Organic Process Research & Development **2001**, *5*, 445−449

Large-Scale Syntheses of FMOC-Protected Non-Proteogenic Amino Acids: Useful Building Blocks for Combinatorial Libraries

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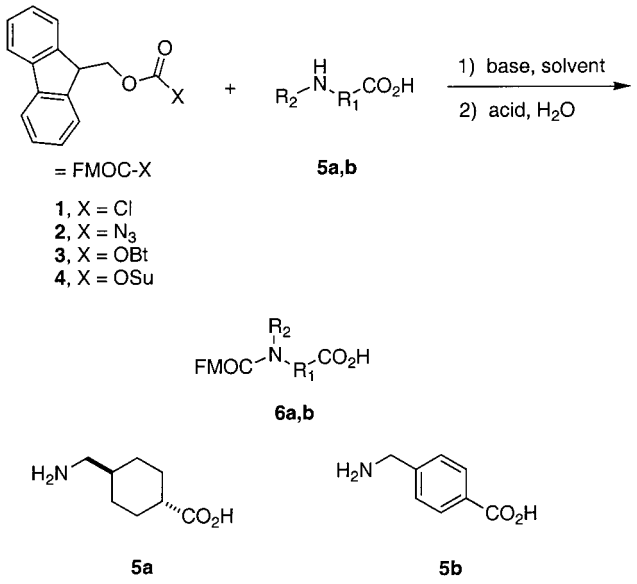
Abstract:

Convenient and reliable large-scale procedures for the protection of various amino acids with *N*-(9-fluorenylmethoxycarbonyl)oxysuccinimide (FMOC-OSu) are described. Commercially available 4-aminomethylbenzoic acid and *trans*-4-(aminomethyl)cyclohexanecarboxylic acid were converted into their corresponding FMOC-derivatives in excellent yields without the need for an extractive workup. In addition, FMOC-*cis*-*β*-amino acids were also prepared, employing a [2 + 2]-cycloaddition strategy between a cyclic olefin and *N*-chlorosulfonyl isocyanate (CSI). The resulting *N*-chlorosulfonyl *β*-lactams were reduced to the parent *β*-lactams with sodium sulfite and then converted to the *cis*-*β*-amino acid hydrochlorides by exposure to aqueous hydrochloric acid. The resulting *cis*-*β*-amino acids were converted to their FMOC-derivatives under conditions similar to those developed for the commercially available amino acids. Differences in the conditions employed between these *β*-amino acids and the commercial derivatives were observed, primarily in the nature of the base required for the reaction. A possible rationale for the differences in behavior is described. These FMOC-amino acid derivatives are valuable intermediates for the solid-phase synthesis of combinatorial libraries.

Introduction

Since its conception over 15 years ago, combinatorial chemistry has become an accepted technique for the identification and optimization of biologically active molecules.[1] The interest in development of combinatorial libraries has spawned a renaissance in solid-phase chemistry, primarily due to the fact that early combinatorial libraries were based on solid-phase peptide synthesis. While target library size may vary, libraries relying on solid-phase chemistry often require the use of excess building blocks and reagents to achieve satisfactory reaction rates and conversion on support.[2,3] Therefore, the need to synthesize sufficient quantities of starting materials (resins and scaffolds) for these libraries necessitates the development of efficient and reliable synthetic procedures, especially for large libraries (>1000 compounds). As part of a program spanning several library development projects, we have developed scalable procedures for the protection of amino acids as their FMOC-derivatives. In addition, we have also investigated large-scale syntheses of three interesting *cis*-*β*-amino acids and their FMOC-derivatives as useful building blocks for the generation of solid-phase combinatorial libraries.

Scheme 1



Results and Discussion

In 1970, Carpino first described the FMOC group as a base-labile protecting group,[4,5] now preferred over Merrifield's BOC-protection strategy for the synthesis of peptides on solid-phase.[6] The initial methodology to introduce this functionality relied upon the use of the 9-fluorenylmethoxyl chloroformate **1**.[7] Other reagents such as the azide (**2**), benzotriazole (**3**), and succinimidyl carbonate (**4**) have also been employed and in some cases preferred since use of **1** can generate dipeptide impurities with some amino acids.[6] Furthermore, cost and stability concerns limit the uses of some of these reagents, in particular azide **2**. For these reasons we chose to use succinimidyl carbonate **4** for our studies.

The general synthetic route for the preparation of the FMOC-derivatives is shown in Scheme 1. The amino acids protected under these conditions are shown below. While

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(2) Frechet, J. M. J. *Tetrahedron* **1981**, *37*, 663−683.
(3) Reaction rates for solid-phase reactions are often determined by the nature of the polymer matrix. For a discussion of this phenomenon, see: Czarnik, A. W. *Biotechnol. Bioeng.* **1998**, *61*, 77−79.
(4) Carpino, L. A.; Han, G. Y. *J. Am. Chem. Soc.* **1970**, *92*, 5748−5749.
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(6) Fields, G. B.; Noble, R. L. *Int. J. Pept. Protein Res.* **1990**, *35*, 161−214.
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10.1021/op010204f CCC: $20.00
Published on Web 06/01/2001

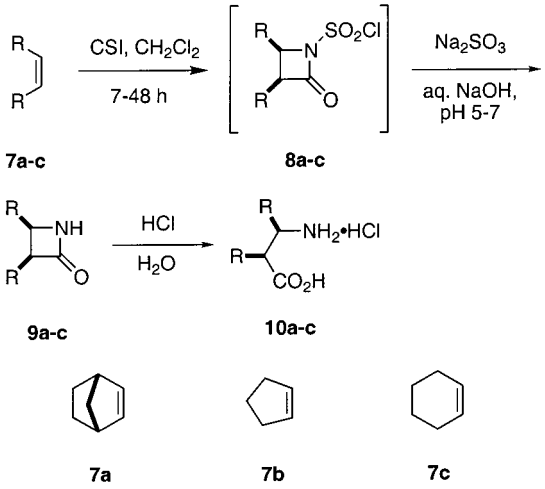
these FMOC-derivatives are commercially available, we required significant quantities (500 g to 1 kg) for library syntheses and therefore found their costs prohibitive given the simplicity of the chemistry involved.

Most reported literature procedures for the formation of FMOC-amino acids employ bicarbonate bases (as their sodium or potassium salts) in aqueous dioxane or acetonitrile solutions.[6,8] We observed that these conditions were unacceptable for large-scale work since the FMOC-amino acid salts would precipitate out and entrain the poorly soluble FMOC-OSu in the solid mass, resulting in slow or incomplete reaction. Even at relatively dilute reaction concentrations (for example, 0.15 M), this phenomenon was immediately apparent. Performing the reactions at higher dilution was not practical for scale-up and complicated by the fact that solubility was still a problem at lower concentrations.

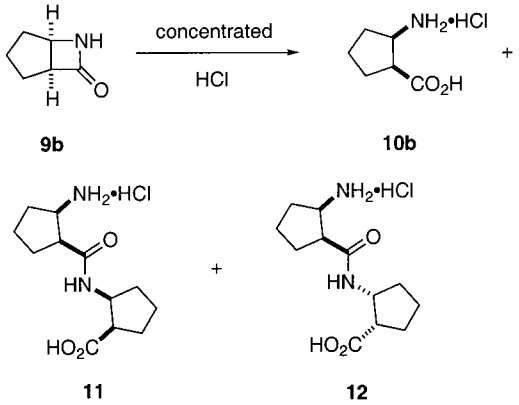
Ultimately, the use of trialkylamine bases in aqueous acetonitrile for this reaction afforded conditions that were suitable for large-scale work.[9] Reaction of either amino acid **5a** or **5b** in aqueous acetonitrile gave stirrable suspensions of the triethylammonium salts of the FMOC-amino acids. By using a 15% molar excess of the amino acid, the reaction could be driven to completion and avoid the need to remove unreacted FMOC-OSu by potentially tedious extractions. Acidification of the reaction with HCl converted the FMOC-amino acid triethylammonium salt to the free acid, in addition to forming the HCl salt of the unreacted amino acid. The free FMOC-amino acids **6a,b** were then isolated by filtration, with the water-soluble salts (triethylamine hydrochloride and amino acid hydrochloride) and *N*-hydroxysuccinimide removed by simply washing the filter cake with water. This procedure is operationally straightforward and has been carried out on a 1.9-mol scale. Furthermore, yields of these FMOC-derivatives ranged from 90 to 95% with HPLC area percent purities greater than 95%.

For another library project we required three *cis*-β-amino acids as library scaffolds, protected as their FMOC-derivatives. The requisite amino acids were prepared by modification of known literature procedures (Scheme 2).[10] Cycloaddition of cyclic olefins **7a**−**c** with *N*-chlorosulfonyl isocyanate (CSI)[11] in dichloromethane gave the *N*-chlorosulfonyl β-lactams **8a**−**c**,[12] which were not isolated but converted directly to the parent β-lactam (**9a**−**c**) by treatment of the crude reaction mixtures with sodium sulfite at pH 5−7.[13] Isolation

Scheme 2. **Preparation of *cis*-β-amino acids**



Scheme 3. **Dipeptide formation during ring-opening of lactam 9b**



of the *N*-chlorosulfonyl lactams was not necessary, and furthermore, use of the dichloromethane solutions containing crude **8a**−**c** directly in the reduction step was convenient and advantageous for large-scale preparation of **9a**−**c**. Subsequently, β-lactams **9a**−**c** were converted to the corresponding racemic β-amino acid hydrochlorides **10a**−**c** by exposure to hydrochloric acid. These conditions had to be performed at high concentrations to avoid product losses since the β-amino acid products were soluble in these solvent mixtures.

Conversion of β-lactam **9b** to the β-amino acid **10b** required different conditions for the ring-opening step relative to the other β-lactams. These modified conditions were necessary to avoid the formation of byproducts that presumably arise from the highly strained nature of this bicyclic system. Use of concentrated HCl afforded the desired product contaminated with a diastereomeric mixture of dipeptides **11** and **12** that was difficult to remove from the desired product (Scheme 3). The formation of **11** and **12** was avoided by suspending the β-lactam in a small volume of water and adding an equal volume of the concentrated HCl.

Protection of the amino acid hydrochlorides **10a**−**c** was performed according to a modification of the procedure

(8) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 3rd ed.; Wiley and Sons: New York, 1999; pp. 506−509.

(9) A related procedure has been reported that requires extractions with ethyl acetate: Milton, R. C.; Becker, E.; Milton, S. C. F.; Baxter, J. E. J.; Ellsorth, J. F. *Int. J. Pept. Protein Res*. **1987**, *30*, 431−432. See also: Ten Kortenaar, P. B. W.; Van Dijk, B. G.; Peeters, J. M.; Raaben, B. J.; Adams, P. J. H. M.; Tesser, G. I. *Int. J. Pept. Protein Res.* **1986**, *27*, 398−400.

(10) (a) Moriconi, E. J.; Crawford, W. C. *J. Org. Chem.* **1968**, *33*, 370−378. (b) Fülöp, F.; Bernáth, G.; Spitzner, R.; Mattinen, J.; Pihlaja, K. *ACH - Models Chem.* **1994**, *131*, 435−443. (c) Stájer, G.; Mód, L.; Szabó, A. E.; Fülöp, F.; Bernáth, G.; Sóhar, P. *Tetrahedron* **1984**, *40*, 2385−2393.

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(12) For other examples, see: (a) Malpass, J. R.; Tweddle, N. J. *J. Chem. Soc., Perkin I* **1977**, 874−884. (b) Bestian, H.; Biener, H.; Clauss, K.; Heyn, H. *Liebigs Ann. Chem*. **1968**, *718*, 94−100.

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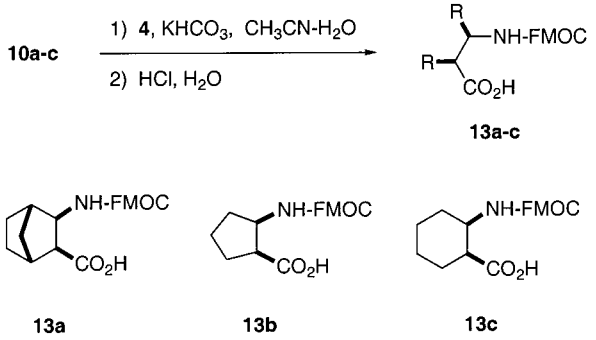
Scheme 4



described for **5a** and **5b** (Scheme 4). For reasons that are not entirely clear, the use of triethylamine was detrimental to the reaction; however, bicarbonate salts in aqueous acetonitrile provided satisfactory results.

The failure of the organic base was likely due to the steric influence of the triethylammonium carboxylate on the acylation of the neighboring *cis*-amine with FMOC-OSu. Furthermore, unlike cyclopentane amino acid **13b**, the cyclohexane derivative **13c** did not crystallize from the reaction mixture upon acidification. Instead, the resulting oily product was extracted into dichloromethane. Despite the procedural variation observed for the preparation of **13c**, this material exhibited reactivity similar to that of **13a** and **13b** under reaction conditions for the solid-phase library synthesis.[14]

In summary we have identified a useful method for the bulk preparation of valuable FMOC-amino acids for the generation of combinatorial libraries. Both commercial and synthetic amino acid derivatives can be converted to these valuable intermediates, generally without an extractive workup.

Experimental Section

General. All starting materials were used as received. ^{1}H NMR data were obtained on a JEOL Eclipse 270 NMR spectrometer at 270 MHz. ^{13}C NMR data were also recorded on a JEOL Eclipse 270 NMR spectrometer at 67.5 MHz. Elemental analyses were performed by Robertson Microlit, Madison, NJ. Reaction progress was monitored by either thin-layer chromatography (TLC) on glass-backed SiO_2 plates, or HPLC−UV analysis on a Hewlett-Packard model HP1100 HPLC equipped with a diode-array detector (DAD) and a 3.0 × 100 mm Phenomenex C18 column, employing acetonitrile−trifluoroacetic acid and water−trifluoroacetic acid as mobile phases. LC−MS data were recorded on a Finnigan TSQ7000 mass spectrometer fitted with a HP1050 HPLC or a PE-Sciex mass spectrometer equipped with a HP1100 HPLC.

***trans*-4-(FMOC-aminomethyl)cyclohexanecarboxylic Acid (6a).** To a 12-L, three-necked flask equipped with a mechanical overhead stirrer were added *trans*-4-(aminomethyl)cyclohexane carboxylic acid (**5a**; 301.8 g, 1.92 mol), 2.4 L of deionized water and triethylamine (268 mL; 1.92 mol). The mixture was stirred at room temperature, and then the solution was diluted with 2.4 L of acetonitrile, and FMOC-OSu (**4**; 539.2 g; 1.6 mol) was added. After 30 min, most of the solids had dissolved, but then the reaction mixture became a thick, translucent gel. Upon increasing the stirring rate, the precipitate whitened and eventually became a very thick, stirrable paste. Within an additional hour, the mixture thinned substantially and the rate of stirring was reduced. The reaction progress was monitored for the disappearance of FMOC-OSu by employing TLC (solvent system: 5% MeOH in CH_2Cl_2). When the reaction was complete (1.5−2 h), the mixture was acidified to pH 2.5 using 6 N aqueous HCl (ca. 410 mL). The mixture was allowed to stir for an additional hour and was filtered in a PP tabletop Büchner funnel (70 μm porosity). The cake was washed with five 2-L portions of deionized water. The cake was analyzed by TLC (solvent system: 5% MeOH in CH_2Cl_2) for the presence of both *N*-hydroxysuccinimide (UV-active), and *trans*-4-(aminomethyl)cyclohexane carboxylic acid (ninhydrin stain). Additional water washes were performed if either of these materials was detected and continued until the filter cake afforded a negative analysis by TLC. The cake was air-dried and then dried to constant weight in a vacuum oven (25 mmHg, 50 °C, N_2 bleed) to afford 576 g (95%) of *trans*-4-(FMOC-aminomethyl)cyclohexanecarboxylic acid (**6a**) as a white powder. ^{1}H NMR (DMSO-d_6) δ 12.0 (s, 1H), 7.89 (d, J = 7.42 Hz, 2H), 7.69 (d, J = 7.18 Hz, 2H), 7.43 (t, J = 7.18 Hz, 2H), 7.32 (dt, J = 7.42, 1.24 Hz, 3H), 4.45 (br d, J = 5.7 Hz, 1H), 4.31 (d, J = 6.93 Hz, 2H), 4.24−4.17 (m, with d at 4.21 ppm, J = 6.19 Hz, 3H), 2.82 (t, J = 6.43 Hz, 2H), 2.10 (tt, J = 12.12, 3.22 Hz, 1H), 1.88 (br d, J = 13.11 Hz, 1H), 1.68 (br d, J = 10.39 Hz, 1H), 1.44−1.09 (m, with br q at 1.25 ppm, J = 12.62 Hz, 3H), 0.87 (br q, J = 12.62, 2H); ^{13}C NMR (DMSO-d_6) δ 177.3, 144.5, 141.3, 128.1, 127.6, 125.7, 120.7, 65.7, 47.4, 46.8, 43.1, 37.8, 29.8, 28.8; MS (ESI) m/z 380.0 [(M + H)$^+$]; Anal. Calcd for $C_{23}H_{26}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.58; H, 6.48; N, 3.70.

4-(FMOC-aminomethyl)benzoic Acid (6b). This material was prepared according to the procedure described for **6a**. ^{1}H NMR (DMSO-d_6) δ 7.95−7.84 (m, with d at 7.89 ppm, J = 8.16 Hz, 5H), 7.70 (d, J = 7.42 Hz, 2H), 7.43 (t, J = 7.18 Hz, 2H), 7.33 (t, J = 6.43 Hz, 4H), 4.38 (d, J = 6.68 Hz, 2H), 4.26−4.21 (m with d at 4.25 ppm, J = 6.19, 3H); ^{13}C NMR (DMSO-d_6) δ 167.7, 157.0, 145.5, 144.4, 141.3, 129.9, 128.2, 127.5, 125.7, 120.7, 65.9, 47.4, 44.1; MS (ESI) m/z 373.8 [(M + H)$^+$]; Anal. Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75. Found: C, 73.65; H, 4.98; N, 3.77.

***cis*-β-amino Acids (9a−c). General Procedure.** A stirred solution of the alkene **7a−c** (2.12 mol) in dichloromethane (300 mL) was cooled in an ice−water bath. To the cold solution was added a solution of 300 g (184.5 mL, 2.12 mol) of CSI in dichloromethane (100 mL) dropwise over a period of 25 min. The reaction was stirred at 0 °C for 1 h, after which the ice bath was removed, and the reaction was allowed to warm to room temperature, with the exception of cyclopentene **7b** which was heated to 40 °C. Table 1 outlines approximate reaction times and reaction temperatures for all three alkenes. The reaction was deemed complete

(14) The specific details for library synthesis involving these intermediates will be described in a separate publication.

Table 1. **Reaction temperatures and approximate reaction times for the reaction of CSI with alkenes 7a−c**

alkene	time (h)	temperature (°C)
7a	7	25
7b	24	40
7c	96	25

when an aliquot of the reaction mixture no longer gave a reaction with water (also monitored by HPLC). The reaction mixture was cooled in an ice bath and was quenched by careful addition of cold water. This mixture was used immediately in the next step.

A suspension[15] of Na_2SO_3 (133.6 g, 1.06 mol) in water (400 mL) was stirred in an ice−water bath. The aqueous suspension was then treated with the dichloromethane solution of the crude *N*-chlorosulfonyl β-lactam **8a−c**, which was added in small portions, keeping the internal temperature below 25 °C. The pH of the aqueous solution was maintained between 5 and 7 by the concurrent addition of 20% aqueous NaOH. After the addition was complete, the reaction mixture was stirred for an additional hour at 0 °C. The organic layer was separated, and the aqueous layer was extracted with dichloromethane, with the exception of cyclohexyl-β-lactam **9c**, which was extracted with ethyl acetate. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the parent β-lactams **9a−c** as stable, crystalline white solids or viscous oils.

(±)-*cis*-6-Azabicyclo[3.2.0]heptan-7-one (9b): isolated as a white powder; ^{1}H NMR (DMSO-d_6) δ 3.88 (m, 1H), 3.34 (m, 1H), 1.79−1.21 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 169.4, 55.1, 52.3, 29.7, 24.8, 22.3. MS (ESI) *m*/*z* 112.0 [(M + H)$^+$].

(±)-*cis*-3-Aminobicyclo[2.2.1]heptane-2-carboxylic Acid Hydrochloride (10a). The norbornane β-lactam **9a** (290.8 g; 2.12 mol) was cooled in an ice−water bath, and to it was added just enough concentrated HCl to cover the solid. After several minutes an exothermic reaction was observed, affording a white solid. The mixture was allowed to stand for an additional 3−4 h and diluted with diethyl ether, and the solid was filtered. The white solid was washed with diethyl ether to afford 333.2 g (82%) of amino acid hydrochloride **10a**. ^{1}H NMR (DMSO-d_6) δ 3.21 (m, 1H), 2.66 (d, J = 8.16 Hz, 1H), 1.86 (d, J = 10.39 Hz, 1H), 1.47 (m, 1H), 1.45 (m, 2H), 1.14 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 171.1, 52.6, 47.3, 39.5, 38.6, 31.8, 26.1, 24.1; MS (ESI) *m*/*z* 155.8 [(M + H)$^+$]; Anal. Calcd for $C_8H_{14}ClNO_2$: C, 50.13; H, 7.36; N, 7.31. Found: C, 50.05; H, 7.24; N, 7.21.

(±)-*cis*-2-Aminocyclopentane-1-carboxylic Acid Hydrochloride (10b). The cyclopentane β-lactam **9b** (115.6 g; 1.04 mol) was dissolved in water (100 mL), and then the mixture was treated with 100 mL of concentrated HCl. The reaction mixture was stirred for 2 h after which it was allowed to stand at room temperature for 12 h. The resulting crystalline solid was isolated by filtration to give 142.9 g (83%) of the β-amino acid hydrochloride **10b**. ^{1}H NMR (DMSO-d_6) δ 3.61 (m, 1H), 3.01 (m, 1H), 1.96 (m, 2H), 1.80 (m, 2H), 1.59 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 174.0, 52.2, 45.7, 29.8, 26.9, 21.2; MS (ESI) *m*/*z* 129.6 [(M + H)$^+$]; Anal. Calcd for $C_6H_{12}ClNO_2$: C, 43.51; H, 7.30; N, 8.46. Found: C, 43.49; H, 7.19; N, 8.39.

(±)-*cis*-2-Aminocyclohexane-1-carboxylic Acid (10c). The cyclohexane β-lactam **9c** (300.4 g; 2.4 mol) was dissolved in water (100 mL), and then the mixture was treated with 100 mL of concentrated HCl. The reaction mixture was stirred for 2 h, and then the solution was allowed to stand at room temperature for 12 h. The solution was concentrated to give an oil which was triturated with a large amount of acetone (∼30:1 volume ratio) to afford 404 g (92%) of crystalline β-amino acid hydrochloride **10c**. ^{1}H NMR (DMSO-d_6) δ 3.24 (m, 1 H), 2.90 (m, 1H), 1.92 (m, 2H), 1.71 (m, 2H), 1.56 (m, 2H), 1.26 (m, 2H);^{13}C NMR (DMSO-d_6) δ 174.1, 49.5, 42.2, 27.4, 22.7, 26.2, 22.7; MS (ESI) *m*/*z* 143.8 [(M + H)$^+$]; Anal. Calcd for $C_7H_{14}ClNO_2$: C, 46.80; H, 7.86; N, 7.80. Found: C 46.90; H, 7.69; N, 7.74.

Other runs to prepare **10c** proceeded in variable yields (48−94%).

General Procedure for FMOC-Protection of *cis*-β-Amino Acids 10a−c. To a 5-L, three-necked flask equipped with a mechanical stirrer was added $KHCO_3$ (301.6 g, 3.01 mol) followed by water (1.5 L). Stirring was initiated, and once all the solids had dissolved, solid amino acid **10a−c** (1.56 mol) was added in small portions over a period of 1−1.5 h. The resulting mixture was stirred at room temperature until complete dissolution was achieved. The reaction mixture was diluted with acetonitrile (1.5 L), followed by the addition of solid FMOC-OSu (**4**; 576 g, 1.5 mol). The white suspension was stirred vigorously at room temperature until TLC analysis indicated that the reaction was complete. The mixture was acidified with concentrated HCl to pH 2 and then stirred at room temperature for 1 h. The white suspension was then filtered through a coarse sintered glass funnel. The cake was suspended in water (5.5 L), filtered, and the process repeated. The FMOC-amino acid was dried to constant weight in a vacuum oven at room temperature.

(±)-*cis*-3-FMOC-aminobicyclo[2.2.1]heptane-2-carboxylic acid (13a): isolated as a white powder, 435.7 g (74%); ^{1}H NMR (DMSO-d_6) δ 7.78−7.21 (m, 8H), 4.18 (s, 2H), 3.89 (m, 1H), 2.56 (m, 1H), 2.37 (m, 1H), 2.09 (m, 1H), 1.96 (m, 1H), 1.47 (m, 2H), 1.17 (m, 4H);^{13}C NMR (DMSO-d_6) δ 173.5, 155.5, 144.6, 144.3, 141.3, 128.2, 127.6, 126.1, 120.6, 66.3, 56.9, 53.4, 47.3, 42.4, 35.7, 28.5, 26.9. MS (ESI) *m*/*z* 378.2 [(M + H)$^+$]; Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found C, 73.06; H, 6.17; N 3.65.

(±)-*cis*-2-(FMOC-amino)cyclopentane-1-carboxylic acid (13b): isolated as a white powder; 535.8 g (94%); ^{1}H NMR (DMSO-d_6) δ 7.94−7.29 (m, 8H), 4.26 (s, 2 H), 4.21 (d, J = 6.68 Hz, 1H), 3.34 (m, 1H), 2.85 (m, 1H), 1.78 (m, 6H);^{13}C NMR (DMSO-d_6) δ 174.4, 155.6, 144.1, 140.7, 127.6, 127.1, 125.3, 120.1, 65.6, 54.3, 47.5, 46.8, 31.4, 26.4, 21.7; MS (ESI) *m*/*z* 352.2 [(M + H)$^+$]; Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.70; H, 5.97; N, 4.05.

(15) In some cases complete dissolution of sodium sulfite was observed.

(±)-*cis*-2-(FMOC-amino)cyclohexane-1-carboxylic Acid (13c). To a 3-L, three-necked round-bottom flask equipped with a mechanical stirrer was added $KHCO_3$ (128.8 g, 1.29 mol) followed by H_2O (800 mL). After the solids had dissolved, amino acid **10c** (120.4 g; 0.67 mol was added over a period of 1−1.5 h, and then the reaction mixture was stirred at room temperature until the solids had dissolved. The reaction mixture was treated with acetonitrile (800 mL), followed by carbonate **4** (216.7 g, 0.64 mol). The white slurry was stirred vigorously, resulting in a clear biphasic solution. Once the reaction was deemed complete by TLC analysis (72 h), the layers were separated, and the acetonitrile was removed by evaporation. The resulting aqueous mixture was extracted with dichloromethane (3 × 1.2 L). The aqueous layer was discarded and the combined organic phase concentrated in vacuo. The resulting yellow oil was dissolved in diethyl ether (200 mL) and was extracted with a saturated sodium bicarbonate solution (3 × 800 mL). The aqueous layer was then cautiously acidified to pH 2 using concentrated HCl. **(Caution: Vigorous Gas Evolution!)** The water layer was decanted from the gummy, pasty product. The crude product was then dissolved in dichloromethane (500 mL) and any residual water was separated. The organic layer was dried (Na_2SO_4), and concentrated in vacuo to afford 170 g (70%) of the FMOC-amino acid **13c** as a white, friable foam. ^{1}H NMR (DMSO-d_6) δ 7.86−7.14 (m, 8H), 4.22 (m, 2H), 4.0 (m, 1H), 3.32 (m, 1H), 2.60 (m, 1H), 1.54 (m, 8H);^{13}C NMR (DMSO-d_6) δ 174.6, 155.6, 144.6, 141.2, 128.2, 127.7, 126.0, 120.6, 65.6, 49.1, 46.8, 44.3, 30.1, 23.9, 23.4, 21.2; MS (ESI) *m*/*z* 366.2 [$(M + H)^+$]; Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C 72.08; H, 6.30; N, 3.89.

Acknowledgment

We thank Mr. Joseph Duimstra for his assistance during this project. We also thank Dr. Liling Fang for analytical support.

Received for review February 5, 2001.

OP010204F