Tetrahedron: Asymmetry Vol. 3, No. 7, pp. 833-836, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

(1R)-Menthoxymethyl ether, a Chiral OH Protecting Group and its use in the Measurement of Enantiomeric Excess.

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(*Received* 21 *May* 1992)

Abstract : The protection of a range of chiral alcohols with chloromethyl-(1R)-menthyl ether is reported. Conditions for the deprotection of (1R)-menthoxymethyl ethers are described which do not lead to racemisation of homochiral alcohols. The usefulness of the (1R)-menthoxymethyl ether group (MM) as a simple means of measuring enantiomeric excess in a reaction sequence starting from ethyl lactate is outlined.

During a synthetic study on the synthesis of homochiral dienes[1] we needed to measure the enantiomeric excess of each intermediate in a reaction sequence starting from ethyl lactate. Application of the Mosher method[2] to this problem was possible, however many intermediates were labile and underwent side reactions. It occurred to us that it would be far more efficient if a chiral protecting group could be introduced at an early stage in the route which would produce diastereoisomers at each stage. The diastereoisomer ratio could be measured for each intermediate and, as long as the protecting group was not influencing the stereochemistry of the reaction, this measurement would monitor the stereochemical integrity of each compound in the sequence.

One of the most convenient ways to protect an OH group[3] is the formation of an acetal derivative by reaction of the alcohol with a chloroether eg., a methoxymethyl ether (MOM ether),[4] a benzyloxymethyl ether[5] or 2-methoxyethoxymethyl ether (MEM ether).[6] One approach to finding a chiral OH protecting group is to prepare homochiral chloroethers and to use them in an analogous way to other ether protecting groups. Chloromethyl-(1R)-menthyl ether is a known compound[7] and it has been used for the resolution of an oxime,[8] an allylic alcohol[9] and an iron acyl complex.[10] We have prepared a series of (1R)-menthoxymethyl ethers of racemic and homochiral alcohols as shown in Table 1.[11] Each alcohol (1.2 m. mol.) was reacted with chloromethyl-(1R)-menthyl ether (3.7 m. mol.) and N,N-diisopropylethylamine (4.9 m. mol.) in dichloromethane. After stirring overnight and standard work up the (1R)-menthoxymethyl ethers were obtained in the yields given in Table 1.

The ratio of diastereoisomers was measured from the proton nmr using the integral of the signal for the proton next to oxygen in the (1R)-menthyl group and the acetal protons as indicated in structure (1). To test the accuracy of the measurements both enantiomers of methyl mandelate were protected and three different mixtures of diastereoisomers were prepared. The diastereoisomer ratio was then determined using the nmr method, the results are shown in Table 2.

Deprotection of the acetal (1) was achieved using zinc bromide in dichloromethane. The (S)-methyl mandelate obtained in this process had the normal specific rotation showing that no racemisation occurred during the protection or deprotection processes.

In order to illustrate the use of the (1R)-menthoxymethyl ether protecting group, chiral diene (7) was

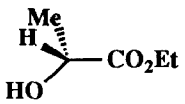
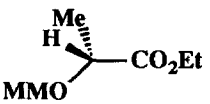
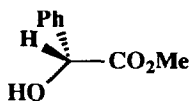
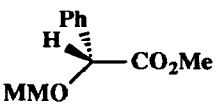
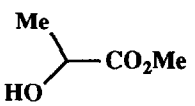
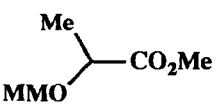
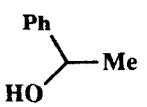
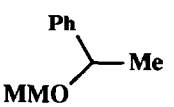
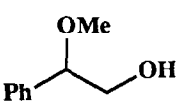
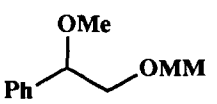
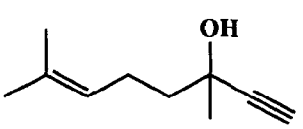
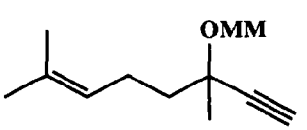
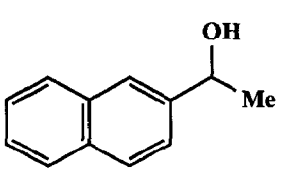
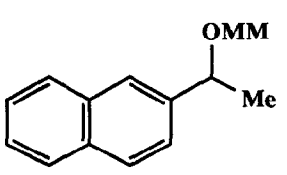
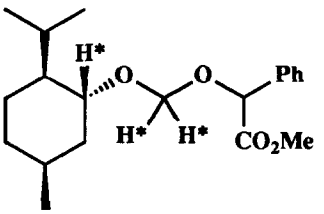
Alcohol	Product	Yield
		85%
		79% Yield of racemic product 90%
		77%
		89%
		65%
		95%
		94%

Table 1 : Alcohols protected with chloromethyl-(1R)-menthyl ether
MM = (1R)-menthoxymethyl ether

synthesised using the reaction sequence shown in the Scheme.[11] (S)-Ethyl lactate was protected as the (1R)-menthoxymethyl ether (2), which was a single diastereoisomer from both ^{1}H and ^{13}C nmr. We are confident that we would have been able to detect the other diastereoisomer from the following control experiment. (S)-

Ethyl lactate was converted into its MM ether as described above. Deprotonation with LDA followed by reprotonation gave an ether which showed peaks for two diastereoisomers in the ratio 56 : 44.

Reduction of the ester (2) with lithium aluminium hydride produced the alcohol (3) as a 90 : 10 mixture



(1)

Diastereoisomer ratio by weight.	Diastereoisomer ratio by nmr of the acetal protons in (1).
75 : 25	74 : 26
50 : 50	51 : 49
25 : 75	24 : 76

Table 2 : Measurement of the diastereoisomer ratio of synthetic mixtures of (1) from the nmr integral of the acetal protons.

of diastereoisomers from the ^1H nmr of the acetal protons. Previous studies[1] had shown that the Mosher ester of (3) with a benzyloxymethyl ether protecting group did not give resolved nmr signals and so enantiomeric excess measurement by this method was not possible in this case. Swern oxidation of alcohol (3) led to the aldehyde (4) which showed a 90 : 10 mixture of diastereoisomers from the ^1H nmr of the acetal protons. Addition of trimethylsilylmagnesium bromide to the aldehyde (4) gave alcohol (5) as one diastereoisomer at the adjacent chiral centres 2 and 3, the ^1H nmr signals were not sufficiently well resolved to measure the diastereoisomeric excess at this stage. Swern oxidation of the alcohol (5) followed by addition of vinyl Grignard reagent led to the unstable alcohol (6) as a 2 : 1 mixture of diastereoisomers at the adjacent chiral centres 2 and 3. The diastereoselectivity of the sequence (4)-(6) was the same when the benzyloxymethyl ether was used as the protecting group, hence the MM ether does not lead to asymmetric induction in these reactions. Peterson elimination using potassium hydride gave the diene (7) as an 88 : 12 mixture of diastereoisomers.

Acknowledgement. We are grateful to the SERC for a studentship (to D.D.) and to the SERC Mass Spectrometry Service at Swansea University for mass spectra on the new compunds mentioned in this paper.

References and Notes

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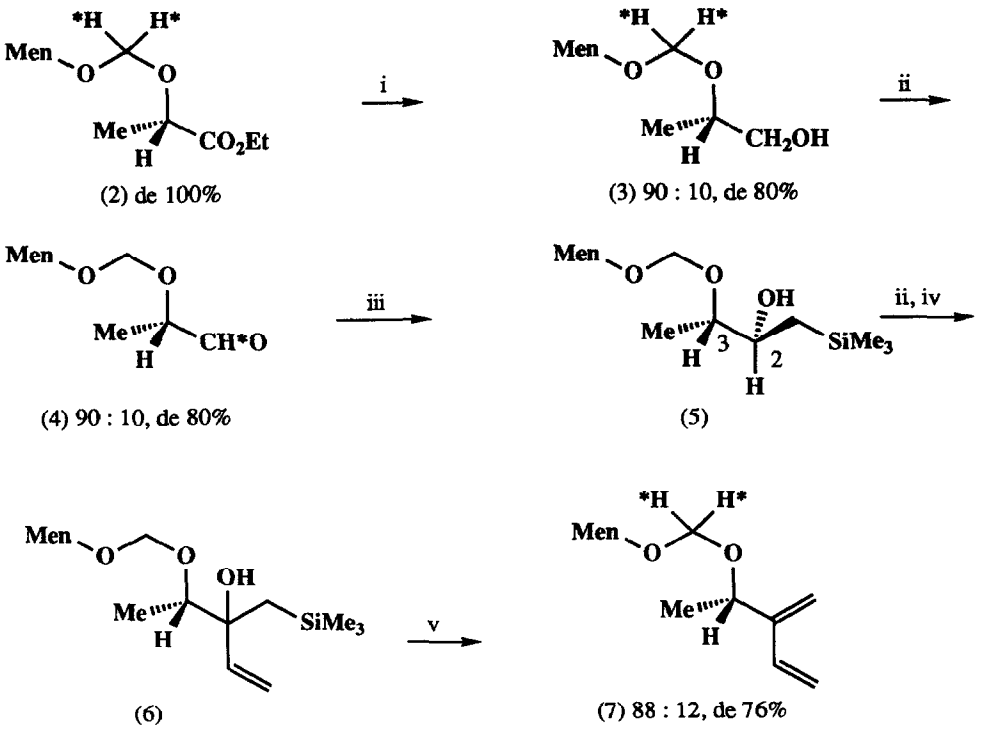

(2) de 100%

(3) 90 : 10, de 80%

(4) 90 : 10, de 80%

(5)

(6)

(7) 88 : 12, de 76%

Scheme Reagents: i, $LiAlH_4$; ii, ClCOCOCl, DMSO, NEt_3; iii, Me_3SiCH_2MgBr; iv, $BrMgCHCH_2$; v, KH.

Signals from the H* protons are used to measure the diastereoisomer ratio

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11. The abbreviation (1R)-menthyl in the text, and Men in the Scheme refer to derivatives of (1R,2S,5R)-(-)-2 isopropyl-5-methylcyclohexan-1-ol. All new compounds gave satisfactory spectroscopic and accurate mass spectral data.