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The Stereochemical Outcome of the Mitsunobu Reactions of *para*-Oxygenated Benzylic Alcohols

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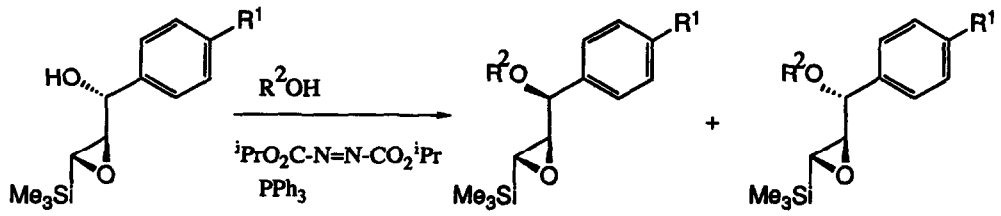
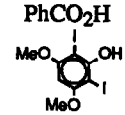
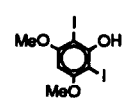
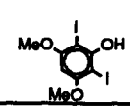
Abstract: Under Mitsunobu reaction conditions a *para*-methoxy benzylic alcohol gave substantially racemic products, whereas a *para*-pivaloyloxy and a *para*-acetoxy benzylic alcohol gave products resulting from inversion.

As part of a program directed towards the synthesis of chiral, naturally occurring, flavan-3-ols with important biological activity e.g. (+)-catechin[1], we were interested in the diastereoselection exhibited in the Mitsunobu reaction[2] of the chiral epoxy alcohols (1) with 2,6-diiodophenol-3,5-dimethoxyphenol[3]. Initial work was directed towards the synthesis of the afzelechin series of flavan-3-ols.



1 2 3

Entry	R^1	R^2OH	ratio 2:3
i	MeO	$PhCO_2H$	60:40
ii	$^tBuCO_2$	$PhCO_2H$	96:4
iii	$MeCO_2$	$PhCO_2H$	>98:2
iv	MeO		50:50
v	$^tBuCO_2$		>98:2
vi	$MeCO_2$		>98:2

The chiral epoxy alcohols (1, R^1=OMe, O_2CBu^t and O_2CMe) were prepared by a Sharpless kinetic resolution[4] and their reaction with benzoic acid was examined under Mitsunobu reaction conditions . Reaction of the *para*-methoxy compound (1, R^1=OMe) with benzoic acid gave the diastereotopic benzoates (2 and 3, R^1=OMe, R^2=COPh) in 86% yield after chromatography. ^1H n.m.r. analysis of the crude reaction mixture indicated the ratio of the isomer resulting from inversion of configuration at the benzylic center (2) to that arising from retention (3) to be 60:40 (entry i). It was thought that the strongly electron donating *para*-methoxy group was responsible for the lack of stereoselectivity in the Mitsunobu reaction and the effect of replacing it by alternative oxygen-bonded substituents was investigated. The *para*-pivaloyloxy compound (1, R^1=O_2CBu^t) was then treated with benzoic acid under Mitsunobu reaction conditions . The benzoate esters (2 and a trace of 3, R^1=O_2CBu^t, R^2=COPh) were obtained in 60% yield after chromatography. ^1H nmr analysis of the total crude product showed predominantly the ester (2), the product of inversion (2:3, ~96:4, entry ii). The small amount of the product of retention of configuration at the benzylic position (3) could be due to small amounts of benzoic anhydride being formed under the reaction conditions, leading to direct acylation of the alcohol (1). When the *para*-acetoxy compound (1, R^1= O_2CMe) was treated with benzoic acid under similar Mitsunobu conditions only the benzoate (2, R^1=O_2CMe, R^2=COPh) was formed in 81% yield (2:3, >98:2, entry iii) after column chromatography. In all cases (entries i, ii and iii) an authentic sample of the product of retention was prepared by esterification of the epoxy alcohols (1) with the appropriate acid using dicyclohexylcarbodiimide.

Attempted preparation of aryl ether (2, R^1=OMe, R^2=2,6-diiodo-3,5-dimethoxyphenyl), a synthetically useful intermediate for flavanol synthesis, using 2,6-diiodo-3,5,-dimethoxyphenol as the nucleophile led to a 1:1 mixture of aryl ethers (2) and (3) in combined yield of 65% (entry iv). Reaction of the *para*-pivaloyloxy (1, R^1=O_2CBu^t) and *para*-acetoxy (R^1=O_2CMe) compounds with 2,6-diodo-3,5-dimethoxyphenol gave a single aryl ether in 92% (entry v) and 83% (entry vi) yields, respectively. The aryl ethers have been assigned the structure (2, R^1=O_2CBu^t or R^1=O_2CMe, R^2=2,6-diiodo-3,5-dimethoxyphenyl) resulting from an inversion at the benzylic centre in keeping with the result obtained from reaction with benzoic acid (entry ii and iii).

In conclusion, the stereochemical outcome of the Mitsunobu reaction of the *para* oxygenated benzylic alcohols discussed in this letter depends on the nature of the *para* substituent. Reactions of phenolic ethers lead to racemisation at the benzylic centre, while reactions of phenolic esters give the products resulting from inversion at the benzylic centre.

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References and Notes

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