All the compounds were commercial, of the highest purity available, dried, and further purified by standard methods. Structures were confirmed by their IR and NMR spectra. Purities were checked by GLC and or TLC. The origin and treatment of c-C_6H_{12} and PyO have also been described.[7]

Acknowledgment. We are grateful to Prof. P. Kebarle (University of Alberta, Edmonton, Canada) for providing a number of unpublished results. Work by J.-L.M.A. was supported by Grant PB87-0357 from CICYT. This work is dedicated in memoriam to Dr. Mortimer J. Kamlet.

Registry No. C_6H_5OH, 108-95-2; 4-FC_6H_4OH, 371-41-5; 4-ClC_6H_4OH, 106-48-9; 3-$(CO_2CH_3)C_6H_4OH$, 19438-10-9; C_6F_5OH, 771-61-9; C_2H_5SH, 75-08-1; n-C_3H_7SH, 107-03-9; i-C_3H_7SH, 75-33-2; t-C_4H_9SH, 75-66-1; C_6H_5CCH, 536-74-3; CH_2Cl_2, 75-09-2; Cl_3CH, 67-66-3; $HCONHCH_3$, 123-39-7; $CF_3CONHC_6H_5$, 404-24-0; Cl_3CCH_2OH, 115-20-8; PyO, 694-59-7; pyrrole, 109-97-7; pyrazole, 288-13-1; 3-methylpyrazole, 1453-58-3; 4-methylpyrazole, 7554-65-6; 3,5-dimethylpyrazole, 67-51-6; 3,4,5-trimethylpyrazole, 5519-42-6; 4-bromopyrazole, 2075-45-8; 3-methyl-4-bromopyrazole, 13808-64-5.

(12) This is in line with recent reports on the acidity and basicity of azoles, both in the gas phase and in solution (see, e.g.: Catalán, J.; Abboud, J.-L. M.; Elguero, J. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1987; Vol. 41, pp 187-274).

An Improved One-Pot Method for the Stereoselective Synthesis of the (2*S*,3*R*)-3-Amino-2-hydroxy Acids: Key Intermediates for Bestatin and Amastatin

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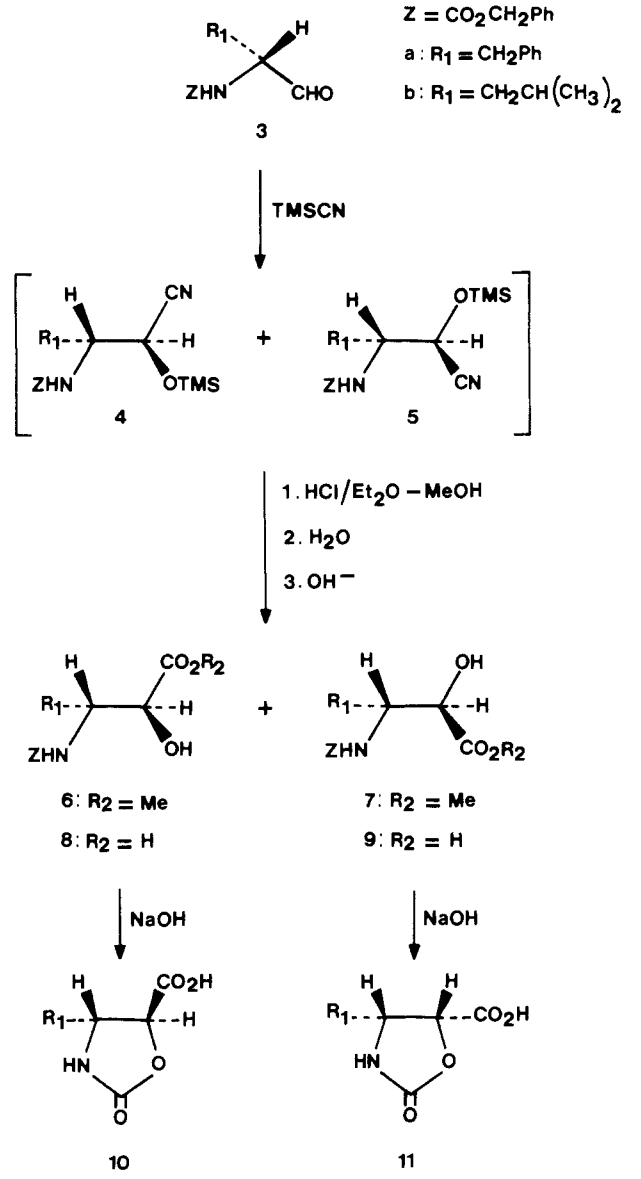
Bestatin (1), an aminopeptidase B and leucine-aminopeptidase inhibitor,[1] and amastatin (2), an aminopeptidase A inhibitor,[2] are two low molecular weight peptidic immunomodifiers,[3-6] with antitumor and antimicrobial activities.[7] The presence and absolute configurations of the (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid [(2*S*,3*R*)-AHPBA] and (2*S*,3*R*)-3-amino-2-hydroxy-5-methylhexanoic acid [(2*S*,3*R*)-AHMHA] residues in **1** and **2**, respectively, are crucial for their bioactivities. Among the several methods reported for the preparation of AHPBA and AHMHA, key intermediates for the preparation of **1** and **2**, that involving aqueous hydrolysis of the cyanohydrin, obtained from the corresponding N-protected α-amino aldehyde, has been the most extensively used.[8,9]

Scheme I



However, this method is not stereoselective, and, as deprotection occurs during hydrolysis, a protection step is required to separate the resulting diastereomers, and to form the peptidic bond. Therefore, the overall yield of N-protected AHPBA or AHMHA is low (<30%). Other methods give either (2*S*,3*R*)-*N*-Z-AHPBA (Z = benzyloxycarbonyl) stereoselectively, but in low overall yield (14%),[10] or as a racemic mixture of the threo[11,12] isomers of AHPBA in less than 30%.

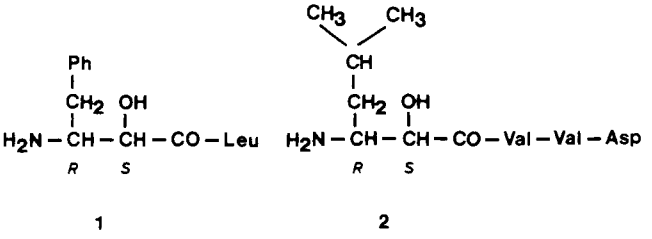


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Table I. Different Reaction Conditions Used in the Cyanohydrin Formation Step

entry	aldehyde	reagent (solvent)	temp, °C/time, h	% yield (6 + 7)[a]	6:7 ratio[b]
1	**3a**	TMSCN (CH_2Cl_2)	−20/5	0	
2	**3a**	TMSCN (CH_2Cl_2)	20/0.5	56	2.5:1
3	**3a**	TMSCN (CH_2Cl–CH_2Cl)	80/5	59	4:1
4	**3a**	TMSCN (CH_2Cl_2)	20/20 days	80	4.3:1
5	**3b**	TMSCN (CH_2Cl_2)	20/0.5	32	2.3:1
6	**3b**	TMSCN (CH_2Cl–CH_2Cl)	80/5	60	3.4:1
7	**3b**	TMSCN (CH_2Cl_2)	20/20 days	75	4:1
8	**3a**	TMSCN/$SnCl_4$ (CH_2Cl_2)	−10/2	70	3.5:1
9	**3a**	TMSCN/BF_3·OEt_2 (CH_2Cl_2)	−10/2	70	1:1

[a] Overall yield from **3**. [b] Due to the overlapping of signals, the diastereomeric ratio of cyanohydrins could not be determined in the 300-MHz ^1H NMR spectra of the mixtures.

Now, we have developed a one-pot procedure for the stereoselective synthesis of (2*S*,3*R*)-Z-AHPBA and (2*S*,3*R*)-Z-AHMHA consisting of reaction of the corresponding *N*-Z-amino aldehyde with (trimethylsilyl)cyanide (TMSCN), followed by hydrolysis of the cyano group via the intermediate imidate hydrochloride. This easy method, which does not require deprotection–protection steps, leads to the desired threo 3-amino-2-hydroxy acids in good yield (60%).

As outlined in the Scheme I, reaction of the amino aldehyde **3**, freshly prepared,[13] free of racemization and side products, by $LiAlH_4$ reduction of the corresponding *N*-methoxy-*N*-methylcarboxamides[14] with TMSCN, under several reaction conditions (Table I) gave a mixture of the threo and erythro *O*-(trimethylsilyl)cyanohydrins **4** and **5**, which could not be separated. This mixture was directly transformed into the corresponding 2-hydroxy esters **6** and **7** by treatment with dry methanolic hydrogen chloride (3:1 Et_2O/MeOH, saturated with HCl, 0 °C, 24 h), followed by in situ hydrolysis (<10 °C, 24–48 h)[15] of the imidate hydrochloride intermediate. The methyl esters **6** and **7** were separated by flash chromatography and saponified (NaOH, dioxane–water) to provide the acids **8** and **9**, respectively. The C-2 configuration of these compounds was unequivocally established on the basis of the ^1H NMR spectrum of the corresponding oxazolidones,[16] obtained by treatment of **6** and **7** with NaOH in methanol. Thus, the threo isomers **6** gave **10** with a H_4, H_5 disposition trans, as indicated by their *J* value of 4.5 Hz, while the erythro isomers **7** gave **11** with a $J_{(H_4,H_5)}$ value of 9 Hz, consistent with a cis disposition. Similarly, the (2*R*,3*S*) and (2*S*,3*S*) enantiomers of **8** and **9** were obtained from the corresponding N-Z-protected L-amino acids.

As the cyanohydrin formation is the determinant step for stereoselectivity, the influence of different reaction conditions on this step was studied (Table I). As shown in the table, the best results in yield and stereoselectivity were obtained using either high temperature (80 °C, entries 3 and 6), or prolonged reaction time (20 h, entries 4 and 7). While our study was in progress, the cyanohydrin-forming reaction of α-*N*,*N*-dibenzylamino aldehydes with TMSCN, using Lewis acids to control the stereoselectivity, was reported.[17] Therefore, we also studied the influence of Lewis acids on the cyanohydrin formation using $SnCl_4$ (1 equiv) and BF_3·OEt_2 (2 equiv) (entries 8 and 9). It has been reported that the employment of the former generally leads to chelation-controlled threo adducts,[17,18] while the utilization of the latter preferentially provides the nonchelation-controlled erythro isomers.[17,18] However, in our case, $SnCl_4$ did not increase the threo:erythro ratio, and BF_3·OEt_2 led to a total loss of stereoselectivity.

In conclusion, the method here reported, involving the combination of the use of TMSCN, and the hydrolysis of the cyano group through the imidate hydrochloride, improves significantly the stereoselectivity and the yield of (2*S*,3*R*)-AHPBA and (2*S*,3*R*)-AHMHA. We are presently engaged in the extension of this method to the preparation of other threo 3-amino-2-hydroxy acids incorporated into bestatin and amastatin analogues, whose synthesis and biological data will be reported elsewhere.

Experimental Section

All reagents were of commercial quality. Solvents were dried and purified by standard methods. Analytical TLC was performed on aluminium sheets coated with a 0.2-mm layer of silica gel 60 F_{254}, Merck. Silica gel 60 (230–400 mesh), Merck, was used for flash chromatography. Melting points were taken using a Reichert-Jung Kofler micro hot stage apparatus and are uncorrected. Microanalyses were obtained using a Heareus CHN-O-RAPID instrument. Optical rotations were determined with a Perkin-Elmer 141 polarimeter at Hg-578 line and at 25 °C, in order to compare with reported data.[8] ^1H NMR spectra were recorded with a Varian EM-390 (90 MHz) and a Varian XL-300 (300 MHz) spectrometers, using Me_4Si as internal standard.

General Procedure for the Synthesis of 3-(*N*-(Benzyloxycarbonyl)amino)-2-hydroxy Methyl Esters 6a, 6b, 7a, and 7b. A mixture of optically pure 2-*N*-(benzyloxycarbonyl)-D-amino aldehyde **3a** or **3b** (5 mmol), obtained in 90% yield from the corresponding 2-*N*-(benzyloxycarbonyl)-D-amino acid,[14] and TMSCN (0.75 mL, 6 mmol) in dry dichloromethane or 1,2-dichloroethane (30 mL) was stirred under different reaction conditions (Table I). Then the reaction mixture was evaporated, and the crude mixture of *O*-(trimethylsilyl)cyanohydrins **4** and **5** was dissolved in a dry and cooled 3:1 Et_2O/MeOH mixture, previously saturated with HCl (70 mL). This solution was stirred below 5 °C for 24 h, then, keeping the temperature below 10 °C, ice water (15 mL) was added, and the stirring was kept at this temperature for 24–48 h [until the disappearance of the imidate intermediate was detected by TLC (5:1, $CHCl_3$–MeOH)]. The reaction mixture was concentrated (10 mL) and extracted with dichloromethane (3 × 50 mL). The organic extracts were washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, and evaporated to yield a crude mixture of the methyl esters **6** and **7**, which were separated by flash chromatography with a 5:1 hexane–ethyl acetate mixture as eluent, in the ratio and yield indicated in Table I. The threo compounds **6** moved a little faster than the corresponding erythro **7**.

(2*S*,3*R*)-3-(*N*-(Benzyloxycarbonyl)amino)-2-hydroxy-4-phenylbutanoic Acid Methyl Ester (6a). From **3a**: mp 94–95 °C (EtOAc–hexane); $[\alpha]^{25}_{578}$ +82° (*c* 0.81, MeOH); ^1H NMR ($CDCl_3$) δ 2.95 (m, 2 H, CH_2Ph), 3.70 (s, 3 H, CH_3), 4.10 (d, 1 H, *J* = 1.8 Hz, C_2-H), 4.34 (m, 1 H, C_3-H), 5.05 (s, 2 H, OCH_2), 5.19 (d, 1 H, *J* = 9.5 Hz, NH), 7.24–7.36 (m, 10 H, Ph). Anal. Calcd

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for $C_{19}H_{21}NO_5$: C, 66.47; H, 6.12; N, 4.08. Found: C, 66.36; H, 6.18; N, 4.33.

(2*R*,3*R*)-3-(*N*-(Benzyloxycarbonyl)amino)-2-hydroxy-4-phenylbutanoic Acid Methyl Ester (7a). From **3a**: mp 121-122 °C (EtOAc-hexane); $[\alpha]^{25}_{578}$ +6° (*c* 0.98, MeOH); ^{1}H NMR ($CDCl_3$) δ 2.80 (m, 2 H, CH_2Ph), 3.56 (s, 3 H, CH_3), 4.34 (d, 1 H, *J* = 2.9 Hz, C_2-H), 4.40 (m, 1 H, C_3-H), 5.05 (s, 2 H, OCH_2), 5.14 (d, 1 H, *J* = 9 Hz, NH), 7.18-7.63 (m, 10 H, Ph). Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.47; H, 6.12; N, 4.08. Found: C, 66.50; H, 6.09; N, 4.15.

(2*S*,3*R*)-3-(*N*-(Benzyloxycarbonyl)amino)-2-hydroxy-5-methylhexanoic Acid Methyl Ester (6b). From **3b**: mp 75-76 °C (EtOAc-hexane); $[\alpha]^{25}_{578}$ +57° (*c* 1, MeOH); ^{1}H NMr ($CDCl_3$) δ 0.93 (d, 3 H, *J* = 6.5 Hz, $CHCH_3$), 1.40-1.52 (m, 2 H, C_4-H), 1.63 (m, 1 H, C_5-H), 3.72 (s, 3 H, CH_3), 4.14 (m, 2 H, C_2-H and C_3-H), 5.04 (s, 2 H, OCH_2), 5.10 (d, 1 H, *J* = 10 Hz, NH), 7.30 (m, 5 H, Ph). Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.14; H, 7.44; N, 4.53. Found: C, 62.23; H, 7.50; N, 4.62.

(2*R*,3*R*)-3-(*N*-(Benzyloxycarbonyl)amino)-2-hydroxy-5-methylhexanoic Acid Methyl Ester (7b). From **3b**: mp 64-65 °C (EtOAc-hexane); $[\alpha]^{25}_{578}$ +10° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 6 H, *J* = 6.5 Hz, $CHCH_3$), 1.29-1.56 (m, 2 H, C_4-H), 1.64 (m, 1 H, C_5-H), 3.81 (s, 3 H, CH_3), 4.16 (m, 1 H, C_3-H), 4.37 (d, 1 H, *J* = 3 Hz, C_2-H), 5.08 (d, 1 H, *J* = 10 Hz, NH), 5.12 (s, 2 H, OCH_2), 7.36 (m, 5 H, Ph). Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.14; H, 7.44; N, 4.53. Found: C, 61.98; H, 7.60; N, 4.71.

General Procedure for the Synthesis of 3-(*N*-(Benzyloxycarbonyl)amino)-2-hydroxy Acids 8a, 8b, 9a, and 9b. To a solution of the methyl esters **6a,b** or **7a,b** (2 mmol), in a 1:1 dioxane-water mixture (50 mL) was added NaOH (2.4 mmol; 1.2 equiv), and the mixture was stirred at room temperature for 1 h. Then the reaction mixture was concentrated (~20 mL), diluted with water (40 mL), and extracted with dichloromethane (3 × 40 mL). The aqueous phase was acidified to pH 3-4 with Dowex 50W-X4 resin. The resin was filtered and washed with dichloromethane (50 mL). The aqueous phase was extracted with dichloromethane (3 × 50 mL), and the organic extracts were dried over Na_2SO_4 and evaporated to give quantitatively the corresponding 3-(*N*-(benzyloxycarbonyl)amino)-2-hydroxy acids **8a,b** or **9a,b**.

(2*S*,3*R*)-3-(*N*-(Benzyloxycarbonyl)amino)-2-hydroxy-4-phenylbutanoic Acid (8a). From **6a**: mp 152-153 °C (EtOAc-hexane) (lit.[8] mp 154-155 °C); $[\alpha]^{25}_{578}$ +83° (*c* 0.69, AcOH) (lit.[8] $[\alpha]^{25}_{578}$ +83.5°); ^{1}H NMR (DMSO-d_6) δ 2.80 (m, 2 H, CH_2Ph), 3.92 (d, 1 H, *J* = 2.5 Hz, C_2-H), 4.10 (m, 1 H, C_3-H), 4.95 (s, 2 H, OCH_2), 7.26 (m, 10 H, Ph).

(2*R*,3*R*)-3-(*N*-(Benzyloxycarbonyl)amino)-2-hydroxy-4-phenylbutanoic Acid (9a). From **7a**: mp 172-174 °C (EtOAc-hexane) (lit.[8] mp 175-176 °C); $[\alpha]^{25}_{578}$ +6° (*c* 0.65, AcOH) (lit.[8] $[\alpha]^{25}_{578}$ +5.7°); ^{1}H NMR (DMSO-d_6) δ 2.74 (m, 2 H, CH_2Ph), 4.06 (m, 2 H, C_2-H and C_3-H), 4.90 (s, 2 H, OCH_2), 7.23 (m, 10 H, Ph).

(2*S*,3*R*)-3-(*N*-(Benzyloxycarbonyl)amino)-2-hydroxy-5-methylhexanoic Acid (8b). From **6b**: mp 91-93 °C (EtOAc-hexane); $[\alpha]^{25}_{578}$ +33° (*c* 0.99, MeOH); ^{1}H NMR (DMSO-d_6) δ 0.85 (d, 6 H, *J* = 6.5 Hz, $CHCH_3$), 1.31 (m, 2 H, C_4-H), 1.55 (m, 1 H, C_5-H), 3.89 (m, 2 H, C_2-H and C_3-H), 4.99 (s, 2 H, OCH_2), 7.34 (m, 5 H, Ph). Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.02; H, 7.12; N, 4.75. Found C, 61.24; H, 7.29; N, 4.51.

(2*R*,3*R*)-3-(*N*-(Benzyloxycarbonyl)amino)-2-hydroxy-5-methylhexanoic Acid (9b). From **7b**: mp 126-128 °C (EtOAc-hexane); $[\alpha]^{25}_{578}$ +17° (*c* 0.8, MeOH); ^{1}H NMR (DMSO-d_6) δ 0.79 (d, 3 H, *J* = 6.5 Hz, $CHCH_3$), 0.84 (d, 3 H, *J* = 6.5 Hz, $CHCH_3$), 1.01 (m, 1 H, C_4-H), 1.50 (m, 2 H, C_5-H and C_4-H), 3.85 (m, 1 H, C_3-H), 3.96 (d, 1 H, *J* = 4.5 Hz, C_2-H), 5.00 (s, 2 H, OCH_2), 7.33 (m, 5 H, Ph). Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.02; H, 7.12; N, 4.75. Found: C, 60.92; H, 7.18; N, 4.68.

General Procedure for the Synthesis of the 2-Oxazolidones 10a, 10b, 11a, and 11b. To a solution of the methyl esters **6a,b** or **7a,b** (3 mmol) in methanol (30 mL) was added 6 N NaOH (1 mL), and after stirring at room temperature for 2 h, the reaction mixture was evaporated. The residue was taken up in water (40 mL), washed with dichloromethane (2 × 20 mL), and acidified to pH 3-4 with Dowex 50W-X4 resin. The resin was filtered off and washed with ethyl acetate (30 mL). The aqueous phase was extracted with ethyl acetate (2 × 30 mL), and the combined organic extracts were dried over Na_2SO_4 and evaporated to yield the corresponding 2-oxazolidones (80%) as foams.

(4*R*,5*S*)-4-Benzyl-2-oxo-5-oxazolidinecarboxylic Acid (10a). From **6a**: IR (KBr) 1760 (NH—C=O); ^{1}H NMR (DMSO-d_6) δ 2.71-2.94 (m, 2 H, CH_2Ph), 3.95 (m, 1 H, C_4-H), 4.20 (d, 1 H, *J* = 5 Hz, C_5-H), 7.21-7.31 (m, 5 H, Ph), 7.70 (s, 1 H, NH). Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.58; H, 5.12; N, 6.25.

(4*R*,5*R*)-4-Benzyl-2-oxo-5-oxazolidinecarboxylic Acid (11a). From **7a**: IR (KBr) 1760 (NH—C=O); ^{1}H NMR (DMSO-d_6) δ 2.51-2.90 (m, 2 H, CH_2Ph), 4.34 (m, 1 H, C_4-H), 5.11 (d, 1 H, *J* = 9 Hz, C_5-H), 7.18-7.31 (m, 5 H, Ph), 7.70 (s, 1 H, NH). Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.61; H, 5.15; N, 6.19.

(4*R*,5*S*)-4-Isobutyl-2-oxo-5-oxazolidinecarboxylic Acid (10b). From **6b**: IR (KBr) 1760 (NH—C=O); ^{1}H NMR (DMSO-d_6) δ 0.87 (d, 3 H, *J* = 6.5 Hz, $CHCH_3$), 0.89 (d, 3 H, *J* = 6.5 Hz, $CHCH_3$), 1.42 (m, 2 H, CH_2), 1.70 [m, 1 H, $CH(CH_3)_2$], 3.73 (m, 1 H, C_4-H), 4.61 (d, 1 H, *J* = 4.5 Hz, C_5-H), 8.00 (s, 1 H, NH). Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.21; H, 7.12; N, 7.44.

(4*R*,5*R*)-4-Isobutyl-2-oxo-5-oxazolidinecarboxylic Acid (11b). From **7b**: IR (KBr) 1760 (NH—C=O); ^{1}H NMR (DMSO-d_6) δ 0.83 (d, 3 H, *J* = 6.6 Hz, $CHCH_3$), 0.87 (d, 3 H, *J* = 6.6 Hz, $CHCH_3$), 1.23 (m, 2 H, CH_2), 1.68 [m, 1 H, $CH(CH_3)_2$], 4.09 (m, 1 H, C_4-H), 5.00 (d, 1 H, *J* = 8.7 Hz, C_5-H), 8.00 (s, 1 H, NH). Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.47; H, 7.10; N, 7.39.

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Registry No. **1**, 58970-76-6; **2**, 67655-94-1; **3a**, 63219-70-5; **3b**, 70853-26-8; **6a**, 124782-04-3; **6b**, 124782-05-4; **7a**, 124782-06-5; **7b**, 124782-07-6; **8a**, 59969-65-2; **8b**, 70853-12-2; **9a**, 62023-58-9; **9b**, 70853-18-8; **10a**, 100564-98-5; **10b**, 124782-08-7; **11a**, 124820-68-4; **11b**, 124782-09-8; Z-D-Phe-OH, 2448-45-5; Z-D-Leu-OH, 28862-79-5.

Monoalkylation vs Dialkylation of a Sulfone-Stabilized Carbanion[1]

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Alkylation of carbanions is one of the most important processes used in organic synthesis for the formation of carbon-carbon bonds. Typically the carbanion is formed through base-promoted abstraction of an activated hydrogen atom. Although carbonyl plays the major role among the electron-withdrawing groups used to "activate" a carbon-hydrogen bond for proton abstraction from the requisite carbon atom,[3] sulfone is one of a variety of heteroatom substituents that has also been used.[4] Sulfone

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(2) (a) Participant in the NIH-MARC program. (b) Participant in the NIH-MBRS program. (c) Participant in the ACS-SEED program.

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