by distillation of the dichloromethane fraction from Florisil chromatography of the crude reaction mixture; bp 70 °C (1 mmHg). Pure **2** could be isolated by GC (10 ft × 0.25 in. column, 5% DEGS on Chromasorb P, 135 °C).

Acknowledgment. We are grateful to Professor R. G. Bergman for advice and encouragement. This research was supported by a grant from the National Institutes of Health (PHS GM26294).

Registry No. 1, 72200-41-0; 2, 39163-29-6; 4, 65909-92-4; 5, 65939-59-5; 6, 14548-31-3; lithiumacetylide-ethylenediamine complex, 39990-99-3; 5-chloro-1-pentene, 928-50-7; 6-chloro-1-hexene, 928-89-2.

N-Methylation of *O*-Benzyl N^{α}-(Alkoxycarbonyl) α-Amino Acid Hydroxamate Derivatives

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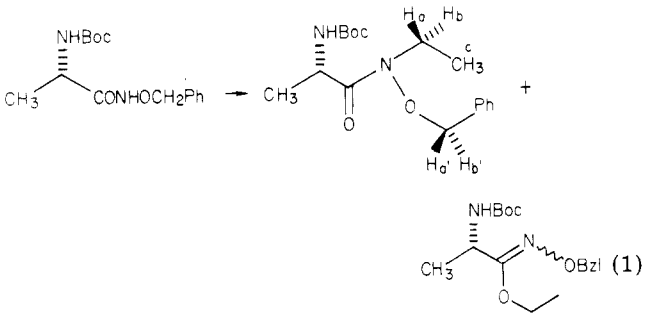
The hydroxamate group is an important functionality in several natural products and is especially prevalent in certain siderophores such as ferrichrome, where it plays a key role in the complexation of ferric ion by these substances.[1] Our interest in the synthesis of siderophore analogues made it desirable to be able to cleanly effect intermolecular N-alkylation of the hydroxamate function of α-amino acid hydroxamate derivatives.

Because of the enhanced acidity (pK_a = 6–10)[2-4] of the hydroxamate NH as compared to an amide or urethane NH group ($pK_a \approx 15$), it would be anticipated that selective N-alkylation should readily occur. The intermolecular N-alkylation by alkyl halides of hydroxamates of simple carboxylic acids has been reported,[5-7] though in some instances O-alkylation also has been observed. Intermolecular alkylation of hydroxamates with alcohols mediated by diethyl azodicarboxylate–triphenylphosphine gives mainly or entirely the O-alkylated product.[6,7b] Clean intramolecular alkylation on nitrogen has been reported[7] in the preparation of β-lactams from β-chloroalanine or serine and threonine hydroxamate derivatives.

The *O*-benzyl N^{α}-(alkoxycarbonyl) α-amino acid hydroxamates (**1**) used in this study were prepared by carbodiimide-mediated condensation of the appropriate N-protected α-amino acids with *O*-benzylhydroxylamine (Table I).[3]

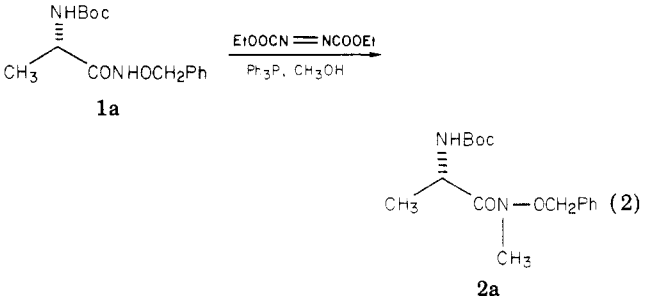
We have observed that *O*-benzyl N^{α}-(alkoxycarbonyl) α-amino acid hydroxamates (**1**) undergo N-methylation on the hydroxamate function with sodium hydride–methyl iodide in dimethylformamide–methylene chloride at 50 °C to form the desired product **2** (Table II). The reaction, if carried out at room temperature, was not complete after 20 h. Analysis of the ^{1}H NMR spectra of the crude reaction products did not show the presence of any O-alkylated product nor of any product resulting from N-methylation of the urethane nitrogen. The *O*-methyl peak would be expected[5,6] to occur at about δ 4.0, while that of the hydroxamate *N*-methyl resonance occurs in the region of δ 3.25 and the urethane N-methyl at about δ 2.8, as described below. We likewise did not observe, upon purification of the *N*-methylhydroxamates by preparative medium-pressure liquid chromatography, other O- or N-methylated products. It appears, therefore, that these products are not formed in the methylation reaction to any significant extent.

Clean N-alkylation of the hydroxamate function apparently is unique for methyl iodide as an alkylation agent. Alkylation of Boc-Ala-NHOBzl (**1a**) with ethyl iodide or benzyl bromide furnished a mixture of products in each case, from which we were able to isolate the *N*- and *O*-alkyl products. For the reaction with ethyl iodide (eq 1), the



N-ethyl and *O*-ethyl products were formed in an approximate ratio of 4:1. The 360-MHz ^{1}H NMR spectrum of the *N*-ethyl product was interesting in that each of the *O*-benzyl protons and the methylene protons of the *N*-ethyl group were nonequivalent. The benzylic protons occurred as an AB quartet centered at δ 4.9, while the *N*-ethyl methylene protons appeared as multiplets at δ 3.4 and 3.95. Decoupling of each of these multiplets caused, in turn, the triplet at δ 1.08 due to the ethyl CH_3 group to collapse to a doublet ($J_{ac} = J_{bc}$ = 7 Hz).

Reaction of **1a** with diethyl azodicarboxylate–triphenylphosphine and methanol provided the N-alkylated hydroxamate **2a** (eq 2) but in only 39% yield. It appears,



1a

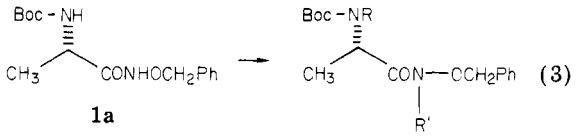
2a

therefore, that alkylation with methyl iodide in dimethylformamide–methylene chloride is the method of choice for preparation of these *N*-methylhydroxamate derivatives.

Methylation of **1a**, when carried out in tetrahydrofuran as the solvent and with 1 equiv of sodium hydride and methyl iodide, gave a low yield of alkylated product accompanied by recovered reactant. Use of 2 equiv each of base and methyl iodide gave an equal mixture of the N^{α}-methyl derivative **3** and N,N^{α}-dimethyl derivative **4** (eq 3). The ^{1}H NMR spectrum of **3** had an *N*-methyl peak at δ 2.83, while **4** had two *N*-methyl peaks at δ 2.93 and 3.23. The monoalkylated product in this case resulted from

(1) Emery, T. "Metal Ions in Biological Systems"; Sigel, H., Ed.; Marcel Dekker: New York, 1978; Vol. 7, p 77.
(2) Exner, D.; Simon, W. *Collect. Czech. Chem. Commun.* **1965**, *30*, 4078.
(3) Miller, M. J.; DeBons, F. E.; Loudon, G. M. *J. Org. Chem.* **1977**, *42*, 1750.
(4) Stolberg, M. A.; Tweit, R. C.; Steinberg, G. M.; Wagner-Jauregg, T. *J. Am. Chem. Soc.* **1955**, *77*, 765.
(5) Johnson, J. E.; Springfield, J. R.; Hwang, J. S.; Hayes, L. J.; Cunningham, W. C.; McClaugherty, D. L. *J. Org. Chem.* **1971**, *36*, 284.
(6) Maurer, P. J.; Miller, M. J. *J. Org. Chem.* **1981**, *46*, 2835.
(7) (a) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026. (b) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. *Ibid.* **1981**, *103*, 2909.

0022-3263/81/1946-5438$01.25/0



1a (3)

3, R = Me; R' = H
4, R = R' = Me

N-methylation at the less acidic, but presumably more reactive, urethane function; this parallels the known N-methylation of the urethane amide nitrogen with sodium hydride–methyl iodide in tetrahydrofuran without methylation of the carboxylate function in N-protected α-amino acids.[8] It is apparent that in tetrahdyrofuran as the solvent, methylation at the hydroxamate nitrogen is slow compared to the rate of methylation at the urethane function. In contrast to the above results, methylation with 2 equiv each of sodium hydride and methyl iodide in dimethylformamide–methylene chloride gave the dialkylated product **4** in 92% yield.

Compounds **2a**, **3**, and **4** also were prepared by independent syntheses as outlined in Scheme I. *O*-Benzyl-*N*-methylhydroxylamine (**5**) was prepared from *O*-benzylhydroxylamine by a sequence of reactions that involved introduction of the *N*-*tert*-butoxycarbonyl (Boc) group, followed by N-methylation and removal of the Boc function. Coupling of **5** with Boc-Ala-OH (**6**) furnished **2a**. N-Methylation of **6** giave the known[8] Boc-MeAla-OH (**7**), which upon reaction with **5** gave the dimethyl derivative **4**. Condensation of **7** with *O*-benzylhydroxylamine furnished **3**. ^{1}H NMR and TLC comparison of **2a**, **3**, and **4** established these to be identical with the respective compounds prepared by N-methylation.

Experimental Section

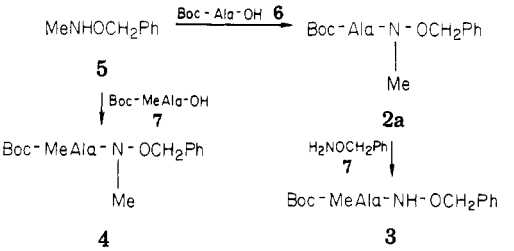
The N-protected L-amino acids and coupling reagents used in this study were commercially available. Tetrahydrofuran was distilled prior to use from sodium benzophenone ketyl. Methylene chloride was distilled from phosphorous pentoxide and stored over Linde 3A molecular sieves. Dimethylformamide was distilled from calcium hydride.

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-360 spectrometer and, in certain instances, on a Nicolet NT-360 spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 automatic polarimeter. Thin-layer chromatography was performed on commerical silica gel on glass plates (1 × 3 in.) developed in hexane–acetone (7:3). Medium-pressure liquid chromatography (MPLC) was performed at 60–100 psi on glass columns packed with silica gel 60 (0.040–0.063 mm). Satisfactory combustion analyses (C, H, and N within ±0.4% of theory) were obtained for all new compounds.

General Procedure for the Preparation of Hydroxamates. To a stirred solution of *O*-benzylhydroxylamine (5–10 mmol) and the *N*-Boc or *N*-Cbz α-amino acid (5–10 mmol) in 50 mL of THF/H_2O (1:4) cooled to 0 °C was added 7–12 mmol of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI). The reaction mixture was stirred at 0 °C for 3 h and at room temperature overnight. The solvent was removed under reduced pressure to give an oil, which was dissolved in EtOAc, washed with saturated $NaHCO_3$, H_2O, and brine, and dried over Na_2SO_4. The residue obtained upon evaporation of the solvent was subjected to chromatography or recrystallization.

General Procedure for N-Methylation of Hydroxamates. An equimolar ratio of a 50% dispersion of sodum hydride (2–5 mmol) was added, in portions, to a solution of hydroxamate (2–5 mmol) and methyl iodide (2–5 mmol) in dry DMF/CH_2Cl_2 (1:1, 20 mL) at room temperature. After the addition of NaH, the reaction temperature was raised to 50 °C, and the reaction mixture was stirred at 50 °C for 12 h. The reaction mixture was cooled and the solvent evaporated under reduced pressure. The residue was acidified with dilute HCl and extracted with EtOAc. The organic extract was washed with water and brine and dried (Na_2SO_4), and the solvent was evaporated in vacuo. The product obtained was purified by using MPLC with elution by hexane–acetone (7:3).

Scheme I



***O*-Benzyl N^{α}-(*tert*-Butoxycarbonyl)-N^{α}-methyl-L-alaninehydroxamate (3).** L-Alaninehydroxamate **1a** (1.5 g, 5 mmol) and CH_3I (1.4 g, 10 mmol) were cooled to 0 °C in dry THF (50 mL). To this cooled, stirred solution was added NaH (10 mmol) in small portions. After the addition of NaH, the reaction mixture was stirred for 1 h at 0 °C and at room temperature overnight. Ethyl acetate (10 mL) and water (5 mL) were added, and the mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate, washed with water and brine, and dried (Na_2SO_4), and the solvent was removed under reduced pressure. Two products, **3** (0.55 g, 35%; mp 91–92 °C) and **4** (0.5 g, 31%), were separated on chromatography with hexane/acetone (7:3) as the eluant. For **3**: ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9 H, Boc), 2.83 (s, 3 H, NCH_3), 4.96 (s, 2 H, CH_2Ph), 7.48 (s, 5 H, phenyl), 9.28 (br s, 1 H, NH). Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.84; N, 9.08. Found: C, 62.36; H, 7.90; N, 8.92.

Methylation of 1a with Methanol–Diethyl Azodicarboxylate–Triphenylphosphine. A mixture of **1a** (0.6 g, 2 mmol), diethyl azodicarboxylate (0.35 g, 2 mmol), triphenylphosphine (0.52 g, 2 mmol), and 0.2 mL of methanol in 20 mL of dry THF was stirred at room temperature for 20 h and concentrated in vacuo. The residue was dissolved in chloroform, washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was chromatographed over silica with hexane/acetone (7:3) as the eluant. Product **2a** (0.25 g, 39.7%) was crystallized from hexane/acetone; mp 78–80 °C.

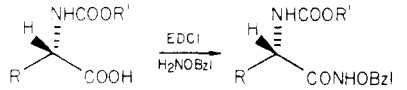
***O*-Benzyl *N*-Methyl-N^{α}-(*tert*-butoxycarbonyl)-N^{α}-methyl-L-alaninehydroxamate (4).** Sodium hydride (0.14 g, 6 mmol) was added in several portions to a stirred solution of **1a** (0.83 g, 3 mmol) and CH_3I (0.85 g, 6 mmol) in 30 mL of dry DMF/CH_2Cl_2 (1:1) at room temperature. The temperature of the reaction mixture was raised to 50 °C, and it was stirred at that temperature for 12 h. The reaction mixture was cooled and treated with ethyl acetate (10 mL) and water (5 mL), and the solvent was evaporated to dryness. The residue was dissolved in ethyl acetate, washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The oil (**4**) obtained was purified by using MPLC with elution by hexane/acetone (7:3): yield 0.84 g (92%); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H, Boc), 2.93 (s, 3 H, NCH_3), 3.23 (s, 3 H, NCH_3), 5.00 (s, 2 H, CH_2Ph), 7.5 (s, 5 H, phenyl). Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.36; H, 8.13; N, 8.69. Found: C, 63.32; H, 8.43; N, 8.67.

***N*-(*tert*-Butoxycarbonyl)-*O*-benzylhydroxylamine.** Di-*tert*-butyl dicarbonate (3.3 g, 18 mmol) was added to an ice-cold (0 °C), stirred solution of *O*-benzylhydroxylamine (1.6 g, 15 mmol) in dioxane/water (2:1, 30 mL), and the mixture was stirred at room temperature for 30 min. The dioxane was evaporated under reduced pressure, and the aqueous solution, at 0 °C, was mixed with ethyl acetate (50 mL) and acidified to pH 2–3 with dilute potassium hydrogen sulfate. The separated water phase was extracted twice with EtOAc, the combined extracts were washed with water and dried (Na_2SO_4), and the solvent was removed. The oil obtained was chromatographed over silica with hexane/acetone (7:3): yield 1.47 g (51%); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9 H, Boc), 4.9 (s, 2 H, CH_2Ph), 7.45 (s, 5 H, phenyl).

***N*-(*tert*-Butoxycarbonyl)-*N*-methyl-*O*-benzylhydroxylamine.** To an ice-cold solution of *N*-(*tert*-butoxycarbonyl)-*O*-

(8) Cheung, S. T.; Benoiton, J. L. *Can. J. Chem.* **1977**, *55*, 906.

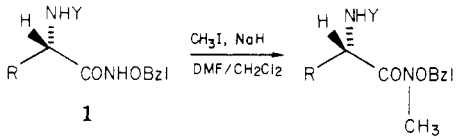
Table I. Preparation of *O*-Benzyl N^{α}-(Alkoxycarbonyl) α-Amino Acid Hydroxamates (1)



substrate	product	mp,[a] °C	yield,[b] %	$[\alpha]^{25}_D$ (c 1, $CHCl_3$), deg
N-Boc-L-alanine	1a	93-95 (AB)	72	−58.3
N-Cbz-L-alanine	1b	153-154 (C)	67	−36.5
N-Boc-L-valine	1c	123-124.5 (AB)	71	−37.6
N-Boc-*O*-Bzl-L-serine	1d	76-77 (A)	82	+13.7
N-Boc-β-Bzl-L-aspartic acid	1e	123-125 (A)	79	−13.2
N-Boc-γ-Bzl-L-glutamic acid	1f	114-115 (AB)	91	−26.5

[a] Recrystallization solvent: A, hexane; B, acetone; C, ethyl acetate. [b] Yields given are for recrystallized product.

Table II. Preparation of *O*-Benzyl *N*-Methyl-N^{α}-(alkoxycarbonyl) α-Amino Acid Hydroxamates (2)



1 2

compd[a]	Y	R	yield,[b] %	$[\alpha]^{25}_D$, deg	^{1}H NMR (in $CDCl_3$), δ
2a	Boc	CH_3	82	+29.5 (c 1, $CHCl_3$)	1.45 (s, 9 H, Boc), 3.26 (s, 3 H, NCH_3), 4.27 (q, 1 H, α-H), 5.01 (s, 2 H, CH_2Ph), 5.51 (d, 1 H, NH), 7.48 (s, 5 H, phenyl)
2b	Cbz	CH_3	84	+31.0 (c 1, $CHCl_3$)	1.33 (d, 3 H, CH_3), 3.23 (s, 3 H, NCH_3), 4.66 (m, 1 H, α-H), 5.00 (s, 2 H, CH_2Ph), 5.16 (s, 2 H, CH_2Ph), 5.85 (d, 1 H, NH), 7.46 (d, 10 H, phenyl)
2c	Boc	*i*-Pr	82	+31.1 (c 1, $CHCl_3$)	0.93 (d, 6 H, CH_3), 1.40 (s, 9 H, Boc), 2.1 (m, 1 H, methine), 3.23 (s, 3 H, NCH_3), 4.73 (m, 1 H, α-H), 4.96 (s, 2 H, CH_2Ph), 5.33 (d, 1 H, NH), 7.46 (s, 5 H, phenyl)
2d	Boc	CH_2OBzl	78	+14.3 (c 1, $CHCl_3$)	1.46 (s, 9 H, Boc), 3.26 (s, 3 H, NCH_3), 3.70 (m, 2 H, CH_2), 4.53 (s, 2 H, CH_2Ph), 4.83 (m, 1 H, α-H), 4.96 (s, 2 H, CH_2Ph), 5.53 (d, 1 H, NH), 7.41 (d, 10 H, phenyl)
2e	Boc	CH_2CO_2Bzl	76	+19.7 (c 1.5, $CHCl_3$)	1.45 (s, 9 H, Boc), 2.73 (m, 2 H, CH_2), 3.21 (s, 3 H, NCH_3), 4.63 (m, 1 H, α-H), 4.96 (s, 2 H, CH_2Ph), 5.13 (s, 2 H, CH_2Ph), 7.41 (s, 10 H, phenyl)
2f	Boc	$(CH_2)_2CO_2Bzl$	80	+12.8 (c 1, $CHCl_3$)	1.43 (s, 9 H, Boc), 2.00 (m, 2 H, CH_2), 2.51 (m, 2 H, CH_2), 3.23 (s, 3 H, NCH_3), 4.83 (m, 1 H, α-H), 4.96 (s, 2 H, CH_2Ph), 5.08 (s, 2 H, CH_2Ph), 7.43 (d, 10 H, phenyl)

[a] All compounds were obtained as oils except **2a**, which has a melting point of 78-80 °C. [b] Yields reported are those for purified product obtained after MPLC on silica gel; see the Experimental Section for general procedure.

benzylhydroxylamine (3.58 g, 15 mmol) and CH_3I (3 mL) in dry THF (50 mL) was added NaH (1.2 g) in small portions. After the addition of NaH, the reaction mixture was stirred at 0 °C for 1 h and at room temperature overnight. Ethyl acetate (20 mL) and water (10 mL) were added, and the mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate, washed with water, sodium thiosulfate, and brine, dried (Na_2SO_4), and concentrated to give product: 3.6 g (94%); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9 H, Boc), 3.06 (s, 3 H, NCH_3), 4.9 (s, 2 H, CH_2Ph), 7.45 (s, 5 H, phenyl).

***N*-Methyl-*O*-benzylhydroxylamine (5).** *N*-(*tert*-Butoxycarbonyl)-*N*-methyl-*O*-benzylhydroxylamine (4.6 g) was dissolved in anhydrous TFA (6 mL), stirred at room temperature for 30 min, and concentrated to a viscous residue. The residue was dissolved in ether, washed with saturated $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated to an oil: 2.2 g (82%); ^{1}H NMR ($CDCl_3$) δ 2.66 (s, 3 H, NCH_3), 4.7 (s, 2 H, CH_2Ph), 5.03 (d, 1 H, NH), 7.35 (s, 5 H, phenyl).

***O*-Benzyl *N*-Methyl-N^{α}-(*tert*-Butoxycarbonyl)-L-alaninehydroxamate (2a).** *N*-(*tert*-Butoxycarbonyl)alanine (0.47 g, 2.5 mmol) and *N*-methyl-*O*-benzylhydroxylamine (0.34 g, 2.5 mmol) were dissolved in dry CH_2Cl_2 (50 mL), and the mixture was cooled to 0 °C. To this cooled solution was added *N*,*N*′-dicyclohexylcarbodiimide (DCC; 0.5 g, 2.5 mmol), and the mixture was stirred at 0 °C for 3 h and at room temperature overnight. The precipitated solid was filtered, and the solvent was removed under vacuo. The residue was dissolved in EtOAc and washed with saturated $NaHCO_3$, H_2O, citric acid (5%), water, and brine. The organic extract, after being dried (Na_2SO_4), was removed under reduced pressure. The oil obtained was chromatographed over silica with hexane–acetone (7:3) to give **2a**: 0.3 g (39%); colorless crystals; mp 78–80 °C. This material was identical (NMR, melting point, TLC) with **2a** prepared by methylation.

***O*-Benzyl *N*-Methyl-N^{α}-(*tert*-Butoxycarbonyl)-N^{α}-methyl-L-alaninehydroxamate (4).** To an ice-cold solution of N^{α}-(*tert*-butoxycarbonyl)-N^{α}-methyl-L-alanine[8] (0.5 g, 2.5 mmol) and **5** (0.34 g, 2.5 mmol) in dry CH_2Cl_2 (30 mL) was added DCC (0.5 g, 2.5 mmol), and the mixture was stirred at 0 °C for 4 h and at room temperature overnight. The solid was filtered and the solvent removed under vacuo. The residue was dissolved in EtOAc, washed with aqueous $NaHCO_3$, H_2O, and citric acid (5%), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified on chromatography with hexane–acetone (7:3) as the eluant to yield **4**, 0.21 g (27%). This material was identical (TLC, NMR) with **4** prepared by methylation.

***O*-Benzyl N^{α}-(*tert*-Butoxycarbonyl)-N^{α}-methyl-L-alaninehydroxamate (3).** *N*-(*tert*-Butoxycarbonyl)-*N*-methyl-L-alanine (2.03 g, 10 mmol) and *O*-benzylhydroxylamine (1.23 g, 10 mmol) were dissolved in 20 mL of THF/H_2O (1:4), and the mixture was cooled to 0 °C. To this cooled solution was added EDCI (2.8 g, 15 mmol), and the mixture was stirred at 0 °C for 3 h and at room temperature overnight. The mixture was concentrated to an oil, extracted with ethyl acetate, and washed with saturated $NaHCO_3$ and brine. The organic extract, after being

dried (Na_2SO_4), was evaporated to an oily product. This oil, on chromatography over silica with hexane–acetone (7:3), gave **3**: 2.1 g (68%); mp 91–92 °C; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H, Boc), 2.81 (s, 3 H, NCH_3), 4.95 (s, 2 H, CH_2Ph), 7.38 (s, 5 H, phenyl), 10.05 (br s, 1 H, NH).

Acknowledgment. We express appreciation to the National Institutes of Health (General Medical Sciences, Grant GM 26711) for support of this research and to the Colorado State University Regional NMR Center, funded by National Science Foundation Grant No. CHE 78-18581, for 360-MHz NMR spectra.

Registry No. 1a, 79722-09-1; **1b**, 27786-77-2; **1c**, 79722-10-4; **1d**, 79722-11-5; **1e**, 79722-12-6; **1f**, 79722-13-7; **2a**, 79722-14-8; **2b**, 79722-15-9; **2c**, 79722-16-0; **2d**, 79722-17-1; **2e**, 79722-18-2; **2f**, 79722-19-3; **3**, 79735-23-2; **4**, 79722-20-6; **5**, 22513-22-0; **7**, 16948-16-6; *O*-benzylhydroxylamine, 622-33-3; *N*-(*tert*-butoxycarbonyl)-*O*-benzylhydroxylamine, 79722-21-7; di-*tert*-butyl carbonate, 34619-03-9; *N*-(*tert*-butoxycarbonyl)-*N*-methyl-*O*-benzylhydroxylamine, 79722-22-8; *N*-Boc-L-alanine, 15761-38-3; *N*-Cbz-L-alanine, 1142-20-7; *N*-Boc-L-valine, 13734-41-3; *N*-Boc-*O*-bzl-L-serine, 23680-31-1; *N*-Boc-β-bzl-L-aspartic acid, 7536-58-5; *N*-Boc-γ-bzl-L-glutamic acid, 13574-13-5.

Convenient Routes to 4,4″-Functionalized *o*-Terphenyls and 2,2′-Functionalized Biphenyls

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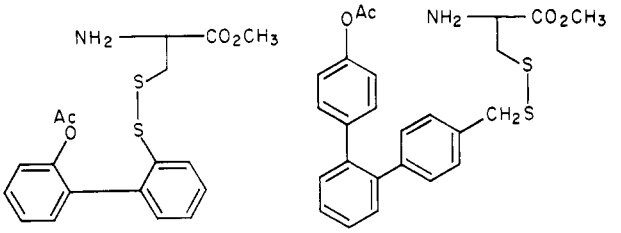
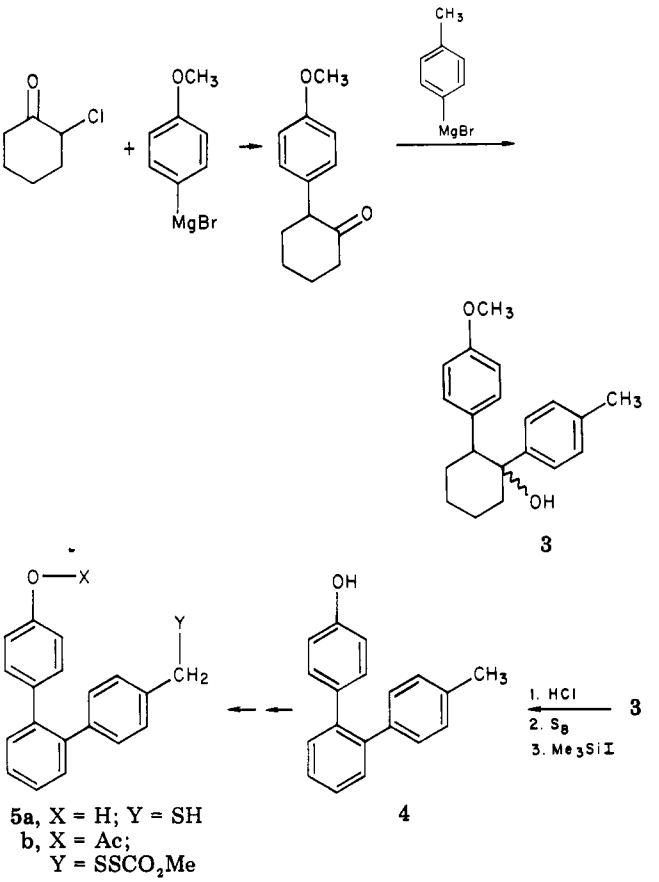
Elsewhere[1,2] we have described a thiol capture strategy for the amide bond-forming step of peptide synthesis and have reported a successful first test of the strategy in the form of a synthesis of a protected derivative of the peptide hormone somatostatin.[3] A key step in the thiol capture process involves an intramolecular acyl transfer involving a medium-sized ring containing a disulfide or a sulfur–mercury bond. Efficient transfer has been shown[2] to require precise geometries, and we here report synthesis of two molecular frameworks, **1** and **2**, which fail to undergo detectable intramolecular acyl transfer and therefore do not meet the geometrical requirements. The syntheses of these species required new routes to functionalized 2,2′-substituted biphenyls and 4,4″-substituted *o*-terphenyls, and these are here reported.



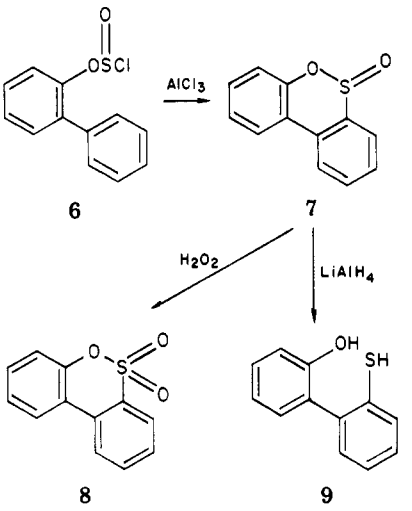
1 2

Although various derivatives of the *o*-terphenyl ring system have been reported, few are known in which both terminal rings are functionalized. Useful synthetic entries

Scheme I



Scheme II



are 2-arylcyclohexanones, reported by Bachmann[4] to result conveniently from the reactions of aryl Grignard reagents with 2-chlorocyclohexanone. Our reaction sequence is outlined in Scheme I.

The dehydrogenation step proceeded satisfactorily only with sulfur fusion; palladium catalysts in our hands resulted in erratic and scale-dependent yields, and also formed the hydrogenolysis product of **3** as a byproduct that was difficult to remove. Subsequent functionalization of the dehydrogenation product followed routine paths. Demethylation with trimethylsilyl iodide gave **4**; acetylation followed by bromination (NBS), and treatment with

(1) Kemp, D. S.; Kerkman, D. J.; Hanson, G.; Leung, S.-L. *J. Org. Chem.* **1981**, *46*, 490. Kemp, D. S.; Kerkman, D. J.; Leung, S.-L. *Tetrahedron Lett.* **1981**, *22*, 181.
(2) Kemp, D. S. *Biopolymers* **1981**, *20*, 1793.
(3) Kemp, D. S.; Galakatos, N.; Bolin, D. "Proceedings of the 7th American Peptide Symposium", Pierce Chemical Co., in press.
(4) Bachmann, W. F.; Fujimoto, G. I.; Nick, L. B. *J. Am. Chem. Soc.* **1950**, *72*, 1995.

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