Design and Asymmetric Synthesis of β-Strand Peptidomimetics

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Received December 28, 1995[⊗]

We describe the asymmetric synthesis of non-peptidic compounds that feature rigid backbone conformations and present various side-chain functions. The key step in the synthesis of these compounds is the C-acylation of an appropriate ketone with a suitably protected aspartic acid derivative. The resulting dipeptide modules may be connected to form tetrapeptide mimics. Specifically is described the mimicry of a four-residue segment of CD4, the cellular receptor of HIV-1. The design was based on molecular modeling and the X-ray crystal structures of CD4 and intended to present the most important side chains and backbone elements of the Phe43-Lys46 segment.

Introduction

One of the fundamental structural elements of proteins and polypeptides is the β-strand. Although this motif represents a very prominant secondary structural class, there have been few small molecule β-strand mimics reported.[1,2] The peptidic mimetics clearly suffer from several therapeutic limitations such as poor oral bioavailability and short half-lives *in vivo*.[3] Non-peptidic mimics, however, may overcome these limitations which, in a general sense, is the ultimate goal for most small molecule approaches. We have sought to develop a strategy of general utility which results in small molecules that adopt specific secondary structures relevant to those found in protein segments or substrate-bound peptides of interest.

In recent years there have been a wide variety of dipeptide-sized, non-peptidic amino acids reported.[4] In general, these molecules either contain a peptide backbone (i.e. N−sp^{3}C−sp^{2}C−N−sp^{3}C−sp^{2}C) or are designed to display properly oriented side chains.[5] We have focused on the development of a methodology that provides both these features as shown in Figure 1. A dipeptide of interest (Figure 1A) is mimicked with a bicyclic vinylamide (Figure 1B) which arises from the condensation of a ketone with an aspartic acid derivative (Figure 1C). If the dipeptide and the dipeptide mimics

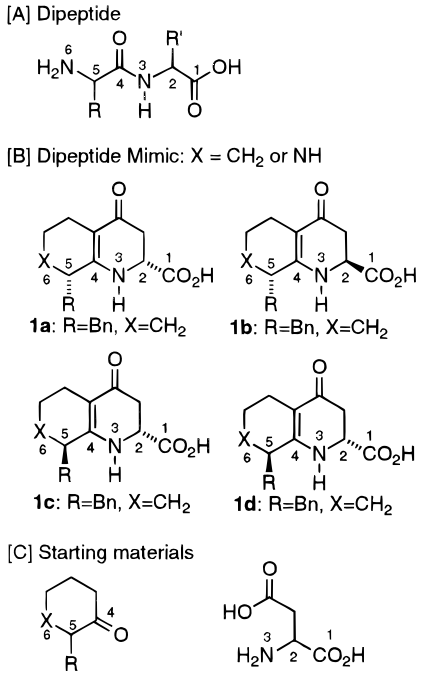

Figure 1. General approach.

are compared, it is clear that C2 and X6 are used to make constraints in a standard fashion while C4 is utilized as part of a vinylamide moiety. The C5 side chain (R) originates from the ketone starting material whereas the second side chain (R′) could arise from either the use of an aspartic acid derivative which contains this group at C2 or from attaching a similar group at a later stage via the C1 carboxylate. The chosen dipeptide mimic may be one of the four possible diastereomers.

In a previous report, cyclohexanones were used to develop a methodology which allows for the asymmetric synthesis of compounds such as **1a**−**d** (Figure 1B).[6] These compounds do not have an available nitrogen for further extension, but present side chains (in this case benzyl) in very specific orientations. In this report, we have extended our methodology to the asymmetric syn-

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1996.

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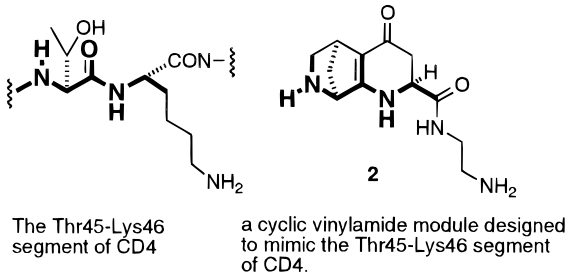


Figure 2. Mimicry of Thr45-Lys46 segment of CD4.

theses of nitrogen-containing analogs (i.e. X = NH) and show that these two types of modules may be used to construct tetrapeptide mimics.

We chose to adapt our general methodology to the mimicry of a four-residue segment found in the first domain of CD4, which, via binding to gp120, serves as the cellular receptor of HIV-1.[7] It has been reasoned that successful disruption of the CD4−gp120 interaction could lead to the prevention of HIV infection,[8] and others have also attempted to inhibit this protein−protein interaction with small molecules.[9] The β-strand segment of CD4 which we targeted includes the residues Phe43 and Lys46, each of which are significant contributors to the gp120 binding event as indicated by mutational analysis.[10]

Our approach, based in part on X-ray crystal structures of CD4,[11] was previously used in the design of vinylamide **1a**,[6,9b] a Phe43-Leu44 module, and a similar process was used to design a Thr45-Lys46 module. Since mutation of Thr45 to Ala has no significant effect on binding there appeared to be no need to mimic the Thr hydroxyl.[10] From a three-dimensional comparison of the Thr45-Lys46 segment and a variety of vinylamide-containing compounds, we identified compound **2** (Figure 2) as having good overlay with respect to the atoms and bonds shown in bold. The tricyclic nucleus of this molecule appropriately directs a lysine-type side chain (in this case derived from ethylenediamine) which, although not as flexible as a 4-aminobutyl group, can adopt the conformations observed for this side chain in the crystal structures of CD4. A subtle but important point for ridge mimicry is that the atoms used to make constraints in the Thr45-Lys46 module, when overlaid appropriately with CD4, reach into the space occupied by the protein itself, and therefore the module does not present structural elements which would sterically preclude binding to gp120.

Connection of module **1a**, module **2**, and ethylenediamine would provide the tetrapeptide mimic **3** (Figure 3). The limited flexibility at this amide juncture allows the four-residue mimic to adopt a set of conformations of which many are close to the native conformations

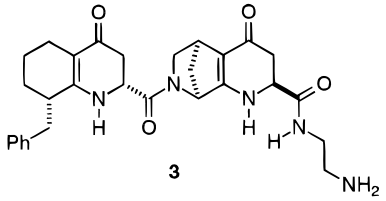
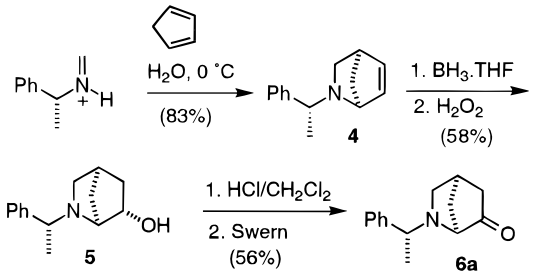


Figure 3. Mimicry of the Phe43-Lys46 segment of CD4: **1a** + **2** + ethylenediamine.

Scheme 1



found in the available X-ray crystal structures of CD4. The synthetic methodology permits access to a variety of related analogs of **3**, differing principally at the Lys- and Phe-type side chains.

Results and Discussion

The synthesis of vinylamide **2** required enantiomerically pure bicyclic ketone **6a**, which was prepared in three steps (Scheme 1). The aza-Diels-Alder reaction between an imminium ion [generated *in situ* from (*R*)-(+)-α-methylbenzylamine and formaldehyde] and cyclopentadiene afforded olefin **4** in 83% yield after separation from the minor diastereoisomer. Hydroboration of olefin **4** with 2.2 equiv of BH_3·THF complex provided alcohol **5**, isolated from a 4:1 diastereomeric mixture, in 58% yield. The regioselectivity of this hydroboration step is in accord with related results reported for 1,2,5,6-tetrahydropyridines.[12] The stereochemistry of **5** was determined by an X-ray crystal structure analysis.[13] Swern oxidation of both the hydrochloride salt of alcohol **5** and the diastereomeric minor product provided ketone **6a**.

The next reaction was C-acylation of ketone **6a** with an aspartic acid derivative. In the synthesis of **1a**−**d** we had accomplished the enolization step with mesityllithium, but this amine-free base simply added to the carbonyl of ketone **6a**.[14] Summarized in Table 1 is a systematic study which concerned the acylation of **6a** (entry 1) as well as **6b** (entry 2) and **6c** (entry 3). The latter two ketones, when subjected to the conditions of method A, similarly condensed with mesityllithium to provide the 1,2-adducts. Enolization of ketones **6a**−**c** with LDA (method B) does occur, but the self-condensation and bis-acylation products predominated after treatment with **7**. The first isolation of a monoacylation product, contaminated with the bis-acylated compound,

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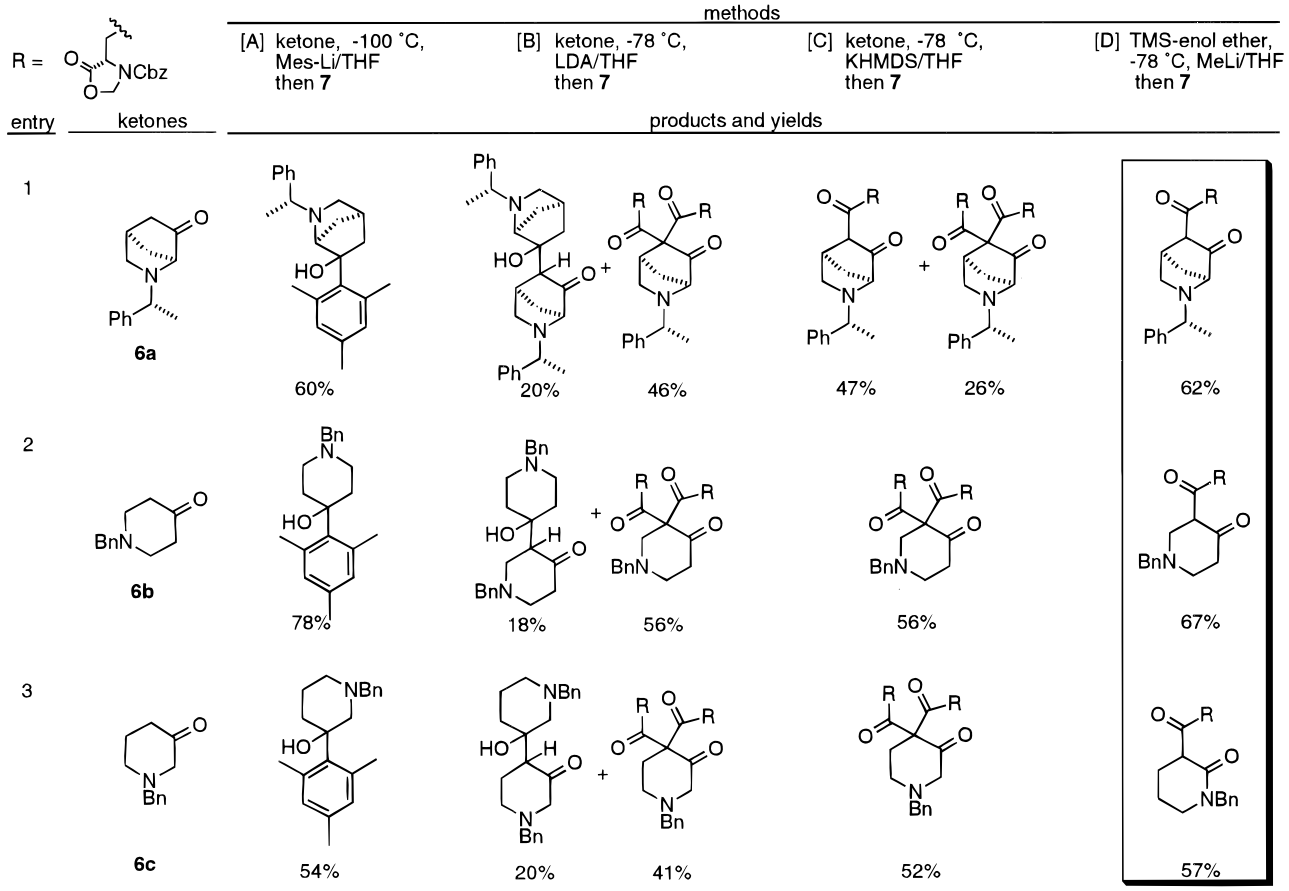
(12) Porthoghese, P. S.; Sepp, D. T. *Tetrahedron Lett.* **1973**, 2253−2256.

(13) An X-ray structure was detemined by Molecular Structure Corporation on the hydrochloride salt of the enantiomer of **5**, prepared identically to **5** except for the use (*S*)-(−)- instead of (*R*)-(+)-α-methylbenzylamine. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(14) Beck, A. K.; Hoekstra, M. S.; Seebach, D. *Tetrahedron Lett.* **1977**, 1187−1190.

Table 1. Acylation of Enolates Derived from Three Amino Ketones

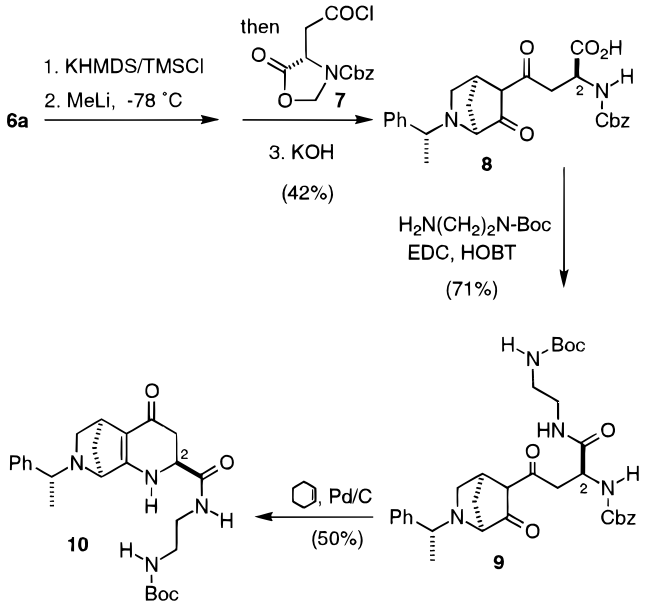


resulted from treatment of ketone **6a** with KHMDS at −78 °C and transfer of the resulting enolate solution to a solution of acid chloride **7** also cooled to −78 °C (method C). Both with ketone **6b** and **6c**, however, the bis-acylated compound proved to be the major product. Ultimately, good yields of *all* the mono-acylation products were obtained when the lithium enolates were generated from the corresponding TMS-enolates by treatment with methyllithium at −78 °C (method D).[15]

The acylation product was saponified *in situ* (1 N KOH) to provide N-Cbz-protected amino acid **8** (Scheme 2). The side chain which mimics that of lysine (in this case ethylenediamine) was introduced by coupling acid **8** with *tert*-butyl *N*-(2-aminoethyl)carbamate in the presence of HOBT and EDC to give diketone **9** in 71% yield (Scheme 2). Removal of the benzyloxy carbonyl protecting group by catalytic hydrogen transfer provided cyclic vinylamide **10** directly as a fully protected version of **2** (Figure 2). The ^{1}H NMR spectrum of compound **10** appeared to be that of a single compound, consistent with the notion that no epimerization had occurred during the synthesis. Indeed, when a mixture of **10** and C2-*epi*-**10** was synthesized by utilizing racemic **7**, the ^{1}H NMR resonances for protons at C2 for the diastereomers were resolved from each other at 250 MHz. As part of a parallel study, all four diastereomers of the free acid derivative of **10** were synthesized independently via the route outlined in Schemes 1 and 2 (data not shown) by choice of the appropriate enantiomers of α-methylbenzylamine and **7**.

Next, the coupling of the Phe43-Leu44 module with the Thr45-Lys46 module was investigated. Removal of the

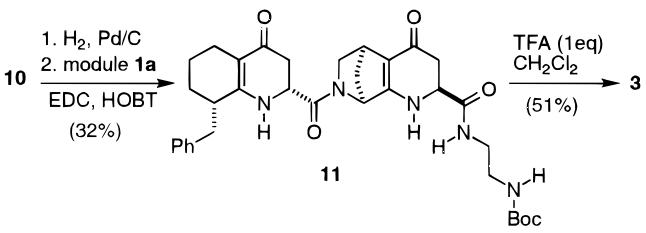
Scheme 2



phenethyl group of **10** gave the corresponding secondary amine which could be coupled with **1a** (EDC, HOBT) to provide compound **11** in 32% overall yield (Scheme 3). When compound **11** was subjected to a conventional method for the removal of *tert*-butyl carboxy protecting groups (1:1 TFA−CH_2Cl_2) complete decomposition occured. Interestingly, both of the analogous compounds derived from ketones **6b** and **6c** (footnote) did not display this acid sensitivity which suggests that decomposition of compound **11** might be via an acid catalyzed retro Diels-Alder reaction of the bridged system. Although

(15) Garst, M. E.; Bongflio, J. N.; Grudoski, D. A.; Marks, J. *J. Org. Chem.* **1980**, *45*, 2307−2314.

Scheme 3



relatively mild conditions (e.g. 0.1 M HCl) also led to immediate disappearance of starting material and no desired product, treatment of a dilute solution of **11** in CH_2Cl_2 with only 1 equiv of TFA resulted in a clean conversion to compound **3**, the final target.

Concluding Remarks

We have described the synthesis of a tetrapeptide mimetic of the Phe43-Lys46 segment of CD4 using a general strategy. It should be noted that the remaining 15 diastereoisomers of **3** are all accessible through connection of **1a**, **1b**, **1c**, or **1d** with one of the four diastereomers of **10**. The further versatility of the strategy has been illustrated by the synthesis of **12** and **13**.[16] Our approach can clearly be applied to a variety of mimetic problems and accommodate unique constraints. We have not been able to demonstrate that compound **3**, our initial tetrapeptide mimic, binds to gp120. We are currently analyzing the solution conformations of our tetrapeptide mimics by NMR.

Experimental Section

General Procedure. All reactions were carried out in an argon inert atmosphere in glassware that was dried in an oven at 120 °C. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 250 NMR at 250 MHz, and 50 MHz, respectively. Chemical shifts are reported in ppm (δ) with TMS as internal standard. Positive and negative FAB spectra were recorded on a JEOL JMS-SX102 instrument. CI spectra were recorded on a JEOL JMS-AX5058 instrument. Elemental analysis was obtained from Atlantic Microlab, Inc; Norcross, GA. Column chromatography was performed on silica gel (60-mesh, Merck). All reagents and dry solvents were used as is from the supplier unless otherwise stated. Abbreviations: HOBT: 1-hydroxybenzotriazole hydrate, EDC: 1-[3-dimethylamino)propyl]-3-ethylcarbodimide, KHMDS: potassium bis(trimethylsilyl)amide.

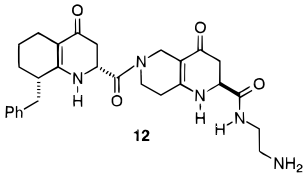
1-Phenethyl-1-azabicyclo[2.2.1]-3-heptene (4). (*R*)-(+)-α-methylbenzylamine (10 g, 83 mmol) was dissolved in 100 mL of water. The solution was acidified to pH = 4 by adding hydrochloric acid (10% by volume), and again the pH was adjusted to 8 with methylbenzylamine. Formaldehyde (4.98 g, 2 equiv) was added dropwise, and the solution was placed in an ice bath (0 °C) and treated with cyclopentadiene (15 mL, 2 equiv). The reaction mixture was stirred overnight at 0 °C and washed with hexane, and the aqueous phase was separated, treated with KOH (5 g in 15 mL of H_2O), extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography eluted with hexane: EtOAc (3:2) to give 13.7 g (83%) of the title compound as a brown oil: $[\alpha]^{20}_D = +23°$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 6.35 (dd, *J* = 5.2, 1.8 Hz, 1 H), 6.18 (dd, *J* = 5.6, 1.8, Hz, 1 H), 4.15 (s, 1 H), 3.15 (q, *J* = 6.5 Hz, 1 H), 2.90 (dd, *J* = 8.8, 3.0 Hz, 1 H), 2.86 (s, 1 H), 1.50 (m, *J* = 8.3 Hz, 2 H), 1.37 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 147.02, 136.62, 130.55, 128.57 (2 C), 127.81 (2 C), 127.01, 63.96, 62.51, 53.02, 48.21, 44.01, 24.12; MS (CI) *m*/*z* (rel intensity) 199 (100). Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.59; N, 7.03. Found: C, 83.75; H, 8.74; N, 7.23.

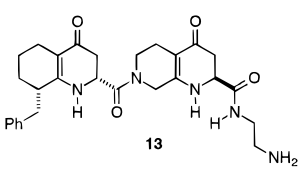
1-Phenethyl-1-azabicyclo[2.2.1]-3-heptanol (5). To a 0 °C solution of olefin **4** (5 g, 25.1 mmol) in THF (100 mL) was added dropwise BH_3·THF (27.6 mL, 1 M solution, 1.1 equiv). The reaction was stirred at room temperature for 30 min and cooled again to 0 °C where another 1.1 equiv of BH_3·THF was added dropwise. After 30 min at room temperature, the reaction mixture was cooled to 0 °C, and NaOH (4.4 g in 5 mL of water) was added. The resulting solution was stirred at 0 °C for 10 min and treated with H_2O_2 (3 mL, 30% solution in H_2O). The cooling bath was removed and the stirring was continued at room temperature for 45 min. Ammonium hydroxide (35 mL) was added, and the mixture was heated at 65 °C for 1 h 30 min. After cooling to room temperature, the reaction was diluted with ethyl acetate (250 mL), washed with NaOH (5%, 40 mL) and brine (40 mL), dried, and concentrated. The crude material was purified by flash chromatography eluted with EtoAC:hexane (1:1) to give 5.3 g (58%) of alcohol **5** as a colorless oil: $[\alpha]^{20}_D = +64°$ (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 5 H), 4.15 (d, *J* = 6.8 Hz, 1 H), 3.63 (q, *J* = 6.5 Hz, 1 H), 3.14 (s, 1 H), 2.65 (dt, *J* = 6.3, 2.4 Hz, 1 H), 2.40 (s, 1 H), 2.34 (d, *J* = 8.7 Hz, 1 H), 1.92 (m, 2 H), 1.61 (s, 2 H), 1.45 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 146.10, 128.96, 128.84, 127.65, 127.36, 126.58, 71.46, 64.09, 63.56, 57.93, 40.17, 36.81, 31.57, 22.97; MS (CI) *m*/*z* (rel intensity) 218 (M + 1, 100), 200 (7). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.44. Found: C, 77.75; H, 8.63 ; N, 6.43.

1-Phenethyl-3-oxo-1-azabicyclo[2.2.1]heptane (6a). To a −78 °C cooled solution of alcohol **5** (5 g, 23 mmol) in anhydrous dichloromethane (100 mL) was added HCl (23 mL, from 1 M in Et_2O, 1 equiv). In a second reaction vessel, oxalyl chloride (4 mL, 46 mmol) was added dropwise to a −78 °C cooled solution of DMSO (6.5 mL, 92 mmol) in anhydrous dichloromethane (100 mL). The mixture was stirred at −78 °C for 15 min and added dropwise *via* cannula to the flask containing alcohol **5.** The reaction mixture was stirred for 50 min during which time the temperature rose to −50 °C. The reaction mixture was cooled again to −78 °C and treated with triethylamine (25.8 mL, 184.3 mmol). The cooling bath was removed, and the reaction was stirred for 1 h, washed with NaOH (5%, 50 mL) and brine (50 mL), dried, and concentrated. Purification by flash chromatography eluted with hexane: EtOAc (3:2) gave 2.77 g (56%) of the title compound as a yellow oil which solidified on standing: $[\alpha]^{20}_D = +12°$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 5 H), 3.64 (s, 1 H), 3.30 (q, *J* = 7.6 Hz, 1 H), 3.05 (dd, *J* = 5.4, 1.5 Hz, 1 H), 2.55 (s, 1 H), 2.15 (m, 1 H), 2.15 - 1.70 (m, 4 H), 1.32 (d, *J* = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 207.7, 146.31, 128.80, 128.47, 127.97, 127.39, 126.02, 64.19, 62.8, 56.03, 44.27, 36.56, 35.21, 23.31; MS (CI) *m*/*z* (rel intensity) 216 (M + 1, 100), 187 (9). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.50. Found: C, 78.46; H, 7.98 ; N, 6.47.

1-Phenethyl-4-[3-(benzyloxycarbonyl)amino]3-carboxy-1-oxopropyl]-3-oxo-1-azabicyclo[2.2.1]heptane (8). Method D. Trimethylsilyl ether was prepared as follows. To LHMDS (1.6 mL, 1.6 mmol) in THF (5 mL) cooled to −78 °C was added dropwise a solution of ketone **6a** (344 mg, 1.4 mmol) in THF (3 mL). The solution was stirred at −78 °C for 30 min, and trimethylsilyl chloride (216 mg, 2 mmol) was added. The solution was stirred for 10 min and warmed rapidly to room temperature, stirred for 10 min, and concentrated. The crude material was partitioned between hexane and 10% Na_2CO_3, the aqueous solution was extracted with hexane, and the organic phases were combined, dried, and concentrated to provide the TMS-enol ether as a clear oil 414 mg (90%) which was used without purification: ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.35 (m, 5 H), 4.94 (d, *J* = 4 Hz, 1 H), 3.92 (s, 1 H), 3.24 (q, *J* = 6.7 Hz, 1 H), 3 (m, 1 H), 2.78 (s, 1 H), 1.68 (m, 2 H), 1.4 (d, *J* = 6.9 Hz, 3 H), 0.30 (s, 9 H).

(16) Compounds **12** and **13** were prepared starting from ketones **6b** and **6c**, respectively, according to Schemes 1−3.





Methyllithium (1 mL, from 1.4 M in diethyl ether) was concentrated under an argon atmosphere and diluted in THF (4 mL) and cooled to −10 °C. A solution of TMS-enol ether (403 mg, 1.4 mmol) in THF (3 mL) was added dropwise. The solution was stirred at −10 °C for 40 min, cooled to −78 °C, and slowly transferred *via* cannula to a solution of acid chloride **7** (1.4 mmol) in THF (5 mL) also cooled to −78 °C. The mixture was stirred at this temperature for 30 min, and potassium hydroxide (2 mL from 2 M solution) was added. The cooling bath was removed, and the solution was stirred at room temperature for 1 h. The aqueous solution was separated, washed with diethyl ether, and acidified with HCl (10%) to pH = 5. The solution was extracted with chloroform (3 × 30 mL), and the organic layers were combined, dried, and evaporated. The crude material was purified by flash chromatography eluted with $CHCl_3$:MeOH (9:1) to give 389 mg (42%) of the title compound as a yellow foam: $[\alpha]^{20}_D = -57°$ (*c* 1.1, MeOH); ^{1}H NMR ($CDCl_3/CD_3OD$) δ 7.51 (m, 10 H), 6.25 (d, J = 5.2 Hz, 1 H), 5.15 (s, 2 H), 4.55 - 4.38 (m, 2 H), 4.05 - 3.62 (m, 6 H), 3.55 (s, 1 H), 3.48 (d, J = 7.8 Hz, 1 H), 3.10 - 2.75 (m, 4 H), 2.65 (s, 1 H), 2.15 - 1.80 (m, 2 H), 1.72 (d, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 215.45, 208.10, 174.82, 154.62, 137.05, 130.64, 130.06, 129.56 (2 C), 129.43, 128.72 (2 C), 128.32, 127.61, 127.50 (2 C), 92.66, 67.50, 60.05, 52.20, 42.66, 38.45, 37.82, 26.89, 22.29, 20.59; MS (FAB) *m*/*z* (rel intensity) 465 (M + 1, 23), 373 (100). Anal. Calcd for $C_{26}H_{28}N_2O_6$: C, 67.22; H, 6.07; N, 6.03. Found: C, 66.96; H, 6.52; N, 6.05.

1-Phenethyl-4-[2-[(benzyloxycarbonyl)amino]-4-[[2-[(*tert*-butoxycarbonyl)amino]ethyl]amino]-1,4-dioxobutyl]-3-oxo-1-azabicyclo[2.2.1]heptane (9). Acid **8** (200 mg, 0.43 mmol) was dissolved in CH_2Cl_2 (5 mL) and treated with HOBT (68 mg, 0.5 mmol) and EDC (96 mg, 0.5 mmol). A solution of *tert*-butyl *N*-(2-aminoethyl)carbamate (80 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) was added. Triethylamine was added until pH = 8 was reached, and the mixture was stirred at room temperature for 15 h. The solution was diluted with CH_2Cl_2 (20 mL) and washed with H_2O and brine. The organic layer was separated, dried, and concentrated. Purification of the crude material by flash chromatography eluted with $CHCl_3$: MeOH (9:1) gave 186 mg (71%) of the title compound as a white foam: $[\alpha]^{20}_D = -62°$ (*c* 1, MeOH); ^{1}H NMR ($CDCl_3/CD_3$-OD) δ 7.43−7.27 (m, 10 H), 5.10 (s, 2 H), 4.31−4.16 (m, 2 H), 3.93−3.39 (m, 6 H), 3.04−2.50 (m, 5 H), 1.9 (m, 1 H), 1.50 (m, 12 H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 210.12, 200.10, 181.34, 171.95, 158.23, 138.30, 136.62, 129.64, 129.56, 129.54, 129.21, 129.18, 129.02, 128.94, 128.83, 128.05, 127.95, 106.98, 81.04 , 67.94, 62.91, 53.54, 51.33, 48.77, 41.92, 31.36, 29.07, 28.99; MS (FAB) *m*/*z* (rel intensity) 607 (M + 1, 12), 509 (100). Anal. Calcd for $C_{33}H_{42}N_4O_7$: C, 65.33; H, 6.97; N, 9.23. Found: C, 65.43; H, 6.75; N, 9.56.

2-[*N*-[2-[(*tert*-Butyloxycarbonyl)amino]ethyl]carbamoyl]-4-oxo-7-phenethyl-1,7-diazatricyclo[6.2.1.0^{10,11}]-11-dodecene (10). To a solution of cyclohexene/methanol (5 mL, 5/1) containing 100 mg of Pd/C (10%) was added compound **9** (100 mg, 0.16 mmol). The solution was refluxed for 20 min and cooled to room temperature. The catalyst was filtered off and washed with methanol, and solvents were evaporated. The residue obtained was partitioned between $CHCl_3$ and $NaHCO_3$, the aqueous layer was extracted with $CHCl_3$ (2×), and the combined organics were dried and concentrated. The crude material was purified by column chromatography $CHCl_3$: MeOH (9:1) to give 43 mg (50%) of the title compound as a clear oil.

$[\alpha]^{20}_D = -32°$ (*c* 0.9, MeOH); ^{1}H NMR ($CDCl_3/CD_3OD$) δ 7.35 (m, 5 H), 4.25 (t, J = 6 Hz, 1 H), 4.19 (t, J = 6.2 Hz, 1H this resonance was observed when racemic **7** was used), 3.55 (q, J = 6.5 Hz, 1 H), 3.15 (m, 2 H), 3.05 (s, 1 H), 2.82−2.50 (m, 6 H), 2.42 (s, 1 H), 2.37 (d, J = 8.7 Hz, 1 H), 1.51 (s, 9 H), 1.34 (d, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 194.72, 181.50, 158.21, 141.02, 138.10, 129.77, 129.69, 129.33, 129.11, 128.26, 128.01, 80.94, 71.03, 65.07, 64.38, 58.21, 40.27, 36.82, 32.10, 28.99 (5 C), 22.28; MS (FAB) *m*/*z* (rel intensity) 455 (M + 1, 25), 413 (35), 240 (70). Anal. Calcd for $C_{25}H_{34}N_4O_4$: C, 66.05; H, 7.53; N, 12.32. Found: C, 66.16; H, 7.49; N, 12.93

Hydrogenation of 10 and Coupling with Module 1a (11). A solution of compound **10** (80 mg, 0.17 mmol) in methanol (10 mL) containing 80 mg of Pd/C (10%) was stirred for 24 h under 1 atm of hydrogen (60 psi). The catalyst was filtered off and washed with methanol and chloroform. Solvents were removed under reduced pressure. The crude material (30 mg) was dissolved in CH_2Cl_2 (2 mL) and treated with EDC (19 mg, 0.1 mmol) and HOBT (13 mg, 0.1 equiv). Compound **1a** (48 mg, 0.17 mmol) dissolved in CH_2Cl_2 (1 mL) was added, triethylamine was added until pH = 8.5 was reached, and stirring was continued for 24 h. The solution was diluted with CH_2Cl_2 (20 mL), washed with water and brine, dried, and concentrated. The crude material was purified by flash chromatography eluted with $CHCl_3$:MeOH (9:1) to give 35 mg (32%) of the title compound as a colorless oil: $[\alpha]^{20}_D = -6°$ (*c* 0.84, MeOH); ^{1}H NMR ($CDCl_3/CD_3OD$) δ 7.35 (m, 5 H), 5.94 (s, 0.5 H), 5.62 (s, 1 H), 4.8 (m, 1 H), 4.25 (m, 1 H), 3.51−3.13 (m, 8 H), 3.02−2.62 (m, 9 H), 2.26 (m, 6 H), 2.24 (m, 3 H), 1.55 (m, 12 H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 190.87, 190.85, 171.61, 171.45, 157.11, 139.95, 138.20, 132.00, 131.68, 129.70, 129.19, 128.04, 127.15, 98.56, 81.20, 55.54, 51.43, 45. 12, 40.48, 30.30, 29.07, 29.05, 22.95; MS (FAB) *m*/*z* (rel intensity) 640 (M + Na, 8), 541 (10), 473 (12), 451 (100). Anal. Calcd for $C_{34}H_{43}N_5O_6$: C, 66.11; H, 7.01; N, 11.33. Found: C, 66.69; H, 7.01; N, 11.79.

***tert*-Butyloxycarbonyl Removal from 11 (3).** To compound **11** (15 mg, 0.024 mmol) in dry dichloromethane (10 mL) was added TFA (2 μL, 0.026 mmol). The solution was stirred under 1 atm of argon for 5 h. The solution was diluted further with CH_2Cl_2, washed several times with saturated solution of NaCl, dried, and concentrated. The crude material (12 mg) was purified by preparative TLC eluted with $CHCl_3$:MeOH (8: 2) to give 5 mg (51%) of the title compound as a yellow solid: $[\alpha]^{20}_D = -15°$ (*c* 0.9, MeOH); ^{1}H NMR ($CDCl_3/CD_3OD$) δ 7.50−7.15 (m, 5 H), 4.60 (t, J = 6.1 Hz, 1 H), 4.12 (t, J = 5.9 Hz, 1 H), 3.65 (m, 6 H); 3.40 (m, 6 H), 3.28−2.80 (m, 4 H), 2.50 (m, 4 H), 2.10 (m, 3 H), 1.77 (m, 5 H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 190.87, 190.85, 171.6, 171.39, 157.11, 139.95, 138.20, 132.00, 131.72, 129.70, 129.19, 128.00, 127.15, 98.56, 81.20, 55.54, 51.43, 45.12, 40.48, 30.30, 29.07, 29.05, 22.95; MS (FAB) *m*/*z* (rel intensity) 616 (M − 1, 100), 416 (13), 316 (40), 274 (38). Anal. Calcd for $C_{29}H_{35}N_5O_4$: C, 67.29; H, 6.81; N, 13.33. Found: C, 67.10; H, 6.46; N, 12.89.

Analog 12: $[\alpha]^{20}_D = -24°$ (*c* 1, MeOH); ^{1}H NMR ($CDCl_3/CD_3OD$) δ 7.25 (m, 5 H), 4.17 (m, 2 H), 3.21−2.90 (m, 7 H), 2.83−2.50 (m, 6 H), 2.35−2.00 (m, 5 H), 1.78−1.67 (m, 6 H), 1.5 (m, 3 H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 192.41, 192.36, 172.60, 171.93, 140.05, 139.20, 132.13, 131.70, 129.46, 128.94, 128.07, 127.35, 126.62, 106.28, 56.74, 52.13, 47.02, 38.48, 30.30, 28.05, 27.14, 25.73, 22.95; MS (FAB) *m*/*z* (rel intensity)-506 (M + 1, 32), 477 (64), 413 (100), 335 (88). Anal. Calcd for $C_{28}H_{35}N_5O_4$: C, 66.50; H, 6.97; N, 12.85. Found: C, 66.06; H, 6.48; N, 12.89.

Analog 13: $[\alpha]^{20}_D = -18°$ (*c* 1, MeOH); ^{1}H NMR ($CDCl_3/CD_3OD$) δ 7.25 (m, 5 H), 4.15 (m, 2 H), 3.30−3.06 (m, 6 H), 2.85−2.55 (m, 6 H), 2.35−2.00 (m, 4 H), 1.85−1.70 (m, 6 H), 1.5 (m, 3 H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 190.79, 190.43, 172.42, 172.00, 141.15, 140.30, 132.32, 131.74, 129.52, 128.71, 128.00, 127.56, 126.12, 108.04, 55.95, 52.31, 46.21, 38.40, 29.45, 27.95, 27.04, 25.73, 23.00; MS (FAB) *m*/*z* (rel intensity) 506 (M + 1, 10), 477 (45), 335 (100). Anal. Calcd for $C_{28}H_{35}N_5O_4$: C, 66.50; H, 6.97; N, 12.85. Found: C, 66.10; H, 6.42; N, 12.89.

Acknowledgment. This investigation was made possible in part by the financial support provided by the National Institutes of Health (grant AI 27336. project 3) to whom we are grateful.

Supporting Information Available: An ORTEP drawing derived from the crystal structure of *ent*-**5** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9522771