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Synthetic Studies Toward (−)-FR901483 Using a Conjugate Allylation To Install the C-1 Quaternary Carbon

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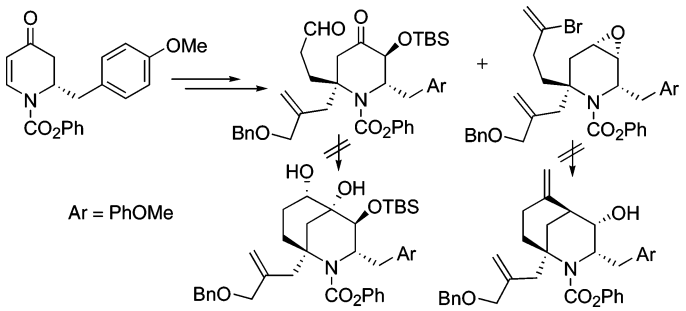

Two approaches to the aza-tricyclo dodecane skeleton of (−)-FR901483 are reported. Both routes utilized a Grignard addition to an *N*-acylpyridinium salt to establish the absolute stereochemistry at C-6 and a highly diastereoselective conjugate allylation reaction to form the quaternary center at C-1 of the natural product in an excellent yield. Although the desired polysubstituted piperidine intermediates were prepared regio- and stereoselectively, the construction of the C-8/C-9 bond connectivity could not be achieved. All attempts at a pinacol cyclization or an intramolecular *6-exo-tet* epoxide opening were unsuccessful because of an unfavorable $A^{(1,3)}$ strain inherent in the molecule.

Introduction

The immunosuppressive natural products cyclosporine A and FK 506 are leading therapeutic agents in the organ transplant field.[1,2] The mechanism of action of both cyclosporin A and FK 506 is the inhibition of calcineurin, a calcium-dependent serine/threonine phosphatase. Calcineurin, in turn, leads to the inhibition of interleukin-2 production, which is a signal molecule that induces cytotoxic T-cells. In high doses these two compounds exhibit serious side effects such as neurotoxicity and adverse reactions in diabetic patients.[3] Because of this, the search for less toxic immunosuppressants with a different mechanism of action has emerged. These efforts led to the isolation of (−)-FR901483 (**1**) from the fermentation broth of the fungal strain *Cladobotrium* species No. 11231 by the Fujisawa research group, and it was shown to significantly prolong the graft survival time in the rat skin allograft model.[4] More importantly, it was suggested that the mechanism of action is quite different as compared to cyclosporin A and FK 506; namely, (−)-FR901483 inhibits the *adenylosuccinate synthetase* and/or *adenylosuccinate lyase* enzymes in the purine biosynthesis. Because of the high degree of bioactivity and the unprecedented azatricyclic structure of (−)-FR901483, it has become a popular target of synthetic interest.[5]

(1) *Cyclosporin A*; Borel, J. F., Ed.; Elsevier Biochemical Press: Amsterdam, 1982.

(2) Schreiber, S. L. *Cell* **1992**, *70*, 365.

(3) (a) Schreiber, S. L. *Science* **1991**, *251*, 283. (b) Kannedy, M. S.; Deeg, H. J.; Storb, N.; Thomas, E. D. *Transplant. Proc.* **1983**, *15*, 471.

(4) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *46*, 37.

(5) 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 syntheses 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,; Fukujama, T. *Org. Lett.* **2004**, *6*, 2729. (f) Brummond, K. M.; Hong, S.-P. *J. Org. Chem.* **2005**, *70*, 907. For approaches to FR901483 and its analogues, see: (g) Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391. (h) Yamazaki, N.; Suzuki, H.; Kibajashi, C. *J. Org. Chem.* **1997**, *62*, 8280. (i) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E.-M. *Tetrahedron Lett.* **1998**, *39*, 4667. (j) Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442. (k) Bonjoch, J.; Diaba, F.; Puigbo, E.; Sole, D.; Segarra, V.; Santamaria, L.; Beleta, J.; Ryder, H.; Palacios, J.-M. *Bioorg. Med. Chem.* **1999**, *7*, 2891. (l) Brummond, K. M.; Lu, J. *Org. Lett.* **2001**, *3*, 1347. (m) Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 2353. (n) Bonjoch, J.; Diaba, F.; Puigbo, E.; Sole, D. *Tetrahedron Lett.* **2003**, *44*, 8387. (o) Panchaud, P.; Ollivier, C.; Renaud, P.; Zigmantas, S. *J. Org. Chem.* **2004**, *69*, 2755. (p) Kropf, J. E.; Meigh, I. C.; Bebbington, M. W. P.; Weinreb, S. M. J. *Org. Chem.* **2006**, *71*, 2046. (q) Simila, S. T. M.; Reichelt, A.; Martin, S. F. *Tetrahedron Lett.* **2006**, *47*, 2933.

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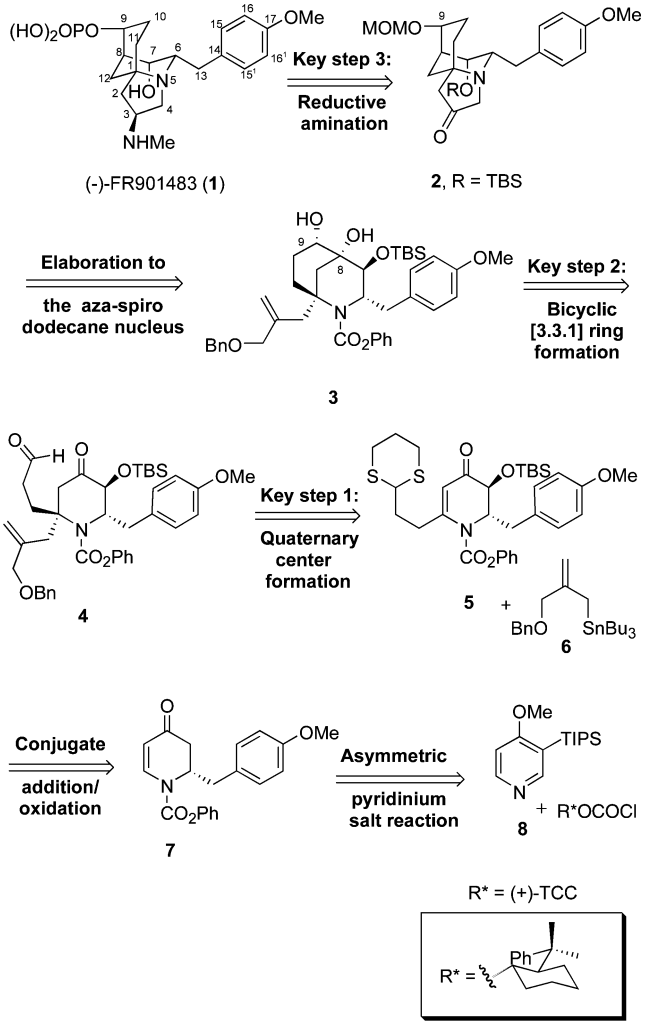
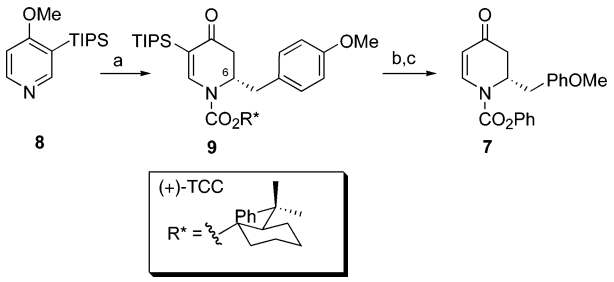
SCHEME 1. First Generation Retrosynthetic Analysis of (−)-FR901483



In the previous syntheses of (−)-FR901483 (**1**), the pyrrolidine portion of the aza-tricyclo dodecane nucleus was installed utilizing a nitrone cycloaddition/hydrogenolysis,[5a] an oxidative spiroannulation,[5b,c] a Diels−Alder cycloaddition/aldol cyclization,[5d] a Michael addition/hydrogenolysis,[5e] or an aza-Cope rearrangement/Mannich cyclization tactic.[5f] Most of the approaches to the bicyclic [3.3.1]-ring system of **1** utilized an intramolecular aldol cyclization reaction.[5a−e] Alternatively, the bicyclic [3.3.1]-ring system can be installed through an intermediate bridgehead imminium ion, followed by an intramolecular aza-Cope rearrangement[5f] or an intermolecular alkylation.[5h] The [3.3.1]-nonane nucleus was also successfully introduced utilizing an intramolecular carboradical cyclization.[5g,m] Our approach to the synthesis of **1** significantly differs from the previous synthetic endeavors in both strategy and execution. Retrosynthetically, we envisioned that target **1** could be derived via a reductive amination of ketone **2**, followed by phosphorylation at C-9 (Scheme 1). Ketone **2**, in turn, could be synthesized from diol **3** by the selective formation and reduction of a tertiary carbocation at C-8. Unlike the other approaches to **1**, we chose to exploit a Mitsunobu-type cyclization to construct the pyrrolidine portion of the aza-tricyclo dodecane nucleus. This would then be followed by an oxidative cleavage of the double bond to give compound **2**. Diol **3**, in turn, could be obtained by performing an intramolecular pinacol cyclization of keto-

SCHEME 2. Synthesis of Dihydropyridone 6[a]



[a] Reaction conditions: (a) (+)-TCC chloroformate, −78 °C; then *p*-OMeBnMgCl; then H_3O^+ (89%, dr = 95:5); (b) NaOMe, MeOH; then H_3O^+ (90%); (c) *n*-BuLi, THF; then PhOCOCl (98%).

aldehyde **4**, which could be accessed by a conjugate addition of an allylsilane or allyltin reagent, such as **6** to dihydropyridone **5**. Vinylogous amide **5** can be accessed via a tandem conjugate addition/oxidation in dihydropyridone **7**. Finally, Grignard addition to the chiral 1-acylpyridinium salt **8** is expected to furnish enantiopure **7**.

Results and Discussion

Our approach to the synthesis of (−)-FR901483 (**1**) commenced with Grignard addition to the chiral 1-acylpyridinium salt prepared from 3-triisopropylsilyl-4-methoxypyridine (**8**) and the chloroformate of (+)-*trans*-2-(α)-cumylcyclohexanol (TCC), thus establishing the absolute stereochemistry at the C-6 position of the resulting dihydropyridone **9** (90%, dr 95:5, Scheme 2).[6,7] The resulting dihydropyridone **9** was obtained as a single diastereomer after recrystallization from ethyl acetate/hexanes. A one-pot reaction with sodium methoxide in methanol to remove the chiral auxiliary, followed by protodesilylation with 10% aqueous HCl, yielded an intermediate vinylogous amide,[8] which in turn was reacylated by exposure to *n*-BuLi and phenyl chloroformate to give dihydropyridone **7** as a single enantiomer.

After establishing a practical route to the optically active dihydropyridone **7**, we turned our attention to the synthesis of racemic intermediates for initial studies of the feasibility of the proposed pinacol coupling and of reductive amination reactions (Scheme 1). Use of the enantiopure **7** would lead to the asymmetric synthesis of **1**, since once the absolute stereochemistry at C-6 is established, the rest of the stereocenters will be introduced relative to the one at C-6 in the same manner as in the racemic route. The addition of *p*-methoxybenzylmagnesium chloride to the 1-acylpyridinium salt, prepared from 4-methoxypyridine (**10**) and phenyl chloroformate, provided dihydropyridone **11** in a 77% yield (Scheme 3).[6] Copper-mediated addition of the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxolane to compound **11** in the presence of trimethylsilylchloride (TMSCl) afforded the desired silyl enol ether **12**, which was then subjected to catalytic $Pd(OAc)_2$ oxidative rearrangement conditions to give vinylogous amide **13** in a 70% yield (two steps).[9] A reaction of dihydropyridone **13** with $Pb(OAc)_4$ resulted in C-3 acetoxylation to give acetate **15a** as the

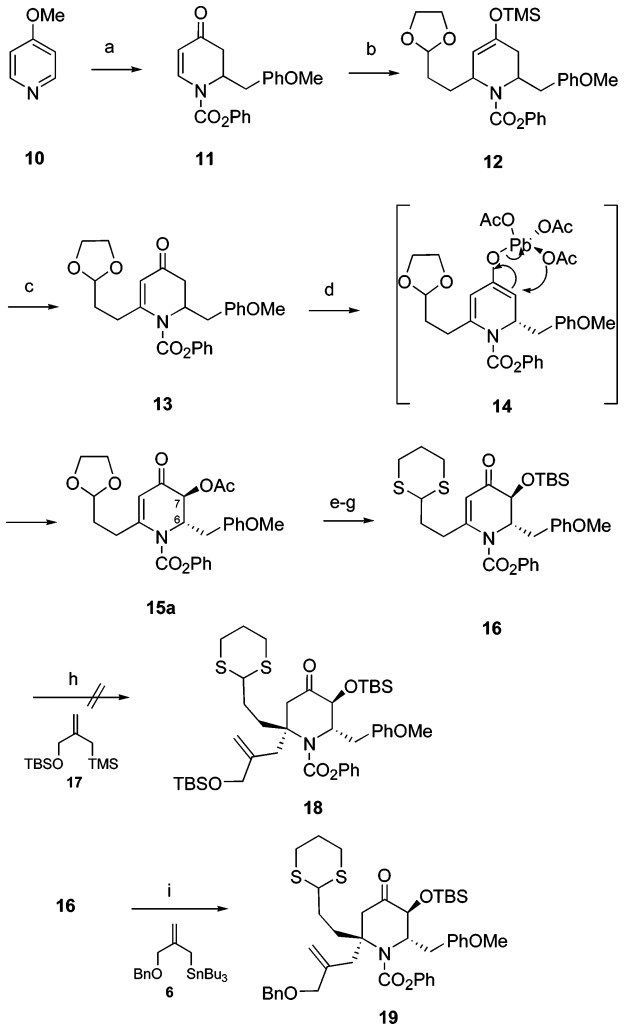
(6) (a) Comins, D. L.; Zhang, Y.-M.; Joseph, S. P. *Org. Lett.* **1999**, *1*, 657. (b) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719.

(7) The numbering scheme adopted is based on the accepted numbering for the natural product (−)-FR901483 (compound **1**, Scheme 1).

(8) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549.

(9) Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. *Tetrahedron Lett.* **1995**, *36*, 2423.

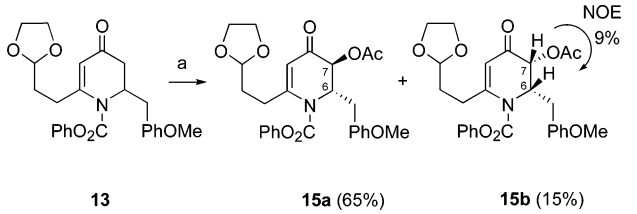
SCHEME 3. C-1 Quaternary Center Installation via Conjugate Allylation[a]



[a] Reactions conditions: (a) PhOCOCl, −78 °C; then *p*-MeOBnMgCl; then H_3O^+ (91%); (b) CuBr·SMe_2, TMSCl, Et_3N, (2-[1,3]dioxolan-2-yl-ethyl)-magnesium bromide (used crude); (c) $Pd(OAc)_2$ (0.1 equiv), CuCl (1 equiv), O_2, CH_3CN, 65 °C (70%, two steps); (d) $Pb(OAc)_4$, toluene, reflux (75%, dr = 15:1); (e) $ScOTf_3$ (0.2 equiv), H_2O:MeOH 1:4 (100%); (f) TBSCl, imidazole (90%); (g) BF_3·OEt_2, $HS(CH_2)_3SH$ (95%); (h) $TiCl_4$, CH_2Cl_2; (i) TMSOTf, CH_2Cl_2 (65%, dr = 5.5:1).

major diastereomer (75%, dr 15:1).[10] The resulting trans stereochemistry can be explained by stereoelectronic control: in order to maintain a chairlike transition state, intramolecular delivery of the acetate group from the enol-lead triacetate intermediate **14** takes place from the axial direction (Scheme 3).[10] The C-6 substituent is in an axial orientation due to the $A^{(1,3)}$ strain, with the *N*-acyl group leading to the observed major diastereomer **15a**.[11] The stereochemistry of the major diastereomer **15a** was confirmed by subjecting vinylogous amide **13** to a mixture of $Pb(OAc)_4$ and 5% of AcOH for 3 days at reflux to give a 4:1 mixture of C-7 acetates (Scheme 4). A large NOE (9%) between H-6 and H-7 was observed in *cis*-acetate **15b**. No NOE was observed in the *trans*-acetate **15a** between H-6 and H-7. In addition, $J_{H6-H7} = 4.9$ Hz in **15b** and $J_{H6-H7} = 2.0$ Hz in **15a** were observed, confirming the assignment of **15a**.

SCHEME 4. Confirmation of the C-7 Stereochemistry[a]



[a] Reaction conditions: (a) $Pb(OAc)_4$, AcOH (5 mol %), toluene, reflux, 3 days.

After considerable experimentation, hydrolysis of *trans*-acetate **15a** was achieved by treatment with $Sc(OTf)_3$ in a 4:1 MeOH/H_2O mixture to afford the corresponding α-hydroxy ketone (Scheme 3).[12,13] Protection of the resulting secondary alcohol as a *tert*-butyldimethylsilyl (TBS) ether, followed by acetal exchange, gave dihydropyridone **16** in an 86% yield (three steps).[14] We then turned our attention to finding suitable reaction conditions to effect the conjugate allylation of compound **16** with the known allylsilane reagent **17**.[15] To our disappointment, the use of Sakurai's conjugate allylation conditions resulted only in the recovery of the starting materials, even at temperatures as high as −20 °C.[16]

In order to enhance the reactivity of the allylation reagent in the conjugate addition, we prepared the known allylstannane compound **6**.[17] The choice of compound **6** as the nucleophilic partner was deliberate, as allylstannane reagents of this type are known to be more reactive than the corresponding allylsilanes. This is due to the presence of a more anionic character on the carbon atom in the C−Sn bond, which makes it a weaker bond.[18] To our delight, conjugate allylation of dihydropyridone **16** with stannane **6** gave the desired piperidone **19** as the major product in a 65% yield (dr 5.5:1).[19] The observed stereochemistry of the major diastereomer can be explained by stereoelectronic-controlled axial approach of the nucleophile, where the incoming allyl group adds syn to the axial substituent at C-6.[20] The use of TMSOTf as the Lewis acid source in this type of transformation proved to be extremely important, as both the employment of BF_3·OEt_2 and $TiCl_4$ resulted in the isolation of

(10) Comins, D. L.; Stoltze, D. A.; Thakker, P.; McArdle, C. L. *Tetrahedron Lett.* **1998**, *39*, 5693.

(11) For reviews on $A^{(1,3)}$ strain, see: (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. (b) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(12) Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1999**, *40*, 1689.

(13) A variety of basic hydrolysis conditions (K_2CO_3, MeOH; KCN, MeOH) resulted in acetate hydrolysis together with carbamate removal or significant decomposition (DBU, MeOH; NH_3, MeOH). Other acidic type hydrolysis conditions (10% aqueous HCl, EtOH; 10% aqueous H_2SO_4, EtOH; HBF_4·OEt_2, MeOH) resulted in significant polymerization upon scale up.

(14) Acetal exchange was necessary as subjection of the (1,3)-dioxolane acetal protected version of compound **16** to the Sakurai conjugate allylation conditions (allyl silane **17**, $TiCl_4$, CH_2Cl_2) resulted in the Lewis acid coordinating to the acetal moiety leading to an attack at the side chain.

(15) (a) Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org. Synth.* **1984**, *62*, 58. (b) Marcó, I. E.; Plancher, J.-M. *Tetrahedron Lett.* **1999**, *40*, 5259. (c) Dumeunier, R.; Markó, I. E. *Tetrahedron Lett.* **2000**, *41*, 10219.

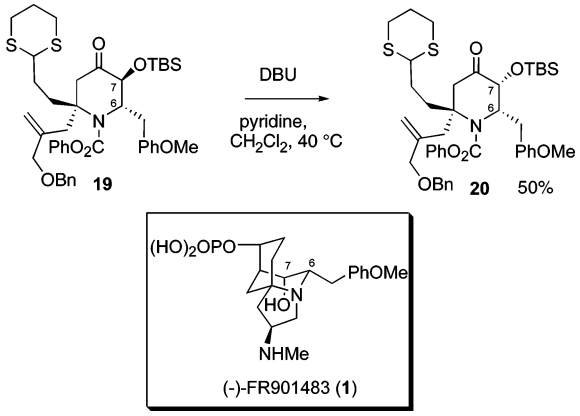
(16) Sakurai, H.; Hosomi, A.; Hayashi, J. *Org. Synth.* **1984**, *62*, 86.

(17) (a) Evans, D. A.; Rajapakse, H. A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4569. (b) Kelly, D. R.; Mahdi, J. G. *Tetrahedron Lett.* **2002**, *43*, 511.

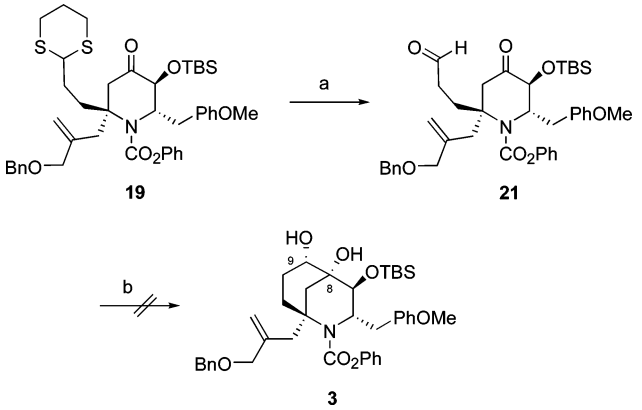
(18) Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954.

(19) The stereochemistry of the major diastereomer **19** is believed to be as depicted on the basis of an analogy with the allylation reaction in **25**, yielding the structurally similar compound **31** with unambiguously established stereochemical correlation of the substituents on the piperidone ring (see Scheme 8).

SCHEME 5. Epimerization of the Silyl Ether in Dihydropyridone 19



SCHEME 6. Attempted Pinacol Coupling of Keto-Aldehyde 21[a]



[a] Reaction conditions: (a) $CaCO_3$, MeI, H_2O:CH_3CN 1:9 (100%, crude); (b) see reagents in text.

starting material **16**. This, to the best of our knowledge, represents the first example of a Lewis acid mediated conjugate allylation performed on a substituted dihydropyridone to give the requisite quaternary carbon α to the nitrogen atom (C-1 in this case).[21] The conjugate allylation is unplagued by 1,2-addition and gives exclusively the 1,4-product. The reaction proceeds with good stereocontrol, making it an attractive way to establish quaternary centers stereoselectively in appropriately substituted dihydropyridone systems.

Next, we turned our attention to the epimerization of the C-7 silyl ether in piperidone **19**, since there is a cis stereochemical relationship between the two substituents at C-6 and C-7 in the natural product (Scheme 5). After considerable experimentation,[22a] we obtained the desired *cis*-epimer **20** on treatment with DBU, but only as a 1:1 mixture of stereoisomers at C-7. In an attempt to increase the yield of the desired compound, piperidone **19** was subjected to more forcing epimerization conditions (DBU, pyridine, $CHCl_3$, 80 °C); however, a complex mixture of products was observed, and the ratio of **20** to **19** did not improve. Apparently, our optimal conditions led to a 1:1 thermodynamic mixture of epimers at C-7.[23] At this point we decided to epimerize the C-7 center at a later stage in the synthesis.[24]

Next, hydrolysis of piperidone **19** in an aqueous iodomethane solution gave keto-aldehyde **21** in a quantitative yield, which was subsequently used without further purification (Scheme 6).[25] We were now in a position to investigate the proposed intramolecular pinacol coupling which would simultaneously set the stereocenters at C-8 and C-9 of diol **3**.[26] Unfortunately, after considerable effort using various conditions (VCl_3/Zn; $TiCl_3$/Zn−Cu; SmI_2), we were unable to achieve the desired transformation. All attempts led to the recovery of the starting materials or a complex mixture of products.

As a result of our inability to obtain the desired pinacol cyclization product **3**, we turned our attention to a second generation retrosynthetic approach to (−)-FR901483 (**1**; Scheme 7). Our analysis suggested that the targeted compound **1** could be derived via reductive amination in ketone **22**, followed by phosphorylation at C-9. The C-8/C-9 bond connectivity would, this time, be established by taking advantage of an intramolecular *6-exo-tet* epoxide opening of vinyl bromide **23**. This will again be followed by a Mitsunobu-type cyclization to construct the pyrrolidine portion of the aza-tricyclo dodecane nucleus in ketone **22**. Vinyl bromide **23** in turn would arise from α-hydroxy ketone **24** via a stereoselective carbonyl reduction, monomesylation of the less hindered alcohol at C-7 and from epoxide formation. Piperidone **24** would be accessed by the conjugate addition of allyltin reagent **6** to dihydropyridone **25**, once again providing the C-1 quaternary center stereoselectively. Vinylogous amide **25** would be synthesized from dihydropyridone **7** by our tandem conjugate addition/oxidative rearrangement protocol, followed by a regioselective installment of the vinyl bromide group and by introduction of the alcohol function at C-7.

Our second generation approach to the target began with exposure of dihydropyridone **11** to copper-mediated addition of the known Grignard reagent **26**[27] in the presence of TMSCl to give silyl enol ether **27** in a quantitative yield (Scheme 8).

(20) (a) Comins, D. L.; LaMunyon, D. H.; Chen, X. *J. Org. Chem.* **1997**, *62*, 8182. (b) Kuethe, J. T.; Comins, D. L. *Org. Lett.* **1999**, *1*, 1031. For discussions on stereoelectronic control in reactions of this type, see: (c) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry;* Pergamon: New York, 1983; Chapter 6. (d) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289.

(21) For a few examples of conjugate allylations in dihydropyridones unsubstituted α to the nitrogen at the vinylogous amide portion of the molecule, see: (a) Sato, M.; Aoyagi, S.; Yago, S.; Kibayashi, C. *Tetrahedron Lett.* **1996**, *37*, 9063. (b) Comins, D. L.; Killpack, M. O.; Despagnet, E.; Zeller, E. *Heterocycles* **2002**, *58*, 505. (c) Kranke, B.; Hebrault, D.; Schultz-Kukula, M.; Kunz, H. *Syn. Lett.* **2004**, *4*, 671.

(22) (a) See Table 1 in Supporting Information. (b) See Table 2 in Supporting Information.

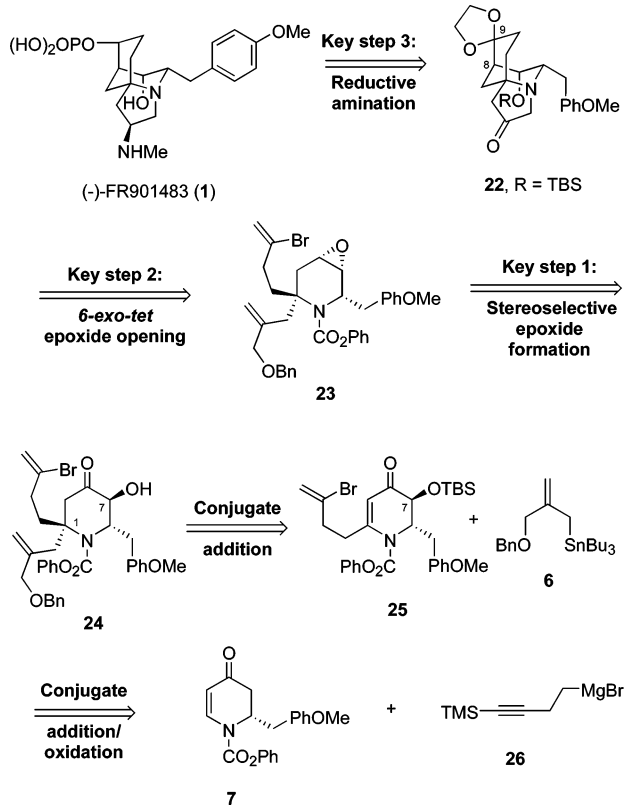
(23) MacSpartan Pro minimization employing MMFF conformer distribution of ketone **19** revealed that the compound existed in a twist-boat conformation with no apparent thermodynamic bias for the desired epimerization to take place.

(24) We could epimerize the C-7 acetate functionality **15a**, by prolonged exposure to acetic acid, and prepare the C-7 epimer of **16**. However, all our attempts at the conjugate allylation reaction to install the C-1 quaternary center failed, presumably resulting from the fact that the bulky TBS ether (which is now epimeric at C-7 in dihydropyridone **16**) blocks the α face during the addition step. Since this is the face the nucleophile has to approach in order to maintain a low energy, chairlike transition state, an attack does not occur.

(25) White, J. D.; Hanselmann, R.; Wardrop, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 1106.

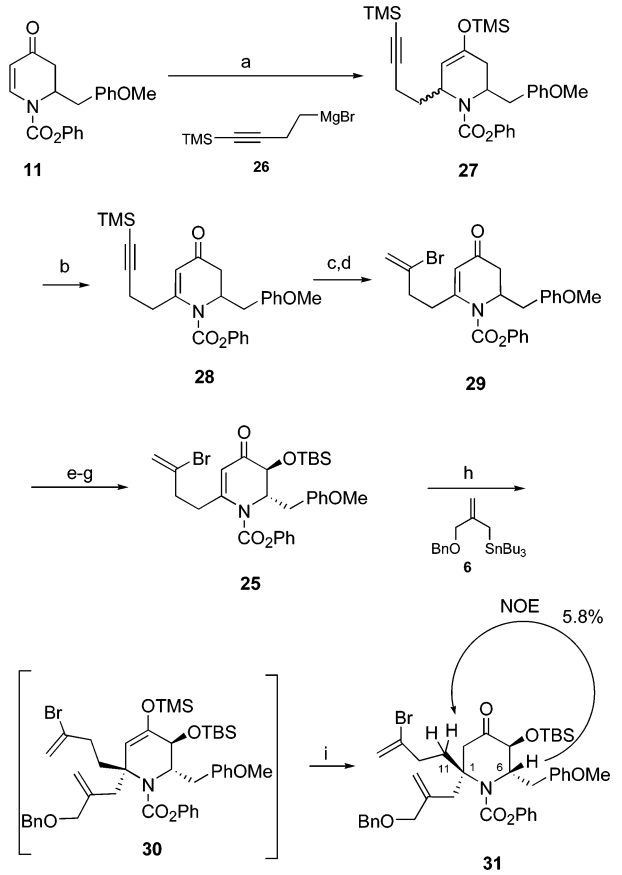
(26) (a) Dobler, M. R.; Bruce, I.; Cederbaum, F.; Cooke, N. G.; Diorazio, L. J.; Hall, R. G.; Irving, E. *Tetrahedron Lett.* **2001**, *42*, 8281. (b) Takahara, P. M.; Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *Tetrahedron Lett.* **1989**, *30*, 7177. (c) Matsumoto, T.; Yamaguchi, H.; Tanabe, M.; Yasui, Y.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 8393. (d) Kawatsura, M.; Kishi, E.; Kito, M.; Sakai, H.; Shirahama, H.; Matsuda, F. *Synlett* **1997**, *55*, 479. (e) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1988**, *53*, 2132. (f) Fleming, M.; McMurry, J. E. *Org. Synth.* **1982**, *60*, 113. (g) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513. (h) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321.

SCHEME 7. Second Generation Retrosynthetic Analysis



Subjection of **27** to premixed *o*-iodoxybenzoic acid (IBX) and 4-methoxypyridine *N*-oxide (MPO) afforded the desired dihydropyridone **28** in a 55% yield.[28,29] The versatility of this transformation is exemplified by the fact that the sensitive acetylene functionality is well tolerated under the reaction conditions.[30] Removal of the terminal trimethylsilyl group in **28** yielded the corresponding acetylene, which was then subjected to *B*-bromo-9-BBN to yield vinyl bromide **29** as a single regioisomer.[31] Reaction of **29** with $Pb(OAc)_4$ resulted in the corresponding *trans*-acetate.[32] $Sc(OTf)_3$-mediated hydrolysis of the acetate group was followed by protection of the resulting secondary alcohol as the TBS ether to yield dihydropyridone **25** (57%, three steps). Conjugate allylation with allylstannane **6** gave the desired trimethylsilyl enol ether **30** as a single diastereomer at C-1. Interestingly, compound **30** proved to be stable to silica gel chromatography and had to be subjected to acidic hydrolysis to yield the desired piperidone **31** in an 85% yield (two steps). We proceeded to establish the stereochemical relationship between the allylic group at C-1 and the benzylic substituent at C-6 in compound **31**. Irradiation of H_6 showed a large NOE correlation to H_{11} (5.8%), thus confirming the assigned stereochemistry. This result confirmed our working model that the conjugate addition of allylstannane **6** to C-6 substituted dihydropyridones indeed operated under stereoelectronic-approach control, where the incoming allylgroup adds syn to the axial substituent at C-6 in order to maintain a chairlike transition state.[20]

SCHEME 8. C-1 Quaternary Center Installation in Piperidone 31[a]



[a] Reaction conditions: (a) $CuBr\cdot SMe_2$, TMSCl, Et_3N, **26** (used crude); (b) IBX (1.2 equiv), $MPO\cdot H_2O$ (1.2 equiv), DMSO (55%, two steps); (c) TBAF, THF, −40 °C (93%); (d) *B*-9-BBN, CH_2Cl_2 (85%); (e) $Pb(OAc)_4$, toluene, reflux (69%, dr = 15:1); (f) $ScOTf_3$ (0.2 equiv), H_2O:MeOH 1:4 (100%); (g) TBSCl, imidazole (90%); (h) TMSOTf, **6**, CH_2Cl_2 (crude); (i) silica gel (50 equiv), oxalic acid (0.1 equiv), $MeOH:H_2O$ 10:1 (85%, two steps, dr > 99:1).

Having successfully installed the C-1 quaternary center with the desired stereochemical orientation, we then focused on the synthesis of key epoxide intermediate **23** (Scheme 9). Deprotection of the TBS ether in **31** was followed by intramolecular, stereocontrolled reduction at C-8 with tetramethylammonium triacetoxyborohydride to give the 1,2-diol **32** as a single stereoisomer. The selective derivatization of the C-8 position of *trans*-diol **32** by reaction with benzoic anhydride yielded the C-8 benzoate ester **33** as the major product of a 3:1 mixture of C-8/C-7 regioisomers.[33] The direction of the acylation was determined by examination of the ^1H NMR spectra of diol **32** and benzoate ester **33**. The H_8 hydrogen atom frequency in **33** shifted downfield as compared to the chemical shift of H_7. This

(27) (a) Crimmins, M. T.; Gould, L. D. *J. Am. Chem. Soc.* **1987**, *109*, 6199. (b) Rossi, R.; Carpita, A.; Ciofalo, M.; Lippolis, V. *Tetrahedron* **1991**, *47*, 8443.

(28) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996.

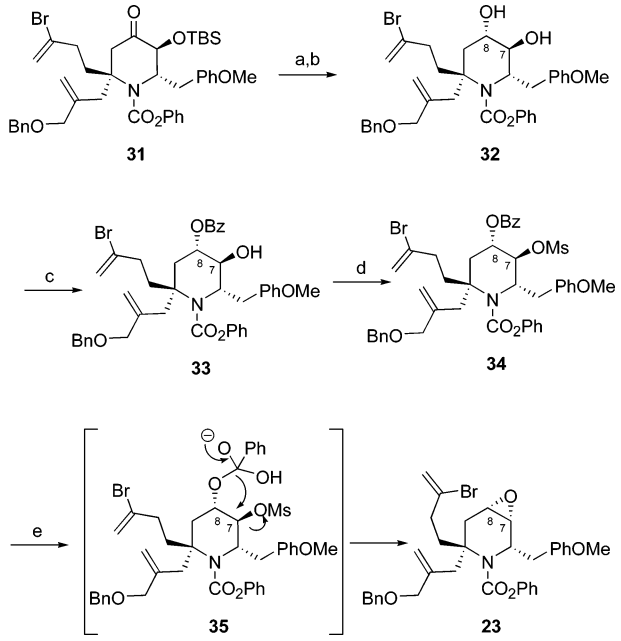
(29) During the course of the oxidation of **27** to **28**, we observed a small amount (15%) of the piperidone product resulting from hydrolysis of the silyl enol ether functionality.

(30) During the course of the oxidation of **27** to **28**, we were surprised to see that exposure to our earlier catalytic oxidation conditions ($Pd(OAc)_2$ (0.1 equiv), CuCl (1 equiv), O_2, CH_3CN, 65 °C) gave only the undesired piperidone byproduct resulting from the hydrolysis of the silyl enol ether moiety.

(31) (a) White, J. D.; Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop. D. L. *J. Am. Chem. Soc.* **2001**, *123*, 8593. (b) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731.

(32) The product showed a small coupling constant (J_{H6-H7} = 2.0 Hz) in its ^1H NMR, consistent with its trans stereochemistry.

SCHEME 9. Synthesis of Key Epoxide Intermediate 23[a]

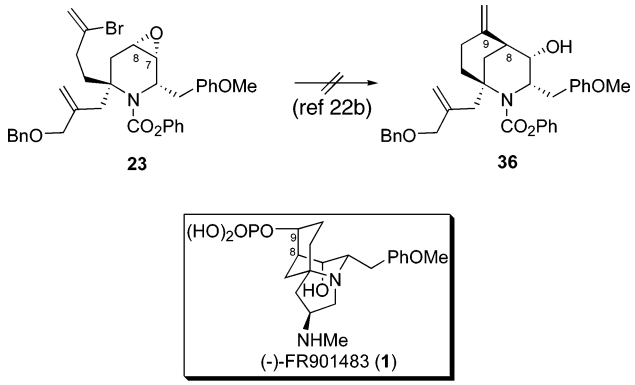


[a] Reaction conditions: (a) TBAF (1.2 equiv), THF, −40 °C (crude); (b) $Me_4N^+BH(OEt)_3$, AcOH (92%, two steps); (c) $(PhCO)_2O$ (1.0 equiv), Et_3N (2.0 equiv), DMAP (cat), CH_2Cl_2, 0 °C (56%); (d) MsCl, Et_3N (2.0 equiv), DMAP (cat), CH_2Cl_2 (97%); (e) NaOH, MeOH (94%).

is to be expected as the electron withdrawing benzoate ester group exerts a larger deshielding effect on the H_8 than on the H_7, causing the observed downfield shift in its resonance. During the course of the acylation, we also discovered that subjection of the corresponding undesired C-7 benzoate ester to methanolic NaOH resulted in the quantitative formation of diol **32**, allowing the C-7 isomer to be recycled. Mesylation of **33** was followed by subjection of the benzoate ester moiety in **34** to basic hydrolysis to give the tetrahedral intermediate **35**, which, upon collapse, yielded the desired epoxide **23** in a one-pot event.[34]

With epoxide **23** in hand, we turned our attention to finding suitable conditions to afford the C-8/C-9 bond connectivity in (−)-FR901483 by effecting an intramolecular epoxide ring opening (Scheme 10). This type of intramolecular opening of an epoxide with an aryllithium to form a six-membered ring has been reported.[35] Unfortunately, all of our efforts to achieve the desired *6-exo-tet* epoxide opening to afford product **36** were unsuccessful.[22b] Exposure to *n*-butyllithium or dibutylcopper lithium led to the recovery of the starting materials together with products resulting from an attack at the carbamate. Similar results were observed when *tert*-butyllithium was used at −78 °C. Gratifyingly, lithium−bromide exchange was achieved by reaction with *t*-BuLi at −120 °C for 1 h; however, all attempts to obtain the desired epoxide opening product **36** via formation of a higher-order cuprate or a lower-order cuprate gave the corresponding debrominated product exclusively. A likely reason for the cyclization failure is an inherent $A^{(1,3)}$ strain in the molecule that produces a conformation unfavorable to the desired bond formation.

SCHEME 10. Attempted *6-exo-tet* Epoxide Opening in 23



Summary

Although the investigated routes to the bicyclic [3.3.1]-ring system of (−)-FR901483 did not result in the formation of the C-8/C-9 bond connectivity, diastereoselective methodology for the installation of the quaternary center at C-1 utilizing a conjugate allylation reaction was developed, and several highly substituted piperidine derivatives were prepared regio- and stereoselectively. Most of the stereoselective transformations were designed based on a conformational bias caused by an $A^{(1,3)}$ strain present in the molecules. Unfortunately, failure of the attempted C-8/C-9 formation is also attributed to an allylic strain. If an N-acyl group of a late intermediate can be selectively removed to relieve an $A^{(1,3)}$ strain, ring closure may be feasible. Further studies will be needed to determine if the synthetic routes attempted can be modified to allow the key bond formation.

Experimental Section

6-(2-[1,3]Dioxolan-2-yl-ethyl)-2-(4-methoxybenzyl)-4-oxo-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Phenyl Ester (13). Magnesium turnings (7.57 g, 311 mmol) were mechanically activated by stirring at rt overnight under argon, and then 50 mL of anhydrous THF was added. A portion of 2-(2-bromoethyl)-1,3-dioxolane (9.7 mL, 83 mmol) in 50 mL of anhydrous THF was slowly added to the mixture. Once the reaction was initiated, the mixture was cooled to 10 °C, and the remaining bromide was continuously added over a period of 2 h. After the addition was complete, the reaction mixture was stirred at 10 °C for 9 h to form the corresponding Grignard reagent. In a separate flask, a copper bromide−dimethyl sulfide complex (22.6 g, 110 mmol) was mixed with 50 mL of freshly distilled THF under argon and was cooled to −78 °C. A solution of 2-(4-methoxybenzyl)-4-oxo-3,4-dihydro-2*H*-pyridine-1-carboxylic acid phenyl ester (**11**; 7.40 g, 20.7 mmol) in THF (30 mL) was added and was followed by a premixed solution of TMSCl (30.6 mL, 241 mmol) and Et_3N (35.2 mL, 252 mmol). A solution of the above prepared Grignard reagent in THF was then added dropwise over a period of 1 h. Once the addition was complete, the resulting slurry was stirred at −78 °C for 2 h and then warmed to −45 °C. After 24 h, the reaction mixture was quenched with 100 mL of a carefully buffered solution of NH_4OH and NH_4Cl (pH 8), and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 150 mL), and the combined organic layers were washed with 10% NH_4OH until no further blue color was observed in the aqueous layer. The organic layers were combined,

(33) In a previous experiment we had discovered that exposure of diol **32** to MsCl (1.0 equiv) in the presence of Et_3N and DMAP resulted in the formation of the C-8 mesylate as the major compound of a 3:1 mixture of C-8/C-7 regioisomers. Thus, in order to obtain the desired epoxide **23** we needed to selectively derivatize the C-8 hydroxyl first. This led to the C-8 benzoate ester formation/C-7 mesylation route.

(34) Mashimo, K.; Sato, Y. *Tetrahedron* **1970**, *26*, 803.

(35) (a) Gauthier, D. R., Jr.; Bender, S. L. *Tetrahedron Lett.* **1996**, *37*, 13. (b) Hudlickly, T.; Rinner, U.; Gonzalez, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T. A.; Pettit, G. R. *J. Org. Chem.* **2002**, *67*, 8726.

dried over K_2CO_3, filtered through Celite, and concentrated in vacuo to yield crude silyl enol ether **12**.

To a solution of the above enol ether **12** in 100 mL of anhydrous CH_3CN under argon was added $Pd(OAc)_2$ (15 mol %, 0.74 g, 3.3 mmol), followed by CuCl (2.95 g, 29.8 mmol). The solution was purged with oxygen, was warmed to 60 °C under an O_2 balloon pressure atmosphere, and was stirred vigorously overnight. Upon completion, the reaction mixture was cooled to rt and filtered through Celite with CH_2Cl_2, and the solvent was removed in vacuo to yield the crude product **13**. Purification by silica gel chromatography (20 to 30% EtOAc in hexanes) gave 6.75 g (70%, two steps) of the desired product **13** as a yellow foam: IR (neat) 2922, 2851, 1719, 1512, 1494, 1453, 1248, 1203, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38 (dt, J = 1.2 Hz, 5.7 Hz, 2 H), 7.26 (d, J = 3.9 Hz, 1 H), 7.10 (d, J = 6.0 Hz, 2 H) 7.00 (d, J = 6.0 Hz, 2 H), 6.85 (d, J = 6.9 Hz, 2 H), 5.63 (s, 1 H), 5.07 (q, J = 5.1 Hz, 1 H), 4.93 (t, J = 3.3 Hz, 1 H), 3.96 (m, 2 H), 3.86 (m, 2 H), 3.79 (s, 3 H), 3.08 (m, 2 H), 2.81 (m, 3 H), 2.43 (d, J = 12.6 Hz, 1 H), 1.97 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.0, 158.5, (157.3 r), 151.5, 150.3, 130.5, 129.4, 128.8, 126.1, 121.3, 114.0, 113.2, 103.2, 64.9, 57.0, 57.2, 55.2, 39.7, 35.5, 32.3, 30.1. HRMS: $(M + H)^+$ calcd for $C_{25}H_{27}NO_6$ + H, 438.1917; found, 438.1904.

(2*S,3*S**)-3-Acetoxy-6-(2-[1,3]dioxolan-2-yl-ethyl)-2-(4-methoxybenzyl)-4-oxo-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Phenyl Ester (15a).** To a stirred solution of **13** (121 mg, 0.277 mmol) in 8 mL of toluene at rt was added lead(IV) acetate (160 mg, 0.36 mmol). The resulting mixture was refluxed for 3 h and cooled to rt, and additional lead(IV) acetate (160 mg, 0.36 mmol) was added. The mixture was refluxed for 3 h. After cooling to rt, the solution was filtered through Celite with CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$ (30 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was dried over Na_2SO_4, filtered through Celite, and concentrated in vacuo to yield crude **15a**. Purification by silica gel chromatography (20 to 30% EtOAc in hexanes) gave 103 mg (75%) of **15a** as a colorless oil: IR (neat) 2934, 1741, 1678, 1592, 1513, 1401, 1248, 1181, 1032, 911, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36 (t, J = 7.4 Hz, 2 H), 7.22 (d, J = 7.3 Hz, 1 H), 7.12 (d, J = 8.3 Hz, 2 H), 6.86 (t, J = 8.7 Hz, 4 H), 5.70 (s, 1 H), 5.23 (dt, J = 1.5, 6.6 Hz,1 H), 4.93 (m, 2 H), 3.96 (m, 2 H), 3.86 (m, 2 H), 3.79 (s, 3 H), 3.13 (m, 1 H), 2.97 (m, 2 H), 2.82 (m, 1 H), 2.09 (s, 3 H), 2.01 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.6, 169.9, 159.4, (159.0 r), 151.9, 150.3, 130.6, 129.7, 127.8, 126.5, 121.3, 114.4, 112.1, 103.4, 71.4, 65.2, 65.1, 61.9, 55.4, 33.5, 32.3, 30.5, 21.0. HRMS: $(M + H)^+$ calcd for $C_{27}H_{29}NO_8$ + H, 496.1971; found, 496.1959.

(2*S,3*R**)-3-Acetoxy-6-(2-[1,3]dioxolan-2-yl-ethyl)-2-(4-methoxybenzyl)-4-oxo-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Phenyl Ester (15b).** IR (neat) 2934, 1738, 1682, 1593, 1513, 1397, 1289, 1249, 1177, 1033, 913 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.24 (m, 5 H), 6.86 (d, J = 6.3 Hz, 2 H), 6.72 (d, J = 6.3 Hz, 2 H), 5.83 (d, J = 4.5 Hz, 1 H), 5.63 (s, 1 H), 5.25 (m, 1 H), 4.91 (t, J = 3.3 Hz, 1 H), 3.96 (m, 2 H), 3.84 (m, 2 H), 3.79 (m, 3 H), 2.98 (m, 3 H), 2.81 (m, 1 H), 2.19 (s, 3 H), 2.05 (m, 1 H), 1.90 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.1, 169.9, 158.7 (158.8 r), 151.3, 150.3, 130.7, 129.6, 129.1, 126.4, 121.5, 114.2, 111.6, 103.4, 73.0, 65.2, 65.1, 60.7, 55.5, 32.4, 30.7, 30.0, 20.9. HRMS: $(M + H)^+$ calcd for $C_{27}H_{29}NO_8$ + H, 496.1971; found, 496.1961.

(2*S,3*S**)-3-(*tert*-Butyldimethylsilanyloxy)-6-(2-[1,3]dithian-2-yl-ethyl)-2-(4-methoxybenzyl)-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic Acid Phenyl Ester (16).** To a solution of **15a** (23.0 mg, 0.046 mmol) in H_2O:MeOH (1.0 mL, 1:4) was added $ScOTf_3$ (20 mol %, 5.0 mg, 0.0093 mmol). The resulting mixture was stirred at rt for 40 h. Upon completion, the reaction mixture was poured into H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried over Na_2SO_4 and filtered through Celite with CH_2Cl_2, and the solvent was removed in vacuo. Purification by silica gel chromatography (20 to 30% EtOAc in hexanes) gave 21.0 mg (100%) of the desired α-hydroxy ketone as a white solid which was used directly in the next step. Mp 152−154 °C; IR (neat) 3394, 2919, 1737, 1664, 1513, 1410, 1320, 1248, 1179, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40 (t, J = 5.7 Hz, 1 H), 7.27 (d, J = 3.9 Hz, 2 H), 7.10 (d, J = 6.3 Hz, 2 H), 7.01 (d, J = 6.0 Hz, 2 H), 6.83 (d, J = 6.9 Hz, 2 H), 5.60 (s, 1 H), 5.09 (dt, J = 2.1, 8.1 Hz, 1 H), 4.92 (t, J = 7.2 Hz, 1 H), 3.96 (m, 2 H), 3.87 (m, 2 H), 3.79 (s, 3 H), 3.04 (m, 2 H), 2.81 (m, 2 H), 2.70 (d, J = 4.2 Hz, 1 H), 1.97 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.9, 158.4 (159.2 r), 152.2, 150.4, 130.6, 129.6, 128.4, 126.3, 121.5, 114.3, 110.3, 103.4, 70.7, 65.1, 65.0, 64.2, 55.4, 33.5, 32.3, 30.5. HRMS: $(M + H)^+$ calcd for $C_{25}H_{27}NO_7$ + H, 454.1866; found, 454.1873.

To a solution of the above α-hydroxy ketone (550 mg, 1.22 mmol) in DMF (20 mL) at 20 °C was added imidazole (165 mg, 2.43 mmol) and *tert*-butyldimethylsilyl chloride (275 mg, 1.82 mmol). The resulting mixture was stirred at rt for 12 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and filtered through Celite with CH_2Cl_2, and the solvent was removed in vacuo. Purification by silica gel chromatography (30 to 40% EtOAc in hexanes) gave 620 mg (90%) of the desired TBS-protected alcohol as a colorless oil which was used directly in the next step. IR (neat) 2953, 1738, 1674, 1597, 1512, 1323, 1249, 1184, 1100, 1035, 841 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37 (dt, J = 1.0, 7.4 Hz, 2 H), 7.23 (t, J = 8.4 Hz, 1 H), 7.10 (d, J = 8.4 Hz, 2 H), 6.95 (d, J = 7.7 Hz, 2 H), 6.85 (d, J = 6.6 Hz, 2 H), 5.59 (s, 1 H), 5.09 (dt, J = 2.0, 7.2 Hz, 1 H), 4.92 (t, J = 4.4 Hz, 1 H), 3.95 (m, 2 H), 3.84 (m, 2 H), 3.79 (s, 3 H), 3.69 (s, 1 H), 3.11 (m, 1 H), 3.01 (m, 1 H), 2.85 (m, 2 H), 1.99 (m, 2 H), 0.83 (s, 9 H), 0.07 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.9, 157.8 (158.8 r), 152.5, 150.5, 130.5, 129.7, 128.7, 126.3, 121.6, 114.3, 111.0, 103.6, 71.6, 65.7, 65.2, 65.1, 55.5, 33.2, 32.5, 30.5, 25.8, 18.2, −4.6, −5.0. HRMS: $(M + H)^+$ calcd for $C_{31}H_{41}NO_7Si$ + H, 568.2731; found, 568.2741.

To a solution of the above TBS-protected alcohol (620 mg, 1.04 mmol) in CH_2Cl_2 (10 mL) at 20 °C were added neat $BF_3{\cdot}OEt_2$ (60 μL, 0.44 mmol) and then 1,3-propanedithiol (170 μL, 1.64 mmol). The resulting mixture was stirred at rt for 8 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL) and was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered through Celite with CH_2Cl_2, and the solvent was removed in vacuo to yield the crude product **16**. Purification by silica gel chromatography (10 to 20% EtOAc in hexanes) gave 637 mg (95%) of **16** as a colorless oil: IR (neat) 2929, 1738, 1673, 1597, 1249, 1182, 1096, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37 (t, J = 7.6 Hz, 2 H), 7.22 (t, J = 6.8 Hz, 1 H), 7.10 (d, J = 8.4 Hz, 2 H), 6.92 (d, J = 6.4 Hz, 2 H), 6.84 (d, J = 6.8 Hz, 2 H), 5.56 (s, 1 H), 4.99 (dt, J = 3.2, 11.2 Hz, 1 H), 4.00 (t, J = 9.6 Hz, 1 H), 3.80 (s, 3 H), 3.71 (d, J = 2.4 Hz, 1 H), 3.19 (m, 1 H), 2.91 (m, 1 H), 2.81 (m, 6 H), 2.05 (m, 3 H), 1.97 (m, 1 H), 0.84 (s, 9 H), 0.04 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.8, 158.9, 157.0, 152.4, 150.6, 130.5, 129.7, 128.54, 126.3, 121.6, 114.4, 111.2, 71.7, 65.5, 55.5, 46.7, 34.1, 33.2, 33.1, 30.3, 26.0, 25.8, 18.3, −4.6, −5.0. HRMS: $(M + H)^+$ calcd for $C_{32}H_{43}NO_5S_2Si$ + H, 614.2430; found, 614.2439.

(2*R,5*S**,6*S**)-2(2-Benzyloxymethylallyl)-5-(*tert*-butyldimethylsilanyloxy)-2-(2-[1,3]dithian-2-yl-ethyl)-6-(4-methoxybenzyl)-4-oxo-piperidine-1-carboxylic Acid Phenyl Ester (19).** A well-stirred solution of dihydropyridone **16** (0.560 g, 0.912 mmol) in 20 mL of dry CH_2Cl_2 was cooled to −78 °C. TMSOTf (490 μL, 2.73 mmol) was added in one portion, giving rise to a deep orange color. After 5 min, neat (2-benzyloxymethylallyl)tributylstannane reagent **6** (1.00 g, 1.82 mmol) was added dropwise over a 10 min period. The reaction mixture was stirred for 4 h at −78 °C, warmed up to −45 °C, and stirred for an additional 6 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL) and warmed to rt, during which time it became colorless. The mixture

was extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were dried over Na_2SO_4 and filtered through Celite. The solvent was removed in vacuo to yield the crude product **19**. Purification by silica chromatography (0 to 20% EtOAc in hexanes) gave 458 mg (65%) of **19** as a colorless oil: IR (neat) 2929, 2856, 1720, 1513, 1348, 1250, 1201, 1098, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39 (m, 12 H), 6.82 (d, J = 9.2 Hz, 2 H), 5.34 (d, J = 1.2 Hz, 1 H), 5.08 (s, 1 H), 4.67 (dd, J = 1.8, 10.8 Hz, 1 H), 4.50 (s, 2 H), 4.00 (t, J = 6.4 Hz, 1 H), 3.96 (s, 2 H), 3.78 (s, 3 H), 3.74 (s, 1 H), 3.21 (bs, 1 H), 3.19 (d, J = 14.0 Hz, 1 H), 2.98 (bs, 1 H), 2.80 (m, 6 H), 2.52 (bs, 1 H), 2.13 (m, 2 H), 1.90 (m, 2 H), 1.85 (m, 2 H), 0.78 (s, 9 H), −0.10 (s, 3 H), −0.24 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.3, 158.8, 151.1, 141.8, 141.4, 138.5, 130.3, 129.7, 129.4, 128.6, 128.5, 127.6, 125.9, 122.2, 120.7, 114.4, 73.9, 72.5, 71.3, 70.6, 64.2, 55.5, 47.4, 30.8, 30.4, 30.3, 30.2, 26.1, 25.8, 25.6, 18.1, −4.9, −5.6. HRMS: $(M + H)^+$ calcd for $C_{43}H_{57}NO_6S_2Si$ + H, 776.3475; found, 776.3439.

(2*R,5*R**,6*S**)-2-(2-Benzyloxymethylallyl)-5-(*tert*-butyldimethylsilanyloxy)-2-(2-[1,3]dithian-2-yl-ethyl)-6-(4-methoxybenzyl)-4-oxo-piperidine-1-carboxylic Acid Phenyl Ester (20).** Compound **19** (120 mg, 0.155 mmol) in CH_2Cl_2 (5 mL) was treated with pyridine (1 μL, 0.02 mmol) and DBU (20 μL, 0.077 mmol), and the resulting mixture was refluxed for 60 h. The solution was cooled to rt and quenched with 1 N aqueous HCl (1 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product, a 1:1 mixture of piperidones **19** and **20**, was purified by silica gel chromatography (10 to 20% EtOAc in hexanes) to give 60 mg (50%) of the desired product **20** as a colorless oil: IR (neat) 2927, 2853, 1717, 1512, 1248, 1202, 1161, 1110, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32 (s, 8 H), 7.20 (d, J = 9.2 Hz, 2 H), 6.80 (d, J = 9.2 Hz, 2 H), 6.62 (bs, 1 H), 5.34 (d, J = 1.6 Hz, 1 H), 5.02 (s, 1 H), 4.93 (m, 1 H), 4.62 (d, J = 5.6 Hz, 1 H), 4.50 (s, 2 H), 3.99 (t, J = 7.6 Hz, 1 H), 3.92 (s, 2 H), 3.74 (s, 3 H), 3.06 (bs, 1H), 3.04 (d, J = 14.4 Hz, 1 H), 2.86 (m, 6 H), 2.67 (d, J = 19.2 Hz, 1 H), 2.59 (dt, J = 3.6, 12.4 Hz, 1 H), 2.48 (m, 1 H), 2.13 (m, 1 H), 1.87 (m, 5 H), 0.84 (s, 9 H), 0.08 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.1, 158.4, 150.8, 142.2, 138.1, 131.2, 130.7, 129.7, 129.4, 128.6, 127.9, 125.7, 122.2, 122.0, 118.2, 114.2, 75.8, 73.5, 72.8, 62.2, 60.4, 55.6, 47.5, 47.0, 37.8, 31.2, 30.6, 26.2, 25.9, 18.6, 0.2, −4.4, −5.4. HRMS: $(M + H)^+$ calcd for $C_{43}H_{57}NO_6S_2Si$ + H, 776.3475; found, 776.3439.

(2*R,5*S**,6*S**)-2-(2-Benzyloxymethylallyl)-5-(*tert*-butyldimethylsilanyloxy)-6-(4-methoxybenzyl)-4-oxo-2-(3-oxo-propyl)-piperidine-1-carboxylic Acid Phenyl Ester (21).** To a mixture of **19** (32 mg, 0.41 mmol) and calcium carbonate (100 mg, 0.743 mmol) in aqueous H_2O:CH_3CN (2.0 mL, 1:9) was added CH_3I (2.0 mL, 33 mmol). The mixture was stirred at rt overnight, diluted with EtOAc (10 mL), and filtered through Celite. The filtrate was washed with brine (2 × 10 mL) and was dried over Na_2SO_4, and the solvent was removed in vacuo to yield 28 mg (100%) of the crude product **21** as a colorless oil. The product was used crude in the next step without further purification: IR (neat) 2927, 2854, 1720, 1611, 1512, 1251, 1201, 1097, 841 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.74 (q, J = 7.7 Hz, 1H), 7.32 (m, 8H), 7.12 (t, J = 7.7 Hz, 4H), 6.84 (d, J = 8.8 Hz, 2H), 5.36 (q, J = 1.4 Hz, 1 H), 5.10 (s, 1H), 4.69 (dd, J = 2.2, 9.16 Hz, 1H), 4.50 (s, 2H), 3.95 (s, 2H), 3.78 (s, 3H), 3.76 (s, 1 H), 3.23 (d, J = 12.1 Hz, 1 H), 3.18 (d, J = 14.0 Hz, 1 H), 2.86 (d, J = 13.2 Hz, 2 H), 2.74 (dd, J = 1.5, 15.8 Hz, 2H), 2.53 (m, 2H), 1.7 (bs, 1H), 1.55 (bs, 1H), 0.77 (s, 9H), −0.08 (s, 3H), −0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.9, 159.0, 151.1, 141.3, 138.4, 130.5, 130.3, 129.8, 129.8, 128.57, 128.0, 127.9, 127.8, 126.1, 122.1, 114.6, 74.0, 72.6, 71.3, 70.6, 64.3, 55.6, 45.1, 41.2, 39.7, 29.9, 25.9, 18.1, −4.8, −5.5. HRMS: $(M + H)^+$ calcd for $C_{40}H_{51}NO_7Si$ + H, 685.3435; found, 685.3411.

2-(4-Methoxybenzyl)-4-oxo-6-[4-(trimethylsilanyl)but-3-ynyl]-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Phenyl Ester (28). Magnesium turnings (2.16 g, 889 mmol) were mechanically activated by stirring at rt overnight under argon, and then 40 mL of anhydrous ether was added. A portion of 4-bromo-1-trimethylsilyl-1-butyne (3.65 g, 178 mmol) in 20 mL of anhydrous ether was slowly added to the mixture. Once the reaction was initiated, the mixture was cooled to 10 °C, and the remaining bromide was continuously added over a period of 2 h. After the addition was complete, the reaction mixture was stirred at 10 °C for 3 h, warmed up to rt, and stirred for an additional 4 h to form the Grignard reagent **26**. In a separate flask, a copper bromide−dimethyl sulfide complex (6.09 g, 296 mmol) was mixed with 20 mL of freshly distilled THF under argon and was cooled to −78 °C. To a solution of 2-(4-methoxybenzyl)-4-oxo-3,4-dihydro-2*H*-pyridine-1-carboxylic acid phenyl ester (**11**; 2.00 g, 593 mmol) in THF (10 mL) was added a premixed solution of TMSCl (8.30 mL, 652 mmol) and Et_3N (9.5 mL, 682 mmol). A solution of the above prepared Grignard reagent **26** in Et_2O (diluted with 50 mL of THF) was added dropwise over a period of 1 h. Once the addition was complete, the resulting slurry was stirred at −78 °C for 2 h and was then warmed to −45 °C. After 24 h, the reaction mixture was quenched with a carefully buffered solution (pH 8) of NH_4OH and NH_4Cl (100 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with 10% NH_4OH until no further blue color was observed in the aqueous layer. After drying over anhydrous K_2CO_3 and filtering through Celite, the solvent was removed under reduced pressure to give 3.4 g of crude **27**, which was dissolved in 10 mL of anhydrous DMSO. In a separate flask, IBX (9.96 g, 356 mmol) and MPO·H_2O (4.45 g, 356 mmol) were dissolved in 20 mL of DMSO at 10 °C. The IBX/MPO mixture was stirred until complete dissolution and was then added in one portion at 0 °C to the crude silyl enol ether **27** solution. The mixture was stirred vigorously at rt overnight. The reaction mixture was carefully diluted with 5% $NaHCO_3$ (50 mL) and was extracted with Et_2O (3 × 100 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and filtered through Celite, and the solvent was removed in vacuo to yield the crude product **28**. Purification by silica gel chromatography (10 to 25% EtOAc in hexanes) gave 2.3 g (55%, two steps) of **28** as a yellow foam: IR (neat) 2955, 2171, 1725, 1666, 1513, 1248, 1201, 1162, 1037, 889 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, J = 7.7 Hz, 2 H), 7.27 (d, J = 7.0 Hz, 1 H), 7.15 (dd, J = 1.8, 6.6 Hz, 2 H), 6.93 (d, J = 7.3 Hz, 2 H), 6.82 (dd, J = 1.8, 6.2 Hz, 2 H), 5.66 (s, 1 H), 5.10 (dq, J = 1.5, 6.2 Hz, 1 H), 3.79 (s, 3H), 3.29 (m, 1 H), 3.10 (dd, J = 7.3, 7.3 Hz, 1 H), 2.89 (dd, J = 8.1, 6.2 Hz, 1 H), 2.84 (d, J = 5.9 Hz, 1 H), 2.71 (m, 1 H), 2.55 (t, J = 6.6 Hz, 2 H), 2.46 (d, J = 17.2 Hz, 1 H), 0.11 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.2, 158.8, 155.4, 151.8, 150.4, 130.8, 129.6, 129.2, 126.5, 121.6 (122.0 r), 114.7, 114.3, 105.0, 87.3, 58.5, 55.5, 40.3, 36.1, 35.0, 19.1, 0.2. HRMS: $(M + H)^+$ calcd for $C_{27}H_{31}NO_4Si$ + H, 462.2101; found, 462.2085.

6-(3-Bromobut-3-enyl)-2-(4-methoxybenzyl)-4-oxo-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Phenyl Ester (29). A solution of **28** (1.43 g, 3.10 mmol) in THF (35 mL) was cooled to −78 °C. Tetrabutylammonium fluoride (1.0 M in THF, 3.72 mL, 3.72 mmol) was added dropwise over a period of 10 min. After the addition was complete, the reaction mixture was stirred at −78 °C for 30 min, warmed to rt, and stirred for an additional 1 h at rt. The reaction mixture was poured into saturated aqueous NH_4Cl (100 mL) and was then extracted with Et_2O (3 × 250 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo to yield the crude acetylene product. Purification by silica gel chromatography (10 to 25% EtOAc in hexanes) gave 1.11 g (93%) of the desired acetylene as a colorless oil which was used directly in the next step. IR (neat) 3286, 2932, 1738, 1665, 1598, 1512, 1402, 1333, 1301, 1247, 1162, 1040, 829, 749, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 7.39 (t, J = 8.0 Hz, 2 H), 7.26 (m, 1 H), 7.13 (d, J = 8.4 Hz, 2 H), 6.94 (d, J = 7.6 Hz, 2 H), 6.84 (d, J = 8.4 Hz, 2 H), 5.68 (s, 1 H), 5.11 (q, J = 7.6 Hz, 1 H), 3.79 (s, 3 H), 3.27 (m, 1 H), 3.10 (dd, J = 7.2, 6.4 Hz, 1 H), 2.90 (dd, J = 8.0, 5.6 Hz, 1 H), 2.87 (dd, J = 6.0, 11.2 Hz,

1 H), 2.76 (m, 1 H), 2.52 (m, 2 H), 2.45 (s, 1 H), 2.07 (t, $J = 2.0$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.2, 158.8, 155.3, 151.7, 150.4, 130.7, 129.7, 129.1, 128.5, 126.5, 121.5 (121.9 r), 114.3 (114.6 r), 82.4, 7.6, 58.3, 55.5, 40.2, 36.0, 34.7, 17.7. HRMS: $(M + H)^+$ calcd for $C_{24}H_{23}NO_4 + H$, 390.1705; found, 390.1711.

A solution of the above acetylene (44.0 mg, 0.113 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C under argon was treated with 9-bromo-9-borobicyclo[3.3.1]nonane (1.0 M in CH_2Cl_2, 0.17 mL, 0.17 mmol). The resulting mixture was allowed to warm to rt and stirred for 24 h. After this time, the mixture was cooled to 0 °C, and ethanolamine (1.1 mL) was added, followed by MeOH (2.5 mL). The mixture was then diluted with Et_2O (15 mL) and was shaken with saturated aqueous potassium sodium tartrate (15 mL). The aqueous phase was extracted with Et_2O (2 × 15 mL), and the combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo to yield the crude product **29**. Purification by silica gel chromatography (10 to 15% EtOAc in hexanes) gave 45.0 mg (85%) of **29** as a colorless oil: IR (neat) 2927, 1736, 1666, 1597, 1513, 1406, 1301, 1248, 1202, 1164, 1035, 890 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (dt, $J = 2.0$, 8.8 Hz, 2 H), 7.27 (t, $J = 1.2$ Hz, 1 H), 7.08 (dd, $J = 2.8$, 8.8 Hz, 2 H), 6.97 (dd, $J = 2.0$, 2.8 Hz, 2 H), 6.84 (dd, $J = 2.8$, 8.8 Hz, 2 H), 5.60 (dd, $J = 0.8$, 1.6 Hz, 2 H), 5.44 (d, $J = 2.4$ Hz, 1 H), 5.07 (dq, $J = 2.0$, 8.0 Hz, 1 H), 3.78 (s, 3 H), 3.20 (m, 1 H), 3.04 (dd, $J = 8.8$, 9.2 Hz, 1 H), 2.81 (m, 4 H), 2.45 (dt, $J = 1.6$, 17.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.9, 158.7, 155.8, 151.6, 150.3, 132.2, 130.6, 129.7, 128.8, 126.5, 121.4, 118.3, 114.3, 114.0, 58.3, 55.6, 40.34, 40.0, 36.1, 34.4. HRMS: $(M + H)^+$ calcd for $C_{24}H_{24}BrNO_4 + H$, 470.0967; found, 470.0959.

(2*S,3*S**)-6-(3-Bromobut-3-enyl)-3-(*tert*-butyldimethylsilanyloxy)-2-(4-methoxybenzyl)-4-oxo-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Phenyl Ester (25).** To a stirred solution of **29** (224 mg, 0.477 mmol) in 5 mL of toluene at rt was added lead(IV) acetate (275 mg, 0.620 mmol). The resulting mixture was refluxed for 3 h and cooled to rt, and additional lead(IV) acetate (275 mg, 0.620 mmol) was added. The mixture was refluxed for 3 h. After cooling to rt, the solution was filtered through Celite with CH_2Cl_2. The filtrate was washed with saturated aqueous $NaHCO_3$ (40 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phase was dried over Na_2SO_4, filtered through Celite, and concentrated in vacuo to yield the crude acetate. Purification by silica gel chromatography (20 to 30% EtOAc in hexanes) gave 173 mg (69%) of the desired product as a colorless oil which was used directly in the next step. IR (neat) 2926, 1743, 1678, 1591, 1514, 1248, 1219, 1182, 1032, 839 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (dt, $J = 1.6$, 7.2 Hz, 2 H), 7.12 (dd, $J = 2.4$, 6.8 Hz, 2 H), 6.84 (m, 5 H), 5.70 (s, 1 H), 5.62 (m, 1 H), 5.47 (d, $J = 2.0$ Hz, 1 H), 5.25 (dt, $J = 2.8$, 7.2 Hz, 1 H), 4.94 (t, $J = 2.0$ Hz, 1 H), 3.20 (m, 1 H), 3.00 (dd, $J = 8.8$, 8.8 Hz, 1 H), 2.93 (m, 4 H), 2.76 (m, 1 H), 2.65 (m, 2 H), 2.11 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.6, 169.6, 159.1, 157.6, 150.2 (152.0 r), 132.1, 130.7, 130.5, 129.9, 127.6, 126.7, 121.3, 118.4, 114.5, 112.6, 71.3, 61.9, 55.5, 40.1, 34.5, 33.5, 21.0. HRMS: $(M + H)^+$ calcd for $C_{26}H_{26}BrNO_6 + H$, 528.1022; found, 528.1022.

To a solution of the above acetate (390 mg, 0.734 mmol) in H_2O:MeOH (20 mL, 1:4) was added $ScOTf_3$ (20 mol %, 72.0 mg, 0.147 mmol). The resulting mixture was stirred at 60 °C for 24 h. The reaction mixture was cooled to rt, poured into H_2O (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and filtered through Celite with CH_2Cl_2, and the solvent was removed in vacuo to yield the crude product. Purification by silica gel chromatography (20 to 30% EtOAc in hexanes) gave 355 mg (100%) of the desired alcohol as a white foam which was used directly in the next step. IR (neat) 3376, 2919, 1738, 1666, 1589, 1513, 1248, 1179, 838 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (t, $J = 8.0$ Hz, 2 H), 7.26 (t, $J = 7.2$ Hz, 1 H), 7.10 (d, $J = 8.8$ Hz, 2 H), 7.00 (d, $J = 7.6$ Hz, 2 H), 6.85 (d, $J = 8.4$ Hz, 2 H), 5.62 (d, $J = 0.8$ Hz, 1 H), 5.60 (s, 1 H), 5.45 (d, $J = 1.2$ Hz, 1 H), 5.11 (dt, $J = 1.6$, 8.0 Hz, 1 H), 3.79 (s, 4 H), 3.20 (m, 1 H), 2.97 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.3, 159.0, 157.3, 152.3, 150.5, 132.2, 130.6, 129.8, 128.2, 126.6, 121.6, 118.4, 114.4, 111.1, 70.9, 64.1, 55.5, 40.2, 34.5, 38.8. HRMS: $(M + H)^+$ calcd for $C_{24}H_{24}BrNO_5 + H$, 486.0916; found, 486.0911.

To a solution of the above alcohol (355 mg, 0.733 mmol) in DMF (10 mL) at 20 °C was added imidazole (100 mg, 1.47 mmol) and *tert*-butyldimethylsilyl chloride (166 mg, 1.10 mmol). The resulting mixture was stirred at rt for 24 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL) and was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and filtered through Celite with CH_2Cl_2, and the solvent was removed in vacuo to yield the crude TBS ether **25**. Purification by silica gel chromatography (30 to 40% EtOAc in hexanes) gave 397 mg (90%) of **25** as a colorless oil: IR (neat) 2929, 2856, 1737, 1676, 1598, 1513, 1249, 1182, 841 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (dt, $J = 1.6$, 7.2 Hz, 2 H), 7.26 (m, 1 H), 7.10 (dd, $J = 2.0$, 6.8 Hz, 2 H), 6.94 (dd, $J = 1.2$, 7.5 Hz, 2 H), 6.86 (dd, $J = 2.0$, 6.4 Hz, 2 H), 5.60 (m, 1 H), 5.55 (s, 1 H), 5.44 (d, $J = 1.6$ Hz, 1 H), 4.98 (dt, $J = 1.6$, 8.0 Hz, 1 H), 3.80 (s, 3 H), 3.70 (d, $J = 1.2$ Hz, 1 H), 3.21 (m, 1 H), 2.79 (m, 5 H), 0.84 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.7, 158.9, 155.9, 152.5, 150.5, 132.4, 130.5, 129.8, 128.5, 126.4, 121.5, 118.3, 114.3, 111.6, 71.5, 65.6, 55.5, 40.3, 34.3, 33.2, 25.8, 18.2, −4.6, −5.0. HRMS: $(M + H)^+$ calcd for $C_{30}H_{38}BrNO_5Si + H$, 600.1781; found, 600.1800.

(2*R,5*S**,6*S**)-2-(2-Benzyloxymethylallyl)-2-(3-bromobut-3-enyl)-5-(*tert*-butyl-dimethylsilanyloxy)-6-(4-methoxybenzyl)-4-oxo-piperidine-1-carboxylic Acid Phenyl Ester (31).** A well-stirred solution of dihydropyridone **25** (57 mg, 0.097 mmol) in 3 mL of dry CH_2Cl_2 was cooled to −78 °C. TMSOTf (40 μL, 0.22 mmol) was added in one portion, giving rise to a deep orange color. After 5 min, neat (2-benzyloxymethylallyl)tributylstannane reagent **6** (76 mg, 0.15 mmol) was added dropwise over a 10 min period. The reaction mixture was stirred for 4 h at −78 °C, warmed to −45 °C, and stirred for an additional 6 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) and was allowed to warm up to rt, during which time it became colorless. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and were filtered through Celite. The solvent was removed in vacuo to yield 110 mg of the crude silyl enol ether product **30**, which was dissolved in wet MeOH (5 mL). Silica gel (100 mg) was added, followed by H_2O (0.5 mL) and oxalic acid (20 mg, 0.22 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was filtered and was then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and filtered through Celite, and the solvent was removed in vacuo to yield the crude piperidone product **31**. Purification by silica gel chromatography (0 to 20% EtOAc in hexanes) gave 62 mg (85%) of **31** as a colorless oil: IR (neat) 2926, 2853, 1722, 1512, 1379, 1250, 1199, 1072, 844 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 7.20 (m, 10 H), 6.89 (t, $J = 7.6$ Hz, 2H), 6.67 (d, $J = 7.6$ Hz, 2H), 5.38 (s, 1H), 5.26 (m, 3H), 4.84 (m, 1H), 4.31 (s, 2H), 3.92 (s, 1H), 3.90 (s, 2H), 3.50 (d, $J = 17.2$ Hz, 1H), 3.27 (s, 1H), 3.25 (s, 3H), 3.07 (dd, $J = 3.2$, 13.6 Hz, 1H), 2.84 (d, $J = 17.2$ Hz, 1H), 2.54 (m, 2H), 2.24 (m, 2H), 1.72 (m, 1H), 1.54 (m, 1H), 0.90 (s, 9 H), 0.00 (s, 3H), −0.20 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 205.6, 159.1, 151.7, 142.0, 138.8, 133.7, 130.5, 129.7, 129.5, 128.4, 128.2, 127.9, 127.7, 127.5, 127.1, 125.5, 122.1, 117.2, 74.1, 72.2, 70.9, 64.5, 62.5, 54.7, 45.2, 41.3, 37.5, 37.4, 25.7, 25.5, 18.2, −4.9, −5.7. HRMS: $(M + H)^+$ calcd for $C_{41}H_{52}NO_6BrSi + H$, 761.2747; found, 761.2709.

(2*R,4*S**,5*S**,6*S**)-2-(2-Benzyloxymethylallyl)-2-(3-bromobut-3-enyl)-4,5-dihydroxy-6-(4-methoxybenzyl)piperidine-1-carboxylic Acid Phenyl Ester (32).** A solution of **31** (57.0 mg, 0.0758 mmol) in THF (4 mL) was cooled to −40 °C. Tetrabutylammonium fluoride (1.0 M in THF, 91 μL, 0.091 mmol) was added dropwise

over a period of 5 min. After the addition was complete, the reaction mixture was stirred at −40 °C for 1 h, warmed to −20 °C, and stirred for an additional 2 h. The reaction mixture was poured into saturated aqueous NH_4Cl (10 mL) and was then extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered through Celite, and concentrated in vacuo to yield the crude alcohol. To a solution of tetramethylammonium triacetoxyborohydride (80.0 mg, 0.303 mmol) in 4.0 mL of freshly distilled acetone at rt was added acetic acid (35.0 μL, 0.607 mmol). After stirring for 15 min, the above crude alcohol compound in 4.0 mL of freshly distilled acetone was added dropwise over a period of 5 min. The reaction mixture was stirred at rt for 16 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (25 mL), and one-half of the acetone was removed in vacuo. The solution was extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, and filtered through Celite, and the solvent was removed in vacuo to yield the crude product. Purification by silica gel chromatography (30 to 50% EtOAc in hexanes) gave 45 mg (92%, over two steps) of **32** as a colorless oil: IR (neat) 3456, 2924, 1693, 1512, 1454, 1248, 1203, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40 (t, $J = 7.6$ Hz, 1H), 7.28 (m, 11H), 7.14 (dd, $J = 1.6$, 7.2 Hz, 2H), 5.58 (d, $J = 1.6$ Hz, 1H), 5.40 (d, $J = 2.0$ Hz, 1H), 5.33 (d, $J = 1.2$ Hz, 1H), 5.16 (s, 1H), 4.50 (dd, $J = 11.6$, 6.0 Hz, 2H), 4.42 (bd, $J = 12.0$ Hz, 1H), 4.14 (bs, 1H), 4.04 (dd, $J = 12.8$, 8.0 Hz, 2H), 3.79 (s, 4H), 3.12 (dd, $J = 2.8$, 12.8 Hz, 1H), 3.02 (dd, $J = 14.0$, 6.8 Hz, 2H), 2.83 (t, $J = 12.4$ Hz, 1H), 2.73 (m, 1H), 2.48 (m, 2H), 2.14 (dd, $J = 6.0$, 14.8 Hz, 1H), 1.95 (m, 2H), 1.83 (m, 1H), 1.63 (d, $J = 3.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.6, 154.6, 151.2, 142.4, 138.2, 133.9, 130.9, 130.2, 129.7, 128.65, 128.1, 128.0, 125.8, 122.1, 118.0, 117.2, 114.3, 74.4, 74.3, 72.4, 69.7, 64.2, 61.2, 55.5, 41.5, 40.0, 38.0, 37.4, 36.8. HRMS: $(M + H)^+$ calcd for $C_{35}H_{40}BrNO_6 + H$, 650.2117; found, 650.2101.

(2*R,4*S**,5*S**,6*S**)-4-Benzoyloxy-2-(2-benzyloxymethylallyl)-2-(3-bromobut-3-enyl)-5-hydroxy-6-(4-methoxybenzyl)piperidine-1-carboxylic Acid Phenyl Ester (33).** A solution of **32** (23.9 mg, 36.9 μmol) in CH_2Cl_2 (1.5 mL) was cooled to −20 °C. Et_3N (6.0 μL, 41 μmol) was added dropwise, followed by a catalytic amount of DMAP. The reaction mixture was stirred at −20 °C for 5 min and was then cooled to 0 °C. A freshly prepared solution of benzoic anhydride (0.044 M in CH_2Cl_2, 0.84 mL, 37 mol) was added over a period of 10 min. The reaction mixture was stirred at 0 °C for 2 h, warmed up to rt, and stirred for an additional 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over Na_2SO_4 and filtered through Celite, and the solvent was removed in vacuo to yield crude **33**. Purification by silica gel chromatography (10 to 25% EtOAc in hexanes) gave 15.5 mg (56%) of **33** as a colorless oil: IR (neat) 3434, 2910, 2848, 1719, 1510, 1451, 1272, 1243, 1200, 1104, 1066, 1024, 860 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.10 (d, $J = 8.4$ Hz, 2H), 7.65 (t, $J = 7.6$ Hz, 1H), 7.53 (t, $J = 7.6$ Hz, 2H), 7.41 (t, $J = 7.6$ Hz, 2H), 7.26 (m, 9H), 6.70 (d, $J = 8.8$ Hz, 2H), 5.59 (s, 1H), 5.41 (d, $J = 1.6$ Hz, 1H), 5.37 (m, 2H), 5.26 (s, 1H), 4.58 (bd, $J = 10.4$ Hz, 1H), 4.51 (s, 2H), 4.08 (dq, $J = 4.4$, 8.8 Hz, 2H), 3.96 (bs, 1H), 3.72 (s, 4H), 3.14 (m, 3H), 2.84 (m, 2H), 2.53 (t, $J = 8.4$ Hz, 3H), 2.40 (d, $J = 7.2$, 6.8 Hz, 1H), 2.36 (t, $J = 9.6$ Hz, 1H), 1.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8, 158.6, 142.1, 138.3, 133.8, 133.7, 130.5, 130.4, 129.9, 129.8, 129.7, 128.8, 128.2, 128.6, 128.0, 127.8, 125.8, 122.1, 118.0, 117.3, 114.3, 75.1, 74.3, 72.4, 71.0, 62.4, 60.4, 55.4, 41.2, 39.0, 37.3, 33.0, 29.9. HRMS: $(M + H)^+$ calcd for $C_{42}H_{44}BrNO_7 + H$, 754.2379; found, 754.2385.

(2*R,4*S**,5*S**,6*S**)-4-Benzoyloxy-2-(2-benzyloxymethylallyl)-2-(3-bromobut-3-enyl)-5-methanesulfonyloxy-6-(4-methoxybenzyl)piperidine-1-carboxylic Acid Phenyl Ester (34).** A solution of **33** (20.0 mg, 26.0 μmol) in CH_2Cl_2 (1.0 mL) was cooled to 0 °C. Et_3N (4.0 μL, 29 μmol) was added dropwise, followed by a catalytic amount of DMAP. The reaction mixture was stirred at 0 °C for 10 min. A freshly prepared solution of *p*-methanesulfonyl chloride (0.253 M in CH_2Cl_2, 0.15 mL, 40 μmol) was added over a period of 10 min. The reaction mixture was stirred at 0 °C for 2 h, warmed to 20 °C, and stirred for an additional 4 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over Na_2SO_4 and filtered through Celite, and the solvent was removed in vacuo to yield crude **34**. Purification by silica gel chromatography (10 to 25% EtOAc in hexanes) gave 21.0 mg (97%) of **34** as a colorless oil: IR (neat) 2923, 1722, 1513, 1450, 1344, 1268, 1177, 1032, 949 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.10 (dd, $J = 0.8$, 8.0 Hz, 2H), 7.66 (dt, $J = 1.2$, 7.2 Hz, 1H), 7.54 (t, $J = 8.4$ Hz, 2H), 7.41 (t, $J = 7.2$ Hz, 2H), 7.26 (m, 9H), 6.79 (d, $J = 8.8$ Hz, 2H), 5.65 (t, $J = 8.4$ Hz, 1H), 5.58 (d, $J = 1.2$ Hz, 1H), 5.41 (d, $J = 2.0$ Hz, 2H), 5.33 (bs, 1H), 4.91 (m, 1H), 4.88 (s, 1H), 4.52 (s, 2H), 4.14 (dd, $J = 12.8$, 40.4 Hz, 2H), 3.77 (s, 3H), 3.24 (m, 2H), 2.92 (m, 3H), 2.77 (s, 3H), 2.53 (m, 3H), 2.37 (t, $J = 11.6$ Hz, 1H), 1.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 159.0, 151.0, 141.6, 138.3, 133.9, 133.3, 130.48, 130.0, 129.7, 129.4, 128.9, 128.6, 128.5, 128.0, 127.8, 126.0, 122.1, 118.8, 118.7, 117.4, 114.6, 78.9, 74.5, 72.41, 71.2, 61.1, 60.4, 55.4, 40.7, 38.6, 37.3, 33.2, 32.1, 29.9. HRMS: $(M + H)^+$ calcd for $C_{43}H_{46}BrNO_9S + H$, 832.2155; found, 832.2145.

(2*S,4*R**,6*S**,7*R**)-4-(2-Benzyloxymethylallyl)-4-(3-bromobut-3-enyl)-2-(4-methoxybenzyl)-7-oxa-3-aza-bicyclo[4.1.0]heptane-3-carboxylic Acid Phenyl Ester (23).** A solution of **34** (14.0 mg, 16.8 μmol) in MeOH (1.0 mL) was cooled to 0 °C. Solid NaOH (4.7 mg, 0.12 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 30 min, warmed up to rt, and stirred for an additional 10 min. Solid K_2CO_3 (100 mg) was added, followed by CH_2Cl_2 (15 mL). The resulting heterogeneous mixture was filtered through Celite, and the solvent was removed in vacuo to yield crude **23**. Purification by silica gel chromatography (5 to 15% EtOAc in hexanes) gave 10 mg (94%) of **23** as a colorless oil: IR (neat) 2923, 2855, 1713, 1515, 1456, 1379, 1250, 1203 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39 (t, $J = 7.6$ Hz, 1H), 7.30 (m, 9H), 7.12 (d, $J = 7.2$ Hz, 2H), 6.83 (d, $J = 8.8$ Hz, 2H), 5.58 (s, 1H), 5.39 (d, $J = 2.0$ Hz, 1H), 5.32 (d, $J = 1.2$ Hz, 1H), 5.10 (s, 1H), 4.78 (m, 1H), 4.49 (dd, $J = 18.4$, 5.2 Hz, 2H), 3.98 (q, $J = 12.8$ Hz, 2H), 3.80 (s, 3H) 3.38 (m, 1H), 3.09 (dq, $J = 4.4$, 2.8 Hz, 1H), 2.93 (d, $J = 13.6$ Hz, 1H), 2.87 (dd, $J = 3.2$, 12.0 Hz, 1H), 2.75 (m, 2H), 2.58 (d, $J = 13.6$ Hz, 1H), 2.37 (m, 3H), 1.80 (dd, $J = 4.0$, 4.4 Hz, 1H), 1.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.5, 151.1, 142.8, 138.1, 133.8, 130.7, 130.1, 129.7, 129.7, 128.7, 128.1, 128.0, 125.9, 122.1, 117.4, 117.2, 114.1, 73.6, 72.6, 59.9, 55.9, 55.4, 49.3, 48.8, 42.3, 39.0, 38.3, 37.1, 34.7 (29.9 r). HRMS: $(M + H)^+$ calcd for $C_{35}H_{38}BrNO_5 + H$, 632.2012; found, 632.2033.

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Supporting Information Available: General experimental methods, Tables 1 and 2, and ^1H and ^{13}C NMR spectra for compounds **13**, **15a**,**b**, **16**, **19**−**21**, **23**, **25**, **28**, **29**, and **31**−**34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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