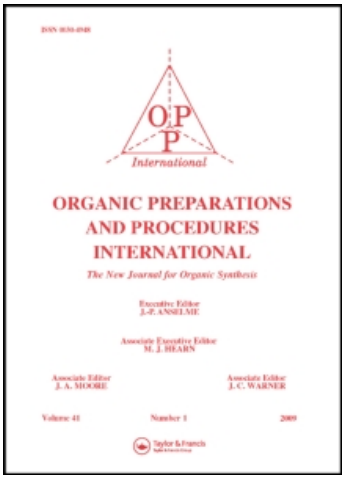


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

PREPARATION OF THE RACEMATE AND ENANTIOMERS OF 3-HYDROXY-5,5-DIMETHYLHEXANOIC ACID

Wayne J. Brouillette[a]; Ahmed S. Abuelyaman[a]; Carla A. Hosmer[b]; Robert N. Comber[b]; Ashraf Saeed[a]
[a] Department of Chemistry, University of Alabama at Birmingham, Birmingham, AL [b] Organic Chemistry Department, Southern Research Institute, Birmingham, AL

To cite this Article Brouillette, Wayne J. , Abuelyaman, Ahmed S. , Hosmer, Carla A. , Comber, Robert N. and Saeed, Ashraf(1993) 'PREPARATION OF THE RACEMATE AND ENANTIOMERS OF 3-HYDROXY-5,5-DIMETHYLHEXANOIC ACID', Organic Preparations and Procedures International, 25: 2, 243 — 246
To link to this Article: DOI: 10.1080/00304949309457956
URL: http://dx.doi.org/10.1080/00304949309457956

REFERENCES

1. J. Mathieu and J. Weil-Raynal, "*Formation of Carbon-Carbon Bond*", Verlag Chemie, Stuttgart, Vol. **2**, 152 ff (1975).

2. R. S. Taylor and R. Connor, *J. Org. Chem.*, **6**, 696 (1941).

3. S. Hashimoto, K. Matsumoto, S. Otani, J. Hayami and H. Yoshida, *Synthesis*, 164 (**1984**).

4. E. P. Kohler and H. M. Chadwell, *Org. Synth., Coll. Vol.* **1**, 78 (1932).

****

PREPARATION OF THE RACEMATE AND ENANTIOMERS OF 3-HYDROXY-5,5-DIMETHYLHEXANOIC ACID†

Submitted by (06/29/92)

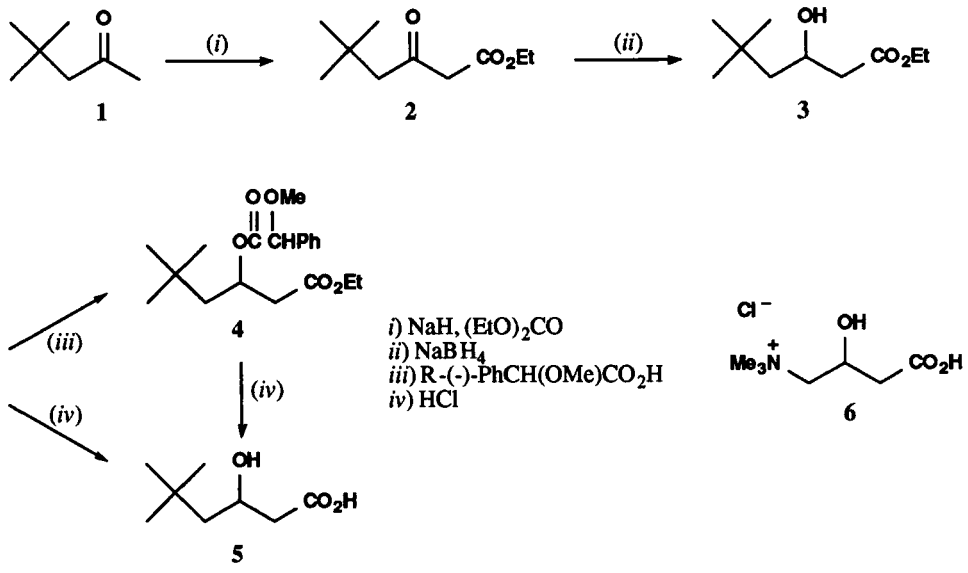
Wayne J. Brouillette*, Ahmed S. Abuelyaman, Carla A. Hosmer,†† Robert N. Comber†† and Ashraf Saeed

Department of Chemistry
University of Alabama at Birmingham
Birmingham, AL 35294-1240

Carnitine (**6**) is important in mammalian systems as an acceptor (and donor) of acyl groups, which may vary in chain length from acetate to long chain fatty acids. Several carnitine acyltransferases, which differ in acyl chain length specificity, catalyze the acylation of the β-hydroxy group on carnitine.[1] As part of a study to compare the carnitine binding requirements for these related enzymes, we required the uncharged racemic carnitine analog **5** and each of its enantiomers, whose preparations have not been previously reported.

Racemic **5** was synthesized from commercially available 4,4-dimethyl-2-pentanone (**1**). The synthesis of intermediate **2** was previously reported by House[2] in three steps: the acid chloride of 3,3-dimethylbutanoic acid was prepared in 86% yield from the acid, and diethylmalonate was hydrolyzed to the half ester in 78% yield. The acid chloride and ethyl malonate (as the dianion) were then condensed to give **2** in 84% yield. We more conveniently prepared **2** in one step (79% yield after distillation) via the acylation of **1** with NaH and diethyl carbonate. Ketoester **2** was then reduced with $NaBH_4$ to give hydroxyester **3** (77% yield), which was hydrolyzed in HCl (aq) to give racemic **5** (82% yield; 50% overall isolated yield from **1**).

For careful comparisons in enzyme kinetics assays, we required both enantiomers of **5** in high optical purity. These were thus prepared via a conventional chromatographic resolution of



diastereomeric covalent derivatives of intermediate hydroxyester **3**. Compound **3** was esterified with R-(-)-α-methoxyphenylacetic acid[3] (using DCC and DMAP). The resulting two diastereomers were readily distinguished using ^{1}H NMR since the *tert*-butyl groups resonate as singlets at 0.87 and 0.63 ppm. This mixture was then separated on a silica flash chromatography column. (We previously reported a similar chromatographic resolution for a synthetic precursor to carnitine).[4] The absolute configuration for each diastereomer was determined by ^{1}H NMR spectroscopy using the model originally proposed by Dale and Mosher[5] for mandelate esters of secondary alcohols and later extended by Trost[6] to include O-methylmandelate esters. (We previously reported the application of this method for assigning the absolute configuration of synthetic intermediates for carnitine).[7] Thus the leading diastereomer of **4** (R_f 0.40) contained the 3R,2'R configuration, and the trailing diastereomer (R_f 0.36) contained the 3S,2'R configuration. Each pure diastereomer was then hydrolyzed in HCl to provide the enantiomers of **5**.

EXPERIMENTAL SECTION

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 360 (60 MHz) or GE 300-WB FT-NMR (300 MHz) spectrometer. IR spectra were obtained on a Beckman Acculab-1 spectrometer, and optical rotations were obtained on a Perkin Elmer 141 polarimeter in 1 dm cells of 1 mL capacity. Flash chromatography used Baker silica gel (40μ), and TLC was performed on Fisher brand silica gel GF plates (0.2 mm layer, 5 x 10 cm). Elemental analyses were performed by Atlantic Microlabs of Atlanta, Georgia.

(R,S) 3-Hydroxy-5,5-dimethylhexanoic Acid (5).- A solution of **3** (1.1 g, 5.9 mmol) in 10% HCl (25 mL) was heated at reflux for 3 hrs. The mixture was concentrated under vacuum to provide racemic **5** as a white fluffy solid (0.77 g, 82%), mp. 110.5-111.5° (H_2O). ^{1}H NMR (D_2O): δ 0.95 (s,

9 H, *t*-Bu), 1.25-1.4 (m, 2 H, H4), 2.25-2.35 (m, 2 H, H2), 3.9-4.25 (m, 1 H, H3); IR (KBr): 3300 (OH), 1675 (C=O) cm^{-1}.

Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.93; H, 10.09

R-(+)-5 and S-(-)-5.- Each diastereomer of **4** (400 mg, 1.12 mmol) was suspended in 5.0 N HCl (10 mL). This mixture was heated at reflux for 5 hrs, kept at room temperature for 5 hrs, and extracted with ether (5 x 15 mL). The extracts were dried (Na_2SO_4) and concentrated under vacuum to give 300 mg of a solid residue. This was placed on a silica gel preparative TLC plate (20 x 20 x 0.2 cm) and eluted with 2% acetic acid-ether to give 120 mg (63%) of either R-(+)- or S-(-)-**5** (R_f 0.45, visualized by charring with H_2SO_4). All spectra were identical to those for the racemate. For R-(+)-**5**: mp. 107.5-109° (CCl_4); $[\alpha]_D^{25}$ = +12.3 (c 0.0212, CH_3OH); for S-(-)-**5**: mp. 105-107° (CCl_4); $[\alpha]_D^{25}$ = -11.7 (c 0.0156, CH_3OH).

Ethyl 5,5-Dimethyl-3-oxohexanoate (2).- To a suspension of 50% NaH/mineral oil (2.09 g, 43.7 mmol NaH; washed three times with dry DME) in DME (10 mL) was added diethyl carbonate (5.16 g, 43.7 mmol). The mixture was heated to 80° and a solution of **1** (2.50 g, 22.0 mmol) in DME (2.5 mL) was added in portions during the next 1.5 hrs. Heating was continued for an additional 4 hrs, and the mixture was stirred at room temperature overnight. To this was added, dropwise, glacial acetic acid (5 mL) followed by water (13.5 mL). The resulting mixture was extracted with ether (3 x 25 mL), the extracts were dried (Na_2SO_4), and the solution was concentrated under vacuum to provide a pale yellow oil. This was distilled to give **2** (3.2 g, 79%) as a colorless oil, bp. 56-58°/0.3 mm, lit.[2] bp. 68-70°/1.2 mm.

Ethyl 3-Hydroxy-5,5-dimethylhexanoate (3).- A solution of **2** (3.15 g, 16.9 mmol) in ethanol (5 mL) was chilled to 0°. To this was added $NaBH_4$ (0.319 g, 8.45 mmol), and the reaction was stirred for 4 hrs. The mixture was adjusted to pH 3 by the addition of 10% HCl and the resulting solution extracted with ether (3 x 40 mL). The extracts were dried (Na_2SO_4) and concentrated under vacuum to provide crude **3** (2.95 g, 92.8%) as a pale yellow oil. This was placed on a flash silica column and eluted with ether-hexane (1:1). The appropriate fractions (R_f 0.65; visualized by sulfuric acid charring) were combined and concentrated to give pure **3** as a colorless oil. ^1H NMR ($CDCl_3$): δ 1.0 (s, 9 H, *t*-Bu), 1.15-1.5 (m, 5 H, H4 & $OCH_2\underline{CH_3}$), 2.35-2.55 (m, 2 H, H2), 2.8-3.2 (br s, 1 H, OH), 3.95-4.35 (m, 3 H, H3 & $O\underline{CH_2}CH_3$); IR (neat): 3450 (OH), 1740 (C=O) cm^{-1}.

Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.94; H, 10.65

(3R,2'R)- and (3S,2'R)-Ethyl 3-(2-Methoxy-2-phenylacetoxy)-5,5-dimethylhexanoate (4).- A solution containing hydroxyester **3** (835 mg, 4.50 mmol), DCC (1.38 g, 6.70 mmol), R-(-)-α-methoxyphenylacetic acid (834 mg, 4.98 mmol), and DMAP (596 mg, 4.89 mmol) in CH_2Cl_2 (20 mL) was stirred for 24 hrs at room temperature. This was filtered, the DCU washed on the filter with ether (25 mL), and the filtrate concentrated on a rotary evaporator. The residue was triturated with 1:1 ether/petroleum ether, the mixture filtered, and the filtrate was concentrated to dryness. The trituration was repeated two additional times to provide a diastereomeric mixture of **4** (1.2 g, 79%) as a yellow oil. This was placed on a flash silica column (5 x 15 cm, 95:5 hexane-ethyl acetate) to give (3R,2'R)-**4**

(400 mg, 33.3%; R_f 0.40). ^1H NMR ($CDCl_3$): δ 0.87 (s, 9 H, *t*-Bu), 1.1-1.2 (t, 3 H, $OCH_2\underline{CH_3}$), 1.38-1.72 (m, 2 H, H4), 2.22-2.53 (m, 2 H, H2), 3.37-3.42 (s, 3 H, OCH_3), 3.78-4.04 (m, 2 H, $O\underline{CH_2}CH_3$), 4.64-4.73 (s, 1 H, H2'), 5.25-5.47 (m, 1 H, H3), 7.19-7.5 (m, 5 H, aromatic); IR (neat): 1740 (C=O) cm^{-1}; $[\alpha]_D^{25}$ = -43.5 (c 0.0200, CH_3OH).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.93; H, 8.41

Continued elution gave 500 mg of mixed diastereomers followed by pure (3S,2'R)-**4** (100 mg; R_f 0.36). The mixed fractions were separated on a second flash silica column to give additional pure (3R,2'R)-**4** (70 mg; total yield = 470 mg, 39.2 %) followed by pure (3S,2'R)-**4** (290 mg; total yield, 400 mg, 33%). ^1H NMR ($CDCl_3$): δ 0.63 (s, 9 H, *t*-Bu), 1.15-1.27 (t, 3 H, $OCH_2\underline{CH_3}$), 1.3-1.58 (m, 2 H, H4), 2.26-2.35 (m, 2 H, H2), 3.35-3.4 (s, 3 H, OCH_3), 3.96-4.18 (q, 2 H, $O\underline{CH_2}CH_3$), 4.55-4.77 (s, 1 H, H2'), 5.14-5.4 (m, 1 H, H3), 7.19-7.57 (m, 5 H, aromatic); IR (neat): 1740 (C=O) cm^{-1}; $[\alpha]_D^{25}$ = -52.1 (c 0.0290, CH_3OH).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 68.09; H, 8.46

Acknowledgment.- This work was supported in part by a grant from the National Institutes of Health (HL 44668).

REFERENCES

† Taken in part from the M. S. Theses of C. A. Hosmer, University of Alabama at Birmingham, 1985, and of A. S. Abuelyaman, University of Alabama at Birmingham, 1990.

†† Present address: Organic Chemistry Department, Southern Research Institute, Birmingham, AL 35255-5305.

1. W. J. Colucci and R. D. Gandour, *Bioorg. Chem.*, **16**, 307 (1988).
2. H. O. House, R. J. Outcalt and M. D. Cliffton, *J. Org. Chem.*, **47**, 2413 (1982).
3. E. J. Corey, P. B. Hopkins, S. Kim, S. Yoo, K. P. Nambiar and J. R. Falck, *J. Am. Chem. Soc.*, **101**, 7131 (1979).
4. R. N. Comber and W. J. Brouillette, *J. Org. Chem.*, **52**, 2311 (1987).
5. J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).
6. B. M. Trost, J. L. Belletire, S. Golleski, P. G. McDougal, J. M. Balkovec, J. J. Baldwin, M. E. Christy, G. S. Ponticello, S. L. Varga, and J. P. Springer, *J. Org. Chem.*, **51**, 2370 (1986).
7. R. N. Comber and W. J. Brouillette, *ibid.*, **53**, 1121 (1988).

****