MCPBA Oxidation of π-Allylpalladium Complexes. π-Allylpalladium complex (0.3 mmol) was placed in the reaction vessel under a nitrogen atmosphere. Pyridine (1.5 mmol) in 2 mL of dichloromethane was introduced with stirring at 0 °C. MCPBA (0.36 mmol) in dichloromethane (3 mL) was added dropwise to the solution. The resulting mixture was stirred at 0 °C for 24 h, allowed to warm to ambient temperature, washed with Na_2SO_3 solution, $NaHCO_3$ solution, water, and brine, and dried on anhydrous $MgSO_4$. The solvent-evaporated residue was analyzed by GLC. Except for the cases of **1a** and **6a**, allylic alcohols were not detected and the isomers of allylic *m*-chlorobenzoates were obtained.

2-[(3-Chlorobenzoyl)oxy]-1-methylenecyclohexane (2e): IR (film) 1710, 1430, 1300, 1270, 1122, 1068, 896, 750 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.4 (m, 8 H, CH_2), 4.81 (s, 1 H, =CH), 4.89 (s, 1 H, =CH), 5.4–5.7 (m, 1 H, CHO), 7.2–8.1 (m, 4 H, phenyl).

1-[[(3-Chlorobenzoyl)oxy]methyl]cyclohexene (2f): IR (film) 1715, 1430, 1295, 1260, 1122, 1070, 809, 749 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.1 (m, 8 H, CH_2), 4.67 (s, 2 H, CHO), 5.81 (br s, 1 H, =CH), 7.2–8.1 (m, 4 H, phenyl).

2-[(3-Chlorobenzoyl)oxy]-1-methylenecyclopentane (3e): NMR ($CDCl_3$) δ 1.5–2.7 (m, 6 H, CH_2), 5.14 (s, 1 H, =CH), 5.25 (s, 1 H, =CH), 5.66 (m, 1 H, CHO), 7.3–8.1 (m, 4 H, phenyl).

1-[[(3-Chlorobenzoyl)oxy]methyl]cyclopentene (3f): NMR ($CDCl_3$) δ 1.8–2.6 (m, 6 H, CH_2), 4.87 (s, 2 H, CHO), 5.72 (br s, 1 H, =CH), 7.3–8.1 (m, 4 H, phenyl).

3-[(3-Chlorobenzoyl)oxy]-2-phenyl-1-butene (4e): IR (film) 1715, 1570, 1420, 1285, 1250, 1135, 1073, 908, 749 cm^{-1}; NMR ($CDCl_3$) δ 1.48 (d, J = 6.6 Hz, 3 H, CH_3), 5.35 (s, 1 H, =CH), 5.41 (s, 1 H, =CH), 6.06 (q, J = 6.6 Hz, 1 H, CHO), 7.2–8.1 (m, 9 H, phenyl).

1-[(3-Chlorobenzoyl)oxy]-2-phenyl-2-butene (4f): IR (film) 1720, 1570, 1420, 1280, 1250, 1135, 1073, 830, 749 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (d, J = 7 Hz, 3 H, CH_3), 5.00 (s, 2 H, CHO), 5.98 (q, J = 7 Hz, 1 H, =CH), 7.2–8.1 (m, 9 H, phenyl).

3-[(3-Chlorobenzoyl)oxy]-2-propyl-1-pentene (5e): IR (film) 1740, 1590, 1440, 1305, 1255, 1122 1070, 898, 749 cm^{-1}; NMR ($CDCl_3$) δ 0.8–2.2 (m, 12 H, CH_3 and CH_2), 4.95 (s, 1 H, =CH), 5.08 (s, 1 H, =CH), 5.38 (t, J = 6 Hz, CHO), 7.3–8.1 (m, 4 H, phenyl).

4-[[(3-Chlorobenzoyl)oxy]methyl]-3-heptene (5f): IR (film) 1730, 1585, 1440, 1305, 1250, 1125, 1070, 808, 750 cm^{-1}; NMR ($CDCl_3$) δ 0.8–2.3 (m, 12 H, CH_3 and CH_2), 4.73 (s, 2 H, CHO), 5.57 (t, J = 7 Hz, 1 H, =CH), 7.3–8.1 (m, 4 H, phenyl).

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Registry No. **1a**, 34829-33-9; **1b**, 1674-08-4; **1c**, 16812-40-1; **2a**, 53789-97-2; **2b**, 4065-80-9; **2e**, 84065-05-4; **2f**, 84065-06-5; **3a**, 53789-96-1; **3b**, 20461-31-8; **3e**, 84065-07-6; **3f**, 84065-08-7; **4a**, 31833-54-2; **4b**, 6249-81-6; **4e**, 84065-09-8; **4f**, 84065-10-1; **5a**, 54587-60-9; **5b**, 84065-11-2; **5e**, 84065-12-3; **5f**, 84065-13-4; **6a**, 12090-09-4; **6b**, 822-67-3; **6c**, 930-68-7; **6d**, 26828-73-9; **7a**, 55940-14-2; **7b**, 60041-30-7; MCPBA, 937-14-4; $MoO_2(acac)_2$, 17524-05-9; *t*-BuOOH, 75-91-2.

A Simple and Efficient Synthesis of L-Carnosine

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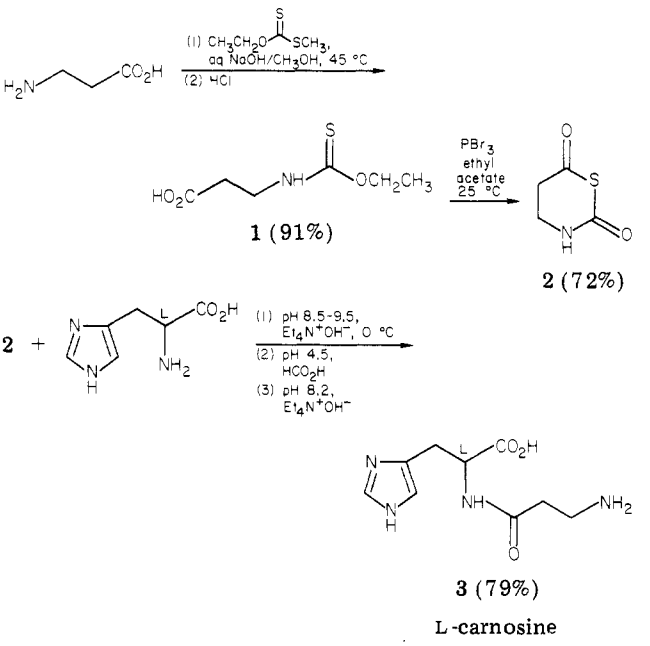
The naturally occurring dipeptide L-carnosine[1,2] (β-alanyl-L-histidine), **3**, is a substance of considerable biological and therapeutic importance. Recent studies[3] suggest that this material is an olfactory neurotransmitter. In addition, L-carnosine possesses the remarkable property of accelerating wound healing,[4] particularly when used following oral surgical procedures.

Scheme I



Previous syntheses of **3**[5] have, in general, required many steps and/or have afforded low overall yields of the final product. We now report a simple, short, high-yield preparation of **3** via the aqueous coupling of L-histidine and the *N*-(thiocarboxy) anhydride (NTA) of β-alanine, **2**.[6,7] This approach relies upon a new method for isolating water-soluble peptides from salt-containing aqueous reaction mixtures.

NTA's of amino acids have not enjoyed extensive utilization in peptide synthesis, principally because of their tendency to suffer some degree of racemization in the coupling process.[6] However, β-alanine, a material without

(1) "The Merck Index", 9th ed.; Merck and Co.: Rahway, NJ, 1976; p 236. L-Carnosine is found in the brain and muscles of man and numerous animals.

(2) For a review article on the skeletal muscle dipeptides L-carnosine and L-anserine, see: Meshkova, N. P. *Usp. Biol. Khim.* **1964**, *6*, 86.

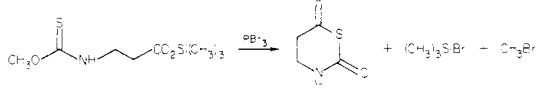
(3) (a) Margolis, F. L. Science (*Washington, D.C.*) **1974** *184*, 909. (b) Margolis, F. L.; Ferriero, D.; Harding, J. *Proc. Int. Congr. Pharmacol., 6th* **1976**, *2*, 61. (c) Brown, C. E.; Margolis, F. L.; Williams, T. H.; Pitcher, R. G.; Elgar, G. *Neurochem. Res.* **1977**, *2*, 555. (d) Wideman, J.; Brink, L.; Stein, S. *Anal. Biochem.* **1978**, *86*, 670. (e) Brown, C. E.; Margolis, F. L.; Williams, T. H.; Pitcher, R. G.; and Elgar, G. *Arch. Biochem. Biophys.* **1979**, *193*, 529.

(4) (a) Fisher, D. E.; Amend, J. F.; Strumeyer, D. H.; Fisher, H. *Proc. Soc. Exp. Biol. Med.* **1978**, *158*, 402. (b) Nagai, K.; Yamane, T. *Heterocycles* **1978**, *10*, 277. (c) Nagai, K.; Kodaira, H.; Kabutake, H.; Takano, H.; Oki, T. *J. Nihon Univ. Sch. Dent.* **1974**, *16*, 29.

(5) (a) Baumann, L.; Ingvaldsen, T. *J. Biol. Chem.* **1918**, *35*, 263. (b) Sifferd, R.; du Vigneaud, V. *Ibid.* **1935**, *108*, 753. (c) Turner, R. A. *J. Am. Chem. Soc.* **1953**, *75*, 2388. (d) Davis, N. C.; Smith, E. L. *Biochem. Prep.* **1955**, *4*, 38. (e) Lösse, G.; Müller, G. *Chem. Ber.* **1961**, *94*, 2768. (f) Rinderknecht, H.; Rebane, T.; Ma, V. *J. Org. Chem.* **1964**, *29*, 1968. (g) Glemzha, A. A.; Severin, S. E. *Izv. Akad, Nauk SSR, Ser. Khim.* **1966**, 861. (h) Pinelli, C.; Portelli, M.; Fioretti, M. *Il Farmico Ed. Sci.* **1968**, *23*, 859.

(6) Dewey, T. S.; Schoenewaldt, E. F.; Joshua, H.; Paleveda, W. J., Jr.; Schwam, H.; Barkemeyer, H.; Arison, B. H.; Veber, D. F.; Strachan, R. G.; Milkowski, J.; Denkewalter, R. G.; Hirschmann, R. *J. Org. Chem.* **1971**, *36*, 49. This paper provides an elegant and definitive account of the use of α-amino acid NTA's in peptide synthesis.

(7) Kricheldorf, H. *Chem. Ber.* **1971**, *104*, 3146. Kricheldorf has prepared β-alanine NTA by the reaction of *N*-(methoxythiocarbonyl) β-alanine trimethylsilyl ester with PBr_3:



The use of this NTA in a peptide coupling reaction has not been reported.

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intrinsic optical activity, is not vulnerable to possible racemization and is a priori an attractive substrate for an NTA-based coupling reaction.

The synthetic sequence employed is depicted in Scheme I.

Treatment of β-alanine with methyl ethylxanthate (1.05 equiv) at 45 °C for 1 h in aqueous sodium hydroxide (1 equiv)/methanol afforded a 91% yield of thionourethane derivative **1** (mp 72–74 °C). Compound **1** was readily cyclized to NTA **2**[7,8] with PBr_3 (0.5 mol, 1.5 equiv) in ethyl acetate (25 °C, 15 min; brine quench). The yield of analytically pure material was 72% [mp 88–90 °C dec (lit.[7] mp 90–92 °C dec)]. The key coupling reaction was carried out by adding **2** to an aqueous solution of L-histidine under conditions of carefully controlled pH (see Experimental Section for specific details). A reaction of this type can be quite impractical when the resulting product is very water soluble. The necessary pH manipulations (addition of aqueous NaOH solution during the reaction and subsequent acidification with 12 N HCl) generate substantial quantities of sodium chloride. In our initial studies we found that it was virtually impossible to isolate L-carnosine that was not contaminated with varying amounts of salt. The crude, salt-containing dipeptide was difficult to purify by recrystallization; such efforts inevitably resulted in seriously diminished yields. To solve this problem, we used tetraethylammonium hydroxide and formic acid in place of NaOH and HCl. Tetraethylammonium formate, obtained as the side product, is soluble in ethanol and can easily be separated from the desired L-carnosine as follows: Water is evaporated from the reaction mixture and replaced with ethanol. The $Et_4N^+HCO_2^-$ dissolves, and L-carnosine slowly crystallizes from solution. This methodology may be of general utility in the isolation of water-soluble peptides when isoelectric point pH adjustments must be made. Using this technique, we isolated a 79% yield of crude L-carnosine which was readily purified by recrystallization.

The above route to **3** is not only a highly efficient preparation of this interesting compound but also serves to illustrate the potential value of NTA's in peptide synthesis. Further studies are in progress.

Experimental Section

General Procedures. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer. NMR spectra were obtained with a Varian XL-100 or EM 360L spectrometer with Me_4Si as an internal standard. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. Microanalyses were performed by the Pfizer Analytical Department.

L-Carnosine (3). L-Histidine (6.2 g, 40 mmol) was stirred as a suspension at 0–5 °C in 60 mL of water. The pH was adjusted to 9.2 with 20% aqueous tetraethylammonium hydroxide, and **2** (10.5 g, 80 mmol) was added portionwise with vigorous stirring. Tetraethylammonium hydroxide was added as needed to maintain pH 8.7–9.2. After completion of the NTA addition, the mixture was stirred until the pH stabilized at 9.2 (1 h) and then acidified with 98% formic acid to pH 4.0–4.5.[9] The pH was adjusted to 8.2 (L-carnosine isoelectric pH) with tetraethylammonium hydroxide and the water evaporated in vacuo. The yellowish, gummy residue was stirred in 600 mL of absolute ethanol; fine white crystals formed, with were collected by filtration, washed with ethanol and then ether, and dried. The isolated yield of L-carnosine was 7.20 g (79%).

A sample of material was recrystallized from aqueous ethanol to give analytically pure **3**: mp 262 °C dec (lit.[5d] mp 260 °C dec); $[\alpha]^{25}_D$ +21.0° (*c* 1.5, H_2O) [lit.[5d] $[\alpha]^{25}_D$ +20.5° (*c* 2, H_2O)]; IR (KBr) 3174, 1639, 1575, 1563 cm^{-1}; ^1H NMR (D_2O) δ 2.64 (t, 2 H, *J* = 6 Hz), 3.04 (AB of ABX, 2 H, J_{AB} = 16 Hz), 3.20 (t, 2 H, *J* = 6 Hz), 4.44 (X of ABX, 1 H, $J_{AX} + J_{BX}$ = 14 Hz), 6.94 (s, 1 H), 7.70 (s, 1 H).

Anal. Calcd for $C_9H_{14}N_4O_3$: C, 47.78; H, 6.24; N, 24.76. Found: C, 47.32; H, 5.82; N, 24.55.

Registry No. **1**, 84040-82-4; **2**, 34653-21-9; **3**, 305-84-0; L-histidine, 71-00-1; β-alanine, 107-95-9; methyl ethylxanthate, 623-54-1.

(8) The NTA can be stored at 0 °C for indefinite periods of time; at 25 °C slow decomposition is observed.

(9) At pH 4.0–4.5 the protecting/activating group is released as COS gas.

Fluorinated Carbohydrates. Use of (Diethylamino)sulfur Trifluoride in the Synthesis of Fluorinated Sugars†

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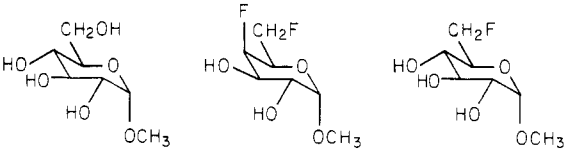
Fluorinated carbohydrates have been widely utilized in biochemical investigations (enzyme–carbohydrate interactions, etc.).[1-3] However, the synthesis of fluorinated sugars is both tedious and time consuming because of the requisite protection and deprotection steps.[4,5] As part of a program concerned with the synthesis of modified carbohydrates, we became interested in facile syntheses of fluorinated derivatives. In particular, we hope to synthesize specifically fluorinated carbohydrates, from unprotected or only partially protected substrates, by use of (diethylamino)sulfur trifluoride (DAST).[6] The simple and selective fluorination of methyl α-D-glucopyranoside presented here is an initial demonstration of this specificity. In addition, we also report preparations of methyl 4,6-dideoxy-4,6-difluoro-α-D-talopyranoside and methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-fluoro-α-D-glucopyranoside.

Somawardhana and Brunngraber[7] recently reported that methyl α-D-glucopyranoside (**1**) reacts with neat DAST to



1 **2** **3**

afford methyl 4,6-dideoxy-4,6-difluoro-α-galactopyranoside (**2**) in 60% yield. Sidhu[8] has also reported a similar observation. In contrast to these reports, we have found that treatment of a suspension of **1** in dichloromethane with 6 equiv of DAST, initially at −30 °C and then 1 h at room temperature, gave the monofluorinated product methyl 6-deoxy-6-fluoro-α-D-glucopyranoside[9] (**3**) in 70–88% yield (see Experimental Section). Only a trace of **2** was detected by thin-layer chromatography and use of longer reaction times did not significantly affect the yields of **2** or **3**. However, when added to neat DAST, **3** was cleanly converted into the difluoro derivative **2**. Compound **2** was identical in all respects with material prepared as previously reported.[7] Thus, use of dichloromethane as a reaction solvent instead of neat DAST allows for the selective monofluorination of **1**.

† Contribution no. 3097.

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