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A SHORT ASYMMETRIC SYNTHESIS OF *N*-α-FMOC-*N*-δ-BOC-α-METHYL-D-ORNITHINE

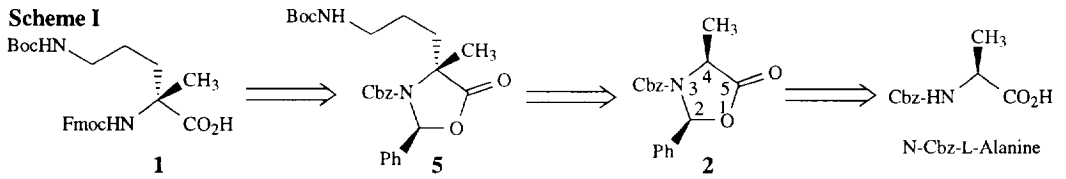
William D. Shrader†, Charles K. Marlowe*

†Department of Chemistry, University of California, Berkeley, CA 94720
*Chiron Corporation, 4560 Horton Street, Emeryville, CA 94608

Abstract: The title compound was synthesized in six steps from *N*-Cbz-L-alanine through asymmetric alkylation of a *cis*-2-phenyl-4-methyl-5-oxazolidinone with *tert*-butyl 4-iodobutyrate. The *cis*-2-phenyl-4-methyl-5-oxazolidinone was obtained via a new BF_3•Et_2O mediated condensation with benzaldehyde dimethyl acetal and *N*-Cbz-L-alanine. The δ-carboxylate was converted to the δ-*N*-Boc derivative **5** through a Curtius rearrangement. Hydrogenation yielded *N*-δ-Boc-α-methyl-D-ornithine **6**, which was protected as the α-*N*-Fmoc derivative for incorporation into solid phase peptide synthesis.

Difficulties in the preparation of unnatural α,α-disubstituted amino acids via manipulation of the natural amino acids have historically limited the number of compounds available for use in biological studies. Seebach and coworkers have developed an elegant enantio-selective approach to the synthesis of α,α-disubstituted amino acids from amide 5-oxazolidinones and 4-imidazolidinones.[1] Karady *et al.* then extended Seebach's concept to carbamate 5-oxazolidinones, which are derived from *N*-Cbz phenylalanine and function as a template for the asymmetric synthesis of α-methyl phenylalanine.[2] One advantage of carbamate derived oxazolidinones is that they offer a wide choice of α-amino and carboxyl protection/deprotection strategies, while retaining orthogonally protected side chain functionality. Methods which utilize amide 5-oxazolidinones or 4-imidazolidinones as templates to obtain α,α-disubstituted amino acids do not preserve the common protecting groups utilized in peptide coupling chemistry, thereby requiring elaborate procedures to selectively differentiate the diverse functionalites found in amino acids.

Scheme I

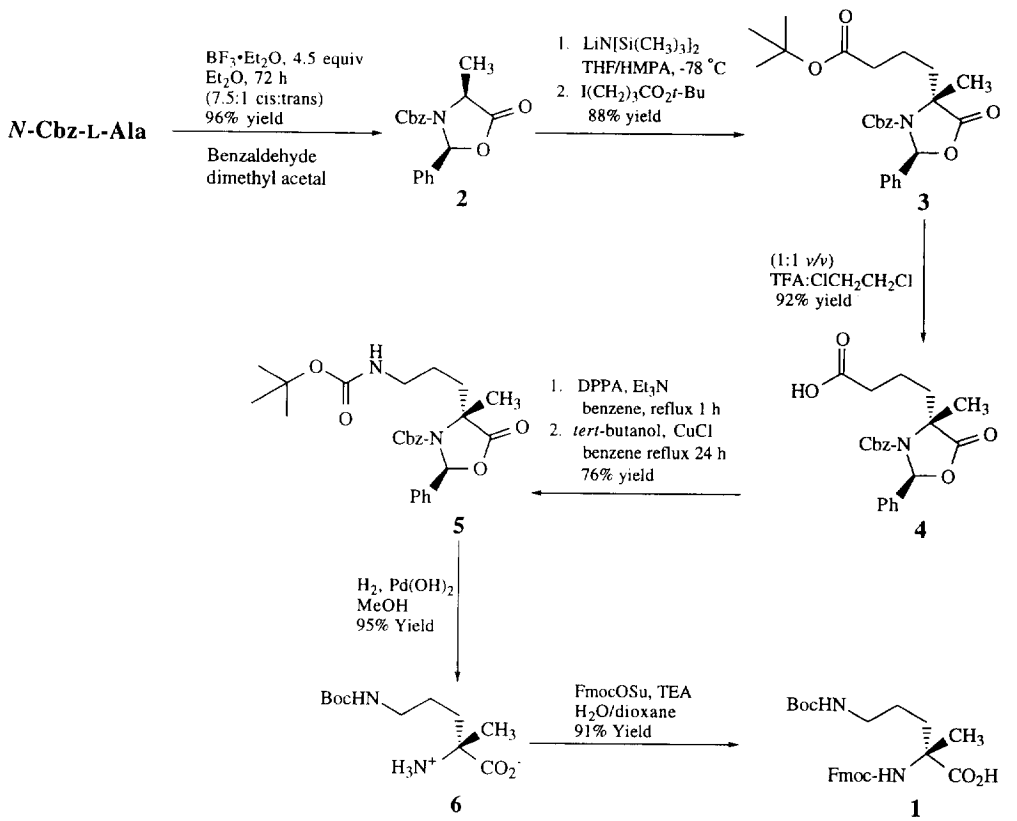


The synthesis of the unnatural D-α-methyl arginine was required for studies of conformationally restricted cyclic peptides as mimics of growth factors.[3] Since arginine can be readily obtained by *in situ* guanidinylation of ornithine using standard techniques, our initial target became the optically active ornithine derivative **1**. Herein we report a short, stereoselective synthesis of the title compound **1** using a simple *N*-Cbz-alanine derived oxazolidinone **2** as a versatile carbamate template for the synthesis of α-methyl amino acids. Furthermore,

* Current address: COR Therapeutics, Inc., 256 E. Grand Avenue, South San Francisco, CA 94080.
† Current address: California Institute of Technology, Department of Chemistry, Mail Code 164-30CH, Pasadena CA 91125

oxazolidinone **2** was obtained via a new efficient condensation reaction between benzaldehyde dimethyl acetal and *N*-Cbz-L-alanine, mediated by boron trifluoride etherate (Scheme I).[4]

Scheme II



Commercially available *N*-Cbz-L-alanine was converted to the 5-oxazolidinone **2** by an improved method over that previously reported[2,5] which utilized benzaldehyde as the aldehyde component (Scheme II). In this new procedure, boron trifluoride etherate cleanly effects the condensation of *N*-Cbz-L-alanine with benzaldehyde dimethyl acetal to yield a 7.5:1 cis:trans mixture of 5-oxazolidinone **2** in 96% yield. Recrystallization from 25:75 (Et_2O:hexanes) gives a 75% recovery of pure *cis*-5-oxazolidinone **2**. The absolute stereochemistry of **2** was confirmed by X-ray crystallography. Alkylation of **2** was accomplished by the addition of 1.25 equiv of *tert*-butyl 4-iodobutyrate[6] to the lithium enolate at -78 °C, formed in 20% HMPA/THF with 1.0 equiv of 1 *N* lithium bis(trimethylsilyl)amide in THF for 20 min (Scheme II).[7] Alkylation of **2** provided **3** in 88% yield. The stereochemistry of **3** arises from electrophilic addition to the face opposite the phenyl group[1] which is confirmed by a single-crystal X-ray structure of **3**. No trace of the other diastereomer was detected by 500 MHz ^1H NMR analysis. Oxazolidinone **3** was then converted to the free acid **4** in 92% yield by treatment with TFA. Acid **4**

underwent a Curtius rearrangement in refluxing benzene in the presence of triethylamine (TEA) and diphenylphosphoryl azide (DPPA), and the intermediate isocyanate was trapped with *tert*-butanol.[8] The efficiency of the trapping step was substantially increased by the addition of 1 equiv of cuprous chloride, doubling the isolated yield of **5** from 30% to 76%.[9] The synthesis was completed by conversion of oxazolidinone **5** to amino acid **6** in a single step by hydrogenation with $Pd(OH)_2/C$ in CH_3OH. Subsequent Fmoc protection using 1.0 equiv of succinimidyl-9-fluorenylmethyl carbonate (FmocOSu) and 1.5 equiv of TEA in dioxane/H_2O afforded **1** in 86% yield for the final two steps (Scheme II).[10,11,15]

Although literature methods exist for the resolution of D,L-α-methylornithine[12,13] and D,L-α-methylarginine,[13] such approaches are impractical due to the extensive protecting group manipulations required to differentiate the α from the δ amino groups of ornithine (or the η^2-amino group in Arg). Alternative methods have been reported for the asymmetric alkylation of α-amino acids to yield chiral ornithine derivatives.[2,7] However, the 7-step asymmetric synthesis of D-α-methylornithine from L-ornithine using an *N*-methyl imidazolidinone as an asymmetric template[14] requires harsh conditions (6 *N* HCl at 180 °C) to liberate the free amino acid removing all protecting groups. Further manipulations were therefore required to differentiate and selectively protect the α and δ amino groups. In contrast, our method provides a more efficient route to a fully protected α-methylorithine derivative which can be utilized in solid phase peptide synthesis. An extensive study of the alkylation step as well as subsequent manipulations will reveal the scope and limitations of this method.

Acknowledgments

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3. A partial communication of this strategy was presented: "Broccoli: A Systematic Method for Designing Conformationally Constrained Peptide Mimics of a Proposed Protein Binding Site," Michael A. Siani, Charles K. Marlowe, Erin K. Bradley, and Jeffrey M. Blaney, 9th European Symposium on Structure-Activity Relationships: QSAR and Molecular Modeling, Strasbourg, France, September, 1992.
4. Our method parallels the condensation of aldehydes and hydroxy acids with $BF_3 \cdot Et_2O$ yielding 1,3-dioxalan-4-ones reported in Mashraqui, S. H.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 2513, and references therein.
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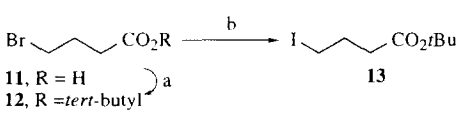
6. *Tert*-butyl 4-iodobutyrate was prepared by the following method from commercially available 4-bromobutyric acid (**8**):



a: Isobutylene, CH_2Cl_2, H_2SO_4, -10 °C, 48 hr
b: 2 equiv. NaI, anhydrous acetone, 23 °C, 48 hr

The physical properties of **13** have been described previously: Krohn, K.; Hemme, C. *Liebigs Ann. Chem.* **1978**, 726. Chang, C. D.; Coward, J. K. *J. Med. Chem.* **1976**, *19*, 684.

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14. Gander-Coquoz, M.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 224.

15. **1**: mp 147° C (dec.); $[\alpha]_D$ = -15.7° (*c* = 0.625 in CH_2Cl_2); IR (KBr): 3387, 3067, 2976, 2937, 1686, 1588, 1493, 1451, 1409, 1366, 1251, 1169, 1088, 1048, 869, 759, 741, 659, 621, 573, 545 cm^{-1}; ^1H NMR (500 MHz in d_6-DMSO): δ 1.20 (m, 2), 1.30 (s, 3), 1.33 (s, 9), 1.61 (dt, 1, J = 5.4, 13.0), 1.87 (m, 1), 2.74-2.84 (m, 2), 4.20 (t, 2, J = 6.8), 4.27 (dd, 1, J = 10.2, 13.7), 6.66 (t, 1, J = 5.7), 6.83 (s, 1), 7.34-7.32 (m, 2), 7.40 (t, 2, J = 7.5), 7.63 (d, 2, J = 7.5), 7.88 (d, 2, J = 7.5); ^{13}C NMR (500 MHz in d_6-DMSO): δ 24.16, 25.27, 28.25, 33.40, 40.20, 46.84, 58.95, 64.79, 77.19, 120.01, 120.10, 125.00, 127.06, 127.27, 127.54, 140.68, 144.01, 155.43; MS (FAB+), parent ion 469 $(M+H)^+$. HRMS: Calculated for $C_{26}H_{33}N_2O_6$: *m/z* = 469.2339; Found 469.2343. **2**: mp 60-61 °C; $[\alpha]_D$ = -23.4° (*c* = 1.0, CH_2Cl_2); IR (film): 3067, 3036, 2984, 2939, 1801 (lactone), 1717 (carbamate), 1457, 1407, 1351, 1249, 1171, 1129, 1010, 767, 697 cm^{-1}; ^1H NMR (500 MHz in d_6-DMSO at 102 °C): δ 1.51 (d, 3, *J* = 7.0), 4.54 (q, 1, *J* = 7.0), 5.11 (s, 2), 6.61 (s, 1), 7.22-7.31 (m, 10); ^{13}C NMR (125 MHz in d_6-DMSO at 102 °C): δ 17.23, 51.43, 66.40, 88.35, 125.89, 126.84, 127.27, 127.99, 128.89, 135.42, 136.88, 152.69, 171.69; MS (EI), parent ion 311 $(M)^+$. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.59; H, 5.68; N, 4.38. **3**: mp 61-62 °C; $[\alpha]_D$ = -55.3° (*c* = 1.0, CH_2Cl_2); IR (film): 2976, 2929, 1793 (lactone), 1724 (ester), 1718 (carbamate), 1407, 1347, 1160, 1014, 697 cm^{-1}; ^1H NMR (500 MHz in d_6-DMSO at 120 °C): δ 1.43 (s, 9), 1.37-1.55 (m, 2), 1.68 (s, 3), 1.84 (dt, 1, *J* = 12.7, 5.0), 2.14 (t, 2, *J* = 7.1), 2.30 (dt, 1, *J* = 12.0, 4.5), 5.05 (q, 2, *J* = 11.6), 6.58 (s, 1), 7.13 (bs, 2), 7.28 (m, 3), 7.42 (s, 5); ^{13}C NMR (125 MHz in d_6-DMSO at 102 °C): δ 18.90, 23.17, 27.25, 33.75, 34.99, 61.30, 66.26, 79.12, 88.13, 126.06, 127.04, 127.29, 127.58, 127.94, 128.96, 135.11, 136.53, 150.91, 170.65, 173.24; MS (FAB+), parent ion 454 $(M)^+$. Anal. Calcd for $C_{26}H_{32}NO_6$: C, 68.70; H, 7.10; N, 3.08. Found: C, 68.97; H, 6.87; N, 3.06. **4**: clear gum; $[\alpha]_D$ = -57.2° (*c* = 1.0, CH_2Cl_2); IR (film): 3567, 3036, 2938, 1798(lactone), 1713, 1699, 1455, 1408, 1349, 1236, 1165, 1094, 1020, 754, 697 cm^{-1}; ^1H NMR (500 MHz in d_6-DMSO at 120 °C): δ 1.39-1.59 (m, 2), 1.68 (s, 3), 1.85 (ddd, 1, *J* = 5.1, 11.4, 13.9), 2.18 (ddd, 2, *J* = 2.76, 7.2, 7.3), 2.33 (ddd, 1, J = 4.7, 11.93, 13.80), 5.05 (abq, 2, *J* = 12.5), 6.59 (s, 1) 7.06-7.20 (bs, 2), 7.23-7.31 (m, 3) 7.39-7.47 (m, 5); ^{13}C NMR (125 MHz in d_6-DMSO at 120 °C): δ 18.87, 23.23, 32.67, 35.19, 61.37, 66.32, 88.17, 126.10, 127.07, 127.33, 127.63, 127.97, 128.99, 135.15, 136.57, 150.98, 172.60, 173.33; MS (FAB+), parent ion 398 $(M+H)^+$. Anal. Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.46; H, 5.95; N, 3.29. **5**: clear gum. $[\alpha]_D$ = -52.8° (*c* = 0.625, CH_2Cl_2); IR (film): 3378, 2977, 2936, 1794 (lactone), 1714, 1695, 1519, 1455, 1404, 1348, 1245, 1169, 1020, 754, 698 cm^{-1}; ^1H NMR (500 MHz in d_6-DMSO at 120 °C): δ 1.30-1.39 (m, 2), 1.40 (s, 9), 1.68 (s, 3), 1.81 (ddd, 1, *J* = 5.1, 11.4, 13.9), 2.18 (ddd, 2, *J* = 2.76, 7.2, 7.3), 2.33 (ddd, 1, *J* = 4.7, 11.93, 13.80), 5.05 (abq, 2, *J* = 6.3, 12.5), 6.59 (s, 1) 7.06-7.20 (bs, 2), 7.23-7.31 (m, 3) 7.39-7.47 (m, 5); ^{13}C NMR (125 MHz in d_6-DMSO at 120 °C): δ 23.24, 24.03, 27.69, 33.24, 39.25, 61.35, 66.27, 77.05, 88.12, 126.05, 126.99, 127.28, 127.60, 127.94, 128.96, 135.08, 136.55, 150.93, 154.92, 173.35; MS (FAB+), parent ion 469 $(M)^+$. Anal. Calcd for $C_{26}H_{33}N_2O_6$: C, 66.51; H, 7.08; N, 5.97. Found: C, 66.32; H, 7.05; N, 5.90. **6**: mp 238-240 °C; $[\alpha]_D$ = 9.04° (*c* = 1.0, H_2O); IR (KBr): 2977, 1688, 1624, 1528, 1457, 1403, 1366, 1251, 1173, 1043, 992, 872, 787, 550 cm^{-1}; ^1H NMR (500 MHz in D_2O): δ 1.24 (s, 9), 1.30 (s, 3), 1.36-1.41 (m, 2), 1.56 (ddd, 1, J = 4.5, 12.6, 14.3), 1.68 (ddd, 1, J = 4.5, 12.9, 14.3), 2.91 (t, 2, J = 6.6); ^{13}C NMR (500 MHz in D_2O): δ 22.06, 23.58, 27.45, 34.23, 39.39, 60.97, 80.71, 158.02, 176.20; MS (FAB+), parent ions 253 $(M+Li)^+$, 247 $(M+H)^+$. HRMS: Calcd for $C_{11}H_{23}N_2O_4$: *m/z* = 247.1655; Found: 247.1658.

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