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A Formal Total Synthesis of (−)-FR901483, Using a Tandem Cationic Aza-Cope Rearrangement/Mannich Cyclization Approach

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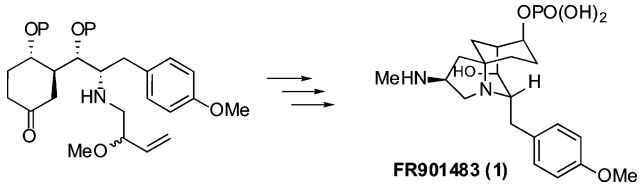
Received September 16, 2004



A formal total synthesis of the immunosuppressant FR901483 has been accomplished. The key step in the synthesis utilizes a tandem cationic aza-Cope rearrangement/Mannich cyclization reaction for accessing the unprecedented bridging tricyclic azaspirane substructure of this compound. The tandem reaction proceeds through a bridgehead iminium ion, a functionality that has rarely been explored in the context of natural product syntheses. Improved stereoselectivity was observed in an aldol reaction when using a Boc-protected amino aldehyde and zinc chloride as an additive. A stereoselective epimerization of the aldehyde-containing stereocenter was achieved with L-phenylalanine upon completion of the Mannich cyclization. Finally, this synthesis is the only one to date that controls the stereochemistry of the oxygen-bearing stereocenters. All other synthetic routes required late stage adjustments to at least one of these stereocenters.

Introduction

FR901483 (**1**) was discovered by researchers at Fujisawa Pharmaceutical Company Ltd as part of an ongoing effort to isolate new compounds that operate as immunosuppressants via a mechanism that is unique from either cyclosporin A or FK506 (Figure 1).[1] Experimental results suggest that FR901483 is likely to operate through an antimetabolite effect on immunocompetent cells by interfering with the enzymes adenylosuccinate synthetase and/or adenylosuccinase. Further information concerning the biological activity of this compound has not been forthcoming. However, one can speculate that the activity may result from FR901483 serving as a competitive inhibitor for inositol monophosphate (IMP) or an analogue of IMP.

This compound has captured the attention of the synthetic community due to its unprecedented bridging tricyclic azaspirane substructure.[2] Nearly all synthetic approaches to FR901483 (**1**) involve initial formation of a spirolactam **2**, followed by a ring closing reaction to form the bicyclic [3.3.1] ring system (pathway a) (Scheme 1). This strategy has been postulated to most closely mimic the biosynthesis of the natural product from tyrosyltyrosine. An alternative strategy involves formation of the [3.3.1] bicyclic ring system **3**, then ring closure to form the pyrrole (pathway b). Our group[2l] and Kibayashi's[2g] have adopted the latter approach, with both routes proceeding through a bridgehead iminium ion. Advantages to pathway b include the ease in which the bicyclic [3.3.1] ring systems can be formed, the conformational immobility of this ring system, and finally the potential to explore bridgehead iminium ion chemistry in the context of natural product synthesis.[3]

(1) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37.

(2) For total syntheses of (−)-FR901483, see: (a) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778. (b) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593. (c) Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett*. **2001**, *3*, 765. For the total synthesis of (±)-FR901483, see: (d) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2001**, *3*, 1125. (e) Kan, T.; Fujimoto, T.; Ieda, S.; Asoh, Y.; Kitaoka, H.; Fukuyama, T. *Org. Lett.* **2004**, *6*, 2729. For approaches to FR901483 and its analogues, see: (f) Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391. (g) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem*. **1997**, *62*, 8280. (h) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E.-M. *Tetrahedron Lett*. **1998**, *39*, 4667. (i) Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442. (j) Kropf, J. E.; Weinreb, S. M. *Abstracts of Papers*, 222nd National Meeting of the American Chemical Society, Chicago, IL, August 26−30, 2001; American Chemical Society: Washington, DC, 2001; ORGN-373. (k) Bonjoch, J.; Diaba, F.; Puigbo, E.; Sole, D.; Segarra, V.; Santamaria, L.; Beleta, J.; Ryder, H.; Palacios, J.-M. *Biorg. Med. Chem.* **1999**, *7*, 2891. (l) Brummond, K. M.; Lu, J. *Org. Lett.* **2001**, *3*, 1347. (m) Bonjoch, J.; Diaba, F.; Puigbo, E.; Sole, D. *Tetrahedron Lett*. **2003**, *44*, 8387 (n) Panchaud, P.; Ollivier, C.; Renaud, P.; Zigmantas, S. *J. Org. Chem.* **2004**, *69*, 2755.

10.1021/jo0483567 CCC: $30.25
Published on Web 12/24/2004

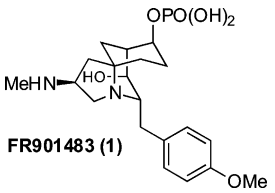
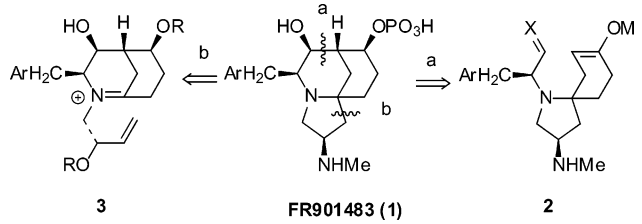


FIGURE 1.

SCHEME 1



Our approach to the core structure of FR901483 (**1**) utilizes the elegant chemistry developed in the Overman group, the tandem cationic aza-Cope rearrangement/Mannich cyclization reaction, to afford formyl pyrroles.[4] Our retrosynthetic strategy was described in an initial communication where it was demonstrated that the bridging tricyclic azaspirane substructure could be obtained by using a tandem cationic aza-Cope rearrangement/Mannich cyclization reaction on a model system possessing only the functionality needed for the rearrangement.[2l] Based upon preliminary results from this successful model system, we set out to prepare a fully functionalized precursor, which upon completing the tandem cyclization reaction, could then be converted to FR901483. The retrosynthetic strategy is shown in Scheme 2. First, it was envisioned that the methylamine group of **1** could be obtained from the aldehyde of **4** via a Curtius rearrangement. Next, the formyl pyrrolidine of **4** should be available via a Mannich cyclization from the intermediate iminium ion **5**. The potential to control the stereochemistry of the aldehyde during the cyclization step seemed possible by way of the flanking axial hydroxyl group. The iminium ion **5**, in turn, is the product of the cationic aza-Cope rearrangement of the bridgehead iminium ion **6**, which is obtained by an intramolecular condensation reaction between the carbonyl group and the secondary amine of compound **7**. The driving force of the aza-Cope rearrangement/Mannich cyclization should be substantial enough to overcome the axial orientation of both protected hydroxyl groups. Finally, compound **7** can be accessed via an aldol reaction between commercially available ketone **8** and a single enantiomer of the Boc-protected amino aldehyde **9**, followed by an amine alkylation with homoallylic halide **10** or a synthetic equivalent thereof.

Results and Discussion

Construction of the rearrangement precursor **7** involves an aldol condensation between a single enantiomer of the amino aldehyde **9** and the monoketal of 1,4-cyclohexanedione **8**. Unfortunately, aldol condensations with *N*-protected α-amino aldehydes are characterized by rather low distereoselectivities.[5] However, the rapid manner in which precursor **7** can be assembled via this aldol condensation was our incentive to investigate this reaction. As anticipated, treatment of ketone **8** with LDA at −78 °C, followed by addition of aminoaldehyde **9** resulted in the aldol condensation as a mixture of products (Scheme 3). However, a major product was obtained and readily isolated from the others via flash chromatography. This compound was determined to possess the stereochemistry of that needed for elaboration of FR901483 by X-ray crystallographic analysis.[6] The stereochemistry obtained for this diastereomer is consistent with a Cram chelation control model in the aldol condensation reaction, thus, a variety of conditions were tried in an effort to increase the selectivity. The highest selectivity was obtained by the formation of the lithium enolate of ketone **8** with LDA, followed by addition of 1 equiv of zinc chloride.[7] Addition of aldehyde **9** to the enolate of **8** afforded a 3.6:1 ratio of the desired isomer to an inseparable mixture of compounds in a combined yield of ∼72%.[8]

Next, the carbonyl of β-hydroxy ketone **11** was reduced with $NaBH_4$ in MeOH to afford the desired diol **14** as a single isomer (Scheme 4).[9] The excellent selectivity was thought to be a result of the appending hydroxymethyl and ketal groups locking the conformation of cyclohexanone **11** then axial delivery of the hydride to the less hindered face. Reaction of the MOM protected ketone **13** with $NaBH_4$ in MeOH at −78 °C also afforded **15** as a single isomer in a nearly quantitative yield. When the Luche reduction protocol was used, both ketones **11** and **13** gave a 1:1 mixture of stereoisomers **14** and **15** in 96% and 99% yield, respectively. The configuration of diol **14** was confirmed by X-ray crystallographic analysis at a later stage in the synthesis and found to be the desired stereochemistry.

Next, diol **14** was protected as the dibenzyl ether **16** with Ag_2O and $^nBu_4NI$ in benzyl bromide (neat). Typical benzyl ether protection protocols (NaH, BnBr, Bu_4NI, DMF or NaH, neat BnBr, Bu_4NI, or Ag_2O, BnBr, Bu_4NI, DMF) afforded only 30−40% yield of **16**.[10] These latter conditions gave significant quantities of cyclic carbamate **17**[11] and an unidentifiable compound. Next, the Boc

(3) Reviews on bridgehead imines: Warner, P. M. *Chem. Rev*. **1989**, *89*, 1067. Eguchi, S.; Okano, T.; Takeuchi, H. *Heterocycles* **1987**, *26*, 3265.

(4) For reviews, see: (a) Overman, L. E.; Ricca, D. J. *Comput. Org. Synth*. **1991**, *2*, 1007. (b) Overman, L. E. *Acc. Chem. Res*. **1992**, *25*, 352. (c) Overman, L. E.; Kakimoto, M.-a.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622.

(5) For a review, see: Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149 and references therein.

(6) The X-ray crystallographic data have been included in the Supporting Information as a CIF file and have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 254173 and 254174.

(7) Pridgen, L. N.; Abdel-Magid, A. F.; Lantos, I.; Shilcrat, S.; Eggleston, D. S. *J. Org. Chem.* **1993**, *58*, 5107.

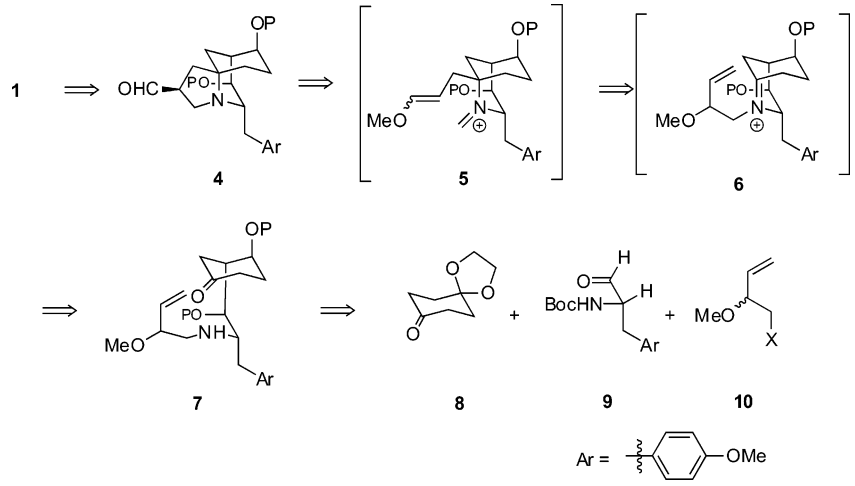
(8) Since the other compounds could not be separated and fully characterized, this yield is based upon the *assumption* that these products are the undesired aldol diastereomers. Indirect support for the diastereomeric aldol adducts is the clean conversion of the mixture compounds to pyrrole **12** upon standing neat at room temperature. Pyrroles have been previously obtained in this manner, see: Konieczny, M. T.; Cushman, M. *Tetrahedron Lett.* **1992**, *33*, 6939.

(9) Thompson, S. H. J.; Mahon, M. F.; Molloy, K. C.; Hadley, M. S.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 379. At this point, we could not determine the newly formed stereocenter, but it was presumed that axial attack occurred predominantly.

(10) Kuhn, R.; Trishmann, H. *Chem. Ber.* **1957**, *90*, 203. Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, *17*, 3535.

(11) Tom, N. J.; Simon, W. M.; Frost, H. N.; Ewing, M. *Tetrahedron Lett.* **2004**, *45*, 905.

SCHEME 2



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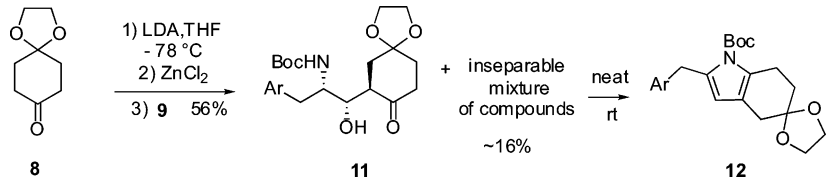

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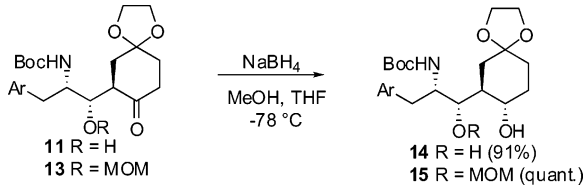

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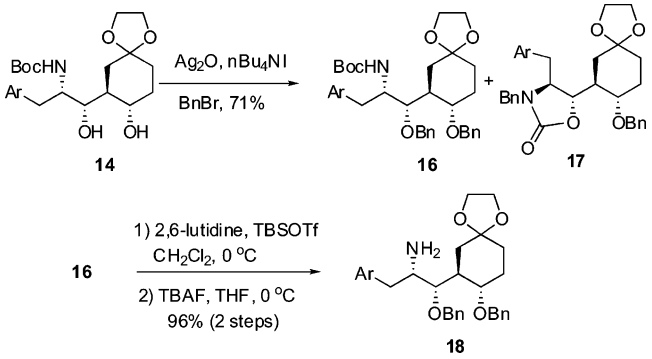
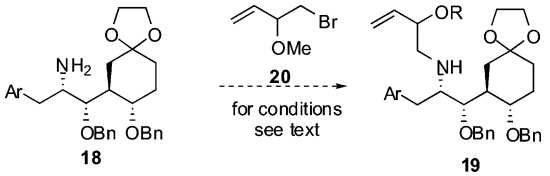


protecting group of **16** was selectively removed from the amine in the presence of the ketal protecting group by using a two-step procedure: first, treatment of protected amine **16** with 2,6-lutidine and TBDMSOTf at 0 °C smoothly afforded the corresponding silyl carbamate, then exposure of the crude silyl carbamate to TBAF in THF at 0 °C afforded amine **18** in 96% yield for two steps Scheme 5).[12]

Next, alkylation of the primary amine of **18** was investigated (Scheme 6). A number of conditions were used in an effort to directly alkylate **18** with homoallyl bromide **20**. Initially, Jung's protocols using CsOH/DMF[13] and Cs_2CO_3/DMF[14] were tried but only starting material was recovered. Moreover, several attempts to alkylate amine **18** with homoallyl bromide **20**, using different bases (K_2CO_3, $NaHCO_3$, DIPEA, ^{n}BuLi, NaH or KH) in a variety of solvents (DMF, DMSO, CH_2Cl_2, or THF), did not afford the secondary amine. Addition of a catalytic amount of $^n Bu_4NI$ to activate electrophile **20** was not successful. If the reaction was done in neat bromide **20** at 80 °C, decomposition of the starting material **18** was observed. The recalcitrant nature of this amine toward alkylation was somewhat surprising since the model system gave low yields of the desired alkylated product due to over-alkylation.[2l]

SCHEME 6



Due to these unforeseen alkylation problems, we turned to the acylation of amine **18** with 2-(*tert*-butyldimethylsilyloxy)but-3-enic acid **21**[15] using EDCI in CH_2Cl_2 that afforded the corresponding α-silyloxy amide (Scheme 7). Removal of the silyl protecting group gave the α-hydroxy amide **22**, which was reduced with 6 equiv of $LiAlH_4$ in refluxing THF affording amino alcohol **23** in 60% yield. Removal of the ketal protecting group from

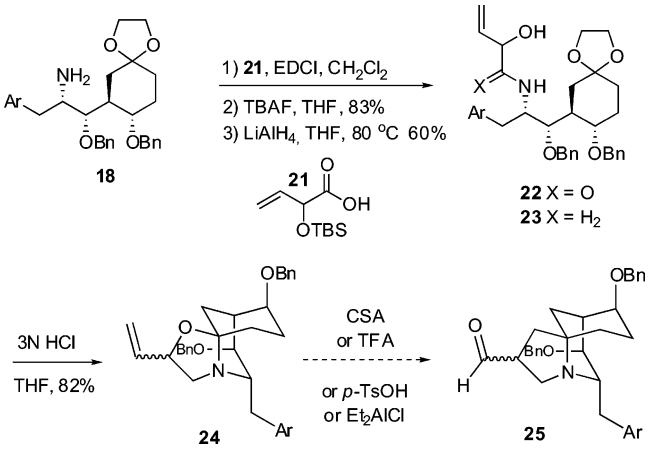
(12) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870.

(13) Salvatore, R. N.; Nagle, A. S.; Schmidt, S. E.; Jung, K.-W. *Org. Lett*. **1999**, *1*, 1893.

(14) Salvatore, R. N.; Shin, S.-I.; Flanders, V. L.; Jung, K.-W. *Tetrahedron Lett.* **2001**, *42*, 1799.

(15) Compound **21** was prepared by treating 2-hydroxybut-3-enoic methyl ester with TBSCl and imidazole in DMF and subsequent hydrolysis with LiOH in THF/H_2O. Stach, H.; Huggernberg, W.; Hesse, M. *Helv. Chim. Acta* **1987**, *70*, 369.

SCHEME 7



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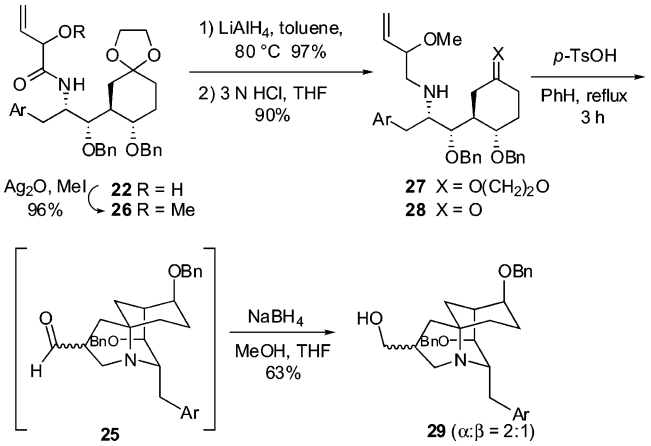


23 with 3 N HCl provided a compound that upon silica gel chromatography gave vinyl oxazolidine **24**. The ^{1}H NMR clearly showed the resonances of the vinyl protons and ^{13}C NMR showed the characteristic signal of the quaternary carbon of the oxazolidine at 93.3 ppm in C_6D_6. Unfortunately, all attempts to rearrange vinyl oxazolidine **24** to the formyl pyrrolidine **25** by using several different protic and Lewis acids resulted in either no reaction or complex mixtures of unidentifiable compounds.[16]

Thus, the hydroxyl group of **22** was reacted with Ag_2O in neat MeI to afford two diastereomers of compound **26** in 96% yield (Scheme 8).[17] Attempts to convert **22** to **26** with NaH/MeI in THF or Ag_2O/MeI in CH_2Cl_2 resulted in isomerization of the double bond into conjugation with the amide as indicated by the resonances at 6.41 (quartet) and 1.91 ppm (doublet) in ^{1}H NMR of the crude product. The stereochemistry of a single diastereomer of **26** was determined by X-ray crystallographic structure analysis.[6] The α-methoxy amide **26** was readily reduced with $LiAlH_4$ in *toluene* to afford **27** in 97% yield. Attempted reduction of **26** with $LiAlH_4$ in *THF* resulted in a complex mixture of compounds. The ketal group of amine **27** was removed with 3 N HCl to afford aminoketone **28**. Next, the aminoketone **28** was subjected to the same reaction conditions that were used on the model system[2l] for effecting the tandem aza-Cope/Mannich cyclization reaction. To our delight, treatment of amino ketone **28** with 1.2 equiv of *p*-TsOH in refluxing benzene afforded aldehyde **25** in 3 h as indicated by two resonances at 9.81 and 9.82 ppm in the ^{1}H NMR. Since aldehyde **25** was unstable to column chromatography, it was directly reduced with $NaBH_4$ to afford the amino alcohol **29**. Extensive NMR studies of the major and minor isomer of **29** including ^{1}H NMR, ^{13}C NMR, ^{1}H−^{1}H COSY, DEPT, and difference nOe showed the desired tricyclic substructure was generated as a 2:1 mixture of diastereomers. The stereochemistry of the hydroxymethyl group on the pyrrolidine **29** was not discernible, so both isomers were advanced through the synthetic sequence independently. At a later stage in the synthesis, it was determined that the desired stereoisomer **29**β was the minor isomer.

Efforts were then made to obtain predominantly pyrrolidine **29**β. For example, ketene **30** was prepared via an oxidation of the major diastereomer of amino alcohol **29**α with Jones' reagent to afford the corresponding amino acid (Scheme 9). The crude amino acid was converted to acid chloride with $SOCl_2$ and reaction of the acid chloride with Et_3N[18] in THF followed by addition of aq NaN_3 at 0 °C afforded the corresponding acyl azide **31**. Unfortunately, Curtius rearrangement of **31** and reduction of the resulting methyl carbamate with $LiAlH_4$ gave a 1:1 diastereomeric mixture of diamine **32** in 18% yield for the 6 steps.

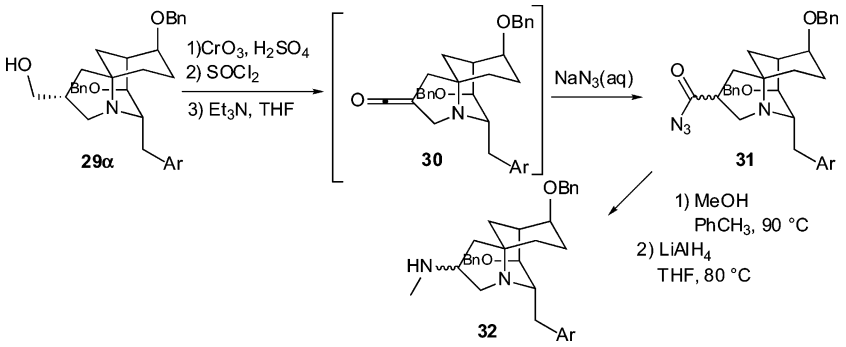
Next, it was thought that the stereochemistry of aldehyde **25** could be controlled by the formation of an enamine that would be selectively protonated from one face then hydrolyzed to give a single stereoisomer of the aldehyde (Scheme 10).[19] Indeed, addition of L-phenylalanine to aldehyde **25** resulted in a 1:2 mixture of diastereomers favoring the desired aldehyde **25**β in 71% combined yield for two steps (entry 2, Table 1). The addition of glycine resulted in no change in the stereoselectivity of **25** (entry 3). L-Proline was also tested and gave only an inseparable mixture of products (entry 4). Curiously, D-phenylalanine afforded a 1:1 mixture of **25**α:**25**β in 68% yield (entry 5). Addition of L-*N*,*N*-dimethylphenylalanine had no effect on the stereochemistry, suggesting that enamine formation is essential for isomerization (entry 6). It is assumed that there is a conformational preorganization of the enamine, imparted by a hydrogen bond between the carboxylic acid and the tertiary amine, that results in a selective protonation from the α face of the enamine.

Next, aldehydes **25**α and **25**β were reduced with $NaBH_4$ in MeOH/THF to afford alcohol **29**α and **29**β (Scheme 11). The major and desired diastereomer, alcohol **29**β, was readily separated from the minor diastereomer **29**α by column chromatography. Oxidation of alcohol **29**β with Jones' reagent afforded the amino acid **33**β in a quantitative crude yield.

Treatment of amino acid **33**β with Et_3N and ethyl chloroformate in acetone, followed by addition of aqueous NaN_3, afforded acyl azide **31**β.[20] The crude acyl azide was heated at 90 °C in toluene for ~45 min and the trans-

(16) Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241.
(17) Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455
(18) Baigrie, L. M.; Seiklay H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 5391.
(19) (a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (b) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450.

SCHEME 9



SCHEME 10

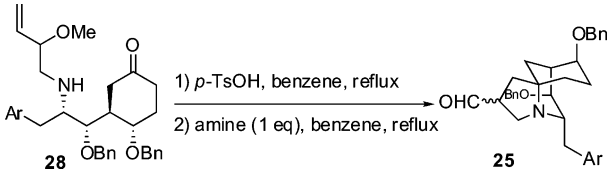


TABLE 1. Isomerization of Aldehyde 25

entry	amine	ratio (25β:25β)[a]	yield,[b] %
1	none	2:1	63
2	**L-phenylalanine**	**1:2**	**71**
3	glycine	2:1	72
4	L-proline		—[c]
5	D-phenylalanine	1:1	68
6	L-*N,N*-dimethyl phenylalanine	2:1	68

[a] Isolated ratio. [b] Combined yield for two steps. [c] Complex mixtures.

formation of the acyl azide (1714, 2138 cm^{-1}) to the isocyanate (1699, 2265 cm^{-1}) was monitored by IR. Once the acyl azide stretch had disappeared, methanol was added to the reaction mixture to afford methylcarbamate **34**β in 78% yield for two steps. Carbamate **34**β was reacted with $LiAlH_4$ in refluxing THF to provide diamine **32**β in 82% yield. Removal of the benzyl protecting groups of diamine **32**β with $Pd(OH)_2$/C in MeOH at 50 psi of hydrogen pressure afforded a diol that has been prepared previously by Ciufolini.[2c] Unfortunately, the solid compound that we obtained from this reaction was insoluble in $CDCl_3$, a solvent that was used by Ciufolini to characterize this compound.[21] Therefore, the secondary amine of **32**β was protected with a Boc group then removal of the benzyl protecting groups was accomplished with H_2 and $Pd(OH)_2$/C in MeOH giving diol **35**β in 78% yield. The more accessible hydroxyl group of diol **35**β was selectively phosphorylated by using a two-step procedure.[22] The ^1H and ^{13}C NMR spectral data of phosphoric ester **36**β were identical with a compound previously synthesized by Sorensen.[2b] Sorensen converted **36**β to FR901483 using a two-step deprotection sequence (Scheme 12).

(20) Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164.

(21) At this time the solubility differences cannot be explained. However, large quantities of palladium catalyst were used in the removal of the benzyl ether groups that may be a contributing factor.

(22) Yu, L.-L.; Fraser-Reid, B. *Tetrahedon Lett.* **1988**, *29*, 979.

Conclusions

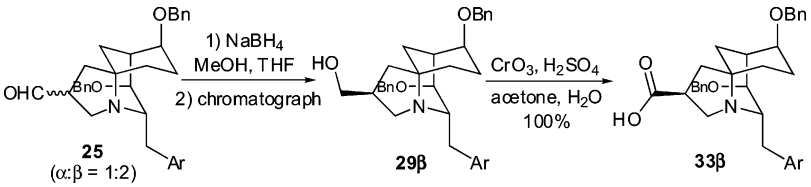
In summary, we have demonstrated an efficient formal total synthesis of FR901483 in 2.5% overall yield in 18 steps from commercially available ketone **8** and the Boc-protected aminoaldehyde **9**. An aldol condensation reaction between the zinc enolate of ketone **8** and Boc-protected α-amino aldehyde **9** afforded the desired amino alcohol **11** with 3.6:1 diastereoselectivity in 56% yield. The selectivity can be explained via a Cram chelation model. Interestingly, there are very few reports of diastereoselective aldol reactions for Boc-protected aminoaldehydes. Our strategy features a tandem aza-Cope/Mannich reaction proceeding through a bridgehead iminium ion to rapidly construct the unique tricyclic core structure of FR901483. The tandem aza-Cope/Mannich reaction and subsequent epimerization of the aldehyde bearing carbon using L-phenylalanine afforded the desired amino aldehyde as a major product with 2:1 selectivity. Finally, the stereochemistry of the oxygen bearing stereocenters of FR901483 was controlled at the outset, without need for late-stage adjustments.

Experimental Section

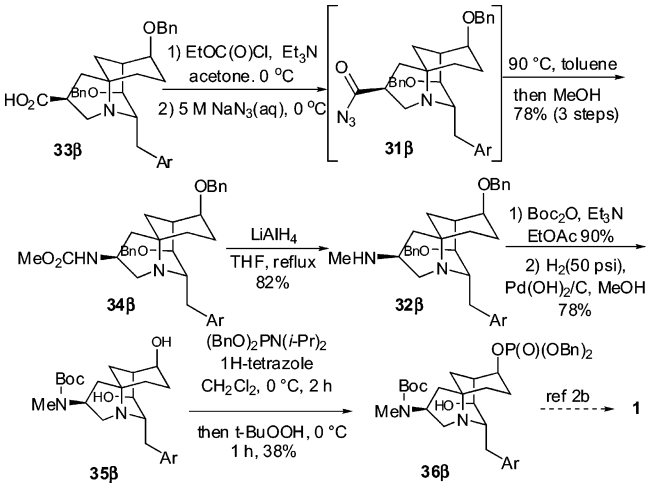
General Comments. All reactions were carried out under nitrogen atmosphere. All commercially available compounds were used as received, unless otherwise specified. Tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (CH_2Cl_2) were purified with alumina, using a solvent purification system. Toluene and diisopropylamine were freshly distilled from CaH_2 prior to use. Flash chromatography was performed with silica gel (32−63 mm particle size, 60 Å pore size). An eluting solution used for the chromatographic purification of the amines **18**, **27**, **29**α, **29**β, **32**β, **34**β, and **36**β was prepared by adding 480 mL of CH_2Cl_2, 20 mL of MeOH, and 20 mL of commercial 28−30% NH_4OH into a separatory funnel. The mixture was shaken and allowed to stand for 20 min. The aqueous phase was separated, and the organic phase was used without further manipulations. All ^1H and ^{13}C spectra were obtained on a 300-MHz spectrometer, and chemical shifts (δ) are reported relative to residual solvent peaks of $CHCl_3$ or C_6H_6. EI mass spectrometry was performed on a micromass spectrometer. Melting points are uncorrected.

[2-Hydroxy-1-(4-methoxybenzyl)-2-(8-oxo-1,4-dioxaspiro[4.5]dec-7-yl)ethyl]carbamic Acid *tert*-Butyl Ester (11). Li enolate: To a solution of diisopropylamine (1.68 mL, 12.0 mmol) in THF (100 mL) was added *n*-BuLi (7.50 mL of a 1.6 M solution in hexanes, 12.0 mmol) at −78 °C. This solution was stirred for 15 min at −78 °C, then cyclohexanedione monoketal **8** (1.25 g, 8.00 mmol) in THF (50 mL) was added dropwise over 10 min at −78 °C. The mixture was maintained at this temperature for 10 min, then freshly prepared amino

SCHEME 11



SCHEME 12



aldehyde **9**[23] (2.23 g, 8.00 mmol) in THF (30 mL) was added. The resulting solution was stirred for 20 min at −78 °C, then saturated NH_4Cl solution was added at that temperature. The aqueous layer was separated then extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (30 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash column chromatography over silica gel eluting with 20:80 ethyl acetate:hexanes to give hydroxyl ketone **11** (1.45 g, 42%) along with 1.21 g of an inseparable mixture of presumed diastereomers.

Zn enolate: To diisopropylamine (0.375 mL, 2.67 mmol) in THF (20 mL) was added *n*-BuLi (1.67 mL of a 1.6 M solution in hexanes, 2.67 mmol) at −78 °C. This solution was stirred for 15 min at −78 °C, then cyclohexanedione monoketal **8** (0.380 g, 2.43 mmol) in THF (10 mL) was added dropwise over 10 min at −78 °C. The mixture was maintained at this temperature for 30 min, then $ZnCl_2$ (4.87 mL of a 0.5 M solution in THF, 2.43 mmol) was added. The reaction was held at −78 °C for 30 min to ensure transmetalation, then amino aldehyde **9** (0.679 g, 2.43 mmol) in THF (30 mL) was added. The solution was stirred for 20 min at −78 °C, then a saturated NH_4Cl solution was added at that temperature. The aqueous layer was separated then extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude material was purified by a flash column chromatography over silica gel eluting with 20:80 ethyl acetate:hexanes to give ketone **11** (0.596 g, 56%) along with 0.165 g of an inseparable mixture of presumed diastereomers (16%).

Mp 120 °C; $[\alpha]^{25}_D$ −60.41 (*c* 0.058, $CHCl_3$); IR (film) 3507, 3382, 2974, 1704, 1513, 1246 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J = 8.3 Hz, 2H), 6.77 (d, J = 8.3 Hz, 2H), 5.12 (d, J = 10.2 Hz, 1H), 4.03−3.72 (m, 7H), 3.72 (s, 3H), 2.80 (d, J = 7.6 Hz, 2H), 2.75−2.58 (m, 2H), 2.36−2.21 (m, 2H), 2.00−1.89 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.1, 158.1, 155.7, 130.5, 130.3, 113.9, 106.8, 79.1, 77.5, 70.6, 64.9, 64.4, 55.2, 51.8, 49.3, 39.1, 37.9, 35.4, 34.9, 28.4; MS (*m/z*) 436, 417, 399, 362, 240, 213, 197, 150, 121, 99, 86, 57; EI-HRMS calcd for $C_{23}H_{33}NO_7$ $[M + H]^+$ (*m/z*) 436.2338, found 436.2335.

[2-Hydroxy-2-(8-hydroxy-1,4-dioxaspiro[4.5]dec-7-yl)-1-(4-methoxybenzyl)ethyl]carbamic Acid *tert*-Butyl Ester (14). $NaBH_4$ (195 mg, 5.17 mmol) was placed in a flask, followed by MeOH (20 mL) at −78 °C. The mixture was stirred at that temperature for 10 min. Next, ketone **11** (1.45 g, 3.33 mmol) in THF (50 mL) was cannulated into this mixture over 15 min at −78 °C. The reaction was held at this temperature for an additional 10 min, then warmed to room temperature. After 20 min at room temperature, ice water was added to the reaction and stirring was continued for an additional 30 min. The aqueous layer was separated and extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with water (2 × 10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash column chromatography over silica gel eluting with 50:50 ethyl acetate:hexanes to give diol **14** (1.33 g, 91%) as a single diastereomer.

Mp 160 °C; $[\alpha]^{25}_D$ −30.40 (*c* 0.015, $CHCl_3$); IR (film) 3382 (br), 2963, 1683, 1513, 1247 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.01 (d, J = 9.8 Hz, 1H), 4.86 (s, 1H), 3.98−3.80 (m, 5H), 3.79 (s, 3H), 3.70−3.55 (m, 1H), 3.53 (d, J = 9.0 Hz, 1H), 2.89−2.76 (m, 3H), 1.97−1.50 (m, 7H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 156.1, 131.0, 130.6, 114.2, 108.1, 79.4, 77.5, 75.9, 64.7, 64.4, 55.5, 52.9, 43.1, 38.0, 34.2, 33.5, 33.2, 28.6; MS (*m/z*) 436, 377, 359, 329, 315, 275, 91; EI-HRMS calcd for $C_{23}H_{35}NO_7$ $[M - H]^+$ (*m/z*) 436.2335, found 436.2329.

[2-Benzyloxy-2-(8-benzyloxy-1,4-dioxaspiro[4.5]dec-7-yl)-1-(4-methoxybenzyl)ethyl]carbamic Acid *tert*-Butyl Ester (16). To diol **14** (468 mg, 1.07 mmol) in benzyl bromide (6 mL) was added *n*-Bu_4NI (39 mg, 0.11 mmol) at room temperature. After 20 min, Ag_2O (990 mg, 4.28 mmol) was added in a single portion and the reaction was stirred for 12 h at room temperature. The mixture was filtered through Celite and the filter cake was washed with Et_2O (30 mL). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography over silica gel eluting with hexanes and 20:80 ethyl acetate:hexanes to give dibenzyl ether **16** (470 mg, 71%) as a colorless oil.

$[\alpha]^{25}_D$ +22.38 (*c* 0.048, $CHCl_3$); IR (film) 3457, 2934, 1709, 1512, 1247 cm^{-1}; ^1H NMR (300 MHz,C_6D_6) δ 7.20−7.00 (m, 10H), 6.85 (d, J = 8.3 Hz, 2H), 6.55 (d, J = 8.3 Hz, 2H), 5.18 (d, J = 9.6 Hz, 1H), 4.43 (d, J = 11.6 Hz, 1H), 4.35−4.25 (m, 1H), 4.15 (d, J = 11.6 Hz, 1H), 4.14 (d, J = 11.6 Hz, 1H), 3.98−3.96 (m, 1H), 3.81 (d, J = 11.6 Hz, 1H), 3.50−3.41 (m, 4H), 3.40−3.30 (m, 1H), 3.18 (s, 3H), 2.88−2.80 (m, 1H), 2.72−2.51 (m, 2H), 2.23−2.14 (m, 1H), 1.92−1.76 (m, 2H), 1.75−1.60 (m, 2H), 1.55−1.47 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 158.7, 155.4, 139.9, 139.1, 131.1, 130.7, 128.6, 128.5, 127.6, 127.3, 114.2, 109.0, 78.8, 77.2, 76.3, 71.5, 70.4, 64.4, 54.7, 52.3, 41.9, 40.7, 33.6, 33.0, 28.7, 28.6; MS (*m/z*) 617, 544, 518, 496, 396, 334, 121, 91; EI-HRMS calcd for $C_{37}H_{47}NO_7$ $[M]^+$ (*m/z*) 617.3352, found 617.3332.

2-Benzyloxy-2-(8-benzyloxy-1,4-dioxaspiro[4.5]dec-7-yl)-1-(4-methoxybenzyl)ethylamine (18). To dibenzyl ether **16** (900 mg, 1.46 mmol) in CH_2Cl_2 (50 mL) was added 2,6-lutidine (0.51 mL, 4.4 mmol), then TBDMSOTf (0.670 mL, 2.92 mmol) at 0 °C. The reaction was allowed to warm to room temperature and after 2 h a 0.5 N HCl solution (10 mL) was added. The organic layer was separated and the aqueous layer

(23) Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P. *Tetrahedron* **1998**, *54*, 6051. Jegham, S.; Das, B. C. *Tetrahedron Lett.* **1988**, *29*, 4419. When the Swern oxidation was allowed to warm to room temperature, complete racemization of the aldehyde was observed.

was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with water (1 × 20 mL) and brine (1 × 20 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude residue was dissolved in THF (100 mL) and cooled to 0 °C, then TBAF (4.37 mL of a 1.0 M in THF solution, 4.37 mmol) was added. After 10 min, saturated NH_4Cl was added and the resulting solution was extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with brine (20 mL), dried with $MgSO_4$ and concentrated in vacuo. The crude residue was purified by a flash chromatography over silica gel eluting with 50:50 ethyl acetate:hexanes and a solution of $NH_4OH/MeOH/CH_2Cl_2$ (see general comments) to give amine **18** (725 mg, 96%) as a colorless oil.

$[\alpha]^{25}_D$ +39.32 (*c* 0.053, $CHCl_3$); IR (film) 3200 (br), 2960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.26 (m, 10 H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.35 (d, *J* = 11.5 Hz, 1H), 3.96 (s, 4H), 3.75 (s, 3H), 3.67−3.52 (m, 2H), 3.32−3.24 (m, 1H), 2.84 (dd, *J* = 4.4, 13.3 Hz, 1H), 2.50−2.40 (m, 2H), 2.19−2.14 (m, 1H), 2.01−1.95 (m, 1H), 1.91−1.79 (m, 2H), 1.75−1.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 139.1, 139.0, 131.6, 130.3, 128.5, 128.4, 127.8, 127.7, 127.6, 127.5, 113.9, 108.7, 82.4, 73.6, 70.5, 64.5, 64.4, 55.3, 54.5, 41.9, 41.6, 35.3, 32.4, 27.8; MS (*m/z*) 518, 484, 396, 290, 247, 150, 91; EI-HRMS calcd for $C_{32}H_{39}NO_5$ $[M]^+$ (*m/z*) 517.2828, found 517.2877.

2-Hydroxybut-3-enoic Acid [2-Benzyloxy-2-(8-benzyloxy-1,4-dioxaspiro[4.5]dec-7-yl)-1-(4-methoxybenzyl)ethyl]amide (22). To amine **18** (580 mg, 1.12 mmol) in CH_2Cl_2 (50 mL) was added EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 645 mg, 3.36 mmol) then acid **21** (730 mg, 3.36 mmol) at room temperature. The reaction was stirred for 3 h at room temperature, then 0.5 N HCl was added (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude residue was immediately dissolved in THF (50 mL) and cooled to 0 °C. Next, TBAF (3.36 mL of a 1.0 M in THF solution, 3.36 mmol) was added and the reaction was maintained at 0 °C. After 30 min, saturated NH_4Cl was added then the aqueous phase was separated and extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude residue was purified by a flash column chromatography over silica gel eluting with 50:50 ethyl acetate:hexanes to give amide **22** (560 mg, 83% as a 1:1 mixture of diastereomers) as a colorless oil.

IR (film) 3407(br), 2932, 1655, 1512, 1247 cm^{-1}. Isomer 1: $[\alpha]^{25}_D$ +18.72 (*c* 0.033, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.20 (m, 8H), 7.13 (m, 2H), 6.95−6.86 (m, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 8.6 Hz, 2H), 5.94−5.84 (m, 1H), 5.42 (d, *J* = 17.1 Hz, 1H), 5.28 (d, *J* = 10.3 Hz, 1H), 4.68 (d, *J* = 11.6 Hz, 1H), 4.47−4.41 (m, 2H), 4.32 (d, *J* = 11.6 Hz, 1H), 4.33−4.22 (m, 1H), 3.97−3.85 (m, 6H), 3.63 (s, 3H), 3.55−3.30 (br s, 1H), 3.27−3.18 (m, 1H), 2.75−2.61 (m, 2H), 2.41−2.31 (m, 1H), 2.14−2.00 (m, 1H), 1.88−1.78 (m, 1H), 1.75−1.67 (m, 1H), 1.64−1.42 (m, 2H), 1.40−1.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 158.4, 139.2, 138.6, 136.3, 130.6, 130.3, 128.8, 128.5, 128.4, 128.1, 127.5, 118.0, 114.1, 108.6, 76.8, 75.7, 73.5, 71.8, 70.5, 64.6, 55.3, 51.0, 41.7, 39.7, 33.4, 32.5, 28.2. Isomer 2: $[\alpha]^{25}_D$ +22.26 (*c* 0.027, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.20 (m, 8H), 7.13 (m, 2H), 6.90−6.86 (m, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 8.5 Hz, 2H), 5.93−5.84 (m, 1H), 5.42 (d, *J* = 17.1 Hz, 1H), 5.28 (d, *J* = 10.2 Hz, 1H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.52−4.41 (m, 2H), 4.32 (d, *J* = 11.6 Hz, 1H), 4.30−4.20 (m, 1H), 3.90 (s, 4H), 4.00−3.86 (m, 2H), 3.62 (s, 3H), 3.30−3.18 (m, 1H), 2.77−2.57 (m, 2H), 2.52−2.31 (m, 1H), 2.14−2.00 (m, 1H), 1.92−1.80 (m, 1H), 1.78−1.67 (m, 1H), 1.66−1.22 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 158.4, 139.2, 138.6, 136.4, 130.6, 130.3, 128.8, 128.6, 128.4, 128.1, 127.5, 118.1, 114.1, 108.7, 77.6, 76.7, 75.4, 73.4, 71.6, 70.5, 64.6, 55.3, 51.0, 41.6, 39.6, 33.5, 32.5, 28.2; MS (*m/z*) 602, 544, 480, 409, 253, 234,181, 150, 139, 121; EI-HRMS calcd for $C_{36}H_{43}NO_7$ $[M + H]^+$ (*m/z*) 602.3118, found 602.3106.

7,9-Bisbenzyloxy-6-(4-methoxybenzyl)-3-vinyl-2-oxa-5-azatricyclo[6.3.1.0^{1,5}]dodecane (24). To $LiAlH_4$ (97 mg, 2.6 mmol) in THF (10 mL) was cannulated amide **22** (256 mg, 0.426 mmol) in THF (10 mL) over 5 min at 0 °C. The reaction was refluxed for 12 h, then cooled to room temperature. Next, water (0.2 mL) was added followed by $MgSO_4$ and the resulting mixture was filtered through Celite. The filtrate was concentrated in vacuo to give amine **23** (150 mg, 60%). To amine **23** (90 mg, 0.15 mmol) in THF (5 mL) was added 3 N HCl (5 mL) at room temperature. After the reaction was stirred for 5 h, 1 N NaOH (16 mL) was added, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash column chromatography over silica gel eluting with 50:50 ethyl acetate:hexanes and ethyl acetate to give vinyl oxazolidine **24** (66 mg, 82%) as a colorless oil and a 1:1 mixture of diastereomers. (Data for the isomer with a lower R_f are shown below.)

IR (film) 2925, 1512, 1246, 1092 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.43−7.10 (m, 12H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.11, (ddd, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.27 (d, *J* = 17.0 Hz, 1H), 5.07 (d, *J* = 11.6 Hz, 1H), 4.55−4.45 (m, 1H), 4.38 (d, *J* = 11.6 Hz, 1H), 4.33 (d, *J* = 12.1 Hz, 1H), 4.24 (d, *J* = 12.1 Hz, 1H), 4.03 (d, *J* = 11.6 Hz, 1H), 3.78−3.68 (m, 1H), 3.65 (t, *J* = 8.5 Hz, 1H), 3.41 (s, 3H), 3.16 (dd, *J* = 13.0, 9.4 Hz, 1H), 3.12−3.04 (m, 2H), 2.97 (m, 1H), 2.88 (dd, *J* = 8.8, 4.1 Hz, 1H), 2.73 (m, 1H), 2.38−2.25 (m, 2H), 2.18−2.02 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 158.8, 140.4, 139.6, 139.3, 131.8, 130.4, 127.5, 115.1, 114.3, 92.7, 77.9, 76.3, 74.6, 71.2, 70.5, 60.0, 54.9, 52.2, 39.4, 35.8, 30.2, 27.4, 24.9; MS (*m/z*) 526, 404, 376, 312, 192, 121, 91; EI-HRMS calcd for $C_{34}H_{39}NO_4$ $[M + H]^+$ (*m/z*) 526.2957, found 526.2934.

2-Methoxybut-3-enoic Acid [2-Benzyloxy-2-(8-benzyloxy-1,4-dioxaspiro[4.5]dec-7-yl)-1-(4-methoxybenzyl)ethyl]amide (26). To amide **22** (713 mg, 1.19 mmol) in MeI (10 mL) was added $CaSO_4$ (800 mg, 5.88 mmol), then Ag_2O (550 mg, 2.37 mmol) in a single portion. The reaction was stirred for 12 h at room temperature then filtered through Celite. The filter cake was washed with Et_2O (30 mL) and the filtrate was concentrated in vacuo to give methoxy amide **26** (700 mg, 96%) as a white solid. The white solid was purified by flash column chromatography over silica gel eluting with 50:50 ethyl acetate:hexanes.

IR (KBr) 3426, 2939, 1668, 1506, 1248 cm^{-1}. Isomer 1: mp 142 °C; $[\alpha]^{25}_D$ +32.30 (*c* 0.020, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.25 (m, 7H), 7.20−7.13 (m, 3H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 8.5 Hz, 2H), 5.91−5.79 (ddd, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.47 (d, *J* = 17.2 Hz, 1H), 5.35 (d, *J* = 10.4 Hz, 1H), 4.72 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.36−4.25 (m, 2H), 4.10 (d, *J* = 6.0 Hz, 1H), 3.97 (d, *J* = 4.0 Hz, 1H), 3.94−3.85 (m, 6H), 3.61 (s, 3H), 3.38 (s, 3H), 3.24−3.17 (m, 1H), 2.81−2.64 (m, 2H), 2.44−2.34 (m, 1H), 2.15−2.03 (m, 1H), 1.91−1.83 (m, 1H), 1.75−1.65 (m, 1H), 1.65−1.45 (m, 2H), 1.40−1.28 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 158.4, 139.4, 138.8, 133.6, 130.7, 130.5, 128.8, 128.6, 128.4, 128.1, 127.5, 127.4, 118.7, 114.1, 108.7, 83.4, 76.8, 75.3, 71.4, 70.4, 64.6, 64.5, 57.7, 55.3, 50.4, 41.5, 39.7, 33.4, 32.7, 28.4. Isomer 2: $[\alpha]^{25}_D$ +22.58 (*c* 0.012, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.50−7.23 (m, 7H), 7.22−7.13 (m, 3H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 8.5 Hz, 2H), 5.81−5.69 (ddd, *J* = 17.2, 10.3, 6.2 Hz, 1H), 5.40 (d, *J* = 17.2 Hz, 1H), 5.30 (d, *J* = 10.3 Hz, 1H), 4.72 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.36 (d, *J* = 11.6 Hz, 1H), 4.39−4.25 (m, 1H), 4.07 (d, *J* = 7.2 Hz, 1H), 4.00 (d, *J* = 4.4 Hz, 1H), 3.94 (d, *J* = 11.8 Hz, 1H), 3.92−3.91 (m, 4H), 3.62 (s, 3H), 3.42 (s, 3H), 3.38−3.25 (m, 1H), 2.76−2.61 (m, 2H), 2.48−2.37 (m, 1H), 2.18−2.05 (m, 1H), 1.97−1.89 (m, 1H), 1.80−1.70 (m, 1H), 1.65−1.40 (m, 4H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 158.1, 139.1, 138.6, 133.8, 130.5, 130.3, 128.6, 128.3, 128.2, 127.9, 127.3, 118.6, 113.8, 108.5, 83.3, 76.5, 75.3, 71.3, 70.3, 64.4, 57.8, 55.1, 50.2, 41.4, 39.5, 33.2, 32.3, 28.0; MS (*m/z*) 616, 544, 494, 409, 253, 181, 121, 91, 71; EI-HRMS calcd for $C_{37}H_{45}NO_7$ $[M + H]^+$ (*m/z*) 616.3274, found 616.3291.

[2-Benzyloxy-2-(8-benzyloxy-1,4-dioxaspiro[4.5]dec-7-yl)-1-(4-methoxybenzyl)ethyl](2-methoxybut-3-enyl)-amine (27). To amide **26** (525 mg, 0.854 mmol) in freshly distilled toluene (20 mL) was added $LiAlH_4$ (195 mg, 2.56 mmol) in one portion at room temperature. The suspension was heated at 80 °C for 2 h and cooled to room temperature, then water was added dropwise until a white solid precipitated. To this mixture was added $MgSO_4$ then it was filtered through Celite. The filter cake was washed with Et_2O (30 mL) and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography over silica gel eluting first with 50:50 ethyl acetate:hexanes then a solution of NH_4OH/MeOH/CH_2Cl_2 (see general comments) to give amine **27** (497 mg, 97%) as a colorless oil.

IR (film) 3345, 2960 cm^{-1}. Isomer 1: $[\alpha]^{25}_D$ +57.32 (*c* 0.042, $CHCl_3$); ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.43−7.18 (m, 10H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.68 (d, *J* = 8.6 Hz, 2H), 5.76−5.64 (m, 1H), 5.23 (d, *J* = 15.8 Hz, 1H), 5.22 (d, *J* = 11.8 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.20 (d, *J* = 11.4 Hz, 1H), 3.93 (s, 4H), 3.71 (s, 3H), 3.64−3.45 (m, 3H), 3.20 (s, 3H), 3.13−3.05 (m, 1H), 2.81−2.70 (m, 3H), 2.65 (dd, *J* = 12.0, 6.8 Hz, 1H), 2.47−2.35 (m, 1H), 2.18−2.07 (m, 1H), 1.95−1.91 (m, 2H), 1.83−1.75 (m, 1H), 1.69−1.50 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 139.4, 139.1, 137.6, 132.1, 130.4, 128.4, 128.3, 127.8, 127.7, 127.5, 127.4, 117.9, 113.8, 108.9, 83.0, 80.4, 77.5, 77.0, 72.8, 70.4, 64.4, 61.4, 56.3, 55.2, 52.6, 41.5, 37.3, 35.3, 32.6, 28.0. Isomer 2: $[\alpha]^{25}_D$ +60.70 (*c* 0.023, $CHCl_3$); ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.43−7.20 (m, 10H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 5.76−5.64 (m, 1H), 5.25 (d, *J* = 15.2 Hz, 1H), 5.24 (d, *J* = 12.4 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 4.18 (d, *J* = 11.4 Hz, 1H), 3.94 (s, 4H), 3.72 (s, 3H), 3.72−3.61 (m, 2H), 3.54−3.46 (m, 1H), 3.29 (s, 3H), 3.13−3.05 (m, 1H), 2.90 (dd, *J* = 11.8, 7.5 Hz, 1H), 2.85−2.72 (m, 2H), 2.61 (dd, *J* = 11.8, 4.5 Hz, 1H), 2.53−2.43 (m, 1H), 2.20−2.11 (m, 1H), 2.00 (d, *J* = 8.2 Hz, 2H), 1.87−1.78 (m, 1H), 1.73−1.53 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 139.6, 139.4, 137.7, 132.4, 130.5, 128.6, 128.5, 128.1, 127.9, 127.7, 127.5, 118.0, 114.0, 109.1, 83.2, 80.0, 77.1, 77.0, 72.9, 70.5, 64.6, 64.5, 61.2, 56.6, 55.4, 52.8, 41.8, 37.3, 35.3, 32.7, 28.1; MS (*m/z*) 602, 570, 530, 480, 234, 139, 121, 91; EI-HRMS calcd for $C_{37}H_{47}NO_6$ $[M + H]^+$ (*m/z*) 602.3482, found 602.3508.

4-Benzyloxy-3-[1-benzyloxy-2-(2-methoxybut-3-enylamino)-3-(4-methoxyphenyl)propyl]cyclohexanone (28). To amine **27** (497 mg, 0.827 mmol) in THF (10 mL) was added 3 N HCl (10 mL) at room temperature and the reaction was stirred for 12 h. The resulting solution was carefully quenched with saturated $NaHCO_3$ solution and extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash column chromatography over silica gel eluting with 20:80 ethyl acetate:hexanes, 50:50 ethyl acetate:hexanes, and ethyl acetate to give ketoamine **28** (414 mg, 90%) as a 1:1 mixture of diastereomers.

IR (film) 3339, 2932, 1713 cm^{-1}. Isomer 1: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, 10H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 5.68−5.57 (m, 1H), 5.22 (d, *J* = 15.7 Hz, 1H), 5.20 (d, *J* = 11.8 Hz, 1H), 4.55 (s, 2H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.35 (d, *J* = 11.6 Hz, 1H), 3.93−3.85 (m, 1H), 3.75 (s, 3H), 3.58−3.50 (m, 1H), 3.46 (t, *J* = 4.7 Hz, 1H), 3.17 (s, 3H), 3.05−2.95 (m, 1H), 280−2.45 (m, 9H), 2.32−2.13 (m, 2H), 2.05−1.88 (m, 1H), 1.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.5, 158.1, 138.6, 138.5, 137.2, 131.4, 130.2, 128.5, 128.0, 127.7, 118.2, 114.0, 82.7, 81.2, 74.1, 73.7, 70.5, 61.4, 56.3, 55.3, 52.5, 43.3, 41.2, 37.0, 36.9, 27.7. Isomer 2: $[\alpha]^{25}_D$ +47.50 (*c* 0.014, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.34 (m, 10H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.79−5.67 (m, 17.5 Hz, 1H), 5.28 (d, *J* = 12.0 Hz, 1H), 5.27 (d, *J* = 15.4 Hz, 1H), 4.66 (s, 2H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.20−3.95 (m, 1H), 3.82 (s, 3H), 3.73−3.63 (m, 1H), 3.57 (t, *J* = 4.6 Hz, 1H), 3.34 (s, 3H), 3.15−3.07 (m, 1H), 2.94−2.55 (m, 9H), 2.42−2.22 (m, 2H), 2.10−1.97 (m, 1H), 1.97−1.75 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.3, 158.1, 138.6, 137.2, 131.4, 130.2, 128.5, 128.0, 127.7, 118.0, 114.0, 82.8, 80.7, 77.0, 74.1, 73.5, 70.5, 61.2, 56.4, 55.3, 52.6, 43.4, 41.1, 37.0, 36.8, 27.7; MS (*m/z*) 558, 526, 436, 234, 121, 91, 71; EI-HRMS calcd for $C_{35}H_{43}NO_5$ $[M + H]^+$ (*m/z*) 558.3219, found 558.3229.

[7,9-Bisbenzyloxy-6-(4-methoxybenzyl)-5-azatricyclo-[6.3.1.01,5]dodec-3-yl]methanol (29). A flask equipped with a Dean Stark apparatus was charged with ketoamine **28** (230 mg, 0.413 mmol), benzene (20 mL), then *p*-TsOH (94 mg, 0.50 mmol) in a single portion. The solution was slowly heated to reflux over 30 min then maintained at that temperature for 3 h. Next, the solution was cooled to room temperature and saturated $NaHCO_3$ was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude residue was dissolved in THF (20 mL) then cannulated into $NaBH_4$ (30 mg, 0.79 mmol) in MeOH (10 mL) at −78 °C over 10 min. The resulting solution was allowed to warm to room temperature. At room temperature, ice water (10 mL) was added to the reaction and the aqueous layer was separated and extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash chromatography over silica gel eluting with a solution of NH_4OH/MeOH/CH_2Cl_2 (see general comments) to give amino alcohol **29** (major **29**α: 91 mg, 42%; minor **29**β: 41 mg, 21%).

In situ epimerization with L-phenylalanine: A flask equipped with a Dean Stark apparatus was charged with ketoamine **28** (20 mg, 0.036 mmol), benzene (20 mL), then *p*-TsOH (8 mg, 0.04 mmol) in a single portion. The reaction was heated to reflux for 3 h. Upon complete consumption of ketoamine **28** by TLC, L-phenylalanine (6 mg, 0.04 mmol) was added and the solution was refluxed for an additional 2 h. The reaction was cooled to room temperature and quenched with saturated $NaHCO_3$. The organic phase was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude residue was dissolved in THF (5 mL) then cannulated into a solution of $NaBH_4$ (10 mg, 0.26 mmol) in MeOH (0.2 mL) at −78 °C. The resulting solution was allowed to warm to room temperature. At room temperature, ice water (5 mL) was added and the aqueous layer was separated and extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried with $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography over silica gel eluting with a solution of NH_4OH/MeOH/CH_2Cl_2 (see general comments) to give amino alcohol **29** (minor **29**α: 4.3 mg; major **29**β: 9.0 mg).

IR (film) 3396, 2928 cm^{-1}. Isomer 1 (**29**α): $[\alpha]^{25}_D$ +73.84 (*c* 0.058, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.24 (m, 10H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.43 (s, 2H), 4.16 (d, *J* = 11.7 Hz, 1H), 3.81 (s, 3H), 3.67 (dd, *J* = 9.9, 5.2 Hz, 1H), 3.56 (dd, *J* = 15.8, 5.8 Hz, 1H), 3.37−3.25 (m, 2H), 3.17 (br s, 1H), 3.08 (dd, *J* = 9.3, 4.0 Hz, 1H), 2.99−2.80 (m, 4H), 2.50 (s, 1H), 2.33 (br s, 1H), 2.03−1.77 (m, 5H), 1.70 (dd, *J* = 12.2, 9.4 Hz, 1H), 1.60−1.48 (m, 1H), 1.47 (dd, *J* = 12.2, 6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 139.3, 139.2, 131.9, 130.5, 128.7, 127.8, 127.7, 114.0, 77.6, 75.7, 74.9, 71.4, 70.5, 67.8, 64.1, 60.8, 59.4, 55.5, 54.6, 51.8, 43.3, 36.7, 36.6, 36.0, 27.8, 27.5. Isomer 2

(**29**β): $[\alpha]^{25}_D$ +42.52 (*c* 0.050, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.24 (m, 10H), 7.07 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 4.54 (d, J = 11.6 Hz, 1H), 4.48 (d, J = 12.1 Hz, 1H), 4.42 (d, J = 12.1 Hz, 1H), 4.16 (d, J = 11.6 Hz,-1H), 3.80 (s, 3H), 3.68 (dd, J = 9.8, 4.3 Hz, 1H), 3.57−3.43 (m, 3H), 3.33 (br s, 1H), 3.07 (dd, J = 12.9, 10.3 Hz, 1H), 2.96−2.89 (m, 2H), 2.84 (dd, J = 13.0, 4.8 Hz, 1H), 2.52 (s, 1H), 2.25 (m, 1H), 2.12−1.95 (m, 2H), 1.95−1.70 (m, 4H), 1.55−1.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 139.3, 139.2, 131.9, 130.5, 130.4, 128.7, 128.6, 127.7, 127.5, 114.1, 76.3, 74.9, 71.4, 70.7, 68.5, 59.2, 58.9, 55.5, 52.1, 43.4, 36.9, 36.1, 36.0, 31.4, 30.0, 27.2, 23.5, 23.0; MS (*m/z*) 526, 436, 406, 314, 121, 91; EI-HRMS calcd for $C_{34}H_{41}NO_4$ $[M - H]^+$ (*m/z*) 526.2957, found 526.2961.

7,9-Bisbenzyloxy-6-(4-methoxybenzyl)-5-azatricyclo-[6.3.1.0^{1,5}]dodecane-3-carboxylic Acid (33β). A flask was charged with CrO_3 (48 mg, 0.48 mmol) then 1.5 M H_2SO_4 (0.64 mL, 0.96 mmol). To this solution was added the amino alcohol **29**β in acetone (5 mL) dropwise over 5 min. The resulting solution was stirred for 5 h at room temperature then 0.2 mL of *i*-PrOH was added and the solution was stirred for an additional 30 min. The mixture was filtered through Celite. The filter cake was washed with $CHCl_3$ (5 mL) and the filtrate was concentrated in vacuo. The residue was diluted with brine and extracted with ethyl acetate (4 × 5 mL). The combined organic phases were washed with water (3 mL) and brine (3 mL), dried with $MgSO_4$, and concentrated in vacuo to give amino acid **33**β (52 mg, 100%) that was used in the next step without further purification. The ^1H NMR of this material showed a broad singlet at 12.1 ppm and the IR showed an absorption at 2925 (OH) and 1732 cm^{-1} (C=O).

[7,9-Bisbenzyloxy-6-(4-methoxybenzyl)-5-azatricyclo-[6.3.1.0^{1,5}]dodec-3-yl]carbamic Acid Methyl Ester (34β). Amino acid **33**β (52 mg, 0.096 mmol) was dissolved in freshly distilled acetone (5 mL) and the solution was cooled to 0 °C. Triethylamine (0.052 mL, 0.37 mmol) and ethyl chloroformate (0.021 mL, 0.22 mmol) were added and the reaction was stirred for 1 h at 0 °C. Next NaN_3 (0.044 mL of a 5.0 M aqueous solution, 0.22 mmol) was added and this solution was stirred for 1 h at 0 °C and 15 min at room temperature, then the solution was diluted with water (3 mL) and extracted with $CHCl_3$ (3 × 5 mL). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was azeotroped once with benzene under reduced pressure. The IR spectra of **31**β showed acyl azide absorptions at 1714 and 2138 cm^{-1}. The acyl azide **31**β was dissolved in freshly distilled toluene (20 mL) and heated at 90 °C for 45 min. Progress of this reaction was followed by taking aliquots and monitoring the formation of the isocyanate by IR (1699 and 2265 cm^{-1}). Upon complete disappearance of the acyl azide absorptions, MeOH (1 mL) was added to the reaction and it was heated at 90 °C for 6 h. The solution was cooled to room temperature and concentrated in vacuo. The crude residue was purified by a flash chromatography over silica gel eluting first with 50:50 ethyl acetate: hexanes then a solution of $NH_4OH/MeOH/CH_2Cl_2$ (see general comments) to give methyl carbamate **34**β (43 mg, 78%) as a colorless oil.

IR (film) 3323, 2930, 1717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.23 (m, 10H), 7.08 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 5.48 (br s, 1H), 4.52 (d, J = 11.5 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.41 (d, J = 12.0 Hz, 1H), 4.29 (br s, 1H), 4.18 (d, J = 11.7 Hz, 1H), 3.82−3.75 (m, 1H), 3.80 (s, 3H), 3.64 (s, 3H), 3.62−3.51 (br s, 1H), 3.34 (br s, 1H), 3.07−2.90 (m, 4H), 2.51 (br s, 1H), 2.20 (m, 1H), 2.10−1.85 (m, 6H), 1.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 156.7, 138.6, 138.3, 130.2, 128.6, 128.5, 127.7, 127.5, 127.4, 114.0, 74.6, 73.7, 71.5, 70.6, 59.2, 55.6, 55.3, 52.1, 47.2, 36.0, 34.8, 30.0, 26.4, 23.2; MS (*m/z*) 569, 530, 479, 464, 449, 417, 91, 71, 57; EI-HRMS calcd for $C_{35}H_{42}N_2O_5$ $[M - H]^+$ (*m/z*) 569.3015, found 569.3007.

[7,9-Bisbenzyloxy-6-(4-methoxybenzyl)-5-azatricyclo-[6.3.1.0^{1,5}]dodec-3-yl]methylamine (32β). A solution of methyl carbamate **34**β (41 mg, 0.072 mmol) in THF (10 mL) was cannulated into $LiAlH_4$ (16 mg, 0.43 mmol) at room temperature and the reaction was refluxed for 3 h. The reaction was cooled to room temperature, then water was added dropwise until a white solid precipitated. To this mixture was added $MgSO_4$ then the solution was filtered through Celite. The filter cake was washed with Et_2O (20 mL) and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography over silica gel eluting first with 50:50 ethyl acetate:hexanes then a solution of $NH_4OH/MeOH/CH_2Cl_2$ (see general comments) to give amine **32**β (31 mg, 82%).

$[\alpha]^{25}_D$ +38.40 (*c* 0.015, $CHCl_3$); IR (film) 3309 (br), 2929 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, 10H), 7.08 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 4.50 (d, J = 11.6 Hz, 1H), 4.45 (d, J = 12.1 Hz, 1H), 4.42 (d, J = 12.1 Hz, 1H), 4.17 (d, J = 11.6 Hz, 1H), 3.82 (s, 3H), 3.56 (dd, J = 9.7, 7.6 Hz, 1H), 3.49−3.42 (m, 1H), 3.30 (m, 1H), 3.22−3.13 (m, 1H), 3.02 (dd, J = 13.0, 10.2 Hz, 1H), 2.93−2.85 (m, 2H), 2.72 (dd, J = 9.8, 3.6 Hz, 1H), 2.48 (m, 1H), 2.36 (s, 3H), 2.20−1.92 (m, 1H), 1.97 (dd, J = 12. 9, 8.6 Hz, 1H), 1.90−1.75 (m, 4H), 1.62 (dd, J = 12.8, 2.8 Hz, 1H), 1.44−1.33 (m, 1H), 1.27 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 139.0, 138.9, 131.8, 130.2, 128.5, 127.5, 113.8, 75.9, 74.6, 71.3, 70.3, 59.5, 58.9, 56.5, 55.3, 54.6, 49.7, 47.7, 36.4, 35.7, 35.0, 30.1, 26.9, 24.5; MS (*m/z*) 525, 435, 405, 149, 91, 69; EI-HRMS calcd for $C_{34}H_{42}N_2O_3$ $[M - H]^+$ (*m/z*) 525.3117, found 525.3110.

[7,9-Bisbenzyloxy-6-(4-methoxybenzyl)-5-azatricyclo-[6.3.1.01,5]dodec-3-yl]methylcarbamic Acid *tert*-Butyl Ester. To amine **32**β (13 mg, 0.027 mmol) in ethyl acetate (5 mL) was added Et_3N (0.1 mL), followed by $(Boc)_2O$ (12 mg, 0.055 mmol) at room temperature. After 7 h, the solution was concentrated in vacuo, and the residue was purified by flash column chromatography eluting with 50:50 hexanes:ethyl acetate to give the corresponding carbamate (15 mg, 90%).

$[\alpha]^{25}_D$ +19.50 (*c* 0.026, $CHCl_3$); IR (film) 2928, 1687, 1247, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.27 (m, 10H), 7.14 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 4.87 (br s, 1H), 4.58 (d, J = 11.7 Hz, 1H), 4.51 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 12.1 Hz, 1H), 4.21 (d, J = 11.7 Hz, 1H), 3.80 (s, 3H), 3.70 (br s, 1H), 3.64−3.53 (m, 1H), 3.39 (br s, 1H), 3.10−2.82 (m, 4H), 2.75 (s, 3H), 2.56 (br s, 1H), 2.18−2.06 (m, 2H), 2.04−1.82 (m, 4H), 1.80−1.65 (m, 2H), 1.58−1.45 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 156.0, 139.1, 138.9, 131.8, 130.1, 128.5, 127.6, 127.5, 127.2, 113.8, 79.3, 74.7, 71.3, 70.4, 58.9, 58.0, 55.3, 51.1, 43.8, 36.5, 35.7, 31.6, 28.7, 26.9; MS (*m/z*) 624, 569, 553, 535, 505, 449, 415, 359, 121, 91, 71; EI-HRMS calcd for $C_{35}H_{41}N_2O_5$ ($C_{39}H_{50}N_2O_5$ − C_4H_9) $[M]^+$ (*m/z*) 569.3015, found 569.3041.

[7,9-Dihydroxy-6-(4-methoxybenzyl)-5-azatricyclo-[6.3.1.0^{1,5}]dodec-3-yl]methylcarbamic Acid *tert*-Butyl Ester (35β). To the carbamate (13 mg, 0.029 mmol) in MeOH (5 mL) was added $Pd(OH)_2/C$ (119 mg). The vessel was flushed with H_2 and shaken for 12 h under 50 psi of H_2 pressure in a Parr hydrogenation apparatus. The resulting solution was filtered through Celite (5 g) and the filtrate was concentrated in vacuo to give diol **35**β (7 mg, 78%) as colorless oil. The ^1H NMR spectrum shows very broad signals except for the aromatic (doublets), methoxy (singlet), and *tert*-butyl (singlet) resonances. Similar observations were seen by Snider on a closely related substrate.[2a]

[9-(Bisbenzyloxyphosphoryloxy)-7-hydroxy-6-(4-methoxybenzyl)-5-azatricyclo[6.3.1.0^{1,5}]dodec-3-yl]methylcarbamic Acid *tert*-Butyl Ester (36β). To a solution of diol **35**β (4 mg, 0.009 mmol) in dry CH_2Cl_2 (2 mL) was added 1*H*-tetrazole (61 μL of a 3% in CH_3CN solution, 0.021 mmol), followed by addition of *N,N*-diisopropyl dibenzyl phosphoramidite (6.0 μL, 0.054 mmol). The reaction was stirred at room temperature for 2 h then cooled to 0 °C before adding *t*-BuOOH (2.0 μL of 5−6 M in decane, 0.090 mmol). After 45 min, a saturated $Na_2S_2O_3$ solution was added, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic phases were washed with

water (2 mL) and brine (2 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography eluting with a solution of $NH_4OH/MeOH/CH_2Cl_2$ (see general comments) to give phosophate **36**β (2 mg, 38%). The ^1H NMR and ^{13}C NMR spectral data completely matched that reported by Sorensen.[2b]

$[\alpha]^{25}_D$ +7.4 (*c* 0.002, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.28 (m, 10H), 7.16 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.03−4.98 (m, 4H), 4.75 (br s, 1H), 4.33 (br s, 1H), 3.81 (s, 3H), 3.41 (m, 1H), 3.31 (m, 1H), 3.15 (br s, 1H), 2.80 (m, 2H), 2.73 (s, 3H), 2.70 (m, 1H), 2.12 (br s, 1H), 2.02 (m, 1H), 1.87 (dd, J = 13.3, 10.4 Hz, 1H), 1.87−1.75 (m, 4H), 1.64−1.50 (m, 2H), 1.46 (s, 9H), 1.41 (dd, J = 13.1, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 156.0, 136.1, 130.9, 130.2, 128.7, 128.1, 114.0, 79.6, 75.1, 69.4, 67.0, 58.6, 58.5, 55.4, 51.5, 50.3, 43.6, 43.1, 35.9, 29.9, 28.9, 28.7; MS (*m/z*) 706, 675, 661, 647, 633, 619, 585, 379, 274, 207, 163, 147, 105, 91, 79; EI-HRMS calcd for $C_{39}H_{52}N_2O_8P$ $[M + H]^+$ (*m/z*) 707.3461, found 707.3452.

Acknowledgment. We thank the University of Pittsburgh and the National Institutes of Health for supporting this research and Dr. Steven Geib, University of Pittsburgh, and Dr. Jeff Petersen, West Virginia University, for X-ray crystallographic analysis. We also thank Professor Eric Sorensen for generously providing of ^1H and ^{13}C spectra of compound **36**β. We also would like to thank Li Sha for early investigations of this project.

Supporting Information Available: Spectra for all new compounds and X-ray crystallographic data (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

JO0483567