Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 10, pp. 2871-2878, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00378-3

Differentiation and Assignment of the Proton NMR Signals in the Bis-MTPA Ester of *Meso*-α,α'-Dimethyl-1,4-benzenedimethanol

Bruce W. Baldwin and Cary J. Morrow*

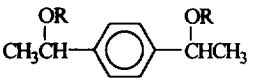
Department of Chemistry, University of New Mexico, Albuquerque, NM 87131

Abstract: $NaBH_4$ reduction of one ketone in 1,4-diacetylbenzene followed by Amano PS catalyzed acylation of the R enantiomer, separation of the R acetate from the S alcohol, and reduction of the remaining ketone in each with $NaBD_4$ has provided two mixtures of monodeuterated diol diastereomers: R,R(d) plus R,S(d) and S,R(d) plus S,S(d). Conversion of the unseparated diols into their bis-(R)-MTPA (Mosher's) esters has allowed the NMR signals arising from the C-methyl groups at the R and the S ends of *meso*-α,α-dimethyl-1,4-benzenedimethanol bis-(R)-MTPA ester to be assigned unequivocally. Copyright © 1996 Published by Elsevier Science Ltd

Recently, there has been renewed interest in the NMR analysis of diol stereoisomers.[1,2,3,4] Procedures developed by Resnick, Torok, and Gibson,[1] by Burgess and Porte,[2] and by Tokles and Snyder,[4] all rely on conversion of the diol to a cyclic ester of a boronic acid enantiomer, and, hence, are useful in those cases where the two hydroxyls are arranged 1,2 or 1,3. Our own interest was in the analysis of the symmetric α,α'-dimethybenzenedimethanol stereoisomers, **1a,b,c,** which we[3] and others[5] have separated using an enzymatic process. In these diols, the two alcohol functions are at stereogenic centers sufficiently far removed from each other to preclude forming a cyclic boronate. For that reason, we have adopted the older technology of converting the two alcohols to their α-methoxy-α-trifluoromethylphenylacetates,[6,7] the bis (R)-MTPA ester (or bis Mosher's ester), **2 a,b,c**.[8,9,10]

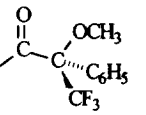
The stereoisomers of **1** isolated in our work may include as stereoisomeric impurities, in the case of **1a** or **1b**, the enantiomer of the major stereoisomer, its *meso* diastereomer, **1c**, or both. Similarly, compound **1c** may be contaminated with **1a**, **1b**, or both. In our earlier work, we were able to show that, at 250 MHz, proton NMR signals characteristic of both the stereocenter being analyzed and the one across the ring from it could be identified in the spectra of each of compounds **2**.[3] Integration of the signals provided a quantitative estimate of the mole fraction of the major stereoisomer and each of the minor stereoisomers present in the sample.

Because of our interest in converting diols **2** into polycarbonates having extensive, well-defined backbone stereochemistry[11] it is important to know how the NMR signals of a given stereocenter are impacted by stereo-



1 R=H

a R,R
b S,S
c R,S (meso)



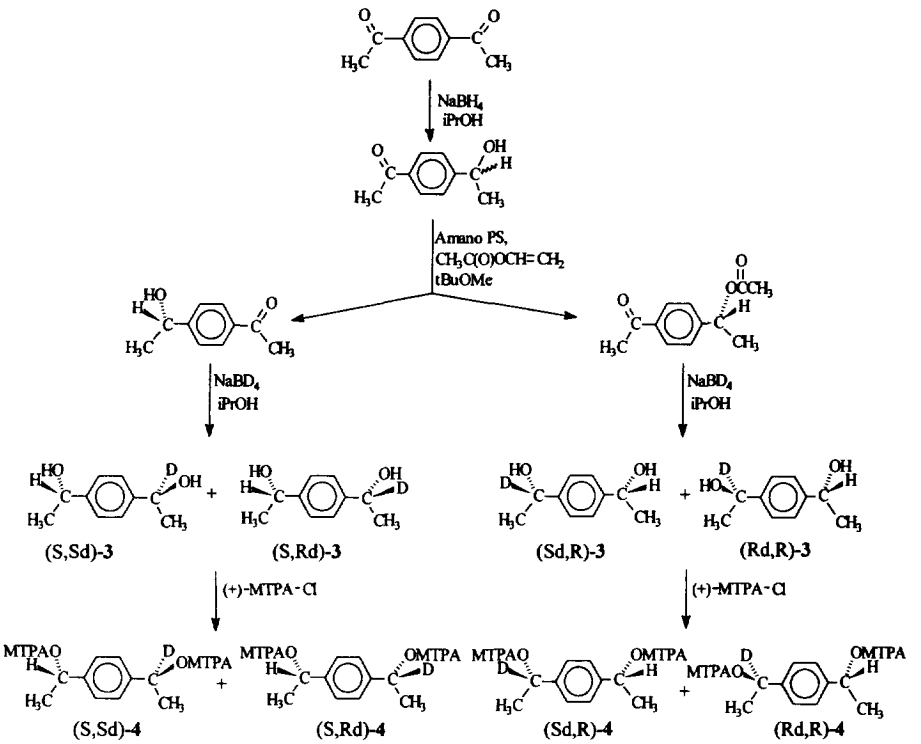
2 R=

a R,R
b S,S
c R,S

chemistry in an esterifying group as well as by the transannular stereochemistry. The availability of highly enriched samples of the C_2 symmetric R,R and S,S enantiomers permitted ready assignment of the signals associated with the bis MTPA ester of each of these compounds, **2a** and **2b**. However, in the analysis of the C_S symmetric meso compound, **2c**, it was possible only to speculate, on the basis of Mosher's rules[7] which absorptions to assign to the MTPA ester of the R stereogenic center in the diol, and which to assign to the MTPA ester of the S stereogenic center. The experiments described here allow those assignments to be made elegantly and unequivocally in the case where the esterifying group is (R)-MTPA.

To make the assignments, syntheses were carried out which resulted in two diastereomer mixtures each of which consisted of one enantiomer, either R,R or S,S, plus the *meso* diastereomer. In each mixture, a different end, either the R or the S, of the *meso* diol, **1c**, was modified by the methine hydrogen at that end being replaced by deuterium in a stereochemically known way. While the C-methyl region in the spectrum of the undeuterated stereoisomer, **2c**, displayed two doublets differing in chemical shift by about 0.06 ppm, replacing the methine proton at one end of the diol with a deuteron changed the C-methyl proton NMR signal for that end, from a doublet to a broadened singlet. (The coupling constant $J_{D\text{-}C\text{-}C\text{-}H}$ is too small for a triplet to be seen.) Since the stereochemistry, R or S, was known at the deuterated end of the *meso* diol, the doublet that collapsed to a singlet could be assigned to the end of the diol having that stereochemistry.

The required stereoselectively labeled, mono-deuterated diols were prepared by initial $NaBH_4$ reduction of one ketone in 1,4-diacetylbenzene followed by enzymatic resolution using Amano PS catalyzed, stereoselective acetylation of the R enantiomer with vinyl acetate.[12,13] Following chromatographic separation of the resulting S keto alcohol from the R keto acetate, the remaining ketone in each compound was reduced with $NaBD_4$, and the resulting mixture of two diols was converted to a mixture of the bis MTPA esters of each. (The conditions used in this last step were also found to remove the acetate group put on during the resolution.) This synthetic sequence is illustrated in Scheme 1. (To simplify the analysis below, the following convention was chosen in designating the structures in Scheme 1: The stereogenic center to the left is indicated first and the center on the right is indicated second. The location of the deuterium is indicated with a letter d immediately after the stereochemical designator for the carbon on which it is located. The MTPA group always has the R configuration so its stereo-



Scheme 1

chemistry is not shown.) Although each pair of diastereomeric diols, **3**, resulting from the sequence could have been separated by a second enzymatic acylation step, ^{1}H NMR analysis of the mixtures of bis MTPA esters **2a** with **2c** and **2b** with **2c**, the undeuterated analogues of the mixtures prepared according to Scheme 1, showed that to be unnecessary.

The C-methyl region of the spectrum given by an unequal mixture of **2a** and **2c** is shown in figure 1a while the same region of the spectrum given by an unequal mixture of **2b** and **2c** is shown in figure 2a. Through comparison with the spectra given by highly stereochemically pure **2a** and **2c**, the doublet labeled R,R in figure 1a can be assigned to **2a**, while the doublets labeled R,S can be assigned to **2c**. Likewise, the doublet labeled S,S in figure 2a is given by **2b**, while the doublets labeled R,S arise from **2c**. Thus, the C-methyl region of the ^{1}H NMR spectra for the two pairs of undeuterated stereoisomeric bis MTPA esters shows the peaks representing the four different magnetic environments (R,R; S,S; $R_{observed}S$, and $S_{observed}R$) to be sufficiently resolved to allow the different stereoisomers in the mixture to be identified and quantitated. In the spectra from undeuterated compounds **2**, the peaks arising from the bis (R)-MTPA esters of the enantiomeric R,R and S,S diols are readily

assigned, for both ends of each have the same stereochemical environment. Each of these environments leads to observation of one doublet which is labeled RR or SS in figures 1a and 2a, respectively. In contrast, **2c**, the bis MTPA ester of the *meso* diastereomer, has two different magnetic environments, R and S, each of which gives rise to a doublet. Independently of how the undeuterated *meso* diol is prepared, this same S,R stereochemical outcome obtains. However, when deuterated *meso* diol is prepared according to the two pathways in Scheme 1, two different diols result for which the bis MTPA esters, **4**, can be designated SRd and SdR.

To simplify this discussion further, a different way of designating the stereochemistries leading to each C-methyl signal in the proton NMR spectra will be used. Again, the (R)-MTPA is invariant and not shown. The stereochemistry leading to an observed C-methyl NMR signal can then be designated in terms of the stereochemistry at the stereogenic center to which the observed methyl is attached and the stereochemistry at the stereogenic center across the ring from it. The stereocenter to which the observed methyl is attached will be designated as R or S while the stereocenter across the ring will be designated r or s. Using these designations, the absorptions labeled R,R and S,S in figures 1a and 2a can be assigned to the Rr and Ss stereoisomers, respectively. The two stereocenters in the bis MTPA ester of the meso structure are then designated sR and Sr. Each of these signals may arise from observing the C-methyl at a stereogenic center having a deuterium replacing the methine H or having a deuterium replacing the methine at the stereogenic center across the ring. These situations will be designated with the letter d following the R, r, S, or s. Each of the pathways in Scheme 1 then requires consideration of four different NMR signal designations for the resulting mixture of bis MTPA esters, **4**: (a) (R)-keto acetate reduction and MTPA acylation leads to Rdr, Rrd, Sdr, and sdR. (S)-keto alcohol reduction and MTPA acylation leads to Sds, Ssd, Srd, and sRd.

If one assumes that the substitution by deuterium has little effect on chemical shifts but causes a methyl attached to the same carbon to appear as a broadened singlet rather than a doublet, the doublet assigned to Rr and labeled R,R in figure 1a should become a broadened singlet for Rdr but remain a doublet for Rrd in figure 1b. The two signals corresponding to these two cases are labeled Rdr and Rrd in figure 1b. It should be noted that the singlet for the methyl on the deuterated carbon is shifted about 0.01 ppm upfield of the centroid for the doublet given by the methyl that is in the same chemical and stereochemical environment, but that is located on a protonated carbon. It is also important to note that, whereas the C-methyls in the R,R compound gave a single doublet in the spectrum of the undeuterated material, figure 1a, it now gives two signals, one for methyls attached to deuterated carbons and one for methyls attached to protonated carbons. Similarly, Ssd and Sds, as expected, give a nearly unchanged doublet and a broadened singlet, and are so labeled in figure 2b. Continuing this same logic, the signals assigned to Sdr and sdR are expected to appear as a singlet and a doublet, respectively. Thus, the doublet that should be assigned to Sr in figure 1a is the one that has collapsed to a singlet and is labeled Sdr

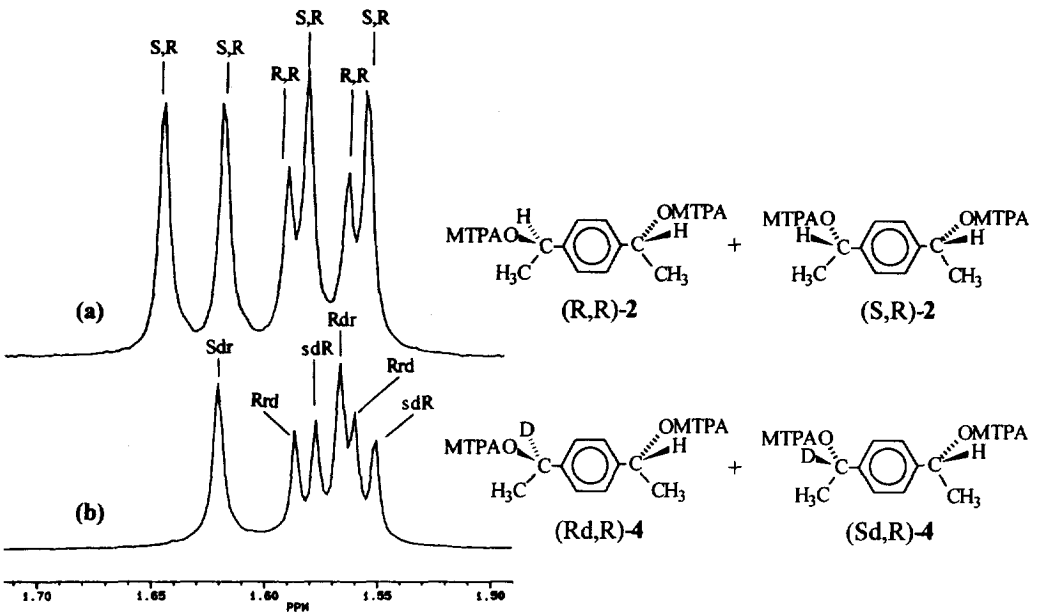


Figure 1. C-methyl region of the 1H NMR spectra of mixtures of: (a) **2a** with **2c** and (b) (Rd,R)-**4** with (Sd,R)-**4**. The doublets labeled S,R in (a) are given by **2c** while the doublet labeled R,R is given by **2a**. See text for discussion of the labels in (b).

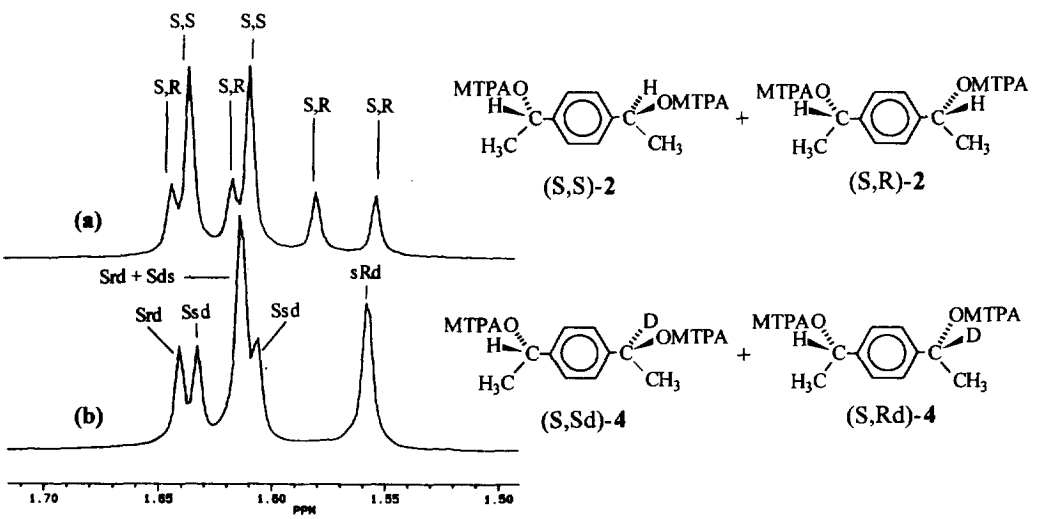


Figure 2. C-methyl region of the 1H NMR spectra of mixtures of: (a) **2b** with **2c** and (b) (S,Sd)-**4** with (S,Rd)-**4**. The doublets labeled S,R in (a) are given by **2c** while the doublet labeled S,S is given by **2b**. See text for a discussion of the labels in (b).

in figure 1b. A second doublet in figure 1a, then should be assigned to sR. As expected, it appears as the doublet labeled sdR in figure 1b. Thus, the doublet at 1.63 ppm in figure 1a may be assigned to the methyl on the S stereogenic center in **2c**, and the doublet centered near 1.57 ppm may be assigned to the methyl on the R stereogenic center.

This conclusion was confirmed by the signals for Srd, and sRd formed in the (S)-keto alcohol reduction and acylation. The methyl signals corresponding to these two designations are expected to appear as a doublet and a singlet, respectively, in figure 2b. Thus, doublet sR in figure 2a is the one that collapses to singlet sRd in figure 2b. Likewise, doublet Sr in figure 1a remains a doublet, only the left line of which is resolved in figure 2b. Thus, again, the doublet at 1.63 ppm may be assigned to the methyl on the S stereogenic center in **2c**, and the doublet centered near 1.57 ppm may be assigned to the methyl on the R center.

With the completion of these studies, the identity of all C-methyl signals in the stereoisomeric MTPA-bis esters **2a**, **b**, and **c** can be assigned with certainty as follows: Sr = 1.63 ppm, Ss = 1.62 ppm, Rr = 1.58 ppm, and sR = 1.57 ppm. A general trend noted in these results is that for the bis MTPA ester of a 1,4-benzene-1,1'-diethanol, the NMR signal of a methyl on a carbon having the S configuration is observed downfield relative to signal observed for a methyl on a carbon having the R configuration, as is expected from Mosher's rules.[7] On the other hand, for these cases, a carbon having an R configuration that is located across the ring from the observed methyl leads to a greater downfield shift of the observed methyl than does a carbon that has an S configuration. Thus, signals arising from observation of the same stereochemistry, e.g.(R), are near the same location regardless of deuterium substitution or the identity of the stereochemistry across the aromatic ring. Signals due to the opposite stereochemistry occur in a different chemical shift region. Although the stereochemistry across the aromatic ring from the observed stereocenter is not the primary determining factor for the location of signals, it too has a small, but potentially useful, impact on the chemical shift of the observed methyl group.

Experimental

(R,S)-4'-(1-Hydroxyethyl)acetophenone. To an ice-bath cooled suspension of 20 g (123.3 mmol) 1,4-diacetylbenzene (Aldrich) in 240 mL isopropyl alcohol was added 2.33 g (62 mmol) $NaBH_4$. The mixture was stirred 4 hours after which TLC(silica gel, 50% ethyl acetate/hexane) showed no starting material remained. To the cooled mixture was added 100 mL of 2.5 M aqueous HCl. The isopropyl alcohol was evaporated and the residue extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to produce an oil. The oil was distilled under high vacuum, and the material boiling at 130-160°C, 0.01 mm Hg collected. (A large fraction of the oil appeared to polymerize during the distillation.) The distillate was subjected to column chromatography on silica gel eluting with 50% ethyl acetate/hexane to yield 2.0 g (9.9% yield) of a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 7.72 Hz, 2H), 7.41 (d, J = 8.07 Hz, 2H), 4.90 (q, J = 6.49 Hz, 1H), 2.53 (s, 3H), 1.46 (d, J = 6.52 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ_c 198.1, 151.5, 135.6, 128.3, 126.0, 125.4,

125.3, 69.3, 26.3, 25.0; IR (neat) 3405, 1676, 1270, 1084 cm^{-1}.

(S)-4'-(1-Hydroxyethyl)acetophenone and (R)-4'-(1-Acetyloxyethyl)acetophenone. Following the general method of Boaz,[13] to a solution of 1.20 g (7.33 mmol) 4'-(1-hydroxyethyl)acetophenone. and 1.26 g (14.66 mmol) vinyl acetate in 40 mL t-butyl methyl ether, was added 0.5 g Amano PS lipoprotein lipase. The mixture was stirred for 24 hours at which time TLC analysis showed approximately 50% conversion of the hydroxy ketone to product. The mixture was filtered to remove the enzyme and the filtrate diluted with diethyl ether. The solution was extracted with saturated aqueous Na_2CO_3 and with water then was dried over $MgSO_4$, filtered, and the ether evaporated. The oily products were separated by column chromatography on silica gel, with a 25-50% ethyl acetate/hexane gradient. The first fraction, 290 mg (19.2%) of a colorless oil, was **(R)-4'-(1-Acetyloxyethyl)acetophenone**: $[\alpha]^{20}_D$ = +96.9; ^{1}H NMR ($CDCl_3$) δ 7.94 (d, J = 8.23 Hz, 2H), 7.44 (d, J = 8.21 Hz, 2H), 5.90 (q, J = 6.62 Hz, 1H), 2.57 (s, 3H), 2.08 (s, 3H), 1.54 (d, J = 6.66 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ_c 197.1, 146.7, 136.3, 128.4, 125.8, 71.4, 26.3, 21.9, 20.9. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.68; H, 6.85. The second fraction, 177.9 mg (15% yield) of colorless needles, was **(S)-4'-(1-hydroxyethyl)-acetophenone**: $[\alpha]^{20}_D$ = -41.6. IR and NMR spectra were identical with those of the starting material. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.23; H, 7.54.

Mixture of (R,R)-α,α'-Dimethyl-α-deuterio-1,4-benzenedimethanol, (Rd,R)-3, and (S,R)-α,α'-Dimethyl-α-deuterio-1,4-benzenedimethanol, (Sd,R)-3. To a solution of 290 mg (1.41 mmol) (R)-4'-(1-acetoxyethyl)aceto-phenone in 2 mL isopropyl alcohol was added 30 mg (0.70 mmol) $NaBD_4$. The mixture was stirred at room temperature for two hours then aqueous HCl was added to pH 7. The mixture was filtered and the filtrate extracted with ether. The ether was dried over $MgSO_4$, filtered, and evaporated to produce white crystals weighing 225.1 mg (76.8% yield): mp 98-115°C; $[\alpha]^{20}_D$ = +41.6; ^{1}H NMR (d_6-acetone) δ 7.31 (s, 4H), 4.83 (q, J = 6.43 Hz, 0.5 H), 4.81 (q, J = 6.42, 0.5 H), 1.38 (d, J = 6.31 Hz, 3H), 1.38 (s, 3H). Anal. Calcd for $C_{10}H_{13}DO_2$: C, 71.83; H, 9.04. Found: C, 71.85; H, 8.91.

Mixture of (S,S)-α,α'-Dimethyl-α-deuterio-1,4-benzenedimethanol, (S,Sd)-3, and (R,S)-α,α'-Dimethyl-α-deuterio-1,4-benzenedimethanol, (S,Rd)-3. To a solution of 100 mg (0.609 mmol) (S)-4'-(1-hydroxyethyl)aceto-phenone in 1 mL isopropyl alcohol was added 12.7 mg (0.305 mmol) $NaBD_4$. Work up as above produced white crystals weighing 60 mg (60% yield): mp 98-118°C; $[\alpha]^{20}_D$ = –38.7; ^{1}H NMR (d_6-acetone) δ 7.31 (s, 4H), 4.82 (q, J = 6.41 Hz, 0.5 H), 4.81 (q, J = 6.43, 0.5 H), 1.38 (d, J = 6.31 Hz, 3H), 1.375 (s, 3H). Anal. Calcd for $C_{10}H_{13}DO_2$: C, 71.83; H, 9.04. Found: C, 71.62; H, 9.09.

Bis (R)-MTPA Esters of α,α'-Dimethyl-α-deuterio-1,4-benzenedimethanol Stereoisomer Mixtures, (S,Sd)-4 + (S,Rd)-4 and (Sd,R)-4 + (Rd,R)-4. (S)-(+)-MTPA chloride was prepared in the usual way from 3.00 g (12.8 mmole) (R)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA), 6 mL thionyl chloride, and 36 mg sodium chloride and shown by IR and NMR to be identical to the literature material.[7] To an oven-dried 12 X 75 mm test tube equipped with rubber septum was added a few crystals 4-(N,N'-dimethylamino)pyridine. The test tube was then flushed with nitrogen gas and 0.54 mmole (S)-MTPA–Cl dissolved in 300 μL pyridine was

added. The solution was visually checked for precipitate, and if absent, 0.18 mmole diol dissolved in 300 μL pyridine was quantitatively transferred to the test tube. The resulting mixture was allowed to stand overnight at 40°C in an incubating oven. Complete reaction was confirmed by observing total consumption of the starting diol by TLC. Addition of 1.08 mmole dimethylaminopropylamine (DMAPA) was used to make excess acid chloride acid extractable. After standing five minutes, the solution was diluted with 35 mL diethyl ether and extracted with three 10 mL portions of 5% aqueous HCl, three 10 mL portions of dilute aqueous Na_2CO_3, and two 10 mL portions of distilled water. The organic layer was then dried over $MgSO_4$, filtered, and the solvent evaporated. The residue was dissolved in 1.0 mL $CDCl_3$ and filtered through a glass wool plug into a 5 mm NMR tube at room temperature. ^1H NMR analysis was carried out on a Bruker AC-250 instrument operating at 250.133 MHz using the decoupling coil of a broadband probe. The pulse width was 5 μs and spectral width 3246.753 Hz. Standard samples were observed for 40 scans with an 8 second recycle delay, and the FID transformed with no line broadening. Integration of the spectral lines was performed with instrumental software.

Acknowledgment. Support of this work by the National Science Foundation under grant No. DMR-8912065 and by the University of New Mexico Research Allocations Committee is gratefully acknowledged

REFERENCES

1. Resnick, S. M.; Torok, D. S.; Gibson, D. T. *J. Org. Chem.* **1995**, 60, 3546.
2. Burgess, K.; Porte, A. M. *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1182.
3. Wallace, J. S.; Baldwin, B. W.; Morrow, C. J. *J. Org. Chem.* **1992**, 57, 5231.
4. Tokles, W.; Snyder, J. K.; *Tetrahedron Lett.* **1988**, 29, 6063.
5. Takemura, T.; Saito, K; Mori, N.; *Tetrahedron Lett.* **1992**, 33, 6335.
6. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, 34, 2543.
7. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, 95, 512.
8. Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, 110, 1968.
9. Sharpless, K. B.; Amberg, W.; Beller, M. Chen, H.; Hartung, J.; Kawanami, Y.; Lubben, D.; Manoury, E.; Ogino, Y; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, 56, 4585.
10. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.; Kwong, H.; Morikawa, K.; Wang, Z; Xu, D.; Zhang, X. *J. Org. Chem.* **1992**, 57, 2768.
11. Baldwin, B. W.; Morrow, C. J. manuscript in preparation.
12. Terao, Y.; Murata, M.; and Achiwa, K. *Tetrahedron Lett.* **1988**, 29, 5137.
13. Boaz, N. W. *Tetrahedron Lett.* **1989**, 30, 2061.

(*Received in UK* 9 *July* 1996; *accepted* 3 *September* 1996)