$$\sigma^2(F_o^2) = \sigma(I) + (pF_o^2)P^2$$

where $\sigma(I)$ is the standard deviation of the reduced intensity due to counting statistics and the parameter p is a factor introduced to downweight intense reflections. Here p was set to 0.030. Scattering factors were taken from Cromer and Waber.[17] Anamalous dispersion effects were included in F_c;[18] the values for f' and f'' were those of Cromer.[19] Only the 594 reflections having intensities greater than 2.0 times their standard deviation were used in the refinements. The final cycle of refinement included 65 variable parameters and converged (largest parameter shift was 0.32 times is esd) with unweighted and weighted agreement factors of:

$$R_1 = \sum||F_o| - |F_c||/\sum|F_o| = 0.182$$

$$R_2 = \sqrt{(\sum w(|F_o| - |F_c|)^2/\sum wF_o^2)} = 0.190$$

The standard deviation of an observation of unit weight was 3.46. The highest peak in the final difference Fourier had a height of 0.85 e/Å^3. The high residuals are due to the molecules in the other minor crystals as seen in the omega scans. No attempt was made to include them in this model.

All calculations were performed on a PDP-11/34a computer using DSP-PLUS.[9] A complete listing of crystallographic data can be found in the supplementary material.

Acknowledgment. We are happy to acknowledge the contributions to this work of G. R. Chipman and R. W. Dunlap of Amoco Corporation.

Supplementary Material Available: X-ray data for $C_{26}H_{14}O_6$ (7 pages); table of structure factors for $C_{26}H_{14}O_6$ (4 pages). Ordering information is given on any current masthead page.

(17) Cromer, D. T.; Waber, J. T. *International Tables for X-Ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV, Table 2.2B.
(18) Ibers, J. A.; Hamilton, W. C. *Acta Crystallogr.* **1964**, *17*, 781.
(19) Cromer, D. T. *International Tables for X-Ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV, Table 2.3.1.

Selective Transformation of *O*-2-(Trimethylsilyl)ethyl and *O*-*tert*-Butyl Carbamates into *O*-Benzyl Carbamates Using Benzyl Trichloroacetimidate

Anthony G. M. Barrett* and Daniel Pilipauskas

Department of Chemistry, Northwestern University, Evanston, Illinois 60208

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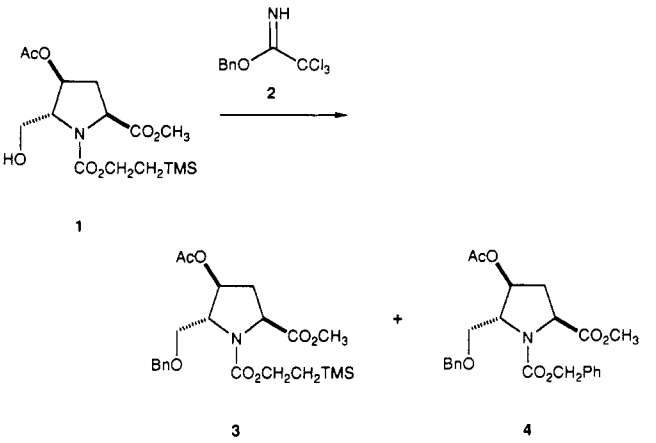
We recently attempted to benzylate the hydroxyl group of the bulgecinine derivative (**1**)[1] with benzyl trichloroacetimidate (**2**) in the presence of a catalytic amount of trifluoromethanesulfonic acid.[2] Upon workup, the expected benzyl ether (**3**) was isolated (50%) along with the *O*-benzyl carbamate benzyl ether (**4**) (20%). To our knowledge, the direct conversion of an *O*-alkyl carbamate into an *O*-benzyl carbamate (Cbz) (**1** to **4**) has not been described. However, a two-step procedure for converting *O*-*tert*-butyl carbamates (BOC) into *O*-benzyl carbamates via the *O*-*tert*-butyldimethylsilyl carbamate has been reported by Ohfune and co-workers.[3] The reactive *O*-*tert*-butyldimethylsilyl carbamate intermediate is also



available from *O*-benzyl carbamates by the reductive cleavage of the benzyl group using *tert*-butyldimethylsilane and palladium acetate.[4] We report that the benzylating agent benzyl trichloroacetimidate (**2**) readily converts *O*-2-(trimethylsilyl)ethyl carbamates (TEOC)[5] and *O*-*tert*-butyl carbamates into the corresponding *O*-benzyl carbamates in moderate yields in a one-step process that proceeds without "racemization". The conversion procedure is compatible with ester, amide, and silyl ether functionalities.

The *cis*-hydroxyproline derivative (**5**) was used in optimizing the reaction conditions for the TEOC to Cbz transformation. Six equivalents of benzyl trichloroacetamidate and a minimum of 0.3 equiv of trifluoromethanesulfonic acid were required to consume **5** and give the Cbz derivative (**6**) in a 56% yield (Chart I). No pyrrolidine-containing compounds were among the components isolated during the purification of **6** by silica gel chromatography. Presumably, the remaining amount of **5** was converted into polar compounds, such as the free and benzylated amine derivatives, and removed by the aqueous workup or not eluted from silica gel. With these conditions, the conversion of **1** to **4** proceeded with a 48% yield while the conversion of TEOC-Leu-OMe (**7**) gave a 68% yield of the Cbz derivative **8**. The above procedure was also found to convert *O*-*tert*-butyl but not *O*-methyl (**9**) carbamates into *O*-benzyl carbamates. A series of *O*-*tert*-butyl carbamates (**10**, **12**, **14**, **16**, **18**, **20**) were converted into the corresponding Cbz derivatives in modest yields. Noteworthy results are the stability of the *tert*-butyldimethylsilyl ether (**21**) and the selective conversion of the *O*-*tert*-butyl carbamate in the presence of a *tert*-butyl ester (**19**). No epimerization was detected by ^{1}H NMR spectroscopy for the Cbz derivatives **4**, **6**, and **17**. In order to detect any racemization in the Cbz derivatives **11**, **13**, and **15**, the Cbz group was removed by hydrogenolysis and the amino esters converted to Mosher amides.[6] In each case only the *R*,*S* diastereoisomer was detected by ^{1}H NMR spectroscopy.

The course of the reaction is rationalized as a nucleophilic attack of the carbamate carbonyl oxygen at the benzylic position of the protonated benzyl trichloroacetimidate to give a cation (Scheme I). If R^2 is a *tert*-butyl group, the intermediate cation fragments to form the *O*-benzyl carbamate plus the *tert*-butyl cation. Alterna-

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(2) Wessel, H.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.
(3) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1985**, *26*, 5543. Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870.
(4) Sakaitani, M.; Kurokawa, N.; Ohfune, Y. *Tetrahedron Lett.* **1986**, *27*, 3753.
(5) Carpino, L. A.; Tsao, J. H.; Ringsdorf, H.; Fell, E.; Hettrich, G. *J. Chem. Soc., Chem. Commun.* **1978**, 358.
(6) Nelson, W. L.; Burke, T. R., Jr. *J. Org. Chem.* **1978**, *43*, 3641. Dale, J. A.; Dull, D. L.; Mosher, H. S. *Ibid.* **1969**, *34*, 2543. Baxter, C. A. R.; Richards, H. L. *Tetrahedron Lett.* **1972**, *13*, 3357.

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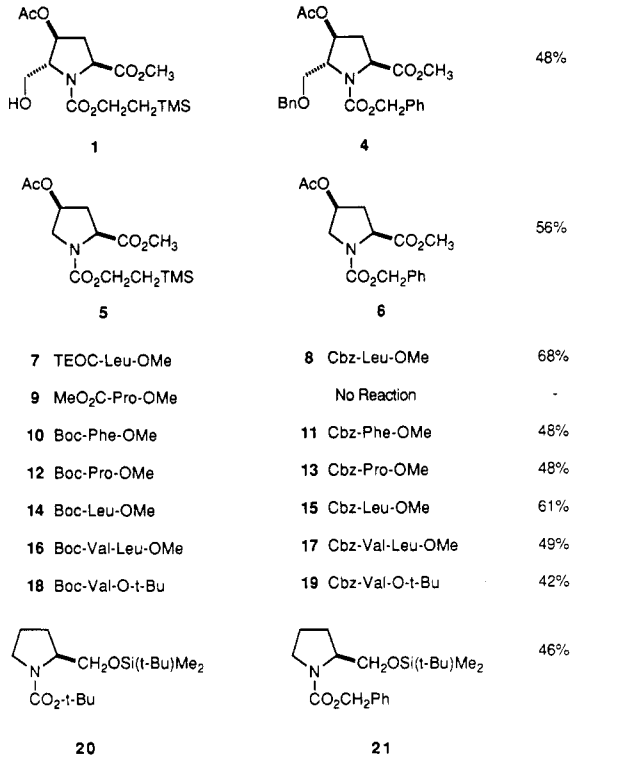
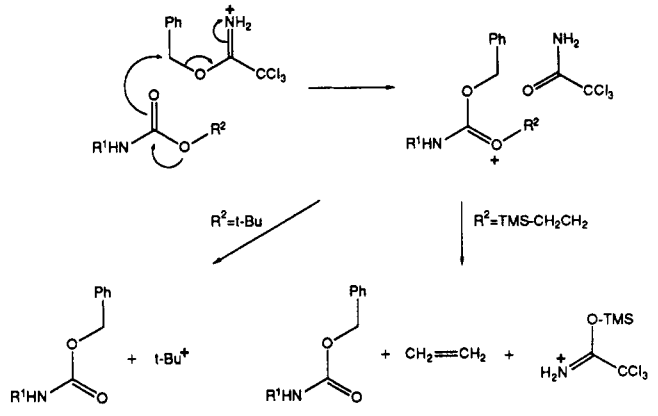
Chart I. Conversion of *N*-Boc and *N*-TEOC Groups to the *N*-Cbz Group



Scheme I



tively, when R^2 is a 2-(trimethylsilyl)ethyl group, S_N1 fragmentation and subsequent nucleophilic attack at silicon by the trichloroacetamide gives the product carbamate, ethylene, and the positively charged TMS adduct. However, when R^2 is a methyl group, cleavage of the cation occurs presumably via debenzylation with the formation of *N*-benzyltrichloroacetamide rather than de-O-methylation with formation of the benzyl carbamate.

Experimental Section

Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Optical rotations were recorded at room temperature. Infrared spectra were recorded as films on a Perkin-Elmer 283 instrument. ^1H (400 MHz) and ^{13}C NMR (101 MHz) spectra were recorded on a Varian XL 400 spectrometer with tetramethylsilane as internal standard. Mass spectra were recorded on a VG70-250SE mass spectrometer. Microanalyses were determined by G. D. Searle and Company, Skokie, IL 60077. Samples for microanalysis that were oils were purified by flash chromatography, rotary evaporated, and subsequently further evaporated at ca. 0.1 mmHg.

Hexane, diethyl ether, and ethyl acetate were purified by distillation. Cyclohexane was dried by filtration through a column of activated neutral alumina, Brockmann grade I. All reactions were carried out under dry N_2. Silica gel for chromatography refers to the Merck product Kieselgel 60 (Art. 9385). Thin-layer chromatography was performed on Merck Kiesegel 60 F254 (Art. 5715).

(2*S*,4*R*)-Methyl 4-Hydroxy-1-[[2-(trimethylsilyl)ethyl]-oxycarbonyl]pyrrolidine-2-carboxylate. To an acetonitrile solution (50 mL) of L-*trans*-hydroxyproline methyl ester hydrochloride (17.9 g, 98.5 mmol) and 2-(trimethylsilyl)ethyl azidoformate[5] (15.6 g, 83.4 mmol) was added triethylamine (13.7 mL, 98.5 mmol) at <12 °C. After being stirred for 16 h at room temperature, the reaction mixture was rotary evaporated, and the residue was mixed with Et_2O and H_2O. The organic layer was separated and washed with H_2O and brine. After drying with $MgSO_4$, the organic layer was rotary evaporated. Flash chromatography (eluant, Et_2O) of the residue gave the product (19.6 g, 82%) as an oil: $[\alpha]_D = -76°$ (c = 1.5, $CHCl_3$); IR (neat) 3460, 2970, 1755, 1710, 1685, 1440, 1365, 1210, 1175, 865, 845 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.52–4.42 (m, 2 H), 4.22–4.05 (m, 2 H), 3.75, 3.73 (2 s, 3 H), 3.67–3.48 (m, 2 H), 3.14, 3.04 (2 s, 1 H), 2.38–2.23 (m, 1 H), 2.11–2.02 (m, 1 H), 1.01 (t, 1 H, J = 8.4 Hz), 0.94 (t, 1 H, J = 9.2 Hz), 0.04, 0.03 (2 s, 9 H); ^{13}C NMR ($CDCl_3$) 173.3, 173.2, 155.4, 155.1, 69.9, 69.1, 63.8, 57.7, 57.6, 54.9, 54.4, 52.3, 52.2, 39.0, 38.3, 17.6, -1.5, -1.6 ppm; HRMS (EI) calcd for $C_{12}H_{23}NO_5Si$ ($M^{\cdot+}$) 289.1346, found ($M^{\cdot+}$) 289.1335. Anal. Calcd for $C_{12}H_{23}NO_5Si$: C, 49.80; H, 8.01; N, 4.84. Found: C, 49.63; H, 8.05; N, 4.84.

(2*S*,4*S*)-Methyl 4-Acetoxy-1-[[2-(trimethylsilyl)ethyl]-oxycarbonyl]pyrrolidine-2-carboxylate (5). To a THF solution (100 mL) of (2*S*,4*R*)-methyl 4-hydroxy-1-[[2-(trimethylsilyl)-ethyl]oxycarbonyl]pyrrolidine-2-carboxylate (19.1 g, 66.1 mmol), triphenylphosphine (17.8 g, 66.1 mmol), and glacial acetic acid (5.67 mL, 99.1 mmol) was added dropwise a THF solution (15 mL) of diethyl azodicarboxylate (10.4 mL, 66.1 mmol) at 25 °C. After 16 h, the reaction was filtered through 400 g of silica, eluting with Et_2O. The eluate was rotary evaporated, and the residue was flash chromatographed (eluant, 0–10% Et_2O/hexanes), giving 20.9 g of an oil that crystallized on standing. Recrystallization from cyclohexane gave 5 (13.8 g, 63%) as white crystals: mp 66–67 °C; $[\alpha]_D = -40°$ (c = 2.5, $CHCl_3$); IR (KBr) 2980, 1765, 1745, 1715, 1420, 1365, 1260, 1210, 1180, 1125, 870, 845 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.30–5.22 (m, 1 H), 4.54, 4.46 (2 dd, 1 H, J = 7.6, 1.6 Hz), 4.26–4.12 (m, 2 H), 3.83–3.72 (m, 1 H), 3.75, 3.74 (2 s, 3 H), 3.63, 3.58 (2 d, 1 H, J = 12.4 Hz), 2.52–2.38 (m, 1 H), 2.38–2.28 (m, 1 H), 2.01, 2.00 (2 s, 3 H), 1.07–0.90 (m, 2 H), 0.04, 0.03 (2 s, 9 H); ^{13}C NMR ($CDCl_3$) 172.1, 171.9, 170.2, 170.1, 154.9, 154.6, 72.7, 71.7, 63.81, 63.76, 57.6, 57.4, 52.3, 52.2, 51.9, 36.4, 35.3, 20.9, 17.7, -1.56, -1.61 ppm; HRMS (EI) calcd for $C_{14}H_{25}NO_6Si$ ($M - Me^+$) 316.1216, found ($M - Me^+$) 316.1222. Anal. Calcd for $C_{14}H_{25}NO_6Si$: C, 50.73; H, 7.60; N, 4.23. Found: C, 50.59; H, 7.55; N, 4.25.

TEOC-Leu-OMe (7). To a stirred mixture of leucine methyl ester hydrochloride (0.91 g, 5.0 mmol) and 2-(trimethylsilyl)ethyl azidoformate[5] (0.94 g, 5.0 mmol) in acetonitrile (3 mL) was added triethylamine (1.4 mL, 10.0 mmol). After 30 h, the reaction mixture was rotary evaporated, and the residue was diluted with Et_2O and water. The organic layer was separated and washed with 1 M sodium bisulfate, brine, 10% aqueous sodium bicarbonate, and brine. The organic layer was dried with $MgSO_4$ and rotary evaporated. Flash chromatography of the residue (eluant, 10–20% Et_2O/hexanes) gave 7 (1.04 g, 72%) as an oil: $[\alpha]_D = -27°$ (c = 2.3, MeOH); IR (neat) 3360, 2970, 1755, 1730, 1535, 1260, 870, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.98 (d, 1 H, J = 9.0 Hz), 4.42–4.32 (m, 1 H), 4.16 (t, 2 H, J = 8.0 Hz), 3.74 (s, 3 H), 1.78–1.43 (m, 3 H), 1.05–0.90 (m, 8 H), 0.04 (s, 9 H); ^{13}C NMR ($CDCl_3$) 173.8, 156.3, 63.3, 52.21, 52.18, 41.7, 24.7, 22.8, 21.7, 17.6, -1.6 ppm; HRMS (EI) calcd for $C_{13}H_{27}NO_4Si$ ($M - Me^+$) 274.1475, found ($M - Me^+$) 274.1486. Anal. Calcd for $C_{13}H_{27}NO_4Si$: C, 53.95; H, 9.40; N, 4.84. Found: C, 54.09; H, 9.40; N, 4.83.

Boc-Val-O-*t*-Bu (18). To a solution of BOC-Val (1.2 g, 5.5 mmol), *tert*-butyl alcohol (856 mg, 11.6 mmol), and 4-(dimethylamino)pyridine (67 mg, 0.55 mmol) in Et_2O was added dicyclohexylcarbodiimide (1.14 g, 5.5 mmol). After 1 week (this length of time may not be necessary), the mixture was diluted with Et_2O and filtered. The filtrate was extracted with 5% acetic acid, water, 10% aqueous sodium bicarbonate, and brine. The organic layer was dried with $MgSO_4$ and rotary evaporated. The

residue was flash chromatographed (eluant, 10% Et_2O/hexanes) to give **18** (1.0 g, 67%) as an oil: $[\alpha]_D$ = +4.5° (*c* = 5.7, $CHCl_3$); IR (neat) 3380, 2980, 1720, 1495, 1365, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.02 (d, 0.9 H, *J*. = 8.2 Hz), 4.75–4.65 (s, 0.1 H), 4.10 (dd, 0.9 H, *J* = 4.4, 9.1 Hz), 3.95–3.85 (s, 0.1 H), 2.20–2.00 (m, 1 H), 1.47 (s, 9 H), 1.45 (s, 9 H), 0.95, 0.89 (2 dd, 6 H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$) 171.4, 155.6, 81.5, 79.3, 58.8, 31.4, 28.2, 28.0, 18.8, 17.4 ppm; HRMS (EI) calcd for $C_{14}H_{27}NO_4$ ($M^{\bullet+}$) 273.1940, found ($M^{\bullet+}$) 273.1986. Anal. Calcd for $C_{14}H_{27}NO_4$: C, 61.51; H, 9.96; N, 5.12. Found: C, 61.17; H, 9.94; N, 5.05.

(2*S*)-1-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)-pyrrolidine. To a toluene solution (10 mL) of *N*-BOC-proline methyl ester (4.3 g, 18.8 mmol) at −78 °C was added 1.5 M diisobutylaluminum hydride (DIBAL) in toluene (25 mL, 37.6 mmol) over a 30-min period. At 40 and 60 min, an additional 10 mL of DIBAL was added. After an additional 1 h, methanol (15 mL) was added cautiously (vigorous foaming) at −78 °C, and the resulting solution was poured onto a mixture of ice (300 mL) and concentrated HCl (20 mL). The mixture was extracted with Et_2O, and the organic layer extracted with 1 M sodium bisulfate until clear. The organic layer was dried with $MgSO_4$ and rotary evaporated to give the aldehyde as an oil. Without further purification, the aldehyde was dissolved in a 1:1 mixture of THF and i-PrOH (30 mL) and cooled in an ice bath before sodium borohydride (2.9 g, 75.0 mmol) was added. After 1 h, 3% HCl (60 mL) was added cautiously (vigorous foaming), and the resulting solution was saturated with NaCl. The mixture was then extracted with Et_2O, and the organic layer was separated and extracted with 10% aqueous sodium bicarbonate. After drying with $MgSO_4$ the organic layer was rotary evaporated, and the resulting residue was flash chromatographed (eluant, 50–60% Et_2O/hexanes) to give the product (2.1 g, 55%) as an oil: $[\alpha]_D$ = −53° (*c* = 1.7, MeOH) [lit.[7] $[\alpha]_D$ = −47.2° (*c* = 1, MeOH)]; IR (neat) 3450, 3000, 1760, 1665, 1400, 1170, 1110, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.78 (d, 1 H, *J* = 6.3 Hz), 4.03–3.25 (m, 5 H), 2.20–1.96 (m, 1 H), 1.90–1.72 (m, 2 H), 1.61–1.40 (m, 1 H), 1.47 (s, 9 H).

(2*S*)-1-(*tert*-Butoxycarbonyl)-2-[(*tert*-butyldimethylsilyl)oxymethyl]pyrrolidine (20). To a DMF solution (1 mL) of (2*S*)-1-(*tert*-butoxycarbonyl)-2-(hydroxymethyl)pyrrolidine (402 mg, 2.0 mmol) and imidazole (272 mg, 4.0 mmol) cooled in an ice bath was added *tert*-butyldimethylsilyl chloride (377 mg, 2.5 mmol). The ice bath was removed after 15 min, and the mixture was stirred at room temperature. After 16 h, the reaction mixture was diluted with Et_2O and extracted with water (3×) and then brine. The organic layer was dried with $MgSO_4$ and rotary evaporated. Flash chromatography of the residue (eluant, 10% Et_2O/hexanes) gave **20** (520 mg, 83%) as an oil: $[\alpha]_D$ = −49° (*c* = 1.7, $CHCl_3$); IR (neat) 2960, 1690, 1390, 1250, 1170, 1090, 835, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90–3.25 (m, 5 H), 2.05–1.70 (m, 4 H), 1.46 (s, 9 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$) 154.5, 151.0, 79.1, 78.8, 63.7, 63.3, 58.3, 47.1, 46.6, 28.5, 28.2, 27.5, 25.8, 23.9, 22.8, 18.2, −5.4 ppm; HRMS (EI) calcd for $C_{16}H_{33}NO_3Si$ (M − Bu^+) 258.1526, found (M − Bu^+) 258.1527. Anal. Calcd for $C_{16}H_{33}NO_3Si$: C, 60.91; H, 10.54; N, 4.44. Found: C, 61.08; H, 10.79; N, 4.29.

General Procedure for *O*-Benzyl Carbamate Formation. To a stirred solution of the *O*-*tert*-butyl or *O*-2-(trimethylsilyl)ethyl carbamate (1 mmol) and benzyl trichloroacetimidate (1.52 g, 6 mmol) in cyclohexane (3 mL) was added trifluoromethanesulfonic acid (29 μL, 0.33 mmol), and the resulting mixture was stirred for 1 h. The thick reaction slurry was diluted with cyclohexane and filtered. The filtrate was diluted with Et_2O and washed with 10% aqueous $NaHCO_3$ and brine, and the organic layer was dried with $MgSO_4$ and rotary evaporated. Flash chromatography of the residue gave the *O*-benzyl carbamate.

(2*S*,4*S*,5*R*)-Methyl 4-Acetoxy-1-(benzyloxycarbonyl)-5-[(benzyloxy)methyl]pyrrolidine-2-carboxylate (4). To a solution of **1** (100 mg, 0.28 mmol) and benzyl trichloroacetimidate (560 mg, 2.22 mmol) in cyclohexane (0.9 mL) was added trifluoromethanesulfonic acid (24 μL, 0.28 mmol), and the mixture was stirred for 1 h. At the end of this time, Et_2O was added to dissolve the thick reaction slurry, and the resulting solution was filtered through a short column of silica. The eluate was rotary evaporated, and the residue was flash chromatographed (eluant, 50% Et_2O/hexanes) to give **4** (60 mg, 48%) as an oil: $[\alpha]_D$ = −59° (*c* = 1.3, $CHCl_3$); IR (neat) 2970, 1760, 1740, 1715, 1415, 1350, 1245, 1215, 1130, 1095, 1060, 1025, 745, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.20 (m, 10 H), 5.20 (m, 1 H), 5.14, 5.12 (2 AB q, 2 H, *J* = 12.1 Hz), 4.60–4.33 (m, 3 H), 4.18 (t, 0.6 H, *J* = 2.8 Hz), 4.10 (t, 0.4 H, *J* = 3.2 Hz), 3.87–3.71 (m, 1 H), 3.75, 3.57 (2 s, 3 H), 3.63–3.56 (m, 1 H), 2.78–2.64 (m, 1 H), 2.19, 2.18 (2 d, 1 H, *J* = 14.4 Hz), 2.00, 1.98 (2 s, 3 H); ^{13}C NMR ($CDCl_3$) 172.4, 171.8, 170.4, 170.2, 154.3, 154.1, 137.9, 137.7, 136.3, 136.1, 128.44, 128.38, 128.35, 128.1, 128.0, 127.9, 127.7, 127.6, 127.4, 77.1, 75.8, 73.3, 73.2, 68.9, 68.1, 67.3, 67.0, 64.7, 63.9, 59.2, 58.9, 52.2, 52.0, 35.6, 34.4, 21.0, 20.9 ppm; HRMS (FAB) calcd for $C_{24}H_{28}NO_7$ (M + H^+) 442.1866, found (M + H^+) 442.1842. Anal. Calcd for $C_{24}H_{27}NO_7$: C, 65.30; H, 6.17; N, 3.17. Found: C, 65.04; H, 6.13; N, 3.20.

(2*S*,4*S*)-Methyl 4-Acetoxy-1-(benzyloxycarbonyl)-pyrrolidine-2-carboxylate (6). Flash chromatography (eluant, 15% Et_2O/PhH) gave **6** (180 mg, 56%) as an oil: $[\alpha]_D$ = −41° (*c* = 1.4, $CHCl_3$); IR (neat) 2960, 1740, 1705, 1410, 1345, 1235, 1205, 1105, 1065, 770, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.40 (m, 5 H), 5.25 (m, 1 H), 5.17 (AB q, 1 H, *J* = 12.1 Hz), 5.14 (AB q, 1 H, *J* = 12.4 Hz), 4.57, 4.50 (2 dd, 1 H, *J* = 2.4, 8.8 Hz), 3.85–3.72 (m, 1 H), 3.76, 3.64 (2 s, 3 H), 3.70–3.60 (m, 1 H), 2.52–2.38 (m, 1 H), 2.34 (d, 1 H, *J* = 14.5 Hz), 2.00, 1.99 (2 s, 3 H); ^{13}C NMR ($CDCl_3$) 172.0, 171.7, 170.2, 170.1, 154.5, 154.1, 136.33, 136.25, 128.42, 128.36, 128.04, 127.98, 127.9, 127.8, 72.6, 71.6, 67.2, 67.1, 57.8, 57.5, 52.4, 52.3, 52.2, 52.1, 36.4, 35.3, 20.9, 20.8 ppm; HRMS (EI) calcd for $C_{16}H_{19}NO_6$ ($M^{\bullet+}$) 321.1213, found ($M^{\bullet+}$) 321.1207. Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.71; H, 6.10; N, 4.28.

Cbz-Leu-OMe from Teoc-Leu-OMe (8). Flash chromatography (eluant, 10% Et_2O/PhH) gave **8** (190 mg, 68%) as an oil: $[\alpha]_D$ = −28° (*c* = 2.1, CH_3OH) [lit.[8] $[\alpha]_D$ = −29.5° (*c* = 1.0, CH_3OH)]; ^1H NMR ($CDCl_3$) δ 7.40–7.28 (m, 5 H), 5.15 (d, 0.9 H, *J* = 7.1 Hz), 5.10 (s, 2 H), 4.92–4.82 (s, 0.1 H), 4.40 (m, 1 H), 3.73 (s, 2.7 H), 3.65 (s, 0.3 H), 1.75–1.47 (m, 3 H), 0.94, 0.93 (2 d, 6 H, *J* = 6.8 Hz).

Cbz-Phe-OMe (11). Flash chromatography (eluant, 5% Et_2O/PhH) gave **11** (150 mg, 48%) as an oil: $[\alpha]_D$ = −16° (*c* = 1.6, CH_3OH) [lit.[3] $[\alpha]_D$ = −14.9° (*c* = 1, CH_3OH)]; ^1H NMR ($CDCl_3$) δ 7.40–7.05 (m, 10 H), 5.22 (d, 0.9 H, *J* = 8.8 Hz), 5.10 (AB q, 2 H, *J* = 12.5 Hz), 5.04–4.96 (s, 0.1 H), 4.63 (dt, 0.9 H, *J* = 6.3, 8.8 Hz), 4.58–4.49 (s, 0.1 H), 3.72 (s, 2.7 H), 3.66 (s, 0.3 H), 3.14, 3.08 (2 dd, 2 H, *J* = 6.3, 12.5 Hz).

Cbz-Pro-OMe (13). Flash chromatography (eluant, 33% Et_2O/hexanes) gave **13** (128 mg, 48%) as an oil: $[\alpha]_D$ = −61° (*c* = 1.2, CH_3OH) [lit.[9] $[\alpha]_D$ = −57.3° (*c* = 1.0, CH_3OH)]; ^1H NMR ($CDCl_3$) δ 7.40–7.25 (m, 5 H), 5.15, 5.12 (2 AB q, 2 H, *J* = 12.7 Hz), 4.40, 4.35 (2 dd, 1 H, *J* = 3.6, 9.1 Hz), 3.75, 3.59 (2 s, 3 H), 3.67–3.44 (m, 2 H), 2.30–2.15 (m, 1 H), 2.05–1.85 (m, 3 H).

Cbz-Leu-OMe from Boc-Leu-OMe (15). Flash chromatography (eluant, 10% Et_2O/PhH) gave **15** (169 mg, 61%) as an oil: $[\alpha]_D$ = −29° (*c* = 1.8, CH_3OH).

Cbz-Val-Leu-OMe (17). Boc-Val-Leu-OMe (177 mg, 0.515 mmol) was dissolved in benzyl trichloroacetimidate (795 mg, 3.15 mmol) before cyclohexane (1.5 mL) was added. To this solution was added trifluoromethanesulfonic acid (25 μL, 0.28 mmol), and the resulting mixture was stirred for 1 h. The reaction slurry was dissolved in Et_2O and washed with 10% aqueous $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$ and rotary evaporated. Flash chromatography (eluant, 25% EtOAc/hexanes) of the residue gave **17** (96 mg, 49%) as a solid. Recrystallization from EtOAc/hexanes gave crystals: mp 99–102 °C (lit.[10] 93–96 °C); $[\alpha]_D$ = −37° (*c* = 1.6, AcOH) [lit.[10] $[\alpha]_D$ = −39.7° (*c* = 1, AcOH)]; ^1H NMR ($CDCl_3$) δ 7.40–7.30 (m, 5 H), 6.12 (d, 1 H, *J* = 9.2 Hz), 5.34 (d, 1 H, *J* = 8.8 Hz), 5.11 (s, 2 H), 4.61 (m, 1 H), 4.01 (dd, 1 H, *J* = 6.4, 8.8 Hz), 3.73 (s, 3 H), 2.20–2.08 (m, 1 H), 1.70–1.50 (m, 3 H), 1.05–0.90 (m, 12 H); ^{13}C NMR ($CDCl_3$) 173.1, 171.0, 156.3, 136.2, 128.5, 128.1, 128.0, 67.0, 60.2, 52.3, 50.7, 41.3, 31.2, 24.8, 22.7, 21.8, 19.1, 17.8 ppm.

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Cbz-Val-O-*t*-Bu (19). Flash chromatography (eluant, 2% Et_2O/PhH) gave **19** (134 mg, 42%) as an oil: $[\alpha]_D$ = −7.7° (*c* = 2.2, MeOH) [lit.[11] $[\alpha]_D$ −4.7° (*c* = 2, MeOH)]; ^1H NMR ($CDCl_3$) δ 7.40–7.26 (m, 5 H), 5.28 (d, 0.9 H, *J* = 8.8 Hz), 5.11–5.06 (s, 2 H), 5.06–4.98 (s, 0.1 H), 4.19 (dd, 0.9 H, *J* = 4.2, 9.0 Hz), 4.08–4.00 (s, 0.1 H), 2.20–2.05 (m, 1 H), 1.46 (s, 9 H), 0.96, 0.88 (d, 6 H, *J* = 6.8 Hz).

(2*S*)-1-(Benzyloxycarbonyl)-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]pyrrolidine (21). Flash chromatography (eluant, 0–4% Et_2O/PhH) gave **21** (160 mg, 46%) as an oil: $[\alpha]_D$ = −44° (*c* = 1.6 , $CHCl_3$); IR (neat) 2960, 1705, 1415, 1095, 835, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.25 (m, 5 H), 5.02–5.00 (m, 2 H), 3.95–3.34 (m, 5 H), 2.05–1.70 (m, 4 H), 0.88, 0.85 (2 s, 9 H), 0.04, 0.02, −0.04 (3 s, 6 H); ^{13}C NMR ($CDCl_3$) 154.8, 137.1, 136.8, 128.4, 128.1, 127.9, 127.7, 66.7, 66.4, 63.8, 63.11, 63.06, 59.0, 58.9, 58.4, 58.3, 47.2, 46.9, 28.2, 27.5, 25.8, 23.8, 22.8, 18.2, −5.47, −5.52 ppm; HRMS (EI) calcd for $C_{19}H_{31}NO_3Si$ (M − Me^+) 334.1839, found (M − Me^+) 334.1833. Anal. Calcd for $C_{19}H_{31}NO_3Si$: C, 65.29; H, 8.94; N, 4.01. Found: C, 65.59; H, 9.11; N, 3.95.

General Synthesis of the Mosher Amides for Entries 11, 13, and 15. 10% Pd/C (10 wt % of the Cbz derivative) in MeOH was prehydrogenated under 1 atm of H_2 for 1 h before adding a MeOH solution of the Cbz derivative and camphorsulphonic acid (1 equiv). After the reduction was complete, the reaction mixture was filtered through Celite and rotary evaporated to a solid. To this solid was added dicyclohexylcarbodiimide (2 equiv), 4-(dimethylamino)pyridine (1.8 equiv), and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (2 equiv) in CH_2Cl_2 (0.25 M in amino ester). When the reaction was complete, the solids were removed by filtration, and the filtrate was washed with 1 M $NaHSO_4$, H_2O, 10% aqueous $NaHCO_3$, and brine. The organic layer was dried with $MgSO_4$ and rotary evaporated to leave a syrup. Additional dicyclohexylurea was removed by dissolving the syrup in Et_2O and filtering. Evaporation gave the crude Mosher amide as an oil, and this was assayed for diastereioisomeric purity by ^1H NMR spectroscopy. For all three Mosher amides, no signals for the *R,R* diastereoisomer were observed. However, signals for the *R,R* diastereoisomer were clearly visible in the spectrum of a mixture of the *R,S* diastereoisomer containing 6% of a 1:1 mixture of *R,R* and *R,S* diastereoisomers. Thus, less than 3% of the *R,R* diastereoisomer could be detected.

***N*-[(*R*)-2-Methoxy-2-(trifluoromethyl)phenylacetyl]-(*R,S*)-Phe-O-Me.** Prepared from DL-phenylalanine methyl ester hydrochloride (0.30 mmol) according to the procedure above. Flash chromatography (eluant, 7–13% EtOAc/hexanes) of the residue gave the amide (105 mg, 88%) as a thick syrup that solidified on standing: $[\alpha]_D$ = −18° (*c* = 2.6, $CHCl_3$); IR (KBr) 3320, 2970, 1750, 1670, 1525, 1360, 1330, 1170, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55–6.85 (m, 11 H), 4.98, 4.91 (2 m, 1 H), 3.76, 3.73 (2 s, 3 H), 3.434, 3.430, 3.217, 3.214 (4 s, 3 H), 3.27–2.98 (m, 1 H).

***N*-[(*R*)-2-Methoxy-2-(trifluoromethyl)phenylacetyl]-(*S*)-Phe-O-Me.** Flash chromatography of the crude amide (eluant, 7–13% EtOAc/hexanes) gave the pure *R,S* amide as a solid: mp 99–101 °C; $[\alpha]_D$ = +6° (*c* = 1.1, $CHCl_3$); IR (neat) 3340, 2980, 1755, 1675, 1545, 1265, 1235, 1185, 1175, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60–7.10 (m, 11 H), 4.96–4.87 (m, 1 H), 3.73 (s, 3 H), 3.213, 3.210 (2 s, 3 H), 3.24 (dd, 1 H, *J* = 5.6, 14.0 Hz), 3.12 (dd, 1 H, *J* = 6.8, 14.0 Hz); HRMS (EI) calcd for $C_{20}H_{20}F_3NO_4$ ($M^{\cdot+}$), 395.1344, found ($M^{\cdot+}$) 395.1345.

***N*-[(*R*)-2-Methoxy-2-(trifluoromethyl)phenylacetyl]-(*R,S*)-Pro-O-Me.** Prepared from DL-proline methyl ester hydrochloride (0.30 mmol) according to the procedure above. Flash chromatography (eluant, 15% EtOAc/hexanes) of the reaction mixture gave the amide (80 mg, 77%) as a thick syrup: $[\alpha]_D$ = +144° (*c* = 0.7, $CHCl_3$); IR (neat) 2980, 1760, 1670, 1425, 1185, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68–7.32 (m, 5 H), 4.65–4.55 (m, 1 H), 3.827, 3.822, 3.655, 3.650 (4 s, 3 H), 3.78, 3.77 (2 s, 3 H), 3.49–3.39 (m, 1 H), 2.84–2.71 (m, 1 H), 2.18–2.06 (m, 1 H), 1.90–1.72 (m, 2 H), 1.58–1.47 (m, 1 H).

***N*-[(*R*)-2-Methoxy-2-(trifluoromethyl)phenylacetyl]-(*S*)-Pro-O-Me.** Flash chromatography of the crude amide (eluant, 20–25% EtOAc/hexanes) gave the pure *R,S* amide as a thick syrup: $[\alpha]_D$ = +73° (*c* = 1.1, $CHCl_3$); IR (neat) 2980, 1755, 1665, 1420, 1270, 1180, 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68–7.35 (m, 5 H), 4.58, 4.56 (2 d, *J* = 4.4 Hz), 3.79 (s, 3 H), 3.658, 3.654 (2 s, 3 H), 3.49–3.39 (m, 1 H), 2.79–2.71 (m, 1 H), 2.19–2.07 (m, 1 H), 1.90–1.71 (m, 3 H); HRMS (EI) calcd for $C_{16}H_{18}F_3NO_4$ ($M^{\cdot+}$) 345.1188, found ($M^{\cdot+}$) 345.1201.

***N*-[(*R*)-2-Methoxy-2-(trifluoromethyl)phenylacetyl]-(*R,S*)-Leu-O-Me.** Prepared from DL-leucine methyl ester hydrochloride (0.30 mmol) according to the procedure above. Flash chromatography (eluant, 15–20% EtOAc/hexanes) gave the amide (73 mg, 68%) as a thick syrup that solidified on standing: $[\alpha]_D$ = +1° (*c* = 1.8, $CHCl_3$); IR (KBr) 3310, 2960, 1755, 1740, 1670, 1540, 1170, 720, 700 cm^{-1}; ^1H NMR ($CDCl_3$) 7.60–7.23 (m, 5.5 H), 6.93 (d, 0.5 H, *J* = 4.4 Hz), 4.75–4.63 (m, 1 H), 3.76, 3.73 (2 s, 3 H), 3.562, 3.558, 3.371, 3.368 (4 s, 3 H), 1.80–1.40 (m, 3 H), 0.97, 0.96 (2 d, 3 H, *J* = 6.0 Hz), 0.89, 0.86 (2 d, 3 H, *J* = 6.4 Hz).

***N*-[(*R*)-2-Methoxy-2-(trifluoromethyl)phenylacetyl]-(*S*)-Leu-O-Me.** Flash chromatography of the crude amide (eluant, 15–20% EtOAc/hexanes) gave the pure *R,S* amide as a solid: mp 47–49 °C; $[\alpha]_D$ = −25° (*c* = 1.0, $CHCl_3$); IR (neat) 3320, 2970, 1765, 1740, 1670, 1525, 1180, 1165, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60–7.24 (m, 6H), 4.72–4.67 (m, 1 H), 3.74 (s, 3 H), 3.373, 3.370 (2 s, 3 H), 1.80–1.60 (m, 2 H), 0.97, 0.96 (2 d, 6 H, *J* = 6.4 Hz); HRMS (EI) calcd for $C_{17}H_{22}F_3NO_4$ (M + H^+) 362.1579, found (M + H^+) 362.1579.

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α-Ketoisocaproate Dioxygenase: The Stereochemical Course of the Hydroxylation Reaction

Hyunsoo Han and Robert A. Pascal, Jr.*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

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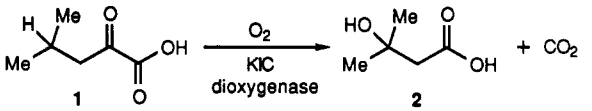
α-Ketoisocaproate (KIC) dioxygenase catalyzes the oxidation of α-ketoisocaproate (1) to β-hydroxyisovalerate (2) in mammals.[1] This cytosolic enzyme is not generally



considered to be part of the "normal" pathway for the degradation of branched-chain α-keto acids, but it has been suggested to function as a "safety valve" to prevent the accumulation of the toxic keto acid **1**, which is produced by the transamination of leucine.[1] The enzyme has been highly purified from rat liver,[1] and ^{18}O-labeling experiments have shown that it is indeed a dioxygenase.[2] Both the C-3 hydroxyl group and one of the carboxyl oxygens of product **2** are derived at least in part from molecular oxygen; labeling of the carboxyl is nearly complete, but more than half of the product molecules contain no label in the hydroxyl group.[2]

The vast majority of biological hydroxylations of aliphatic carbons proceed with retention of configuration,[3] although some stereochemical infidelity has been observed

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