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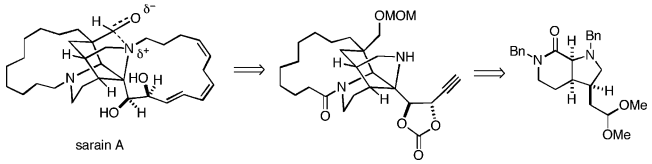
Construction of an Advanced Tetracyclic Intermediate for Total Synthesis of the Marine Alkaloid Sarain A

Sungwoo Hong, Jinhai Yang, and Steven M. Weinreb*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

smw@chem.psu.edu

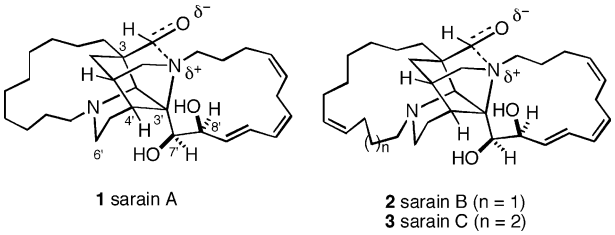
Received December 5, 2005



In work directed toward a total synthesis of the marine alkaloid sarain A (**1**), the advanced intermediate **54**, containing all the key elements and the seven stereogenic centers of sarain A, has been successfully synthesized from bicyclic lactam **4**, previously prepared via an intramolecular stereospecific [3 + 2]-azomethine ylide dipolar cycloaddition. Intermediate lactam **4** could be efficiently converted to *N*-Boc derivative **12**. Introduction of a two-carbon fragment into lactam **12** which eventually becomes the C-7′,8′ syn diol of the "eastern" ring was then achieved by C-acylation of the corresponding enolate with methoxyacetyl chloride followed by a highly stereoselective ketone reduction with $Zn(BH_4)_2$ to afford alcohol **16**. Intermediate **16** has the incorrect C-7′ relative stereochemistry for sarain A, but this problem was conveniently remedied by inverting the C-7′ center via an intramolecular Ohfune-type cyclization of the silyl carbamate derived from Boc mesylate **27** to produce the key cyclic carbamate **28**. It was then possible to convert acetal **28** to allylsilane **32** followed by cyclization to the alkaloid tricyclic core **33** via an allylsilane/*N*-sulfonyliminium ion cyclization. Formation of the "western" macrocyclic ring has been successfully addressed using functional group handles at C-3′ and N-1′ on the tricyclic core via a ring-closing olefin metathesis (RCM) strategy with the second-generation Grubbs ruthenium catalyst to produce intermediate macrolactam **47**. A chelation-controlled addition of ethynylmagnesium bromide to advanced aldehyde **51** afforded a single diastereomeric adduct **53** which is tentatively assigned to have the correct C-7′,8′ *syn*-diol stereochemistry. This adduct could be rearranged to the conveniently protected amino carbonate **54** which is set up for construction of the remainder of the eastern ring of sarain A.

Introduction and Background

Marine sponges produce a fascinating series of complex polycyclic alkaloids which are believed to have a common biogenesis from simple bispyridine macrocycles.[1] This family of alkaloids has been the subject of a considerable amount of innovative synthetic work during the past several years, and we have reviewed the progress in this field.[1] Included among these marine alkaloids are sarain A (**1**), B (**2**), and C (**3**), produced by the sponge *Reniera sarai*.[2] The structures of these three alkaloids were elucidated by Cimino and co-workers using



1 sarain A

2 sarain B (n = 1)
3 sarain C (n = 2)

a combination of spectral analysis and X-ray crystallography.[2] All three sarains contain a pentacyclic structural array with a tightly fused tricyclic core annulated to two large rings, along with seven stereogenic centers. Another unique feature of these marine metabolites is a zwitterionic tertiary amine−aldehyde interaction enforced by the rigidity of the core system, which puts these functional groups in close proximity.[3]

(1) Matzanke, N.; Gregg, R. J.; Weinreb, S. M. *Org. Prep. Proced. Int.* **1998**, *30*, 1, and references cited therein. See also: Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201. For a modified biogenetic proposal, see: Kaiser, A.; Billot, X.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *J. Am. Chem. Soc*. **1998**, *120*, 8026.

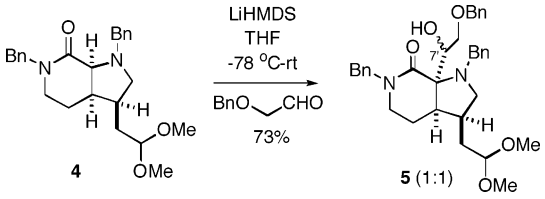
10.1021/jo052504r CCC: $33.50
Published on Web 01/31/2006

Our interest in the synthesis of this group of natural products was spurred by the fact that the sarain alkaloids have an unprecedented molecular architecture along with modest insecticidal, antibacterial, and antitumor activity.[2d] We have previously described a synthetic strategy for construction of the tricyclic core in which the pivotal steps are an intramolecular 1,3-dipolar azomethine ylide/olefin cycloaddition, followed by an allylsilane/*N*-sulfonyliminium ion cyclization.[4] We have also solved the problem of constructing the western 13-membered macrocyclic ring of these exceptionally challenging molecules by making use of an olefin ring-closing metathesis strategy.[4d] Shortly after our inital publication appeared,[4a] Heathcock et al. described some preliminary results based on an azomethine ylide cycloaddition similar to that which we had successfully executed for the synthesis of the tricyclic nucleus found in **1**−**3**.[5] In addition, the Heathcock group has reported some model studies directed toward elaboration of the 14-membered eastern macrocyclic ring of the sarains.[5b] More recently, the Overman[6] group has devised a novel approach for the enantioselective synthesis of the sarain core. Moreover, Cha[7] has published a nice strategy for construction of the tricyclic core of the sarains via a key 3-oxidopyridinium betaine/cyclopentadiene cycloaddition. In 2005, biogenetically patterned studies leading to the sarain core were reported by Marazano and co-workers.[8] Despite all the work in this area, no complete total synthesis of any of these molecules has yet been accomplished. In this paper, we outline the successful application of our synthetic strategy to an advanced intermediate which contains all of the stereocenters of sarain A (**1**), as well as four of the five rings of the alkaloid, and which bears suitable functional handles for attachment of the final ring.[9]

Results and Discussion

Studies on Introduction of the C-7′ Stereogenic Center. Our first goal on this project was to investigate modifications to the original strategy to incorporate the C-7′ center, which eventually would become part of the *syn*-1,2-diol functionality contained in the eastern ring of the sarains. This important issue had not been addressed in our previous studies. Initial experiments were conducted with *N*-benzyllactam **4**, prepared as previously described via a 1,3-dipolar azomethine ylide/olefin intramolecular cycloaddition.[4d] This lactam could be deprotonated with lithium hexamethyldisilazide, but condensation of the resulting enolate with aldehydes such as benzyloxyacetaldehyde unfortunately was nonstereoselective, leading to a 1:1 mixture of aldol products **5** (Scheme 1).

SCHEME 1



SCHEME 2

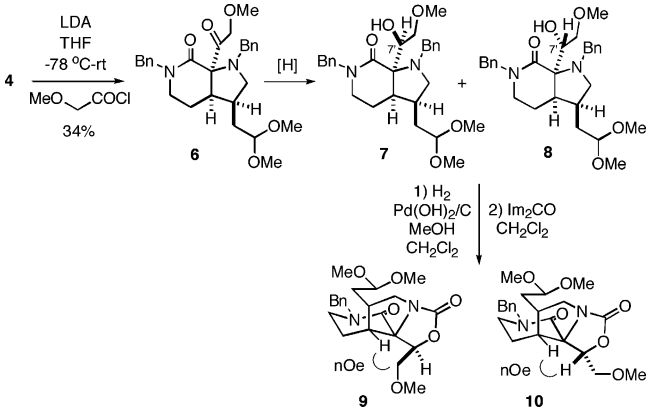


TABLE 1. Hydride Reductions of *β*-Ketolactam 6

entry	reducing agent	solvent	**7**/**8**	yield (%)
1	$NaBH_4$	MeOH	1:1	65
2	$Zn(BH_4)_2$	CH_2Cl_2/Et_2O	6.4:1	71
3	$KB(Et)_3H$	Et_2O	6.0:1	64
4	$KB(Et)_3H$	CH_2Cl_2	4.5:1	62
5	$LiB(Et)_3H$	CH_2Cl_2	1.1:1	63
6	L-selectride	CH_2Cl_2	0.8:1	69
7	K−selectride	CH_2Cl_2	5.1:1	55

In an alternative approach to setting the C-7′ stereochemistry, the enolate of lactam **4** was first acylated with methoxyacetyl chloride to afford *β*-ketolactam **6** (yield unoptimized) (Scheme 2). A number of hydride reagents were then screened to determine whether reduction of the ketone functionality could be affected diastereoselectively (Table 1). It was found that the best yield and highest stereoselectivity were produced with zinc borohydride as reductant. However, the major product in this case proved to be the undesired C-7′ alcohol **7**, with the requisite sarain A compound **8** being the minor isomer. The stereochemistry of these products was secured by chemoselective catalytic hydrogenolysis of **7** and **8** to remove the benzyl group from the amine functionality, followed by conversion to cyclic carbamates **9** and **10**, respectively, with carbonyldiimidazole. Two-dimensional (2D) NOESY NMR analysis of these compounds led to the assignment of their configurations. A possible rationale for the observed selectivity for formation of epimer **7** in the reduction step would involve chelation between the zinc

(2) (a) Cimino, G.; Mattia, C. A.; Mazzarella, L.; Puliti, R.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *Tetrahedron* **1989**, *45*, 3863. (b) Cimino, G.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *J. Nat. Prod.* **1990**, *53*, 1519. (c) Guo, Y.; Madaio, A.; Trivellone, E.; Scognamiglio, G.; Cimino, G. *Tetrahedron* **1996**, *52*, 8341. (d) Caprioli, V.; Cimino, G.; DeGiulio, A.; Madaio, A.; Scognamiglio, G.; Trivellone, E. *Comp. Biochem. Physiol.* **1992**, *103B*, 293.

(3) For a similar aldehyde−amine interaction in a simpler bridged system, see: Kirby, A. J.; Komarov, I. V.; Bilenko, V. A.; Davies, J. E.; Rawson, J. M. *Chem. Commun.* **2002**, 2106.

(4) (a) Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1991**, *56*, 3210. (b) Sisko, J.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4945. (c) Henry, J. R. Ph.D. Thesis, The Pennsylvania State University, 1994. (d) Irie, O.; Samizu, K.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1999**, *64*, 587.

(5) (a) Henke, B. R.; Kouklis, A. J.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 7056. (b) Heathcock, C. H.; Clasby, M.; Griffith, D. A.; Henke, B. R.; Sharp, M. J. *Synlett* **1995**, 467. (c) Denhart, D. J.; Griffith, D. A.; Heathcock, C. H. *Abstracts of Papers*, 216th American Chemical Society Meeting, Boston, MA, 1998; ORGN 526. (d) Denhart, D. J.; Griffith, D. A.; Heathcock, C. H. *J. Org. Chem.* **1998**, *63*, 9616. (e) Blazey, C. M.; Heathcock, C. H. *J. Org. Chem.* **2002**, *67*, 298.

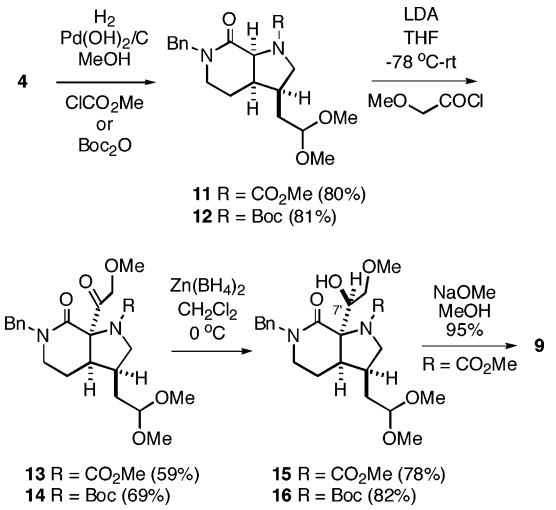
(6) (a) Downham, R.; Ng, F. W.; Overman, L. E. *J. Org. Chem.* **1998**, *63*, 8096. (b) Douglas, C. J.; Hiebert, S.; Overman, L. E. *Org. Lett*. **2005**, *7*, 933.

(7) (a) Sung, M. J.; Lee, H. I.; Cha, J. K. *Org. Lett.* **1999**, *1*, 2017. (b) Sung, M. J.; Lee, H. I.; Lee, H. B.; Cha, J. K. *J. Org. Chem*. **2003**, *68*, 2205. (c) Lee, H. I.; Sung, M. J.; Lee, H. B.; Cha, J. K. *Heterocycles* **2004**, *62*, 407.

(8) Hourcade, S.; Ferdenzi, A.; Retailleau, P.; Mons, S.; Marazano, C. *Eur. J. Org. Chem*. **2005**, 1302.

(9) Taken in part from the Ph.D. Thesis of S. Hong, The Pennsylvania State University, 2004.

SCHEME 3

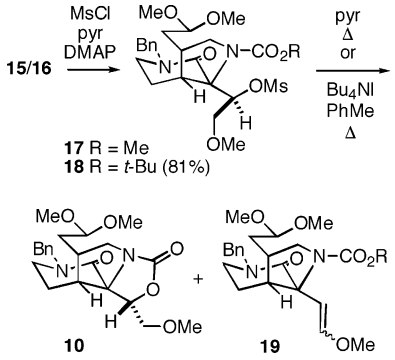


ion and the two carbonyl groups, followed by hydride attack from the least congested face of the complex.

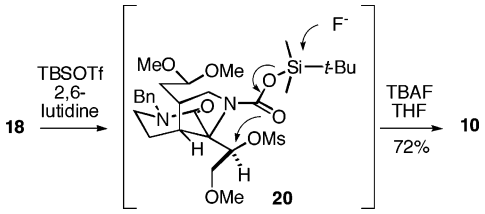
In view of these results, it was decided to next investigate a series of bicyclic lactams analogous to **4** where the amino group is protected as a carbamate. We hoped that a carbamate group in such a system would act as a handle to allow us to easily invert the C-7′ center, producing the correct sarain configuration (vide infra). Therefore, *N*-benzyllactam **4** was hydrogenolyzed using Pearlman's catalyst to the corresponding secondary amine, which was then N-acylated with methyl chloroformate, leading to carbamate **11** in good yield (Scheme 3). It was also possible to efficiently prepare the Boc-protected system **12** from *N*-benzylamine **4** in one operation using the methodology of Ohfune, where the hydrogenolysis is done in the presence of Boc_2O.[10] Deprotonation of lactam **11** with LDA, followed by treatment of the enolate with methoxyacetyl chloride, led to *β*-ketolactam **13** in 59% yield along with 12% of recovered starting material which could be recycled. Similarly, Boc-protected bicycle **12** could be C-acylated to afford *β*-ketolactam **14** (69% yield + 9% recovered starting material). We were pleased to find that reduction of ketones **13** and **14** with zinc borohydride gave alcohols **15** and **16**, respectively, in good yields as *single stereoisomers*. The stereochemistry at C-7′ in **15** was confirmed to be as shown (i.e., unnatural configuration) by conversion to cyclic carbamate **9** with sodium methoxide in methanol. At this point, we are unable to provide a convincing rationale as to why the carbamate-protected *β*-ketolactams **13** and **14** undergo reduction with significantly higher degrees of stereoselectivity than the corresponding *N*-benzyl system **6**.

At this point, we began to explore methodologies for inverting these reduction products to set the requisite C-7′ stereochemistry. However, all attempts to effect a direct Mitsunobu inversion of alcohol **15** were unsuccessful. In general, this alcohol was unreactive under the standard conditions,[11] probably for steric reasons. Alternatively, carbamate alcohols **15** and **16** were first converted to the corresponding mesylates **17** and **18**, respectively (Scheme 4). Heating these compounds in pyridine, however, led to mixtures of the desired inverted cyclic carbamate **10** along with the elimination product **19** in moderate yields. Similarly,

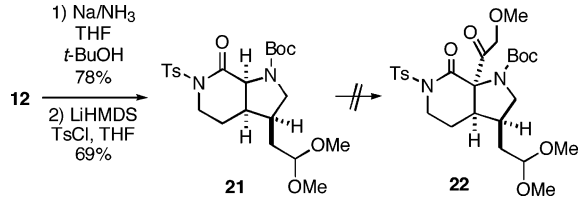
SCHEME 4



SCHEME 5



SCHEME 6



treatment of mesylates **17**/**18** with tetrabutylammonium iodide in hot toluene also afforded mixtures of **10** and **19**.

These disappointing results in effecting the intramolecular cyclizations prompted us to search for alternative conditions. Conversion of *N*-Boc and *N*-Cbz groups to the corresponding *O*-silyl carbamates has been developed by Ohfune et al.[12a] Moreover, the Ohfune group has demonstrated that intramolecular cyclization of silyl carbamates is an efficient way to form cyclic carbamates with inversion of an adjacent stereocenter bearing a sulfonate leaving group.[12b] Thus, initial treatment of the Boc carbamate mesylate **18** with TBSOTf and 2,6-lutidine in methylene chloride gave the silyl carbamate **20**, which without purification was treated with TBAF in THF at 0 °C to furnish the desired cyclic carbamate **10** with inverted stereochemistry in good yield for the two steps (Scheme 5).

To set the stage for construction of the sarain tricyclic core, it was necessary to replace the *N*-benzyl substituent of an intermediate lactam like **10** with a tosyl group. Unfortunately, debenzylation of lactam **10** with sodium/ammonia gave the desired NH product in only low yield (<25%). One alternative sequence which was examined involved debenzylation of lactam **12**, followed by N-tosylation of the resulting NH lactam to produce **21** (Scheme 6). However, all attempts at C-acylating the enolate of **21** to produce ketone **22** failed.

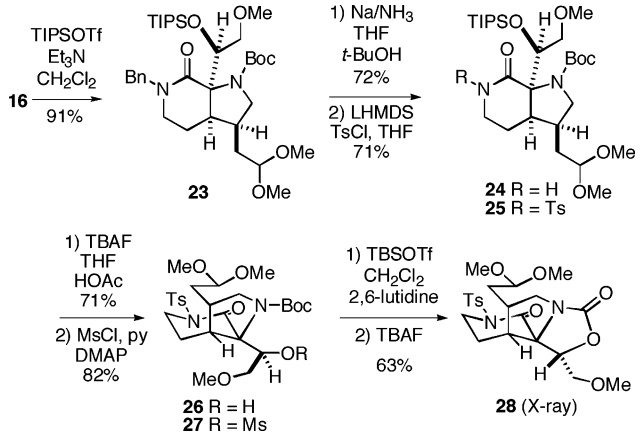
After exploration of a number of other sequences to prepare the requisite *N*-tosyllactam **28**, the route shown in Scheme 7 proved successful. Thus, lactam alcohol **16** was first protected as its TIPS ether **23**, which could be debenzylated under

(10) Sakaitani, M.; Hori, K.; Ohfune, Y. *Tetrahedron Lett.* **1992**, *29*, 2983.

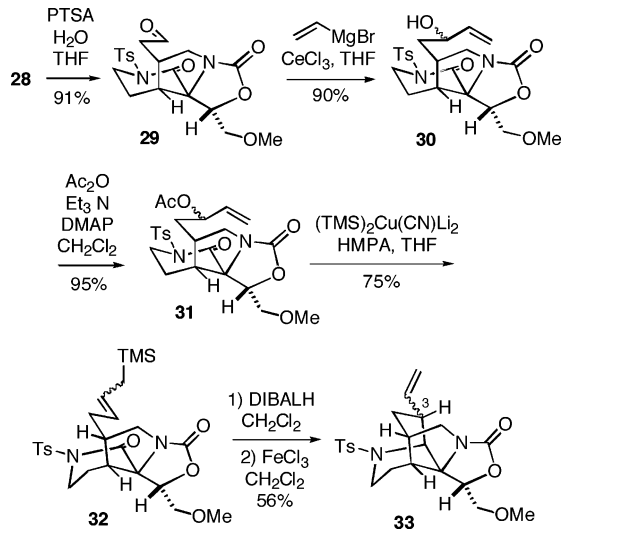
(11) (a) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017. (b) Mitsunobu, O. *Synthesis* **1981**, 1.

(12) (a) Sakaitani, M.; Kurokawa, N.; Ohfune, Y. *Tetrahedron Lett.* **1986**, *27*, 3753. (b) Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150.

SCHEME 7



SCHEME 8

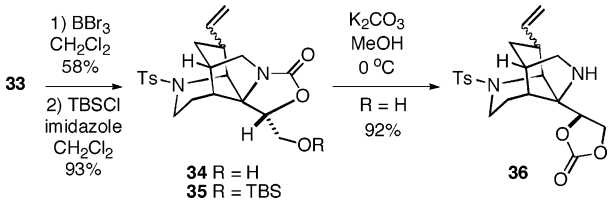


dissolving metal conditions to afford **24**. Subsequent sulfonation of the NH lactam led to *N*-tosyllactam **25**. Removal of the silyl group of **25** proved to be problematic, however, because alcohol **26** is quite prone to retroaldolization under basic conditions. It was eventually found that silyl ether **25** could be deprotected to afford the desired alcohol **26** in good yield with TBAF in THF, provided that the reaction is carefully buffered with acetic acid.[13] This alcohol could then be converted to mesylate **27**, which underwent cyclization via the Ohfune protocol[12] to afford the desired cyclic carbamate **28** which has the correct C-7′ configuration for sarain A. The structure and stereochemistry of **28** were confirmed by X-ray crystallography (see Supporting Information).

Construction of the Tricyclic Core. With key intermediate **28** now in hand, we next explored application of our previously developed *N*-sulfonyliminium ion/allylsilane strategy[4] for formation of the remaining ring of the tricyclic core. Acetal **28** was therefore first hydrolyzed to aldehyde **29**, which underwent addition of vinylmagnesium bromide in the presence of cerium trichloride to afford allylic alcohol **30** as a mixture of stereoisomers (Scheme 8). This mixture was converted to acetates **31**,

(13) Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 9345.

SCHEME 9



and subjection of this intermediate to the Fleming silyl cuprate reagent[14] led to the allylsilane **32** as a mixture of geometric isomers. We were pleased to find that the *N*-tosyllactam functionality in **32** could be partially reduced with DIBALH, and the resulting aminal underwent the desired allylsilane/*N*-sulfonyliminium ion cyclization under ferric chloride catalysis to yield the core fragment **33** as a 2.1:1 mixture of epimers at C-3, which is of no consequence to the synthesis (vide infra).

Studies on Annulation of the Western Macrocyclic Ring. The next goal of this project was to construct the 13-membered western macrocyclic ring found in sarain A (**1**) using the ring-closing metathesis strategy which we had developed in simpler systems.[4d,15] It might also be noted that this early work had been done prior to the invention of the second generation Grubbs metathesis catalyst. On the basis of some exploratory work,[16] it was decided that it would be prudent to replace the methyl ether protecting group at this stage with a more easily removable silyl group. It was found that methyl ether **33** could be cleaved to alcohol **34** in 58% yield under carefully controlled conditions (−78 to −40 °C for 9 h) with boron tribromide (Scheme 9). In an interesting observation which was later put to good use (vide infra), it was found that the rather strained cyclic carbamate moiety in **34** was easily opened, and under mildly basic conditions, rearrangement took place to produce cyclic carbonate amine **36** in high yield. However, it was possible to protect alcohol **34** as the TBS ether **35** without intervention of this rearrangement.

In a simple three-step sequence, olefin **35** could be cleaved and converted via oxime **37** to the C-3 nitrile **38** (Scheme 10). We were gratified to find in accord with our earlier studies that the anion **39**, derived from nitrile **38** via deprotonation with KHMDS, undergoes stereoselective alkylation with the mesylate of 4-pentenol from the least hindered equatorial direction to produce olefin **40**.

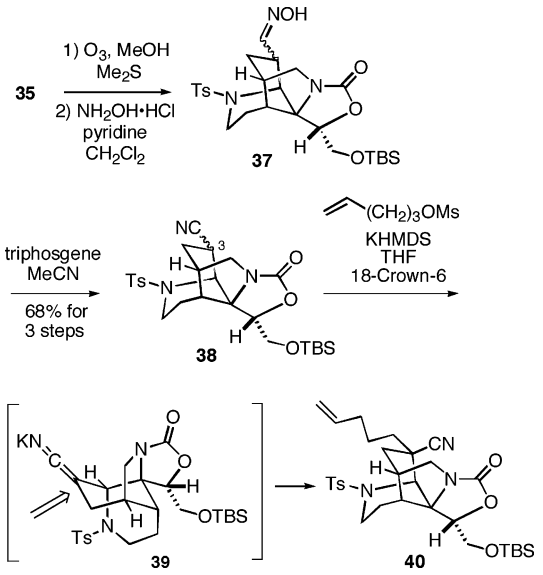
Although we would have much preferred to retain the nitrile functionality throughout the remainder of the total synthesis, this group proved incompatible with removal of the *N*-tosyl moiety via dissolving metal reduction.[17] Thus, nitrile **40** was first reduced with DIBALH to aldehyde **41** (Scheme 11). This intermediate was then further reduced to alcohol **42**, which was subsequently protected as MOM ether **43**. It was then possible to cleanly deprotect sulfonamide **43** to produce the desired

(14) (a) Fleming, I.; Thomas, A. P. *J. Chem. Soc., Chem. Commun.* **1985**, 411. (b) Fleming, I.; Newton, T. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1805.

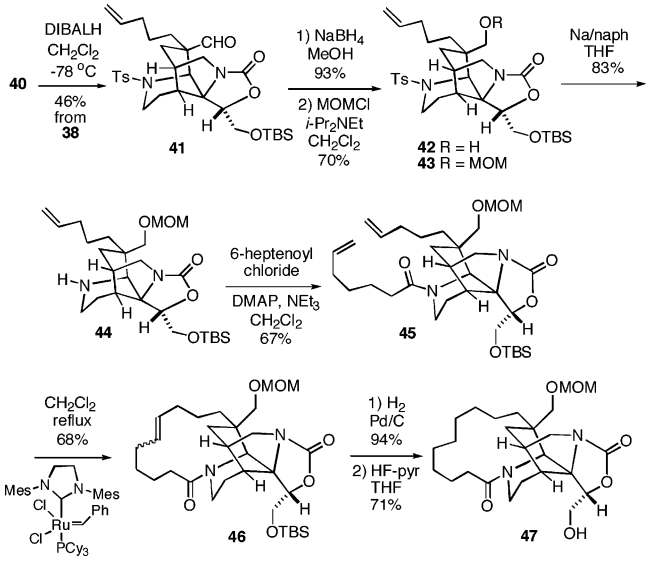
(15) For recent reviews of olefin metathesis, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Furstner, A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3012. (d) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037. (e) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 1900. (f) Walters, M. A. *Prog. Heterocycl. Chem.* **2003**, *15*, 1.

(16) For details, see ref 9.

SCHEME 10

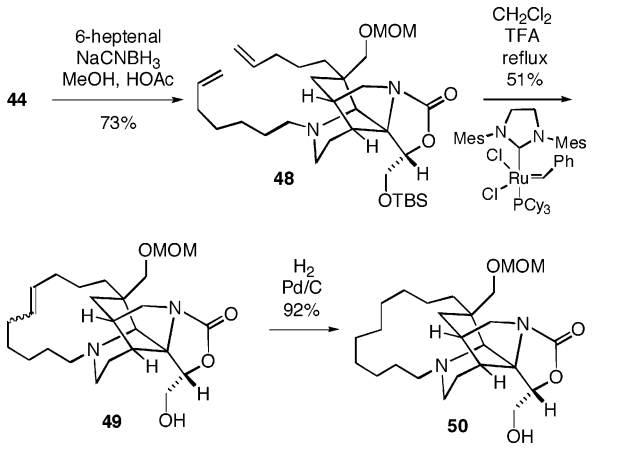


SCHEME 11

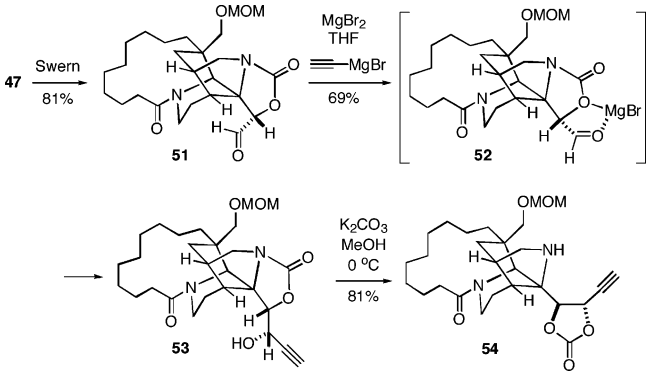


secondary amine **44** using sodium naphthalenide,[18] and subsequent acylation of this amine with 6-heptenoyl chloride led to amide **45**. Upon heating a dilute solution of diene **45** in methylene chloride in the presence of the second generation Grubbs ruthenium metathesis catalyst (25 mol %), macrocycle **46** was formed as a 1:1 mixture of *cis*- and *trans*-alkene isomers in good overall yield. Interestingly, no dimeric product was observed in this reaction, as had been the case when we previously employed the first generation Grubbs catalyst.[4d] This compound could then be hydrogenated to afford the saturated macrolactam, which without purification was desilylated with a HF−pyridine complex to produce alcohol **47**.

SCHEME 12



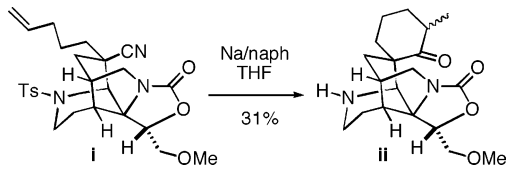
SCHEME 13



We have also found that it is feasible to effect an olefin metathesis to directly access the western ring via a macrocyclic tertiary amine. In this sequence, reductive amination of amine **44** with 6-heptenal using sodium cyanoborohydride was initially effected, leading to diene amine **48** (Scheme 12). This amine was protonated with TFA, and the ring-closing metathesis was then effected in refluxing methylene chloride with the Grubbs catalyst to afford 13-membered macrocyclic olefin **49** as a mixture of geometric isomers in reasonable yield. In the process, the silyl group was conveniently cleaved to produce the corresponding primary alcohol. Catalytic hydrogenation of **49** then afforded the saturated macrocyclic amine **50**.

Formation of the C-7′,8′ *syn*-Diol. Having completed the formation of the western macrocycle, we turned to the introduction of the one remaining sarain stereogenic center at C-8′, which is part of the *syn*-1,2-diol of the eastern ring. For this purpose, alcohol **47** was first subjected to a Swern oxidation to produce aldehyde **51** (Scheme 13). This compound was then treated with anhydrous magnesium bromide in THF, followed by ethynylmagnesium bromide, to afford a single diastereomeric adduct in 69% yield to which we have tentatively assigned the stereochemistry shown in **53**. Although we cannot unambiguously assign configuration at this point, on the basis of literature

(17) In the methyl-protected nitrile series **i**, we were able to isolate amino ketone **ii** in an attempted removal of the *N*-tosyl group with sodium naphthalenide. This transformation presumably occurs via a one-electron reduction of the nitrile to a radical anion followed by cyclization.[18]



(18) Bank, S.; Thomas, S. P. *J. Am. Chem. Soc.* **1977**, *42*, 2858.

precedent,[19] we believe that addition of the Grignard reagent from the least encumbered face of magnesium chelate **52** affords the desired propargylic alcohol **53**. It was then possible to make use of the rearrangement which we had previously observed (cf. Scheme 9) to convert carbamate **53** to cyclic carbonate **54** using potassium carbonate in methanol. This transformation simultaneously frees the amine for annulation of the eastern ring and also protects the 1,2-diol.[20]

Conclusion. In this report we have described an approach to the synthesis of the unique marine alkaloid sarain A (**1**). It has been possible to prepare advanced intermediate **54** which bears all seven stereogenic centers of the alkaloid. This compound, which lacks only one of the five rings of the natural product, has appropriate handles for annulation of the remaining "eastern" 14-membered macrocyclic ring. Key steps in the synthesis of **54** include acylation of lactam **12** to β-ketolactam **14**, followed by stereoselective, chelation-controlled hydride reduction of the carbonyl group to afford alcohol **16**. Using an Ohfune-type cyclization, this alcohol could subsequently be converted to oxazolidinone **28** with inversion, thereby setting the correct sarain C-7′ stereochemistry. The tricyclic core fragment **35** was prepared from **28** utilizing our previously developed *N*-sulfonyliminium ion/allylsilane cyclization strategy. The "western" 13-membered macrocycle was then constructed using a RCM reaction. Finally, a stereoselective chelation-controlled addition of ethynylmagnesium bromide to aldehyde **51** led to adduct **53**, which contains the C-7′,8′ diol functionality of the alkaloid. This oxazolidinone rearranged under mildly basic conditions to cyclic carbonate amine **54**, concurrently protecting the diol and freeing the nitrogen for completion of the "eastern" ring. We hope to utilize intermediate **54** or a closely related analogue in a total synthesis of sarain A.

Experimental Section

General Methods. All nonaqueous reactions were carried out under a positive pressure of dry argon. Air- and moisture-sensitive liquid reagents were added via a dry syringe or cannula. Flash chromatography was performed using silica gel 60 (230−400 mesh). Analytical and preparative thin-layer chromatography were performed on silica gel 60 PF_{254}. THF and ether were dried over and distilled from sodium/benzophenone ketyl. Methylene chloride, toluene, and MeOH were distilled from CaH_2.

6-Benzyl-3-(2,2-dimethoxyethyl)-7-oxooctahydropyrrolo[2,3-*c*]pyridine-1-carboxylic Acid Methyl Ester (11). *N*-Benzyllactam **4** (264 mg, 0.646 mmol) was dissolved in CH_2Cl_2 (4 mL) and methanol (4 mL), and 20% palladium hydroxide on carbon (90 mg) was added to the solution. The reaction mixture was stirred overnight under 1 atm of hydrogen at room temperature and was then filtered through a short plug of Celite eluting with CH_2Cl_2. The filtrate was concentrated in vacuo to produce the secondary amine suitable for use in the next step without purification.

To a solution of the above amine in pyridine (20 mL) was slowly added methyl chloroformate (0.22 mL, 2.85 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 6 h. The pyridine was removed in vacuo, and the residue was diluted with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, gradient 1:2 to 2:1) to give methyl carbamate **11** (194 mg, 80% for two steps): IR (film) 2951, 2831, 1704, 1666, 1451, 1387, 1196, 1125, 1057, 975 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.22 (5H, m), 4.46 (1H, d, J = 8.8 Hz), 4.76 and 4.36 (2H, AB_q, J_{AB} = 14.0 Hz), 4.32 (1H, dd, J = 6.1, 4.9 Hz), 3.80 (1H, dd, J = 10.3, 7.4 Hz), 3.73 (3H, s), 3.29 (3H, s), 3.27 (3H, s), 3.25−3.14 (2H, m), 3.05 (1H, dd, J = 11.1, 8.3 Hz), 2.76 (1H, q, J = 8.5 Hz), 2.29−2.18 (1H, m), 1.75−1.68 (1H, m), 1.66 and 1.50 (2H, AB_q, J_{AB} = 14.0 Hz), 1.45−1.35 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 156.3, 137.0, 128.6, 128.4, 127.6, 103.8, 59.6, 53.4, 53.3, 52.8, 50.9, 50.6, 45.1, 40.1, 37.0, 31.1, 23.3; HRMS (APCI+) calcd for $C_{20}H_{29}N_2O_5$ (MH^+) 377.2069, found 377.2076.

6-Benzyl-3-(2,2-dimethoxyethyl)-7a-(2-methoxyacetyl)-7-oxooctahydropyrrolo[2,3-*c*]pyridine-1-carboxylic Acid Methyl Ester (13). *n*-BuLi (5.92 mL, 14.81 mmol, 2.5 M solution in hexane) was added to a solution of diisopropylamine (2.42 mL, 15.01 mmol) in THF (10 mL) at −78 °C, and the mixture was stirred for 50 min. The mixture was warmed to 0 °C, stirred at this temperature for 15 min, and then recooled to −78 °C. To this mixture was added dropwise a solution of methyl carbamate **11** (906 mg, 2.41 mmol) in THF (15 mL) at −78 °C. Once the addition was complete, the reaction mixture was slowly warmed to 0 °C and stirred at this temperature for 50 min. The resulting solution was recooled to −78 °C, and methoxyacetyl chloride (1.37 mL, 15.03 mmol) was added dropwise. The reaction mixture was then slowly warmed to 0 °C and stirred for a further 2 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$, and the two-phase mixture formed was extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, gradient 1:1 to 2:1) to afford the desired lactam **13** (691 mg, 59%) as a yellow oil, along with unreacted starting lactam **11** (103 mg, 12%): IR (film) 2952, 2831, 1728, 1714, 1660, 1483, 1446, 1372, 1198, 1126, 1070, 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.22 (5H, m), 4.65 and 4.57 (2H, AB_q, J_{AB} = 15.0 Hz), 4.41 (2H, s), 4.29 (1H, q, J = 5.4 Hz), 3.83 (1H, dd, J = 10.7, 7.9 Hz), 3.71 (3H, s), 3.44 (3H, s), 3.31 (6H, s), 3.16−3.13 (2H, m), 3.02 (1H, q, J = 11.0 Hz), 2.94−2.91 (1H, m), 2.31−2.25 (1H, m), 1.81−1.74 (1H, m), 1.69 and 1.57 (2H, AB_q, J_{AB} = 14.0 Hz), 1.65−1.56 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 166.7, 155.4, 136.5, 128.6, 128.4, 127.6, 103.7, 75.7, 75.0, 59.4, 53.6, 52.8, 51.7, 50.9, 45.0, 44.5, 35.9, 31.5, 23.1; HRMS (APCI+) calcd for $C_{23}H_{33}N_2O_7$ (MH^+) 449.2279, found 449.2288.

6-Benzyl-3-(2,2-dimethoxyethyl)-7a-(1-hydroxy-2-methoxyethyl)-7-oxooctahydropyrrolo[2,3-*c*]pyridine-1-carboxylic Acid Methyl Ester (15). A solution of $LiBH_4$ (270 mg, 11.81 mmol) and $ZnCl_2$ (5.90 mL, 5.90 mmol, 1.0 M solution in ether) in ether (15 mL) was stirred at room temperature overnight. The supernatant liquid of the above $Zn(BH_4)_2$ solution (5 mL) was added to a solution of ketone **13** (506 mg, 1.13 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After stirring for 30 min, the reaction mixture was diluted with saturated aqueous NH_4Cl. The two-phase mixture formed was diluted with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, gradient 1:1 to 2:1) to provide the desired alcohol **15** (395 mg, 78%) as a yellow oil: IR (film) 3322, 2952, 1693, 1660, 1449, 1378, 1214, 1193, 1129, 1056, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.23 (5H, m), 5.55 (1H, br s), 4.86 and 4.66 (2H, AB_q, J_{AB} = 14.5 Hz), 4.31 (1H, q, J = 5.5 Hz), 4.01 (1H, ddd, J = 11.1, 6.8, 3.9 Hz), 3.79 (1H, dd, J = 10.9, 7.1 Hz), 3.77 (3H, s), 3.65 and 3.56 (2H, AB_q, J_{AB} = 10.2 Hz), 3.40 (3H, s), 3.31 (3H, s), 3.30 (3H, s), 3.28−3.21 (1H, m), 3.11−3.05 (1H, m), 2.90 (1H, dd, J = 11.3, 11.3 Hz), 2.70 (1H, ddd, J = 10.1, 8.3, 8.3 Hz), 2.43−2.30 (1H, m), 1.77−1.71 (1H, m), 1.68 and 1.51 (2H, AB_q, J_{AB} = 14.2 Hz), 1.47−1.40 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 157.0, 136.7, 128.6, 128.4, 127.5, 103.6,

(19) For a review, see: Huryn, D. M. Carbanions of Alkalai and Alkaline Earth Cations: (ii) Selectivity of Carbonyl Addition Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, p 49.

(20) It is possible to effect this same series of transformations in the "western" ring amine series (cf. Scheme 12) to prepare a cyclic carbonate analogous to **54**.[9]

74.5, 73.8, 73.5, 59.3, 53.4, 53.2, 53.1, 52.5, 51.3, 45.5, 44.9, 34.8, 30.9, 25.4; HRMS (APCI+) calcd for $C_{23}H_{35}N_2O_7$ (MH^+) 451.2435, found 451.2444.

8-Benzyl-5-(2,2-dimethoxyethyl)-1-methoxymethylhexahydro-2-oxa-3a,8-diazacyclopenta[*c*]indene-3,9-dione (9). Alcohol **15** (15.7 mg, 0.035 mmol) in methanol (9 mL) was treated with sodium methoxide (4.7 mg, 0.083 mmol). After stirring at room temperature for 10 h, the reaction mixture was diluted with saturated aqueous NH_4Cl. The methanol was removed in vacuo, and the resulting aqueous mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, gradient 1:2 to 1:1) to afford cyclic carbamate **9** (13.9 mg, 95%) as a yellow oil: IR (film) 2935, 1756, 1655, 1126, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (5H, m), 4.72 (1H, dd, J = 8.6, 3.7 Hz), 4.65 and 4.58 (2H, AB_q, J_{AB} = 14.6 Hz), 4.32 (1H, dd, J = 5.5, 5.5 Hz), 3.89 (1H, dd, J = 12.0, 6.8 Hz), 3.61 and 3.46 (2H, AB_q, J_{AB} = 10.4 Hz), 3.36 (3H, s), 3.33 (3H, s), 3.32 (3H, s), 3.28−3.20 (1H, m), 3.14 (1H, ddd, J = 12.7, 3.9, 3.5 Hz), 2.79 (1H, ddd, J = 12.9, 8.1, 5.7 Hz), 2.73 (1H, q, J = 11.8 Hz), 2.26−2.21 (1H, m), 1.83−1.77 (1H, m), 1.71 and 1.54 (2H, AB_q, J_{AB} = 14.0 Hz), 1.49−1.40 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 160.4, 136.4, 128.8, 128.1, 127.8, 103.9, 80.3, 72.7, 70.1, 59.3, 53.8, 53.5, 51.5, 50.4, 44.9, 41.2, 40.2, 30.8, 24.3; HRMS (APCI+) calcd for $C_{22}H_{31}N_2O_6$ ($MH^+ - CH_3OH$) 387.1913, found 387.1920.

6-Benzyl-3-(2,2-dimethoxyethyl)-7-oxooctahydropyrrolo[2,3-*c*]pyridine-1-carboxylic Acid *tert*-Butyl Ester (12). Palladium hydroxide (20%) on carbon (875 mg) and Boc_2O (3.54 mL, 15.38 mmol) were added sequentially to a solution of *N*-benzylamine **4** (3.14 g, 7.69 mmol) in methanol (200 mL). The mixture was stirred overnight under 1 atm of hydrogen at room temperature and was filtered through a short plug of Celite eluting with EtOAc. The filtrate was concentrated in vacuo, and the residue was then purified by flash column chromatography (EtOAc/hexanes, 1:4) to provide *tert*-butyl carbamate **12** (2.61 g, 81%) as a yellow oil: IR (film) 2933, 1694, 1667, 1480, 1393, 1255, 1125, 1057, 905 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.23 (5H, m), 4.74 and 4.41 (2H, AB_q, J_{AB} = 14.4 Hz), 4.38 (1H, d, J = 7.1 Hz), 4.34 (1H, dd, J = 6.1, 5.1 Hz), 3.73 (1H, dd, J = 10.2, 7.5 Hz), 3.32 (3H, s), 3.30 (3H, s), 3.21−3.17 (2H, m), 3.02 (1H, dd, J = 11.0, 8.5 Hz), 2.77 (1H, dddd, J = 8.0, 8.0, 8.0, 8.0 Hz), 2.31−2.31 (1H, m), 1.75−1.54 (3H, m), 1.49 (9H, s), 1.51−1.39 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 155.3, 137.6, 129.0, 128.6, 104.1, 80.3, 60.5, 53.7, 53.5, 51.3, 50.8, 45.5, 40.5, 37.4, 31.7, 28.8, 23.6; HRMS (APCI+) calcd for $C_{23}H_{35}N_2O_5$ (MH^+) 419.2546, found 419.2547.

6-Benzyl-3-(2,2-dimethoxyethyl)-7a-(2-methoxyacetyl)-7-oxooctahydropyrrolo[2,3-*c*]pyridine-1-carboxylic Acid *tert*-Butyl Ester (14). *n*-BuLi (16.11 mL, 40.21 mmol, 2.5 M solution in hexane) was added to a solution of diisopropylamine (6.72 mL, 43.03 mmol) in THF (30 mL) at −78 °C, and the mixture was stirred for 50 min. The mixture was warmed to 0 °C, stirred at this temperature for 15 min, and then cooled to −78 °C. To this mixture was added dropwise a solution of lactam **12** (2.72 g, 6.52 mmol) in THF (20 mL) at −78 °C. Once the addition was complete, the reaction mixture was slowly warmed to 0 °C and stirred at this temperature for 40 min. The resulting solution was recooled to −78 °C, and methoxyacetyl chloride (3.67 mL, 40.21 mmol) was added dropwise. The reaction mixture was then slowly warmed to 0 °C and stirred for a further 2 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$, and the two-phase mixture which formed was extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, gradient 1:1 to 2:1) to afford the desired lactam **14** (2.23 g, 69%) as a yellow oil, along with unreacted starting lactam **12** (0.24 g, 9%): IR (film) 2930, 2829, 1732, 1644, 1454, 1404, 1366, 1257, 1124, 966, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.24 (5H, m), 4.61 (2H, br s), 4.51 and 4.36 (2H, AB_q, J_{AB} = 17.0 Hz), 4.29 (1H, dd, J = 5.5, 5.5 Hz), 3.77 (1H, dd, J = 9.2, 9.2 Hz), 3.48 (3H, s), 3.32 (3H, s), 3.31 (3H, s), 3.20−3.05 (2H, m), 2.97 (1H, t, J = 11.0), 3.00−2.96 (1H, m), 2.24−2.14 (1H, m), 1.80−1.56 (4H, m), 1.48 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 154.0, 136.6, 128.6, 128.3, 127.5, 103.7, 81.2, 75.7, 75.2, 59.4, 53.5, 51.6, 50.5, 44.9, 35.8, 31.7, 28.2, 22.9; HRMS (APCI+) calcd for $C_{26}H_{39}N_2O_7$ (MH^+) 419.2757, found 419.2750.

6-Benzyl-3-(2,2-dimethoxyethyl)-7a-(1-hydroxy-2-methoxyethyl)-7-oxooctahydropyrrolo[2,3-*c*]pyridine-1-carboxylic Acid *tert*-Butyl Ester (16). A solution of $LiBH_4$ (540 mg, 23.62 mmol) and $ZnCl_2$ (11.84 mL, 11.84 mmol, 1.0 M solution in ether) in ether (36 mL) was stirred at room temperature overnight. The supernatant liquid of the above $Zn(BH_4)_2$ solution (25 mL) was added to a solution of ketone **14** (1.43 g, 2.91 mmol) in CH_2Cl_2 (17 mL) at 0 °C. After stirring for 20 min, the reaction mixture was diluted with saturated aqueous NH_4Cl. The two-phase mixture formed was diluted with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, gradient 1:1 to 2:1) to provide the desired alcohol **16** (1.18 g, 82%) as a yellow oil: IR (film) 3322, 3061, 2926, 1688, 1661, 1454, 1392, 1169, 1129, 1072, 967 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24−7.17 (5H, m), 4.82 (1H, d, J = 14.5 Hz), 4.64 and 4.56 (2H, AB_q, J_{AB} = 14.5 Hz), 4.29 (1H, dd, J = 5.5, 5.5 Hz), 3.94 (1H, t, J = 5.9), 3.71−3.60 (2H, m), 3.35 (3H, s), 3.25 (3H, s), 3.24 (3H, s), 3.20−2.96 (2H, m), 2.88 (1H, t, J = 11.4 Hz), 2.70 (1H, q, J = 7.9 Hz), 2.49−2.28 (1H, m), 1.75−1.72 (3H, m), 1.54−1.47 (1H, m), 1.44 (9H, s), 1.42−1.35 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 157.0, 137.1, 129.0, 128.9, 127.8, 104.0, 81.2, 75.2, 74.8, 69.6, 59.7, 53.8, 53.4, 53.3, 51.3, 45.3, 35.2, 28.8, 25.4, 20.5; HRMS (APCI+) calcd for $C_{26}H_{41}N_2O_7$ (MH^+) 493.2914, found 493.2897.

6-Benzyl-3-(2,2-dimethoxyethyl)-7a-(1-methanesulfonyloxy-2-methoxyethyl)-7-oxooctahydropyrrolo[2,3-*c*]pyridine-1-carboxylic Acid *tert*-Butyl Ester (18). Alcohol **16** (1.23 g, 2.49 mmol), DMAP (50 mg, 0.41 mmol), and methanesulfonyl chloride (0.39 mL, 4.56 mmol) in pyridine (20 mL) was stirred at room temperature for 1 h. The reaction mixture was then diluted with saturated aqueous $NaHCO_3$, and the two-phase mixture which formed was extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, gradient 1:1 to 2:1) to provide the desired mesylate **18** (1.09 g, 81%) as a yellow oil: IR (film) 2926, 1694, 1663, 1600, 1363, 1175, 914, 804 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25−7.20 (5H, m), 5.45 (1H, d, J = 6.3 Hz), 4.60−4.56 (2H, m), 4.22 (1H, t, J = 5.6 Hz), 3.99−3.82 (3H, m), 3.31 (3H, s), 3.22 (3H, s), 3.21 (3H, s), 3.01 (3H, s), 3.10−2.88 (3H, m), 2.86−2.68 (1H, m), 2.56 (1H, t, J = 7.2 Hz), 1.72−1.43 (4H, m), 1.36 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 153.3, 137.1, 129.0, 128.8, 127.9, 104.5, 82.9, 81.5, 73.6, 69.7, 58.9, 54.2, 54.0, 50.9, 46.7, 45.0, 39.2, 35.3, 33.3, 28.7, 24.3; HRMS (APCI+) calcd for $C_{27}H_{43}N_2O_9S$ (MH^+) 571.2689, found 571.2677.

8-Benzyl-5-(2,2-dimethoxyethyl)-1-methoxymethylhexahydro-2-oxa-3a,8-diazacyclopenta[*c*]indene-3,9-dione (10). To a solution of mesylate **18** (519 mg, 0.91 mmol) and 2,6-lutidine (0.64 mL, 5.46 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.05 mL, 4.55 mmol). The reaction mixture was stirred at room temperature for 30 min, and saturated aqueous NH_4Cl was added. The two-phase mixture which formed was diluted with H_2O and extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the crude silyl carbamate **20**.

To a solution of the above crude silyl carbamate **20** in THF (25 mL) was added tetrabutylammonium fluoride (1.82 mL, 1.82 mmol, 1.0 M solution in THF) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, and water was added. The two-phase mixture which formed was extracted with ethyl acetate. The combined

extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, gradient 1:1 to 2:1) to afford cyclic carbamate **10** (273 mg, 72%) as a yellow oil: IR (film) 2927, 1760, 1650, 1494, 1452, 1359, 1323, 1199, 1111, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52−7.28 (5H, m), 4.73 and 4.50 (2H, AB_q, J_{AB} = 14.3 Hz), 4.31 (1H, dd, J = 5.4, 5.4 Hz), 4.26 (1H, dd, J = 8.4, 5.6 Hz), 3.81 (1H, dd, J = 11.9, 6.7 Hz), 3.72−3.65 (2H, m), 3.32 (6H, s), 3.2−3.36 (2H, m), 3.20 (3H, s), 2.81 (1H, dd, J = 11.9, 11.9 Hz), 2.38 (1H, ddd, J = 13.4, 7.6, 5.8 Hz), 2.29−2.35 (1H, m), 1.79−1.74 (1H, m), 1.62 (2H, dd, J = 5.5, 5.4 Hz), 1.47−1.36 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 160.6, 136.4, 128.7, 128.6, 127.8, 103.6, 83.8, 71.5, 70.2, 59.2, 53.7, 53.5, 51.3, 50.3, 47.0, 45.1, 40.0, 30.5, 23.8; HRMS (APCI+) calcd for $C_{22}H_{31}N_2O_6$ (MH^+) 419.2174, found 419.2182.

6-Benzyl-3-(2,2-dimethoxyethyl)-7a-(2-methoxy-1-triisopropylsilanyloxyethyl)-7-oxooctahydropyrrolo[2,3-*c*]pyridine-1-carboxylic Acid *tert*-Butyl Ester (23). To a stirred solution of alcohol **16** (4.31 g, 7.75 mmol) in CH_2Cl_2 (25 mL) were added triethylamine (2.87 mL, 20.6 mmol) and triisopropylsilyl triflate (4.17 mL, 15.5 mmol) at 0 °C. The resulting solution was stirred at room temperature for 1 h, and then saturated aqueous NH_4Cl was carefully added. The two-phase mixture which formed was diluted with water and extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, gradient 1:1 to 2:1) to afford silyl ether **23** (4.54 g, 91%) as a colorless oil: IR (film) 2942, 2866, 1705, 1663, 1455, 1365, 1133 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.25 (5H, m), 5.18−5.09 (1H, m), 4.57 (2H, br s), 4.31 (1H, t, J = 5.4 Hz), 3.75 (1H, d, J = 7.0 Hz), 3.59−3.48 (1H, m), 3.32 (3H, s), 3.29 (6H, s), 3.21−3.16 (1H, s), 3.12−2.98 (3H, m), 2.70−2.62 (1H, m), 1.47 (9H, s), 1.77−1.18 (7H, m), 1.22−0.93 (18H, m), 0.74−0.72 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 169.8, 153.2, 137.3, 128.7, 127.4, 103.7, 79.9, 76.5, 72.8, 70.7, 70.4, 60.3, 58.2, 53.7, 52.9, 50.7, 44.9, 41.8, 35.1, 32.2, 28.4, 24.0, 21.0, 19.1, 18.4, 18.0, 17.2, 14.9, 14.2, 13.2; HRMS (APCI+) calcd for $C_{35}H_{61}N_2O_7Si$ (MH^+) 649.4248, found 649.4215.

3-(2,2-Dimethoxyethyl)-7a-(2-methoxy-1-triisopropylsilanyloxyethyl)-7-oxo-6-(toluene-4-sulfonyl)octahydropyrrolo[2,3-*c*]pyridine-1-carboxylic Acid *tert*-Butyl Ester (24). To a solution of sodium metal (1.12 g, 48.81 mmol) in ammonia (70 mL) at −78 °C was added a solution of *N*-benzyllactam **23** (4.51 g, 6.96 mmol) in THF (25 mL) and *tert*-BuOH (1 mL). After 10 min, the cooling bath was removed, and the reaction was quenched with saturated aqueous NH_4Cl. The NH_3 was allowed to evaporate, and the remaining solution was extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, gradient 3:1 to 5:1) to provide debenzylated lactam **24** (2.79 g, 72%) as a yellow oil: IR (film) 2943, 2866, 1682, 1454, 1391, 1365, 1132, 994 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.99 (1H, m), 5.09−5.00 (1H, m), 4.33 (1H, t, J = 5.4 Hz), 4.06 (1H, t, J = 6.6 Hz), 3.76−3.69 (1H, m), 3.56−3.41 (2H, m), 3.30 (6H, s), 3.29 (3H, s), 3.18 (2H, br s), 3.13−2.63 (3H, m), 1.86−1.59 (5H, m), 1.43 (9H, s), 1.27−0.92 (18H, m), 0.74−0.69 (1H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.8, 172.7, 153.5, 103.8, 80.1, 76.4, 76.3, 70.5, 70.2, 64.3, 58.3, 53.5, 52.9, 43.2, 40.2, 35.1, 32.6, 32.5, 30.7, 28.3, 24.9, 24.8, 19.1, 17.8, 17.1, 14.8, 13.0; HRMS (ESI+) calcd for $C_{28}H_{55}N_2O_7Si$ (MH^+) 559.3778, found 559.3775.

3-(2,2-Dimethoxyethyl)-7a-(2-methoxy-1-triisopropylsilanyloxyethyl)-7-oxo-6-(toluene-4-sulfonyl)octahydropyrrolo[2,3-*c*]-pyridine-1-carboxylic Acid *tert*-Butyl Ester (25). LHMDS (8.96 mL, 8.96 mmol, 1.0 M solution in hexane) was added dropwise to a solution of the NH lactam **24** (2.50 g, 4.48 mmol) in THF (20 mL) at 0 °C. After stirring the mixture for 1 h, *p*-toluenesulfonyl chloride (1.71 g, 8.96 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 h, and then saturated aqueous $NaHCO_3$ was carefully added. The two-phase mixture which formed was diluted with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, gradient 1:1 to 2:1) to afford *N*-sulfonyllactam **25** (2.29 g, 71%) as a colorless oil: IR (film) 2944, 1694, 1460, 1368, 1171, 1090, 991, 674, 546 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (2H, d, J = 8.1 Hz), 7.29 (2H, d, J = 7.8 Hz), 4.89−4.83 (1H, m), 4.29 (1H, t, J = 7.8 Hz), 4.14−4.09 (2H, m), 3.80−3.74 (1H, m), 3.58 (1H, d, J = 12.9 Hz), 3.43−3.38 (1H, m), 3.29 (6H, s), 3.19 (3H, d, J = 6.5 Hz), 3.09 (1H, d, J = 10.8 Hz), 2.89 (1H, br s), 2.66−2.57 (1H, m), 2.42 (3H, s), 1.93−1.88 (1H, m), 1.73−1.56 (2H, m), 1.46 (9H, d, J = 2.8 Hz), 1.46−1.35 (2H, m), 1.26 (1H, d, J = 7.1 Hz), 1.10−0.98 (18H, m), 0.75−0.64 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 169.7, 153.0, 144.5, 136.6, 129.6, 129.4, 128.4, 126.8, 103.6, 76.3, 72.5, 72.2, 60.4, 58.3, 53.8, 53.1, 45.3, 42.6, 34.8, 32.5, 32.3, 28.0, 25.1, 25.0, 21.6, 19.0, 18.3, 18.0, 17.1, 14.7, 13.4, 13.0; HRMS (APCI+) calcd for $C_{35}H_{61}N_2O_9SSi$ (MH^+) 713.3867, found 713.3833.

3-(2,2-Dimethoxyethyl)-7a-(1-hydroxy-2-methoxyethyl)-7-oxo-6-(toluene-4-sulfonyl)-octahydropyrrolo[2,3-*c*]pyridine-1-carboxylic Acid *tert*-Butyl Ester (26). To a solution of silyl ether **25** (2.01 g, 2.83 mmol) in THF (20 mL) were added sequentially tetrabutylammonium fluoride (8.49 mL, 8.49 mmol, 1.0 M solution in THF) and glacial acetic acid (0.3 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred until TLC analysis indicated the absence of starting material (∼10 h). After completion of the reaction, saturated aqueous NH_4Cl was carefully added. The two-phase mixture which formed was diluted with water (10 mL) and extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, gradient 1:1 to 2:1) to afford the desired alcohol **26** (1.13 g, 71%) as a colorless oil: IR (film) 2901, 2341, 1718, 1675, 1456, 1394, 1368, 1170, 1123, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 8.3 Hz), 7.31 (2H, d, J = 8.1 Hz), 4.31 (1H, t, J = 5.4 Hz), 4.11−4.03 (1H, m), 3.91 (1H, br s), 3.73 (1H, dd, J = 8.0, 2.3 Hz), 3.60−3.56 (2H, m), 3.37 (3H, s), 3.31 (6H, d, J = 2.1 Hz), 2.96−2.90 (3H, m), 2.77−2.70 (1H, m), 2.43 (3H, s), 1.70−1.62 (4H, m), 1.47 (9H, s), 1.43−1.33 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 170.6, 145.1, 136.2, 130.4, 130.0, 129.2, 128.2, 104.0, 74.5, 73.7, 64.7, 60.7, 59.7, 59.5, 54.3, 53.8, 52.7, 45.5, 35.1, 28.9, 28.1, 25.4, 20.1; HRMS (APCI+) calcd for $C_{26}H_{41}N_2O_9S$ (MH^+) 557.2532, found 557.2507.

3-(2,2-Dimethoxyethyl)-7a-(1-methanesulfonyloxy-2-methoxyethyl)-7-oxo-6-(toluene-4-sulfonyl)octahydropyrrolo[2,3-*c*]pyridine-1-carboxylic Acid *tert*-Butyl Ester (27). A mixture of alcohol **26** (3.23 g, 5.81 mmol), DMAP (100 mg, 0.82 mmol), and methanesulfonyl chloride (0.91 mL, 11.62 mmol) in pyridine (25 mL) was stirred at room temperature for 1 h. The reaction mixture was then diluted with saturated aqueous $NaHCO_3$, and the two-phase mixture which formed was extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, gradient 1:1 to 2:1) to provide the desired mesylate **27** (3.01 g, 82%) as a yellow oil: IR (film) 2934, 1699, 1597, 1456, 1366, 1175, 965, 907, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 8.2 Hz), 7.32 (2H, d, J = 8.1 Hz), 5.45 (1H, br s), 4.31 (1H, t, J = 5.4 Hz), 4.20 (1H, d, J = 13.6 Hz), 3.82 (1H, t, J = 9.7 Hz), 3.79−3.71 (2H, m), 3.49 (1H, d, J = 13.5 Hz), 3.37−3.35 (3H, m), 3.32 (6H, d, J = 1.0 Hz), 3.13−3.10 (1H, m), 3.07 (3H, s), 2.85−2.80 (1H, m), 2.62 (1H, t, J = 7.4 Hz), 2.44 (3H, s), 1.71−1.66 (3H, m), 1.47 (10H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 152.5, 144.9, 130.0, 129.5, 127.7, 103.5, 81.3, 72.2, 70.9, 58.6, 54.0, 53.4, 42.8, 38.4, 35.0, 32.7, 27.8, 27.7, 25.2, 21.7; HRMS (APCI+) calcd for $C_{27}H_{43}N_2O_{11}S_2$ (MH^+) 635.2308, found 635.2278.

5-(2,2-Dimethoxyethyl)-1-methoxymethyl-8-(toluene-4-sulfonyl)hexahydro-2-oxa-3a,8-diazacyclopenta[*c*]indene-3,9-dione (28). To a solution of mesylate **27** (2.56 g, 4.04 mmol) and 2,6-lutidine

(2.82 mL, 24.22 mmol) in dry CH_2Cl_2 (40 mL) was added dropwise *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.71 mL, 16.15 mmol). The reaction mixture was stirred at room temperature for 2 h, and saturated aqueous NH_4Cl was added. The two-phase mixture which formed was diluted with H_2O and extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the desired silyl carbamate.

To a solution of the above crude silyl carbamatein THF (40 mL) was added tetrabutylammonium fluoride (8.08 mL, 8.08 mmol, 1.0 M solution in THF) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, and water was added. The mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 1:1) to afford cyclic carbamate **28** (1.15 g, 63%) as a white solid. Recrystallization of the purified product from MeOH gave crystals suitable for X-ray analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (2H, d, J = 8.2 Hz), 7.34 (2H, d, J = 8.2 Hz), 4.34−4.28 (2H, m), 4.24 (1H, t, J = 3.4 Hz), 3.77−3.50 (4H, m), 3.32 (3H, s), 3.32−3.19 (6H, m), 2.66 (1H, t, J = 11.7 Hz), 2.53−2.48 (1H, m), 2.44 (3H, s), 2.42−2.32 (1H, m), 2.04−1.97 (1H, m), 1.72−1.26 (1H, m), 1.43−1.33 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 159.3, 145.1, 135.6, 129.3, 128.5, 103.4, 81.0, 73.9, 68.9, 58.9, 53.5, 53.4, 49.8, 46.4, 44.4, 39.6, 30.2, 24.9, 20.8; HRMS (APCI+) calcd for $C_{21}H_{27}N_2O_7S$ ($MH^+ - CH_3OH$) 451.1539, found 451.1543.

Hydrolysis of Acetal 28. To a solution of the cyclic carbamate acetal **28** (1.34 g, 2.97 mmol) in THF (50 mL) and H_2O (50 mL) was added *p*-toluenesulfonic acid (150 mg, 0.79 mol), and the resulting solution was heated at reflux for 14 h. After cooling, the reaction mixture was diluted with saturated aqueous $NaHCO_3$. The two-phase mixture formed was diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 2:1) to produce the desired aldehyde **29** (1.18 g, 91%) as a white solid: IR (film) 3050, 2955, 1725, 1700, 1595, 1450, 1370, 1170 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (1H, s), 7.94 (2H, d, J = 8.2 Hz), 7.34 (2H, d, J = 8.1 Hz), 4.38 (1H, dd, J = 15.2, 4.2 Hz), 4.29−4.25 (1H, m), 3.82 (1H, d, J = 4.5 Hz), 3.65−3.45 (3H, m), 3.29 (3H, s), 2.77−2.57 (4H, m), 2.44 (3H, s), 1.81 (1H, d, J = 13.7 Hz), 1.46−1.31 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 166.1, 157.6, 143.7, 134.0, 127.9, 127.1, 81.5, 72.5, 67.4, 57.5, 47.6, 43.9, 42.9, 39.4, 36.0, 22.7, 20.0; HRMS (ESI+) calcd for $C_{20}H_{25}N_2O_7S$ (MH^+) 437.1382, found 437.1387.

Acetic Acid 1-[1-Methoxymethyl-3,9-dioxo-8-(toluene-4-sulfonyl)hexahydro-2-oxa-3a,8-diazacyclopenta[*c*]inden-5-ylmethyl]allyl Ester (30). Cerium chloride heptahydrate (1.70 g, 4.57 mmol) was dried at 140 °C for 2 h in vacuo. THF (20 mL) was added at 0 °C, and the mixture was stirred overnight at room temperature. To this suspension was added a solution of the above aldehyde **29** (1.18 g, 2.69 mmol) in THF (10 mL) at 0 °C, and the reaction mixture was stirred for 30 min. To the resulting solution was added vinylmagnesium bromide (4.03 mL, 4.03 mol, 1.0 M solution in THF) at 0 °C. After being stirred for 2 h at the same temperature, the mixture was diluted with saturated aqueous NH_4Cl and ethyl acetate. The suspension was filtered through a short plug of Celite eluting with EtOAc. The filtrate was diluted with H_2O and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 1:2) to produce a diastereomeric mixture of allylic alcohols **30** (1.12 g, 90%): IR (film) 3463, 2925, 1762, 1698, 1359, 1171, 1089, 1042 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.94 (2H, d, J = 8.3 Hz), 7.34 (2H, d, J = 8.2 Hz), 5.86−5.78 (1H, m), 5.24 (1H, d, J = 17.1 Hz), 5.14 (1H, dd, J = 3.7, 6.7 Hz), 4.34−4.25 (2H, m), 4.09−4.06 (1H, m), 3.80−3.76 (1H, m), 3.68−3.52 (3H, m), 3.32 (1H, d, J = 2.5 Hz), 2.67 (1H, q, J = 11.8 Hz), 2.55−2.43 (2H, m), 2.44 (3H, s), 2.00−1.95 (2H, m), 1.63−1.35 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 158.5, 144.5, 139.7, 139.6, 135.0, 129.0, 127.9, 114.9, 114.8, 82.5, 73.6, 73.4, 71.1, 70.9, 68.4, 58.4, 49.5, 49.1, 46.1, 44.3, 40.3, 40.0, 33.1, 23.8, 23.7, 20.1; HRMS (APCI+) calcd for $C_{22}H_{29}N_2O_7S$ (MH^+) 465.1696, found 465.1709.

Acetic Acid 1-[1-Methoxymethyl-3,9-dioxo-8-(toluene-4-sulfonyl)hexahydro-2-oxa-3a,8-diazacyclopenta[*c*]inden-5-ylmethyl]allyl Ester (31). Allylic alcohol mixture **30** (912 mg, 1.96 mmol) was dissolved in CH_2Cl_2 (40 mL), and the solution was cooled to 0 °C. Acetic anhydride (0.33 mL, 3.53 mmol), triethylamine (0.53 mL, 3.81 mmol), and DMAP (33 mg, 0.30 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 4 h, and then saturated aqueous NH_4Cl was carefully added. The mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 2:1) to afford the desired acetates **31** (939 mg, 95%) as a colorless amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (2H, d, J = 8.3 Hz), 7.34 (2H, d, J = 8.2 Hz), 5.79−5.77 (1H, m), 5.31−5.19 (3H, m), 4.30−4.26 (2H, m), 3.76−3.50 (4H, m), 3.33 (3H, d, J = 4.6 Hz), 2.69 (1H, q, J = 11.9 Hz), 2.44 (3H, s), 2.30−2.17 (1H, m), 2.06 (3H, d, J = 5.2 Hz), 1.79−1.56 (3H, m), 1.42−1.12 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 169.4, 167.2, 167.1, 158.8, 144.7, 135.1, 134.7, 134.3, 129.0, 128.0, 117.7, 117.3, 82.6, 73.6, 73.4, 68.4, 58.5, 49.2, 49.1, 45.9, 44.3, 44.2, 39.8, 39.3, 30.8, 30.7, 23.9, 23.7, 21.0, 20.5; HRMS (APCI+) calcd for $C_{24}H_{31}N_2O_8S$ (MH^+) 507.1801, found 507.1795.

1-Methoxymethyl-8-(toluene-4-sulfonyl)-5-(4-trimethylsilanyl-but-2-enyl)hexahydro-2-oxa-3a,8-diazacyclopenta[*c*]indene-3,9-dione (32). Hexamethyldisilazane (1.56 mL, 7.74 mmol) dissolved in HMPA (4 mL) was cooled to 0 °C and treated with MeLi (5.19 mL, 7.27 mmol, 1.4 M solution in ether). After being stirred for 15 min, the resulting solution was diluted with THF (10 mL), and CuCN (316 mg, 3.51 mmol) was added in one portion. The reaction mixture was stirred for 40 min and cooled to −25 °C, and allylic acetate **31** (782 mg, 1.55 mmol) in THF (7 mL) was added. After being stirred for 1 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and was filtered through a short plug of Celite eluting with ether. The filtrate was diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 1:1) to produce allylsilanes **32** (603 mg, 75%): IR (film) 2952, 1767, 1698, 1359, 1172, 853 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (2H, d, J = 8.3 Hz), 7.35 (2H, d, J = 8.1 Hz), 5.53−5.44 (1H, m), 5.20−5.09 (1H, m), 4.34−4.25 (2H, m), 3.76−3.53 (4H, m), 3.34 (3H, d, J = 1.4 Hz), 2.67 (1H, dd, J = 11.6, 10.2 Hz), 2.45 (3H, s), 2.28−2.23 (1H, m), 2.05−1.96 (4H, m), 1.64−1.35 (3H, m), 0.00 (4.5H, s), −0.02 (4.5H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 161.4, 147.1, 137.6, 131.4, 131.0, 130.5, 130.1, 126.3, 124.8, 85.0, 76.4, 76.3, 71.0, 61.0, 51.8, 48.1, 46.9, 46.2, 32.4, 32.1, 31.5, 26.2, 25.9, 24.6, 20.9, 20.7, 0, −0.2, −0.3; HRMS (APCI+) calcd for $C_{25}H_{37}N_2O_6SSi$ (MH^+) 521.2142, found 521.2160.

Cyclization of Allylsilane 32 to Tricycle 33. To a solution of *N*-tosyllactam **32** (380 mg, 0.73 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added DIBALH (2.94 mL, 2.94 mmol, 1.0 M solution in hexane). After the mixture was stirred for 40 min at the same temperature, saturated aqueous NH_4Cl was carefully added. The reaction mixture was stirred for 1.5 h at room temperature and was filtered through a short plug of Celite eluting with EtOAc. The filtrate was concentrated in vacuo to give the colorless crude aminal as a mixture of diastereomers suitable for use in the next step without purification.

The above aminal mixture was dissolved in CH_2Cl_2 (10 mL) and cooled to −78 °C. Anhydrous ferric chloride (432 mg, 2.65 mmol) was added in one portion, and the resulting solution was warmed to room temperature. After 1 h, the reaction mixture was diluted with 10% NaOH solution (2.5 mL) and stirred for 1 h. The

mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 1:1) to produce the desired tricyclic product **33** (177 mg, 56% for two steps) as a 2.1:1 mixture of diastereomers at C-3: IR (film) 2952, 1698, 1359, 1263, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (2H, d, J = 8.3 Hz), 7.31−7.19 (2H, m), 5.90−5.80 (0.7H, m), 5.26−5.07 (0.3H, m), 4.86−4.81 (1H, m), 4.70 (0.3H, t, J = 3.7 Hz), 4.60−4.46 (1.4H, m), 4.05 (0.3H, d, J = 7.0 Hz), 3.92 (1H, s), 3.74−3.60 (3H, m), 3.55−3.41 (1H, m), 3.33−3.30 (3H, m), 3.00−2.91 (2H, m), 2.64−2.63 (1H, m), 2.52−2.45 (2H, m), 2.37−2.34 (3H, m), 2.22−2.01 (2H, m), 1.85 (2H, dd, J = 5.3, 9.2 Hz), 1.45−1.41 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 159.0, 144.4, 143.8, 142.5, 137.9, 137.5, 136.0, 130.4, 129.9, 129.8, 127.8, 116.2, 115.0, 81.1, 80.8, 72.1, 71.8, 68.0, 67.7, 61.5, 60.7, 60.0, 51.4, 51.0, 42.5, 39.8, 39.4, 39.0, 38.8, 36.1, 35.3, 32.8, 31.7, 22.9, 22.6, 21.9; HRMS (APCI+) calcd for $C_{22}H_{29}N_2O_5S$ (MH^+) 433.1797, found 433.1781.

Formation of Alcohol 34. To a solution of methyl ether **33** (121 mg, 0.28 mmol) in CH_2Cl_2 (15 mL) was added BBr_3 (1.68 mL, 1.68 mmol, 1.0 M solution in CH_2Cl_2) at −78 °C. The resulting mixture was warmed to −40 °C and stirred until TLC analysis indicated the absence of starting material (∼9 h). After completion of the reaction, saturated aqueous $NaHCO_3$ was added. The mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 2:1) to afford the desired alcohol **34** (68 mg, 58%) as a white foam: IR (film) 3450, 2930, 1654, 1454, 1257, 736 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.65 (2H, d, J = 8.3 Hz), 7.27−7.19 (2H, m), 5.91−5.81 (0.6H, m), 5.17−5.16 (0.4H, m), 4.88 (1H, t, J = 8.4 Hz), 4.66−4.53 (2H, m), 4.08−3.70 (4H, m), 3.58−3.48 (0.4H, m), 3.41−3.35 (0.6H, m), 3.05−3.29 (2H, m), 2.69−2.52 (3H, m), 2.38 (3H, d, J = 5.7 Hz), 2.23−2.17 (1H, m), 1.97−1.86 (1H, m), 1.87−1.82 (1H, m), 1.54−1.21 (2H, br s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 158.2, 143.3, 142.8, 136.8, 134.9, 128.3, 126.6, 114.0, 81.2, 80.8, 66.8, 66.7, 61.5, 61.1, 60.5, 59.6, 50.5, 50.2, 41.3, 38.7, 38.3, 37.9, 37.7, 34.8, 34.0, 31.7, 30.7, 21.8, 21.5, 20.8; HRMS (APCI+) calcd for $C_{21}H_{27}N_2O_5S$ (MH^+) 419.1641, found 419.1648.

Preparation of Nitrile 38. To a solution of alcohol **34** (464 mg, 1.11 mmol) in CH_2Cl_2 (30 mL) were added *tert*-butyldimethylsilyl chloride (251 mg, 1.72 mmol) and imidazole (114 mg, 1.72 mmol) at room temperature. After stirring the mixture for 2 h, saturated aqueous NH_4Cl was added. The two-phase mixture formed was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 1:3) to afford silyl ether **35** (548 mg, 93%) as a colorless oil.

A solution of silyl ether **35** (512 mg, 0.96 mmol) in CH_2Cl_2 (15 mL) was cooled to −78 °C and was exposed to ozone gas with efficient stirring for 5 min. While still at −78 °C, the solution was flushed with argon. After 10 min, dimethyl sulfide (0.22 mL, 2.84 mmol) was added, and the resulting solution was gradually warmed to room temperature. After being stirred overnight, the solution was diluted with saturated aqueous $NaHCO_3$. The two-phase mixture formed was diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were washed with brine to produce the crude aldehyde suitable for use in the next step without purification.

To a solution of the above aldehyde in CH_2Cl_2 (15 mL) were added pyridine (0.17 mL, 2.07 mmol) and hydroxylamine hydrochloride (68 mg, 0.98 mmol) at room temperature. After being stirred overnight at room temperature, the mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give the crude oxime **37** suitable for use in the next step without purification.

To a solution of the above oxime **37** in CH_3CN (10 mL) was added triphosgene (483 mg, 1.78 mmol). After stirring the mixture for 24 h, the CH_3CN was removed in vacuo. The residue was diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 2:3) to produce the desired nitrile **38** (347 mg, 68% for three steps): ^1H NMR (360 MHz, $CDCl_3$) δ 7.60−7.57 (2H, m), 7.21−7.11 (2H, m), 4.74−4.72 (1H, m), 4.27 (1H, t, J = 3.4 Hz), 3.79 (2H, m), 3.48−3.45 (2H, m), 3.21−3.17 (3H, m), 3.13−3.11 (1H, m), 2.45−2.14 (3H, m), 2.40−2.02 (3H, m), 1.82−1.62 (2H, m), 0.71 (9H, s), 0.01 (6H, d, J = 14.5 Hz); LRMS (APCI+) calcd for $C_{26}H_{38}N_3O_5SSi$ (MH^+) 532.2, found 532.2.

Conversion of Nitrile 38 to Aldehyde 41. KHMDS (1.62 mL, 0.81 mmol, 0.5 M solution in hexane) was added to nitrile **38** (203 mg, 0.40 mmol) in THF (10 mL) at −78 °C. The mixture was warmed to 0 °C, stirred at this temperature for 30 min, and then cooled to −78 °C. To this mixture was added dropwise the mesylate of 4-pentenol (185 mg, 1.12 mmol) in THF (6 mL). Once the addition was complete, the reaction mixture was slowly warmed to 0 °C. After 30 min, 18-crown-6 (30 mg, 0.12 mmol) was added, and the resulting solution was heated at reflux for 13 h. After cooling the mixture to room temperature, saturated aqueous NH_4Cl was added. The mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 1:1) to afford the desired alkylated nitrile **40** together with some impurities.

To a solution of the above nitrile **40** in CH_2Cl_2 (10 mL) at −78 °C was added DIBALH (0.62 mL, 0.62 mmol, 1 M solution in CH_2Cl_2). After the mixture was stirred at the same temperature for 40 min, 10% HCl solution (10 mL) and ether (15 mL) were added. The mixture was stirred for 2 h at room temperature and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (EtOAc/hexanes, 1:1) to afford the desired aldehyde **41** (110 mg, 46% for two steps): IR (film) 2929, 1764, 1721, 1333, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.21 (1H, s), 7.51 (2H, d, J = 8.0 Hz), 7.14 (2H, d, J = 7.9 Hz), 5.51−5.38 (1H, m), 5.11 (1H, s), 4.75−4.70 (2H, m), 4.34 (1H, d, J = 12.2 Hz), 4.22 (1H, s), 3.92−3.83 (1H, m), 3.40−3.33 (1H, m), 3.03−2.94 (2H, m), 2.88−2.84 (1H, m), 2.36 (2H, br s), 2.25 (3H, s), 1.94−1.87 (2H, m), 1.65−0.83 (9H, m), 0.71 (9H, s), 0.01 (6H, d, J = 14.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 163.5, 144.4, 138.2, 137.1, 130.2, 128.0, 115.2, 80.3, 67.9, 61.8, 56.8, 55.6, 53.8, 41.1, 40.2, 33.9, 33.8, 31.0, 30.0, 26.2, 22.0, 21.9, 18.8, −5.0, −5.1; HRMS (APCI+) calcd for $C_{31}H_{47}N_2O_6SSi$ (MH^+) 603.2924, found 603.2933.

Reduction of Aldehyde 41 to Alcohol 42. To a solution of aldehyde **41** (431 mg, 0.72 mmol) in methanol (15 mL) was added $NaBH_4$ (54 mg, 1.41 mmol) at 0 °C. After stirring the mixture for 1 h, saturated aqueous NH_4Cl was added. The methanol was removed in vacuo, and the resulting aqueous mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford the crude alcohol **42** (405 mg, 93%) suitable for use in the next step without purification: IR (film) 3477, 2929, 1757, 1328, 1156 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.51 (2H, d, J = 8.1 Hz), 7.12 (2H, d, J = 7.8 Hz), 5.57−5.43 (1H, m), 5.12 (1H, br s), 4.75−4.69 (2H, m), 4.54−4.46 (2H, m), 4.27 (1H, s), 3.87−3.83 (2H, m), 2.97 (1H, dd, J = 12.7, 5.0 Hz), 2.82 (1H, d, J = 10.7 Hz), 2.35 (1H, br s), 2.24 (3H, s), 1.92−1.86 (3H, m), 1.62−0.95 (10H, m), 0.78 (9H, s), 0.00 (6H, d, J = 13.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 144.0, 139.0, 137.3, 130.0, 128.2, 114.8, 79.5, 68.9, 65.5, 62.3, 57.2, 55.3, 43.2, 40.3, 40.2, 40.1, 37.3, 34.9, 34.4, 26.2, 22.7, 21.9, 18.9, −5.0, −5.2; HRMS (APCI+) calcd for $C_{31}H_{49}N_2O_6SSi$ (MH^+) 605.3081, found 605.3100.

Preparation of MOM Ether 43. *N,N*-Diisopropylethylamine (0.62 mL, 2.91 mmol) and MOMCl (0.12 mL, 1.50 mmol) were added to a solution of alcohol **42** (301 mg, 0.50 mmol) in CH_2Cl_2 (7 mL), and the reaction mixture was stirred at room temperature for 15 h. The resulting solution was then diluted with CH_2Cl_2, washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 2:3) to yield the MOM ether **43** as a colorless oil (227 mg, 70%): IR (film) 2930, 1760, 1329, 1155, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (2H, d, J = 8.2 Hz), 7.19 (2H, d, J = 8.1 Hz), 5.67−5.53 (1H, m), 4.83−4.76 (2H, m), 4.50 (2H, s), 4.40 (1H, s), 4.32−4.29 (2H, m), 4.05−3.96 (1H, m), 3.62−3.50 (2H, m), 3.40−3.32 (2H, m), 3.26 (3H, s), 3.10−2.90 (2H, m), 2.43 (1H, br s), 2.31 (3H, s), 1.96−1.36 (9H, m), 1.32 (2H, d, J = 6.6 Hz), 0.83 (9H, s), 0.02 (6H, d, J = 11.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ163.1, 143.7, 138.8, 136.9, 129.7, 127.7, 114.3, 97.0, 79.4, 71.7, 68.5, 61.7, 55.8, 55.5, 53.8, 42.1, 41.7, 39.8, 38.9, 34.1, 33.8, 25.8, 22.4, 21.5, 21.2, 18.6, 18.4, 17.3, 12.2, −5.4, −5.5; HRMS (APCI+) calcd for $C_{33}H_{53}N_2O_7SSi$ (MH^+) 649.3337, found 649.3306.

Preparation of Amine 44. To a solution of naphthalene (267 mg, 4.03 mmol) in THF (6 mL) was added sodium metal (96 mg, 4.01 mmol) at room temperature. After stirring for 2 h, part of the mixture (4 mL) was added to a solution of sulfonamide **43** (203 mg, 0.31 mmol) in THF (8 mL) at −78 °C. After 10 min, saturated aqueous NH_4Cl was carefully added. The two-phase mixture which formed was diluted with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 1:1) to afford secondary amine **44** (129 mg, 83%) as a white foam: IR (film) 2928, 1756, 1253, 1044, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81−5.67 (1H, m), 4.97−4.87 (2H, m), 4.50 (1H, s), 4.44 (1H, br s), 4.07 (2H, d, J = 8.7 Hz), 3.57−3.54 (1H, m), 3.41−3.36 (2H, m), 3.26 (3H, s), 3.07−2.98 (3H, m), 2.61−2.58 (1H, m), 2.45 (1H, br s), 2.04−1.96 (4H, m), 1.86−1.78 (2H, m), 1.70 (1H, br s), 1.56−1.02 (5H, m), 0.81 (9H, s), 0.00 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ163.4, 139.0, 115.2, 97.2, 81.1, 71.1, 67.8, 62.0, 56.1, 55.9, 41.6, 41.5, 41.0, 39.0, 35.3, 35.2, 34.8, 26.2, 22.7, 22.4, 19.0, −5.0, −5.1; HRMS (APCI+) calcd for $C_{26}H_{47}N_2O_5SSi$ (MH^+) 495.3249, found 495.3221.

Preparation of Amide 45. To a solution of amine **44** (178 mg, 0.36 mmol) in CH_2Cl_2 (6 mL) was added a solution of 6-heptenoyl chloride (271 mg, 1.82 mmol) in CH_2Cl_2 (6 mL), followed by triethylamine (1.21 mL, 7.21 mmol) and DMAP (4.5 mg, 0.037 mmol). The reaction mixture was stirred for 10 h at room temperature, and saturated aqueous $NaHCO_3$ was carefully added. The mixture was diluted with water and extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 1:1) to afford the desired amide **45** (146 mg, 67%) as a brown oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.69−5.63 (2H, m), 4.92−4.82 (4H, m), 4.51 (2H, s), 4.16 (1H, s), 3.69−3.58 (5H, m), 3.43−3.41 (2H, m), 3.24 (3H, s), 3.03−2.97 (1H, m), 2.49−2.26 (3H, m), 1.94−1.73 (9H, m), 1.55−1.06 (9H, m), 0.80 (9H, s), −0.01 (6H, d, J = 12.5 Hz); HRMS (APCI+) calcd for $C_{33}H_{57}N_2O_6Si$ (MH^+) 605.3986, found 605.3967.

Preparation of Alcohol 47. To a solution of diene **45** (109 mg, 0.18 mmol) in CH_2Cl_2 (450 mL) was added the Grubb's second generation ruthenium catalyst (36 mg, 0.0434 mmol), and the resulting solution was heated at reflux for 11 h. After cooling the mixture to room temperature, CH_2Cl_2 was removed in vacuo. The residue was then purified by flash column chromatography (EtOAc/hexanes, gradient 1:1 to 2:1) to afford macrocyclic lactam **46** (55 mg, 68%) as a 1:1 mixture of cis and trans isomers: ^1H NMR (400 MHz, $CDCl_3$) δ 5.29−5.23 (2H, m), 4.52 (2H, s), 4.48−4.43 (1H, m), 3.86−3.76 (4H, m), 3.62−3.30 (2H, m), 3.29 (3H, s), 3.16 (1H, s), 3.03−2.90 (3H, m), 2.76−2.46 (4H, m), 2.25−1.74 (10H, m), 1.72−1.01 (8H, m); LRMS (APCI+) calcd for $C_{25}H_{41}N_2O_5$ (MH^+) 449.3, found 449.3.

Palladium (10%) on activated carbon (21 mg) was added to a solution of lactam olefin **46** (51 mg, 0.11 mmol) in methanol (12 mL). The mixture was stirred for 10 h under 1 atm of hydrogen at room temperature and was filtered through a short plug of Celite eluting with EtOAc. The filtrate was concentrated in vacuo to produce the crude macrocyclic lactam (48 mg, 94%) as a colorless oil suitable for use in the next step without purification.

HF·pyridine (50 μL) was added dropwise to a stirred solution of the above silyl ether (47 mg, 0.105 mmol) in THF at 0 °C. The reaction mixture was stirred at room temperature for 12 h, and then saturated aqueous $NaHCO_3$ was added. The mixture was diluted with water and extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 2:1) to afford alcohol **47** (35 mg, 71%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.42 (2H, br s), 4.11 (1H, s), 3.77 (1H, br s), 3.61−3.55 (2H, m), 3.40−3.16 (4H, m), 3.15 (3H, s), 2.90−2.77 (2H, m), 2.42 (1H, br s), 2.34−2.16 (3H, m), 1.95−1.23 (8H, m), 1.05−1.00 (11H, m), 0.63 (2H, t, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 162.3, 97.3, 82.3, 80.9, 71.3, 70.8, 61.8, 61.0, 59.0, 57.2, 56.3, 55.9, 51.2, 50.6, 41.7, 40.8, 39.5, 37.7, 35.4, 32.0, 29.9, 29.2, 27.2, 26.8, 26.3, 25.9, 25.0, 24.1, 23.7, 22.9, 22.8, 21.9, 21.7, 21.4, 14.4; HRMS (APCI+) calcd for $C_{25}H_{41}N_2O_6$ (MH^+) 465.2964, found 465.2948.

Preparation of Diene 48. A solution of amine **44** (71.2 mg, 0.0984 mmol), 6-heptenal (48.4 mg, 0.432 mmol), glacial acetic acid (50 μL), and sodium cyanoborohydride (59.8 mg, 0.936 mmol) in methanol (4 mL), containing 3 Å molecular sieves (10 mg), was stirred at room temperature for 12 h. The reaction mixture was then filtered through a short plug of Celite eluting with EtOAc. The filtrate was concentrated in vacuo, diluted with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 2:1) to provide the desired tertiary amine **48** (42.5 mg, 73%) as a colorless oil: ^1H NMR (360 MHz, $CDCl_3$) δ 5.73−5.68 (2H, m), 4.94−4.85 (4H, m), 4.46 (2H, dd, J = 3.3, 6.4 Hz), 4.35 (1H, t, J = 3.0 Hz), 3.91 (1H, t, J = 3.6 Hz), 3.49 (2H, d, J = 2.2 Hz), 3.38−3.34 (2H, m), 3.27 (3H, s), 3.09 (1H, s), 2.92−2.72 (3H, m), 2.56−2.40 (4H, m), 2.00−1.94 (5H, m), 1.90−1.24 (14H, m), 0.83 (9H, s), 0.00 (6H, d, J = 6.5 Hz); HRMS (APCI+) calcd for $C_{33}H_{59}N_2O_5Si$ (MH^+) 591.4193, found 591.4179.

Ring-Closing Olefin Metathesis of Diene 48 to Macrocyclic Alkene 49 and Subsequent Hydrogenation. A solution of diene **48** (31.3 mg, 0.0513 mmol) in CH_2Cl_2 (102 mL) was treated with TFA (4 μL, 0.0513 mmol), followed by the Grubb's second generation ruthenium catalyst (12.9 mg, 0.0172 mmol), and the resulting solution was heated at reflux for 8 h. After cooling the mixture to room temperature, CH_2Cl_2 was removed in vacuo. The residue was then purified by flash column chromatography (EtOAc/hexanes, gradient 1:1 to 3:1) to afford macrocycle **49** (11.8 mg, 51%) as an inseparable mixture of cis and trans isomers: ^1H NMR (400 MHz, $CDCl_3$) δ 5.29−5.23 (2H, m), 4.52 (2H, s), 4.48−4.43 (1H, m), 3.86−3.76 (4H, m), 3.62−3.30 (2H, m), 3.29 (3H, s), 3.16 (1H, s), 3.03−2.90 (3H, m), 2.76−2.46 (4H, m), 2.25−1.74 (10H, m), 1.72−1.01 (8H, m); LRMS (APCI+) calcd for $C_{25}H_{41}N_2O_5$ (MH^+) 449.3, found 449.2.

Palladium (10%) on activated carbon (11.7 mg) was added to a solution of olefins **49** (63.5 mg, 0.141 mmol) in methanol (5 mL). The mixture was stirred for 10 h under 1 atm of hydrogen at room temperature and was filtered through a short plug of Celite eluting with EtOAc. The filtrate was concentrated in vacuo to produce macrocycle **50** (58.5 mg, 92%) as a colorless oil suitable for use without purification: ^1H NMR (300 MHz, $CDCl_3$) δ 4.69−4.67 (1H, m), 4.56 (2H, s), 4.52−4.49 (1H, m), 3.70−3.66 (2H, m), 3.50−3.33 (2H, m), 3.30 (3H, s), 3.28−3.26 (1H, m), 3.10−2.66

(7H, m), 2.55 (1H, s), 2.53−2.41 (3H, m), 2.10−1.76 (10H, m), 1.44−1.16 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 97.3, 82.3, 71.3, 70.8, 61.8, 61.0, 59.0, 57.2, 55.3, 55.4, 53.2, 51.6, 40.8, 39.2, 36.7, 34.4, 32.1, 27.2, 26.5, 25.9, 25.2, 24.1, 23.7, 22.9, 22.8, 21.7, 21.4, 14.2; HRMS (APCI+) calcd for $C_{25}H_{43}N_2O_5$ (MH^+) 451.3172, found 451.3185.

Oxidation of Alcohol 47 to Aldehyde 51. To a solution of oxalyl chloride (44 mg, 0.531 mmol) in CH_2Cl_2 (3 mL) at −60 °C was added dropwise DMSO (63 μL, 0.912 mmol). After being stirred at the same temperature for 15 min, a solution of alcohol **47** (87 mg, 0.191 mmol) in CH_2Cl_2 (2 mL) was added via a cannula. After 15 min, triethylamine (0.24 mL, 1.71 mmol) was added and the reaction mixture was warmed to room temperature over 10 min. The reaction mixture was diluted with water and was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 2:1) to afford aldehyde **51** (20 mg, 81%) as a colorless oil: IR (film) 2930, 1770, 1731, 1634, 1106, 1043 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.53 (1H, s), 5.14 (1H, s), 4.56 (2H, d, J = 10.7 Hz), 3.76 (1H, d, J = 9.7 Hz), 3.68−3.58 (1H, m), 3.48−3.35 (7H, m), 3.32 (3H, s), 3.14−3.06 (1H, m), 2.42 (1H, br s), 2.62 (1H, br s), 2.48−2.35 (3H, m), 2.18−2.05 (1H, m), 2.00−1.93 (3H, m), 1.75−0.76 (12H, m); LRMS (APCI+) calcd for $C_{25}H_{39}N_2O_6$ (MH^+) 463.3, found 463.3.

Preparation of Acetylenic Alcohol 53. To a solution of the aldehyde **51** (41.2 mg, 0.0819 mmol) in CH_2Cl_2 (10 mL) was added $MgBr_2$ (103 mg, 0.411 mmol). After being stirred at room temperature for 1 h, the reaction mixture was cooled to −78 °C and ethynylmagnesium bromide (1.12 mL, 0.561 mmol, 0.5 M solution in THF) was added dropwise. The reaction mixture was stirred at the same temperature for 4 h, and then saturated aqueous NH_4Cl was added. The mixture was diluted with water and extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexanes, 1:1) to afford alcohol **53** (27.7 mg, 69%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (1H, s), 4.58 (2H, s), 4.01−3.92 (1H, m), 3.49−3.45 (3H, m), 3.29 (3H, s), 2.95 (1H, d, J = 10.9 Hz), 2.65 (1H, br s), 2.55 (2H, br s), 2.45−2.37 (4H, m), 2.07−1.60 (3H, m), 1.82−1.70 (4H, m), 1.62−1.04 (11H, m), 0.83−0.79 (4H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.1, 163.3, 98.3, 82.3, 80.9, 71.3, 70.8, 61.8, 61.0, 59.0, 57.2, 56.3, 55.9, 51.2, 42.7, 40.8, 39.5, 37.7, 35.4, 32.0, 29.9, 28.2, 26.9, 26.5, 25.9, 25.1, 24.1, 23.5, 22.2, 21.7; HRMS (APCI+) calcd for $C_{27}H_{41}N_2O_6$ (MH^+) 489.2964, found 489.2956.

Conversion of Oxazolidinone 53 to Cyclic Carbonate 54. K_2CO_3 (29.1 mg, 0.0212 mmol) was added to a solution of oxazolidinone **53** (48.3 mg, 0.0987 mmol) in methanol (8 mL), and the resulting solution was stirred for 1.5 h at 0 °C. The methanol was then removed in vacuo, and the resulting aqueous mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford alcohol **54** (39.1 mg, 81%) as a yellow oil: IR (film) 3310, 2930, 2858, 1692, 1629, 1425, 1106, 1043 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (1H, s), 4.57 (2H, s), 3.95−3.84 (1H, m), 3.64−3.51 (2H, m), 3.49−3.38 (4H, m), 3.31 (3H, s), 3.20 (1H, d, J = 11.1 Hz), 2.65−2.31 (5H, m), 2.21 (1H, br s), 2.03−1.60 (6H, m), 1.53−1.04 (10H, m), 0.82−0.79 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 154.3, 99.3, 83.3, 80.5, 71.5, 70.2, 64.8, 61.1, 59.0, 57.9, 57.3, 55.4, 52.2, 44.7, 41.8, 39.6, 37.5, 36.0, 35.5, 33.0, 29.9, 28.6, 27.9, 26.2, 25.9, 24.3, 23.5, 22.1, 20.7; LRMS (APCI+) calcd for $C_{27}H_{41}N_2O_6$ (MH^+) 489.3, found 489.3.

Acknowledgment. We are grateful to the National Institutes of Health (GM-32299) for financial support of this research. We thank Dr. Louis Todaro (Hunter College, CUNY) for the crystal structure determination.

Supporting Information Available: Copies of proton and carbon NMR spectra of new compounds and X-ray data including an ORTEP drawing for compound **28**. This material is available free of charge on the Internet at http://pubs.acs.org.

JO052504R