selective reduction with three equiv[10] of lithium triethyl borohydride in THF at -70°C (0.4 M in [H]) in 30 min to afford the hydroxy MEM esters 5 and 10 in 90% chromatographed yields. Selectivity of the less hindered ester group was observed for both the bis-MEM ester 3 in THF and the bis methyl ester 4 in DME.

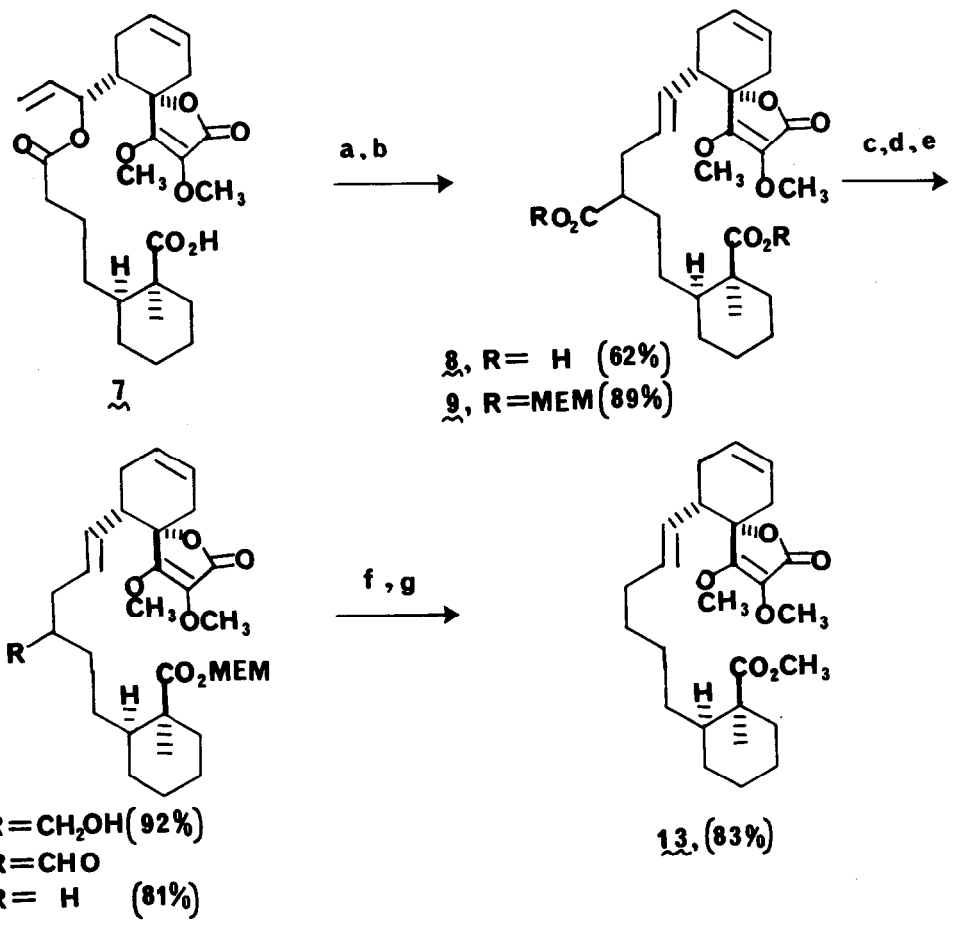


3, R = MEM (THF) 5, R = MEM (90%)
4, R = Me (DME) 6, R = Me (90%)

The MEM esters are easily handled, stable intermediates which survive a variety of reaction conditions as is demonstrated by the oxidation, decarbonylation sequence shown in Scheme I. Finally, the MEM esters can be removed by aqueous acid (3N HCl, THF, 40°C, 12h)[9], which in the case of the hindered ester 6 cannot be accomplished without strong C-nucleophiles such as lithium n-propylmercaptide in HMPA.

The method should find useful application in the synthesis of complex organic substrates containing ester or lactone carbonyls. Application of the efficient sequence shown in Scheme I to the total synthesis of chlorothricolide is presently underway in this laboratory.[13]

Scheme I[a]



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8, R= H (62%)
9, R=MEM(89%)

10, R=CH2OH(92%)
11, R=CHO
12, R= H (81%)

13, (83%)

[a] a, KNTMS$_2$, THF, -70°C; TMSCl, Et$_3$N; b, iPr$_2$EtN, MEMCl, CH$_2$Cl$_2$, 0°C; c, LiEt$_3$BH, THF, -70°C; d, CrO$_3$·C$_5$H$_5$N·HCl; e, [(C$_6$H$_6$P)$_3$P]RhCl, ClCH$_2$CH$_2$Cl, Δ, 2h; f, 3NHCl, THF, H$_2$O, 25°C, 12h; g, CH$_2$N$_2$, Et$_2$O.

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References and Notes

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9) For a recent use of MEM esters see: A. I. Meyers and P. J. Reider, J. Amer. Chem. Soc., 101, 2501 (1979); for the preparation of MEM ethers, see: E. J. Corey, J.-L. Gras, and P. Ulrich, Tetrahedron Lett., 809 (1976); E. J. Corey and R. H. Wollenberg, ibid., 4705 (1976).

10) Use of less than three equiv resulted in recovery of starting material. Complete conversion of the MEM ester to alcohol requires three equiv of hydride, because of generation of one equiv of formaldehyde from the MEM group.

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12) The structures 1 and 2 and all of those on Chart I are depicted as one enantromer for convenience, but are actually a mixture of diastereomers, resulting from the connection of two d,l pairs in the preparation of ester-acid 7 (see ref. 6).

13) All new compounds displayed satisfatory spectral and analytical data.

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