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Analysis of 2-deuterated isopentenyl alcohols by ^{1}H NMR of chiral esters

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Abstract—A convenient procedure is presented whereby the chirality of isopentenyl alcohols labeled with deuterium in the 2-position can be determined by ^{1}H NMR analysis of their chiral esters. The MTPA, MPA and *O*-acetylmandelate esters were investigated in a series of NMR solvents. The best results were obtained using the *O*-acetylmandelates in C_6D_6 with homodecoupling of the 1-position.

The recent discovery of the deoxyxylulose pathway has led to a renaissance in the study of the early steps of isoprenoid biosynthesis.[1,2] Recently an NMR method for the determination of chirality of [2-^{2}H]-isopentenyl alcohols has been reported by Leyes and Poulter involving ^{2}H NMR of the tosylate derivatives in a liquid crystalline medium.[3] In view of various difficulties presented by this method including measurement at −50°C, a better method was desirable. For reasons of sensitivity and convenience, an approach utilizing chiral esters was investigated, although it was reported that no diastereomeric resolution in the ^{1}H NMR spectrum had been achieved using Mosher's MTPA ester.[3]

The MTPA (**1**),[4] MPA (**2**),[5,6] and *O*-acetylmandelate (**3**)[7] esters of isopentenyl alcohol were prepared from the acids by DMAP-catalyzed carbodiimide (EDC) coupling.[5,8] The MPA (**2**) and *O*-acetylmandelate (**3**) esters were obtained nearly quantitatively, whereas the MTPA ester (**1**) was formed in 68% yield. Because ^{1}H NMR chemical shifts are generally solvent dependent, the spectra were investigated using a series of six different NMR solvents (Table 1). Considerable variation was observed in the shapes of the signals of the diastereotopic hydrogens at the isopentenyl 2-position. Analysis of the multiplets as ABX_2 systems ($J_{vic}=6.9$ Hz; $J_{gem}=14.8$ Hz) provided $\Delta\delta$ values ranging from ca. 7 ppb to 31 ppb (Table 1). Although the separation of the signals at the 2-position was poor with the MPA ester (**2**) in $CDCl_3$, this was the best system for resolving the signals of the 1-hydrogens ($\Delta\delta=42$ ppb). The best resolution of the signals of the diastereotopic 2-hydrogens ($\Delta\delta=31$ ppb) was with the *O*-acetylmandelate ester (**3**) in C_6D_6 (Fig. 1a). The signals could be further simplified to an AB multiplet by decoupling of the 1-hydrogens at 4.00 ppm (Fig. 1b).

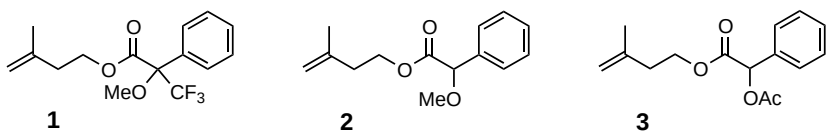

Table 1. ^{1}H NMR resolution ($\Delta\delta$) of the signals for the diastereotopic 2-hydrogens of chiral isopentenyl esters in various NMR solvents

	$CDCl_3$ (ppb)	C_6D_6 (ppb)	$(CD_3)_2CO$ (ppb)	CD_3OH (ppb)	$(CD_3)_2SO$ (ppb)	C_5D_5N (ppb)
1	11	7	12	11	9	9
2	11	11	11	12	15	9
3	20	31	23	23	29	26

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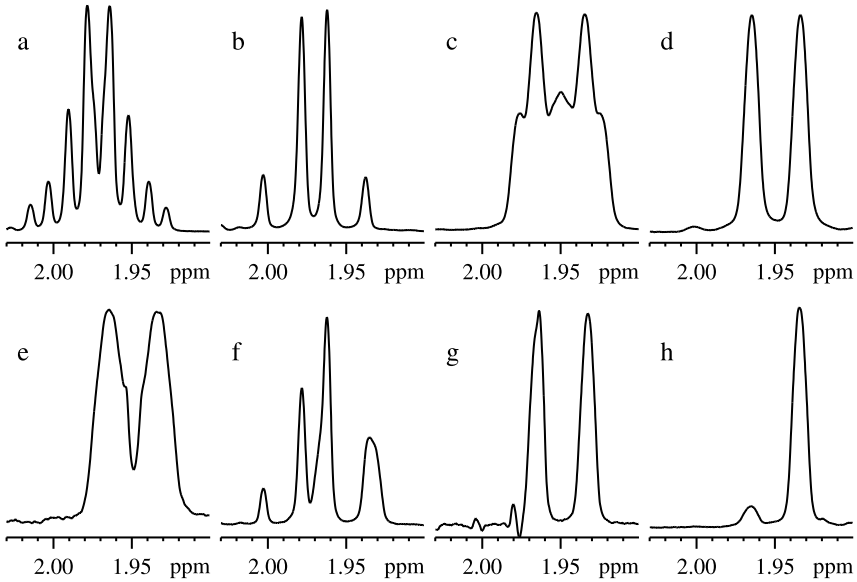
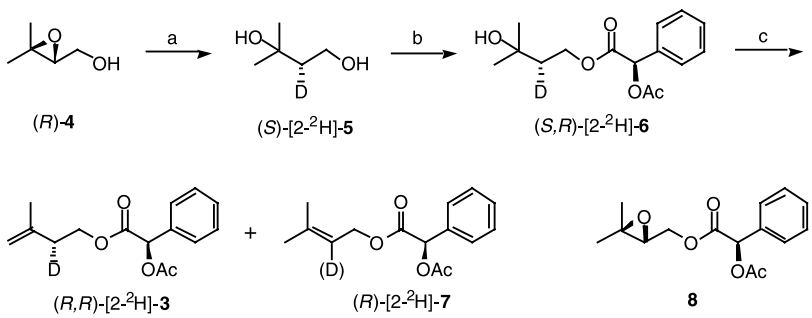


Figure 1. ^{1}H NMR signals of 2-position of **3** (C_6D_6, 30°C, all at 600 MHz except (e). (a) unlabeled **3**; (b) unlabeled **3**, decoupled; (c) [2-^{2}H]-**3**; (d) [2-^{2}H]-**3**, decoupled; (e) [2-^{2}H]-**3**, decoupled, 300 MHz; (f) mixed unlabeled **3** and [2-^{2}H]-**3**, decoupled; (g) difference spectrum (f minus b); (h) (2*R*)-[2-^{2}H]-**3**, decoupled.

Deuterium labeling at the 2-position was achieved by a modification of the method of Suga et al. (Scheme 1).[9] This sequence was first carried out with racemic epoxy alcohol **4** to obtain both diastereomers. We found it convenient to convert the diol (**5**) into the chiral ester (**6**) prior to dehydration. Phosphorus oxychloride dehydration of **6** led to the formation of ca. 33% of the undesired dimethylallyl isomer ([2-^{2}H]-**7**). Since **7** did not interfere with the NMR analysis, it was unnecessary to remove it.[10] The deuterium substitution of **3** resulted in the broadening and simplification of the signals of the hydrogens of the 2-position (Fig. 1c). The homodecoupled spectra showed a baseline resolution of the signals at 600 MHz (Fig. 1d) and a good separation at 300 MHz (Fig. 1e). Deuterium substitution also led to an upfield shift of 21 ppb. By subtracting the signals belonging to unlabeled **3**, mixtures of the [2-^{2}H]-labeled and unlabeled isopentenyl esters can be readily analyzed (Fig. 1f and Fig. 1g).

In order to assign the two signals of the diastereotopic hydrogens at the 2-position of **3**, (*R*)-dimethylglycidol (**4**, from Fluka as the *p*-nitrobenzoate) was reduced with $LiAlD_4$ to give (*S*)-[2-^{2}H]-diol **5** (Scheme 1).[9] ^{1}H NMR analysis as the (*R*)-*O*-acetylmandelate ester (**6**) showed that diol **5** was contaminated with ca. 10% of its (*R*)-enantiomer ((*R*)-[2-^{2}H]-**6**: 1.78 ppm; (*S*)-[2-^{2}H]-**6**: 1.76 ppm). Chiral impurity of the (*R*)-*O*-acetylmandelic acid could be ruled out by ^{1}H NMR examination of its ester with (*R*)-2-phenethyl alcohol (99% e.e.), which showed less than 2% of the diastereomeric ester. The chiral impurity was traced to the starting dimethylglycidol (*R*)-**4** which was found to contain ca. 10% of the (*S*)-enantiomer by ^{1}H NMR analysis as the (*R*)-*O*-acetylmandelate ester **8** ((*R*,*R*)-isomer: 2.87 ppm; (*S*,*R*)-isomer: 2.95 ppm).[11] The ^{1}H NMR spectrum of the (*R*,*R*)-[2-^{2}H]-**3** obtained by this sequence (Fig. 1h) also shows ca. 10% of the (*S*,*R*)-isomer. The peak at 1.934 ppm corresponds to the (2*R*)-isomer, while the peak at 1.965 ppm corresponds to the (2*S*)-isomer.

As a demonstration of the applicability of this method to the analysis of isopentenyl pyrophosphate (IPP), 5 mg of IPP were hydrolyzed with 50 units of bovine



Scheme 1. Synthesis of [2-^{2}H]-isopentenyl *O*-acetylmandelate. (a) $LiAlD_4$; (b) (*R*)-*O*-acetylmandelic acid/EDC/DMAP; (c) $POCl_3$/pyr.

alkaline phosphatase (37°C, 2.5 h, pH 8.2). Extraction with $CDCl_3$ and ^1H NMR analysis indicated an 80% recovery of isopentenyl alcohol, which was converted to its *O*-acetylmandelate ester in quantitative yield. In summary, ^1H NMR analysis of chiral *O*-acetylmandelate esters provides a sensitive and convenient method for the chiral analysis of [2-^2H]-isopentenyl alcohols.

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8. NMR and MS data for nondeuterated, achiral compounds: **1**: ^1H NMR (300 MHz, $CDCl_3$): 7.55–7.50 (2H, m, Ph), 7.43–7.36 (3H, m, Ph), 4.81 (1H, s, C=CH_2), 4.72 (1H, s, C=CH_2), 4.44 (2H, t, $J=6.8$ Hz, CH_2O), 3.55 (3H, d, $J=1.2$ Hz, OMe), 2.41 (2H, t, $J=6.8$ Hz, C-2), 1.74 (3H, s, Me); ^{13}C NMR (75 MHz, $CDCl_3$): 166.5, 140.7, 132.2, 129.5, 128.3, 127.3, 123.2 (q, $J=288.1$ Hz), 112.8, 84.6 (q, $J=28.0$ Hz), 64.6, 55.4 (q, $J=1.6$ Hz), 36.3, 22.2; MS (EI, 70 eV) m/z: 303 ($M+1^+$, 10%), 189 (100), 139 (7), 119 (15), 105 (23), 77 (12), 69 (42). **2**: ^1H NMR (300 MHz, $CDCl_3$): 7.46–7.40 (2H, m, Ph), 7.40–7.30 (3H, m, Ph), 4.75 (1H, s, CHOMe), 4.71 (1H, s, C=CH_2), 4.60 (1H, s, C=CH_2), 4.24 (2H, m, CH_2O), 3.41 (3H, s, OMe), 2.29 (2H, t, $J=6.8$ Hz, C-2), 1.67 (3H, br s, Me); ^{13}C NMR (75 MHz, $CDCl_3$): 170.6, 141.1, 136.2, 128.6, 128.5, 127.2, 112.4, 82.6, 63.3, 57.3, 36.5, 22.2; MS (EI, 70 eV) m/z: 235 ($M+1^+$, 5%), 157 (5), 121 (100), 91 (11), 77 (12). **3**: ^1H NMR (300 MHz, $CDCl_3$): 7.49–7.43 (2H, m, Ph), 7.40–7.35 (3H, m, Ph), 5.90 (1H, s, CHOAc), 4.71 (1H, s, C=CH_2), 4.60 (1H, s, C=CH_2), 4.24 (2H, t, $J=6.8$ Hz, CH_2O), 2.29 (2H, br t, $J=6.8$ Hz, C-2), 2.20 (3H, s, OAc), 1.67 (3H, br s, Me); ^{13}C NMR (75 MHz, $CDCl_3$): 170.2, 168.7, 141.0, 133.8, 129.1, 128.6, 127.6, 112.4, 74.5, 63.7, 36.4, 22.2, 20.6; MS (EI, 70 eV) m/z: 263 ($M+1^+$, 97%), 203 (20), 202 (31), 195 (23), 175 (26), 157 (81), 149 (39), 145 (40), 107 (100).
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10. NMR and MS data for nondeuterated, achiral compounds: **6**: ^1H NMR (300 MHz, $CDCl_3$): 7.48–7.42 (2H, m, Ph), 7.41–7.35 (3H, m, Ph), 5.89 (1H, s, CHOAc), 4.36–4.21 (2H, m, CH_2O), 2.18 (3H, s, OAc), 1.78 (2H, dt, $J=1.3$, 6.7 Hz, C-2), 1.70 (1H, br s, OH), 1.17 (3H, s, Me), 1.16 (3H, s, Me); ^{13}C NMR (75 MHz, $CDCl_3$): 170.3, 168.7, 133.6, 129.2, 128.8, 127.6, 74.6, 69.7, 62.6, 41.2, 29.5, 29.4, 20.6; MS (EI, 70 eV) m/z: 281 ($M+1^+$, 9%), 263 (100), 195 (14), 157 (14), 107 (19), 69 (23). **7**: ^1H NMR (300 MHz, $CDCl_3$): 7.50–7.42 (2H, m, Ph), 7.42–7.34 (3H, m, Ph), 5.93 (1H, s, CHOAc), 5.26 (1H, br t, $J=7.2$ Hz, C=CH), 4.70–4.52 (2H, m, CH_2O), 2.19 (3H, s, OAc), 1.72 (3H, br s, Me), 1.63 (3H, br s, Me); ^{13}C NMR (75 MHz, $CDCl_3$): 170.2, 168.8, 139.7, 133.9, 129.1, 128.6, 127.6, 117.8, 74.5, 62.5, 25.6, 20.7, 17.9; MS (EI, 70 eV) m/z: 263 ($M+1^+$, 15%), 195 (100), 177 (50), 149 (33), 107 (35), 69 (86).
11. **8**: ^1H NMR (300 MHz, $CDCl_3$): 7.51–7.45 (2H, m, Ph), 7.43–7.37 (3H, m, Ph), 5.96 (1H, s, CHOAc), 4.32 (1H, dd, $J=5.0$, 12.0 Hz, CH_2O), 4.14 (1H, dd, $J=6.3$, 12.0 Hz, CH_2O), 2.87 (1H, dd, $J=5.0$, 6.3 Hz), 2.20 (3H, s, OAc), 1.29 (3H, s, Me), 1.24 (3H, s, Me); ^{13}C NMR (75 MHz, $CDCl_3$): 170.2, 168.7, 133.6, 129.3, 128.8, 127.5, 74.4, 64.4, 59.9, 58.1, 24.3, 20.6, 18.7; MS (EI, 70 eV) m/z: 279 ($M+1^+$, 3%), 219 (5), 176 (21), 149 (47), 107 (100), 85 (34); **(*S*,*R*)-diastereomer**: ^1H NMR (300 MHz, $CDCl_3$): 7.51–7.45 (2H, m, Ph), 7.43–7.37 (3H, m, Ph), 5.95 (1H, s, CHOAc), 4.38 (1H, dd, $J=4.8$, 12.0 Hz, CH_2O), 4.08 (1H, dd, $J=6.4$, 12.0 Hz, CH_2O), 2.95 (1H, dd, $J=4.8$, 6.4 Hz), 2.20 (3H, s, OAc), 1.29 (3H, s, Me), 1.25 (3H, s, Me).