mixture of oxalyl chloride (0.44 mL, 5.0 mmol) in methylene chloride (30 mL) under nitrogen was cooled to −78 °C. Dimethyl sulfoxide was added, and the reaction was stirred for 10 min. A solution of **4b** in methylene chloride (10 mL) was added slowly, and the reaction was stirred for 30 min. Triethylamine (4.2 mL, 30.1 mmol) was added dropwise, and after 15 min, the cooling bath was removed, and the reaction was allowed to come to room temperature for 1 h. The reaction was quenched with saturated sodium bicarbonate (30 mL), and the phases were separated. The aqueous phase was extracted with methylene chloride (3 × 40 mL). The combined organic phases were washed with 2% hydrochloric acid (2 × 40 mL), dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue, purified by radial chromatography (silica gel, ethyl acetate), furnished 0.70 g (88%) of **7** as a colorless solid, which sublimes at 160 °C: ^1H NMR ($CDCl_3$) δ 1.62 (m, 1 H), 1.69 (s, 3 H), 1.99 (s, 3 H), 2.29 (s, 3 H), 3.26 (ddd, J = 14.5 Hz, J = 8.6 Hz, J = 7.2 Hz, 1 H), 4.86 (dd, J = 13.1 Hz, J = 7.2 Hz, 1 H), 5.95 (br s, 1 H), 5.98 (dd, J = 8.6 Hz, J = 5.1 Hz, 1 H), 6.93 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.3, 170.2, 146.1, 131.4, 130.6, 126.0, 122.2, 117.5, 92.3, 79.3, 49.2, 31.7, 23.0, 22.0, 20.7; mass spectrum, m/z 275 ($M^{\cdot+}$), 232.

1,2′-Anhydro-2,3,6-trideoxy-3-acetamido-5-*C*-(2-hydroxy-5-methylphenyl)-α-DL-*threo*-hex-4-ulose (8). A solution of **7** (0.45 g, 1.6 mmol) and triethylamine (2 mL) in methylene chloride (30 mL) was stirred overnight at room temperature. The solvent was removed at reduced pressure, and the residue was purified by radial chromatography (silica gel, ethyl acetate) to give 0.45 g (100%) of **8** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.64 (s, 3 H), 1.96 (s, 3 H), 2.27 (s, 3 H), 2.35 (m, 1 H), 3.57 (m, 2 H), 5.40 (br s, 1 H), 5.61 (dd, J = 5.1 Hz, J = 2.6 Hz, 1 H), 6.84 (m, 3 H); mass spectrum, m/z 275 ($M^{\cdot+}$), 232.

1,2′-Anhydro-2,3,6-trideoxy-3-acetamido-4-hydroxy-5-*C*-(2-hydroxy-5-methylphenyl)-α-DL-*arabino*-hexopyranose (9). To a stirred, cold (0 °C) solution of sodium borohydride (0.10 g, 2.6 mmol) in 2-propanol (20 mL) was added a solution of **8** (0.38 g, 1.4 mmol) in 2-propanol (10 mL), and the mixture was stirred at room temperature for 2 h. The solvent was removed at reduced pressure, the residue was dissolved in water (30 mL), and the aqueous phase was extracted with methylene chloride (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated at reduced pressure. The residue was purified by radial chromatography (silica gel, ethyl acetate) to give 0.37 g (95%) of **9** as a colorless solid with mp 193–198 °C: ^1H NMR ($CDCl_3$) δ 1.65 (s, 3 H), 1.87 (m, 1 H), 1.98 (s, 3 H), 2.28 (s, 3 H), 2.31 (m, 1 H), 3.46 (d, J = 10.1 Hz, 1 H), 3.75 (m, 1 H), 5.44 (br s, 1 H), 5.62 (d, J = 2.2 Hz, 1 H), 6.85 (m, 3 H); mass spectrum, m/z 277 ($M^{\cdot+}$). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.31; H, 6.88; N, 4.74.

Acknowledgment. This work was generously supported by the National Cancer Institute of the National Institutes of Health under Grant CA 18141.

Registry No. **1a**, 89177-78-6; **1b**, 112576-13-3; **2**, 112576-14-4; **3a**, 112576-15-5; **3b**, 112576-18-8; **3c**, 112576-19-9; **4a**, 112576-16-6; **4b**, 112576-17-7; **5a**, 112576-20-2; **5b**, 112576-23-5; **5c**, 112576-24-6; **5d**, 112576-25-7; **6**, 112576-21-3; **7**, 112576-22-4; **8**, 112653-33-5; **9**, 112653-34-6.

Assignment of Absolute Configurations for 4-Methylcarnitine Stereoisomers by Proton Nuclear Magnetic Resonance

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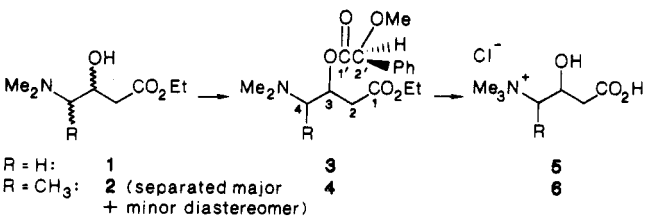
Received August 25, 1987

We recently reported[1] a chromatographic resolution for synthetic precursors of carnitine (**5**) and 4-methylcarnitine (**6**), although at that time the absolute configurations of **6** were not assigned. NMR has been increasingly used for such assignments (see ref 2 for a review), and it became apparent that the NMR method of Trost[3] for determining the absolute configuration of secondary alcohols as their *O*-methylmandelate esters might be applicable in these systems. Here we report the success of Trost's model for predicting the known configurations of carnitine enantiomers and describe a simple ^1H NMR method for establishing the absolute configurations for the two asymmetric centers in the four stereoisomers of 4-methylcarnitine.

Scheme I[a]



[a] See ref 1 for experimental details.

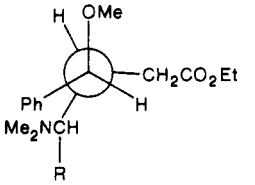
Table I. Summary of ^1H NMR Data for the Configurational Assignments of 5 and 6

configuration	chemical shift (δ) of NMe_2 resonance in precursor **3** or **4** ($CDCl_3$)	$J_{3,4}$ (Hz) for **5** or **6** (D_2O)
(+)-(*S*)-**5**[a]	2.13	1.87 (gauche)[b] 9.83 (anti)
(−)-(*R*)-**5**[a]	2.27	1.87 (gauche)[b] 9.83 (anti)
(−)-(3*S*,4*S*)-**6**[c]	2.07	7.1
(+)-(3*R*,4*R*)-**6**[c]	2.22	7.1
(+)-(3*S*,4*R*)-**6**[d]	2.09	1.0
(−)-(3*R*,4*S*)-**6**[d]	2.22	1.0

[a] Configuration known (ref 4). [b] Values taken from ref 6. [c] From major diastereomer of **2**. [d] From minor diastereomer of **2**.

Results and Discussion

Scheme I summarizes the method that was previously employed[1] for the resolutions of synthetic precursors to carnitine (**5**) and 4-methylcarnitine (**6**). As shown, the resolutions were achieved via chromatographic separation of the *O*-methylmandelate esters of hydroxy ester precursors **1** and **2**, and Trost[3] recently proposed a model that uses such esters for establishing the absolute configuration of secondary alcohols. As illustrated by the extended Newman projections (ester linkage omitted) for **3** and **4**,



(3*S*, 2′*S*)-**3**, R = H
(3*S*, 2′*S*)-**4**, R = CH_3

this model places the ester in a "Mosher-type" conformation. The substituent on the secondary alcohol which is closest to the phenyl group is always shielded in the ^1H NMR spectrum relative to the other secondary alcohol substituent. Thus by using (*S*)-*O*-methylmandelic acid and

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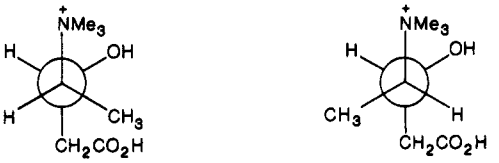
observing the chemical shifts of the NMe_2 singlets for the diastereomers of **3** (see Table I), it was predicted that the upfield resonance resulted from the 3*S* configuration and the downfield resonance from the 3*R* configuration. Chromatographic separation of these diastereomers and conversion to (+)- or (−)-carnitine of known configuration[4] (as in Scheme I) confirmed the assignment and demonstrated that this method is applicable to carnitine systems. This same procedure was then used to assign the configuration at C_3 for each of the diastereomers (**4**) resulting from the major and minor diastereomers of **2**, and the results are summarized in Table I.

Assignment of the configuration at C_3 for **4** (and thus **6**) now allowed for the assignment at C_4 of **6**. This was possible due to a substantial conformational bias for 4-methylcarnitine about the C_3–C_4 bond. Numerous studies including X-ray crystallography,[5] NMR solution measurements,[6,7] molecular mechanics calculations,[7] and molecular orbital calculations[8] have shown that the conformation of carnitine about N–C_4–C_3–OH is nearly 100% gauche. Furthermore, the coupling constants between the C_3 and C_4 hydrogens have been determined for carnitine, with $J_{3,4(anti)}$ = 9.83 Hz and $J_{3,4(gauche)}$ = 1.87 Hz, values consistent with the Karplus relationship. Our examination of Dreiding models revealed that addition of a methyl group at C_4 should not significantly disturb the conformational bias about C_3–C_4. One factor that supports this conclusion is an unfavorable gauche interaction between the quaternary ammonium group and C_2. (The conformations about C_2–C_3 are all highly populated in solution.)[6,7] A second important factor is the gauche effect, which results in a strong conformational preference for a gauche relationship between the hydroxyl and nitrogen of choline, $(CH_3)_3N^+CH_2CH_2OH$.[9] Furthermore, NMR solution studies have shown[10] that acetyl-α-methylcholine, $(CH_3)_3N^+CH(CH_3)CH_2OAc$, is similarly at least 75% gauche. These observations strongly suggest that 4-methylcarnitine largely maintains the gauche conformation about N–C_4–C_3–OH.

Therefore, given the configuration of **6** at C_3, the relative magnitude of $J_{3,4}$ in the ^1H NMR spectrum allows for the assignment of absolute configuration at C_4. This assignment is illustrated in the Newman projections for the two diastereomers of **6** which contain the 3*S* configuration. A



(3*S*,4*R*)-**6** small $J_{3,4}$ (3*S*,4*S*)-**6** large $J_{3,4}$

standard homonuclear decoupling experiment was used to decouple the 4-methyl protons and the residual $J_{3,4}$ coupling constant determined. For one diastereomer of (3*S*)-**6**, $J_{3,4}$ = 1.0 Hz, assigning this isomer as (3*S*,4*R*)-**6**, and the other diastereomer exhibited $J_{3,4}$ = 7.1 Hz, assigning this as (3*S*,4*S*)-**6**. Table I summarizes the assignments.

Finally, the above assignments for **6** were further supported by Cram's rule.[11] The diastereomeric mixture **2** was prepared via $NaBH_4$ reduction of the keto ester precursor.[1] Cram's rule predicts that the major mode of hydride attack should produce (3*S*,4*S*)-**2** and (3*R*,4*R*)-**2** as the major racemic diastereomer, which agrees with the above assignments.

Experimental Section

Compounds **1**–**6** were prepared as previously described.[1] The ^1H NMR spectral data for compounds **3** and **4** were recorded at ambient temperature in $CDCl_3$ on a Varian EM360 spectrometer, and chemical shifts were referenced internally to tetramethylsilane (TMS). The coupling constants for compound **6** were obtained at ambient temperature in D_2O via selective homonuclear decoupling experiments on a GE wide-bore spectrometer (NT series) equipped with an 1180e processor and 293c pulse programmer operating at 300.1 MHz. The latter measurements were obtained at pD 2.6 with sodium 3-(trimethylsilyl)-1-propanesulfonate (DSS) as internal reference.

Acknowledgment. We thank Ken Hope for performing the homonuclear decoupling experiments. Helpful comments from one of the reviewers are also gratefully acknowledged.

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