Further Studies on Total Synthesis of Sarain A. Efforts Toward Annulation of the Macrocyclic Rings

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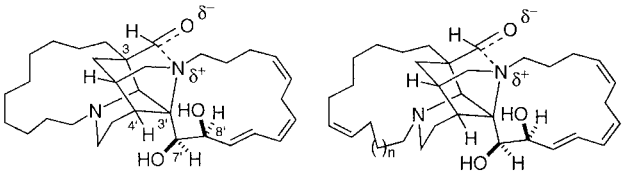
Studies have been conducted on testing strategies for annulation of the two macrocyclic rings onto the central tricyclic nucleus of sarain A (**1**). In particular, methodology has been developed for introduction into the core of C-3′ and C-3 substituents, which are necessary for construction of the "eastern" and "western" macrocyclic rings of **1**, respectively. Formation of the western ring has been successfully addressed via a ring-closing olefin metathesis strategy utilizing the Grubbs ruthenium catalyst. With this macrocyclization approach, a key intermediate lactam has been prepared which will be utilized in a total synthesis of the natural product.

Marine sponges produce a series of complex polycyclic alkaloids which appear to have a common biogenesis from simple bis-pyridine macrocycles. This group of alkaloids has spurred a considerable amount of innovative synthetic work worldwide, particularly with regard to the manzamines, and we have recently 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 unusual



1 sarain A

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

alkaloids were elucidated by Cimino and co-workers using a combination of spectral methods and X-ray crystallography. The sarains **1**−**3** were also found to have moderate antitumor, antibacterial, and insecticidal activity.[2d] We have previously reported some initial synthetic studies directed toward constructing the tricyclic core of these exceptionally challenging and interesting molecules.[3] Heathcock et al.[4] also revealed some preliminary results based on a dipolar cycloaddition strategy similar to that which we successfully executed for synthesis of the nucleus of **1**−**3**. In addition, the Heathcock group has reported some interesting model studies directed toward synthesis of the "eastern" macrocyclic ring of the sarains.

Our strategy for building the tricyclic core of the sarains was to prepare a bicyclic system like **4** via a stereospecific [3 + 2]-azomethine ylid/olefin cycloaddition (vide infra), which would undergo an allyl silane/*N*-sulfonyliminium ion cyclization (cf. **5**) to give a tricycle **6** (Scheme 1). In fact, this concept has proven viable, and sarain tricycle **6** could be prepared efficiently.[3] To continue the synthetic route, it was necessary to next introduce functional handles at some stage for attachment of the "eastern" and "western" macrocyclic rings at C-3′ and C-3, respectively. In this paper, we describe recent work toward this end and, in addition, report on some modifications of our initial route[3] to simplify and improve the overall sequence of steps.

The starting point for the synthesis was commercially available dihydroanisole (**7**), which was ozonized to afford ester acetal **8** (Scheme 2). The ester was converted to alcohol **9** and then via the mesylate **10** to *N*-benzylamine **11** (54% from **7**). Condensation of this amine with the aziridine mixed anhydride **12** yielded amide **13** in excellent yield. Thermolysis of aziridine olefin **13** at 325 °C in *o*-DCB led to a stereospecific cyclization via [3 + 2]-dipolar cycloaddition of azomethine ylid **14** to bicyclic lactam **15**.[5] It might be noted that in our previous work[3] we had employed a protected alcohol in the side chain due to concerns as to whether an acetal moiety would survive the high temperatures required for the cycloaddition step. Introduction of a functionalized C-3′ substituent into the system proved quite easy. Thus, lactam **15** was first deprotonated with LiHMDS followed by alkylation with bromomethyl methyl ether, leading to the desired *cis*-fused bicycle **16** in good yield.

Before continuing with the synthesis, we decided to explore the possibility of incorporating the C-3′ substituent into an early intermediate prior to the cycloaddition step. Thus, aziridine ester **17**[3c,6] was combined with

(1) Matzanke, N.; Gregg, R. J.; Weinreb, S. M. *Org. Prep. Proced. Int.* **1998**, *30*, 1 and references 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.

(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) (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.

(4) (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.

(5) cf. (a) DeShong, P.; Kell, D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, *50*, 2309. (b) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* **1987**, *109*, 5523. Takano, S.; Tomita, S.; Iwabuchi, Y.; Ogasawara, K. *Heterocycles* **1989**, *29*, 1473. Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1204.

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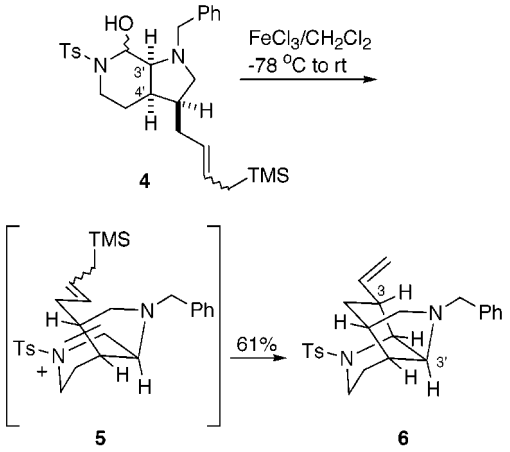
Scheme 1



amine **18**[3] in the presence of trimethylaluminum[7] to afford amide **19** (Scheme 3). Attempts at thermolysis of compound **19** at >320 °C led only to recovery of starting material. Because it seemed possible that this lack of reactivity might be due to an unfavorable amide conformation, secondary amide **19** was *N*-benzylated to afford aziridine olefin **20**. In this case, heating substrate **20** at 320 °C for 2.5 h indeed led to the desired bicylic lactam **21**. Despite the success of these experiments, however, it was deemed simpler and more convenient to proceed via the lactam alkylation route shown in Scheme 2 and this alternative sequence was therefore not pursued.

At this point, lactam **16** was selectively mono-debenzylated by a dissolving metal reduction, and the resulting lactam **22** was *N*-tosylated to afford **23** (Scheme 4). Because we have experienced some difficulties in exploratory work[3c] due to the presence of a basic nitrogen in various intermediates, it was decided to replace the remaining *N*-benzyl group with a carbamate function at this point. Therefore, the benzyl compound **23** was hydrogenolyzed to the corresponding secondary amine, which was converted to the methyl carbamate derivative. Hydrolysis of the acetal moiety then afforded aldehyde carbamate **24** in good overall yield. Addition of vinylmagnesium bromide to this aldehyde in the presence of cerium trichloride afforded a diastereomeric mixture of allylic alcohols **25**, which was acetylated to yield acetates **26**. Application of the Fleming silyl cuprate methodology[8] allowed conversion of allylic acetates **26** to allyl silane **27** as a 1:1 mixture of geometric isomers. We were pleased to find that the C-3′ substituent which had been installed did not adversely affect the *N*-sulfonyl imine/allylsilane addition step. Thus, selective partial reduction of the *N*-tosyl lactam carbonyl group of **27**, followed by treatment of the resulting α-hydroxy sulfonamide with anhydrous ferric chloride led to the sarain A tricyclic nucleus **28** (3:2 mixture of diastereomers) in high yield.

Our initial plan was to next cleave the double bond of tricycle **28** to produce ester **32** and then to alkylate the derived ester enolate at C-3. Treatment of intermediate **28** with OsO_4/Jones reagent[9] led to the desired carboxylic acid, which could be converted to ethyl ester **32** with diazoethane (54%).[3c] However, despite extensive effort, we were unable to alkylate this ester. In addition, the ester substrate bearing an *N*-benzyl group rather than the methyl carbamate functionality was also resistant to alkylation at C-3.[3a] We therefore turned to the nitrile **31** as an alternative. This compound was prepared in excellent yield by ozonolysis of alkene **28** to aldehyde **29**, followed by formation of oxime **30**, and dehydration with triphosgene.

Nitrile **31** has in fact proven quite amenable to C-3 alkylation. Treatment of **31** with KHMDS and iodo acetal **33** led to a single stereoisomeric alkylation product **35** (Scheme 5). The stereochemistry of this product was established as shown by ^{1}H NMR NOE experiments after conversion to benzyl ether **36**.[10] It therefore appears that alkylation of nitrile carbanion **34** occurs from a preferred equatorial direction, as is observed in cases of simpler exocyclic cyclohexyl nitrile anions.[11] Attempts were also made to utilize acetal **36** in construction of the "western" macrocyclic ring of sarain A. Removal of the *N*-tosyl group (Na/naphthalene) and cleavage of the acetal with TFA provided amino aldehyde **37**. However, we have been unable to effect a reductive amination of **37** to afford macrocycle **38**.[12,13]

Another strategy which was briefly examined for annulation of this ring involved an intramolecular nitrile carbanion alkylation.[14] Thus, iodonitrile **39** was prepared (Scheme 6), but we have unfortunately been unable to effect closure to macrocycle **40**.[15]

In view of these disappointing results, we next turned to a ring-closing olefin metathesis strategy for building the "western" macrocyclic ring.[16] Alkylation of nitrile **31** with mesylate **41** afforded a single stereoisomeric product **42** (70%) along with a small amount of recovered starting material (Scheme 7). It was then possible to convert this alkylated nitrile to the benzyl ether **43** in three steps. Selective cleavage of the *N*-tosyl group of **43** could be effected with sodium naphthalenide, and acylation of the resulting amine with 6-heptenoyl chloride afforded amide

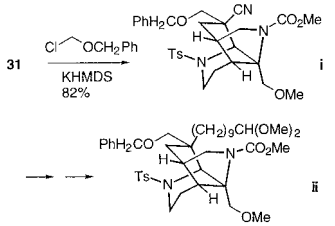
(6) Anderson, G. T.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1991**, *56*, 6946.

(7) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171. Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth.* **1979**, *59*, 49.

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

(9) Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4745.

(10) To confirm this assignment, nitrile **31** was converted via alkylation product **i** to compound **ii**, which is the epimer of **36**. ^{1}H NMR NOE experiments on **ii** established its stereochemistry.



(11) Evans, D. A. Stereoselective Alkylation Reactions of Chiral Metal Enolates. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, p 1.

(12) See, for example: Ina, H.; Ito, M.; Kibayashi, C. *J. Org. Chem.* **1996**, *61*, 1023.

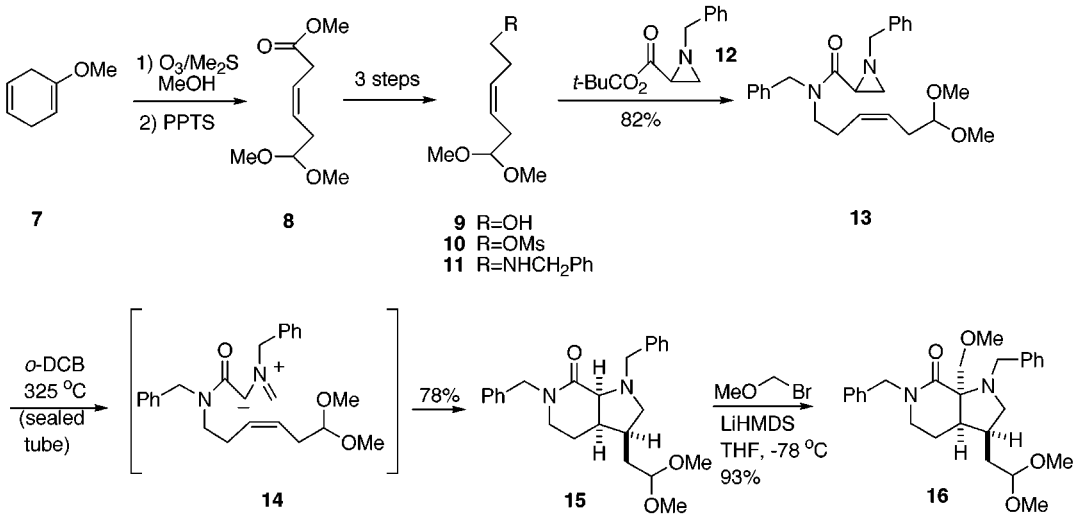
(13) Meng, Q.; Hesse, M. Ring Closure Methods in the Synthesis of Macrocyclic Natural Products. In *Topics in Current Chemistry*; Steckhan, E., Ed.; Springer-Verlag: Berlin, 1991; *161*, p 107.

(14) For some examples of macrocycle formation via intramolecular nitrile anion alkylations, see: Takahashi, T.; Nemoto, H.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 2005. Takahashi, T.; Nagashima, T.; Ikeda, H.; Tsuji, J. *Tetrahedron Lett.* **1982**, *23*, 4361.

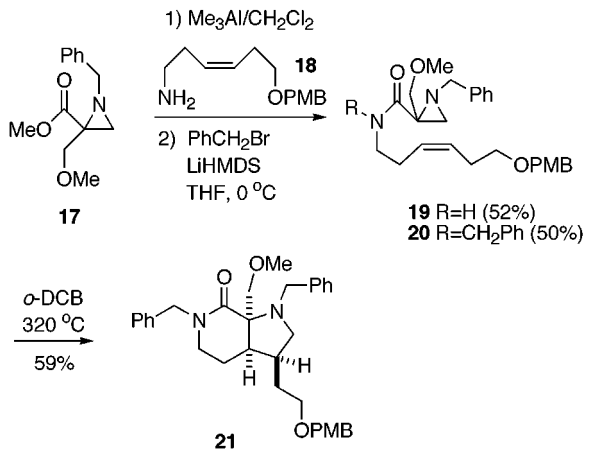
(15) Samizu, K.; unpublished results.

(16) For ring-closing olefin metathesis reviews, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.

Scheme 2



Scheme 3



44. Exposure of diene amide **44** to the Grubbs ruthenium catalyst **45** in refluxing methylene chloride (0.5 mM) for 2 days led to the desired macrocyclic lactam **46** as a mixture of geometric isomers (49%) along with a dimeric product (39%) and some recovered starting material (7%). The dimer appears to be a macrocycle derived from either head-to-head or head-to-tail coupling of diene **44**.[17] It was then possible to hydrogenate **46** to produce the macrolactam alcohol **47**, which we hope to use in the total synthesis of sarain A.

We have briefly examined two other permutations of this metathesis strategy for construction of the "western" ring. Thus, by use of the chemistry described for synthesis of diene **44**, diene **48** was prepared (Scheme 8). Treatment of **48** with the Grubbs catalyst led to formation of an inseparable mixture of the desired macrocycle **49** along with a linear dimer in poor overall yield. The metathesis reaction proved sluggish in this case, and a considerable amount of starting material was also recovered. We believe that in diene **48** the C-3 alkenyl chain is positioned too close to the tricylic core, thus slowing the metathesis process. This may also explain why a noncyclic dimer is formed in this particular case.

One other diene system which was explored is **50** (Scheme 9). Metathesis of this compound gave the desired macrolactam **51**, along with a macrocyclic dimer and some starting material. Although this particular substrate has not yet been examined in detail, the results to date appear to be quite similar to those obtained with diene **44**.

In conclusion, we have developed a successful strategy for preparation of the key macrocyclic intermediate **47** for the total synthesis of sarain A (**1**). Work is currently in progress on improving the metathesis process for construction of the "western" macrolactam ring of **47** and on developing appropriate chemistry for efficient annulation of the functionally complex "eastern" ring.

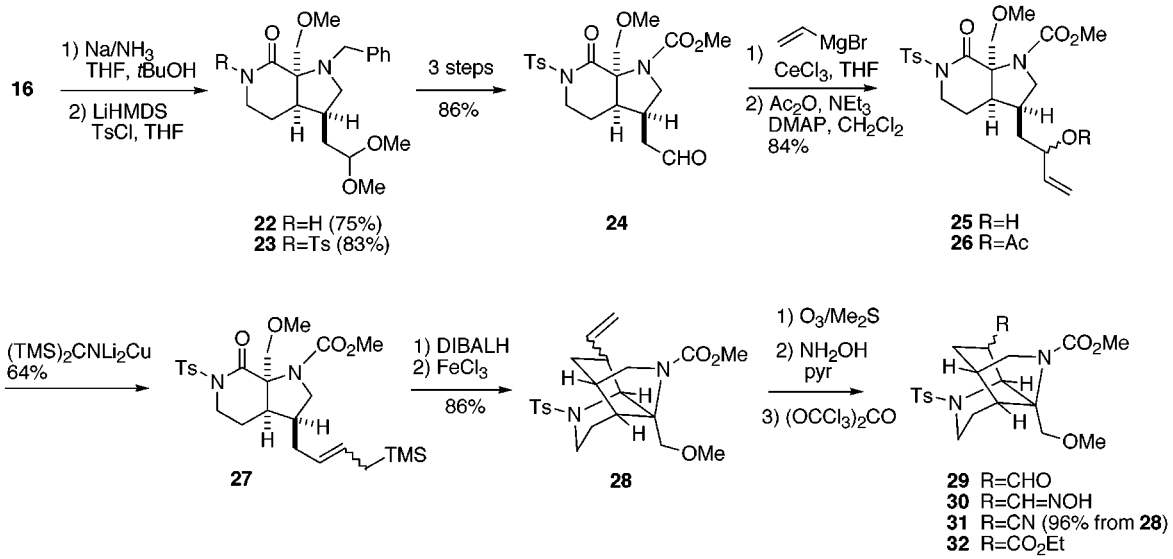
Experimental Section

Preparation of Benzylamine 11. A solution of 1-methoxy-1,4-cyclohexadiene (**7**, 21.25 g, 0.19 mol) in 50 mL of methanol was cooled to −78 °C and was exposed to ozone gas with efficient stirring for 2 h. While still at −78 °C, the solution was flushed with argon. After 10 min, dimethyl sulfide (17.6 mL, 0.24 mol) was added and the resulting solution was gradually warmed to room temperature over 2 h. Methanol and excess dimethyl sulfide were removed in vacuo, and 100 mL of methanol followed by pyridinum *p*-toluenesulfonate (2.32 g, 9.22 mmol) was added to the residue. The mixture was heated at reflux for 2 h, and methanol was then removed in vacuo. The residue was diluted with 50 mL of saturated $NaHCO_3$ solution and extracted with ether (2 × 100 mL). The organic extract was dried (K_2CO_3) and concentrated to give the crude ester **8** as a brown oil: IR (film) 2950, 1740, 1435, 1125 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.67 (2H, m), 4.36 (1H, t, J = 5.7 Hz), 3.68 (3H, s), 3.32 (6H, s), 3.11 (2H, d, J = 6.8 Hz), 2.37 (2H, t, J = 5.7 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.4, 127.6, 123.8, 104.3, 53.4, 52.1, 33.3, 31.6; CIMS *m*/*z* (relative intensity) (M^+ − OMe) 157 (95), 127 (18), 97 (20), 75 (100).

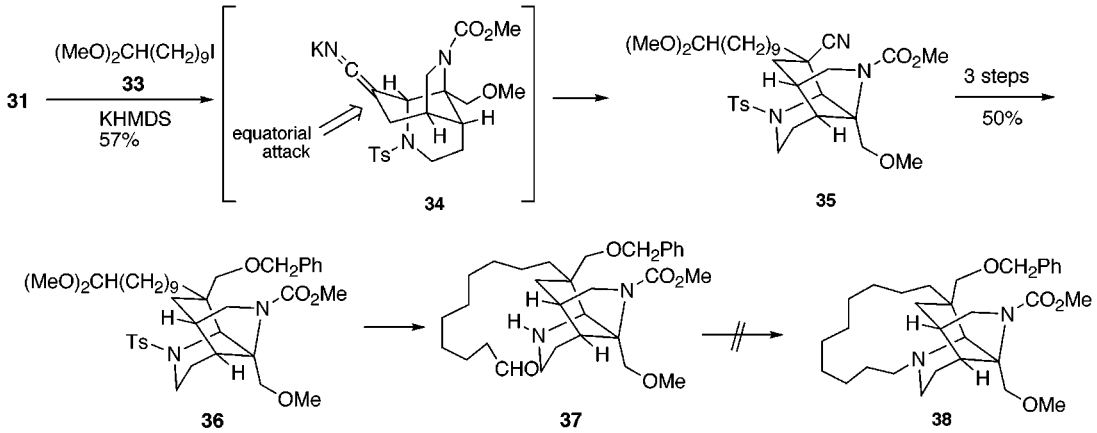
The above crude ester **8** was dissolved in 50 mL of THF and was added to a solution of $LiAlH_4$ (4.20 g, 0.10 mol) in 100 mL of THF over 30 min at 0 °C. After 10 min, 15 mL of a 50% KOH solution and 100 mL of ether were added at 0 °C. The solution was stirred overnight at room temperature and was filtered through a pad of Celite which was further washed with ether. The organic phase was concentrated to produce alcohol **9** as a yellow oil suitable for use in the next step without purification: IR (film) 3420, 2940, 1125, 1055 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.58 (2H, m), 4.36 (1H, t, J = 5.7 Hz), 3.75 (2H, m), 3.34 (6H, s), 2.43 (2H, t, J = 5.7 Hz), 2.32 (2H, q, J = 6.1 Hz), 2.14 (1H, br s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 128.8, 126.7, 104.5, 62.2, 53.6, 31.5, 31.3; EIMS *m*/*z* (relative intensity) (M^+ − OMe) 129 (7), 109 (6), 97 (12), 75 (100).

(17) Ozonolysis of this cyclic dimer followed by treatment with $Ph_3P{=}CH_2$ gave back diene **44**.

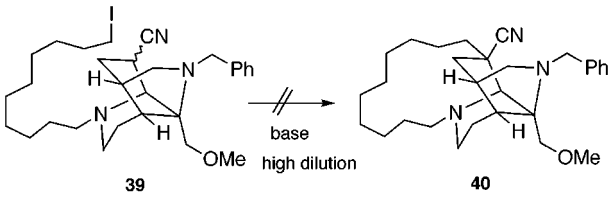
Scheme 4



Scheme 5



Scheme 6

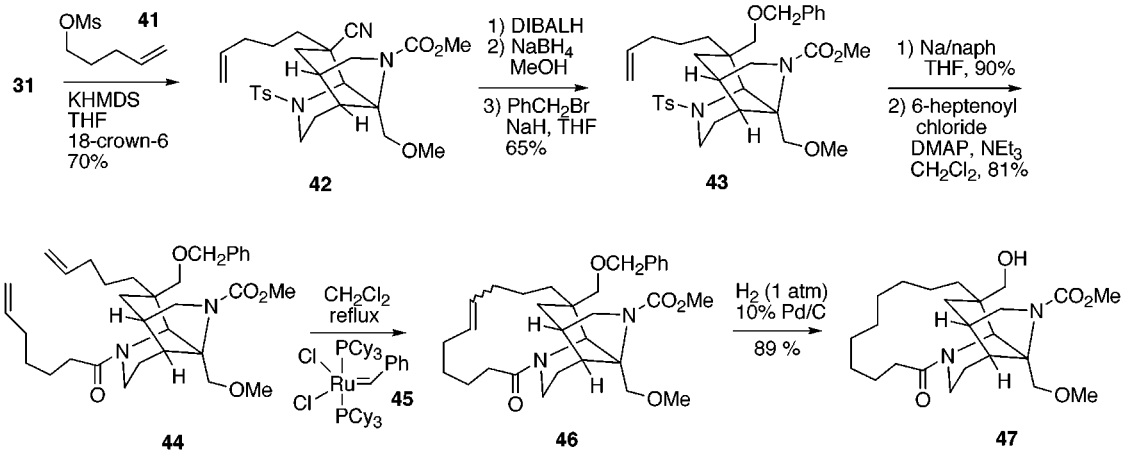


The above alcohol **9** was dissolved in 100 mL of CH_2Cl_2, and the mixture was cooled to 0 °C. Et_3N (18.27 mL, 0.13 mol) and methanesulfonyl chloride (9.7 mL, 0.13 mol) were added sequentially via syringe, and the resulting solution was stirred for 10 min. The mixture was washed with H_2O (2 × 100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated to give the unstable mesylate **10** as a brown oil: IR (film) 2940, 1355, 1175, 1125 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.55 (2H, m), 4.36 (1H, t, J = 5.7 Hz), 4.21 (2H, t, J = 6.7 Hz), 3.32 (6H, s), 2.98 (3H, s), 2.49 (2H, q, J = 6.7 Hz), 2.36 (2H, t, J = 5.7 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 128.3, 126.2, 104.6, 69.9, 53.8, 37.8, 31.9, 28.1; CIMS m/z (relative intensity) ($M^+ + 1$) 237 (10), 207 (100), 111 (30), 85 (40), 75 (95).

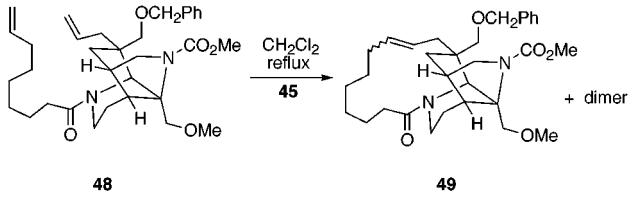
To a solution of the above mesylate **10** and Et_3N (51.8 mL, 0.37 mol) in 100 mL of THF was added benzylamine (42.14 mL, 0.39 mol), and the mixture was heated at reflux overnight. The solution was cooled to 0 °C, and 50 mL of ether was added. The resulting salts were filtered, and the organics were concentrated. The residue was extracted twice with 100 mL of ether. The extract was washed with brine (100 mL), dried (K_2CO_3), and concentrated. Flash chromatography of the residue eluting with ethyl acetate yielded 28.03 g (51% overall from **7**) of amine **11** as a yellow oil: IR (film) 3310, 2935, 2830, 1455, 1125 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.31 (5H, m), 5.48 (2H, m), 4.36 (1H, t, J = 5.7 Hz), 3.78 (3H, s), 3.29 (6H, s), 2.66 (2H, t, J = 6.7 Hz), 2.38 (2H, t, J = 5.7 Hz), 2.26 (2H, q, J = 6.7 Hz), 1.57 (1H, br s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 140.7, 130.1, 128.8, 128.5, 127.3, 125.9, 104.5, 54.3, 53.4, 49.2, 31.5, 28.5; CIMS m/z (relative intensity) ($M^+ + 1$) 250 (100), 218 (78), 186 (10), 120 (40), 91 (32).

Conversion of Amine 11 to Aziridine Amide 13. Potassium trimethylsilanolate (3.33 g, 25.92 mmol) was added in one portion to a solution of methyl *N*-benzylaziridine-1-carboxylate[5a] (4.95 g, 25.92 mmol) in 100 mL of THF. After 14 h, the solution was concentrated in vacuo. The residue was dissolved in 70 mL of CH_2Cl_2 and cooled to 0 °C. Pivaloyl chloride (3.16 mL, 25.67 mmol) was added slowly, and the resulting solution was gradually warmed to room temperature over 2 h. After the mixture was recooled to −78 °C, a solution of amine **11** (6.40 g, 25.67 mmol) in 30 mL of CH_2Cl_2 was added over 30 min. The solution was stirred for 30 min at −78 °C, diluted with 50 mL of saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2 (100 mL). After drying (K_2CO_3) and concentration of the extract, flash chromatography of the residue eluting with hexanes/ethyl acetate (1:2) provided aziridine amide **13** (8.59 g, 82%) as a yellow oil: IR (film) 3480, 2935, 1645, 1450, 1120, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (10H, m), 5.43 (2H, m), 4.72 (0.5H, d, J = 14.8 Hz), 4.51 (0.5H, d, J = 14.8 Hz), 4.51 (1H, t, J = 7.4 Hz), 4.33 (0.5H, d, J = 11.3 Hz), 4.31 (0.5H, d, J = 11.3 Hz), 3.72 (0.5H, d, J

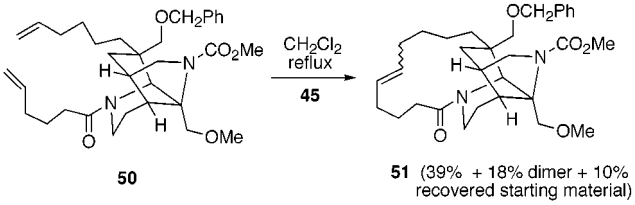
Scheme 7



Scheme 8



Scheme 9



= 13.8 Hz), 3.51 (0.5H, d, J = 13.4 Hz), 3.48 (0.5H, d, J = 13.4 Hz), 3.35 (0.5H, d, J = 13.8 Hz), 3.34 (1H, m), 3.30 (6H, s), 3.21 (1H, m), 2.33 (6H, m), 1.73 (0.5H, d, J = 6.2 Hz), 1.62 (0.5H, d, J = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 169.4, 138.5, 138.4, 137.7, 137.2, 129.7, 128.7, 128.6, 128.4, 128.3, 128.2, 127.7, 127.6, 127.5, 127.5, 126.8, 126.6, 126.1, 104.4, 104.2, 64.5, 53.5, 53.3, 51.3, 49.1, 46.8, 46.3, 37.2, 36.9, 34.6, 34.3, 31.5, 31.2, 27.3, 26.0; FABMS m/z (relative intensity) (M^+ + 1) 409 (38), 408 (2), 407 (2), 407 (5), 393 (6), 363 (3); HRMS calcd for $C_{25}H_{33}N_2O_3$ (M^+ + 1) 409.2491, found 409.2477.

Cyclization of Aziridine 13 to Lactam 15. A solution of aziridine **13** (2.21 g, 5.41 mmol) in 13 mL of *o*-dichlorobenzene in a resealable glass tube was degassed twice and sealed under vacuum. The tube was heated at 325 °C for 25 min and cooled to room temperature. The solvent was removed by vacuum distillation, and the product was isolated by flash chromatography eluting with hexanes/ethyl acetate (1:1) to yield 1.61 g (73%) of lactam **15** as a yellow oil: IR (film) 3485, 2935, 1645, 1450, 1125 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (10H, m), 4.88 (1H, d, J = 14.7 Hz), 4.67 (1H, d, J = 13.8 Hz), 4.36 (1H, d, J = 14.7 Hz), 4.26 (1H, t, J = 5.7 Hz), 3.60 (1H, d, J = 13.8 Hz), 3.27 (3H, m), 3.29 (3H, s), 3.27 (3H, s), 2.74 (1H, t, J = 9.5 Hz), 2.65 (1H, t, J = 9.5 Hz), 2.32 (2H, m), 1.85 (1H, m), 1.61 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 140.6, 137.5, 128.8, 128.7, 128.3, 128.1, 127.5, 126.7, 103.9, 65.9, 59.4, 56.6, 53.2, 49.9, 46.9, 41.1, 35.8, 32.4, 21.2; FABMS m/z (relative intensity) (M^+ + 1) 409 (100), 408 (41), 407 (86), 393 (20), 377 (53), 317 (14); HRMS calcd for $C_{25}H_{33}N_2O_3$ (M^+ + 1) 409.2491, found 409.2468.

***C*-Alkylation of Lactam 15.** A 1.68 M solution of *n*BuLi in hexane (7.87 mL, 13.22 mmol) was added to a solution of bis(trimethylsilyl)amine (2.79 mL, 13.22 mmol) in 40 mL of THF at 0 °C. After 10 min, lactam **15** (4.50 g, 11.01 mmol) in 25 mL of THF was added over 30 min at −78 °C. The solution was stirred for 30 min at 0 °C and recooled to −78 °C, and bromomethyl methyl ether (1.20 mL, 13.22 mmol) was added in one portion. The mixture was stirred for 2 h at room temperature, diluted with 100 mL of saturated $NaHCO_3$ solution, and extracted with ethyl acetate (2 × 75 mL) and brine (100 mL). The organic extract was dried (K_2CO_3) and concentrated. Flash chromatography of the residue eluting with hexanes/ethyl acetate (1:1) provided lactam **16** (4.65 g, 93%) as a yellow oil: IR (film) 3415, 2930, 1635, 1455, 1125 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (10H, m), 4.89 (1H, d, J = 14.9 Hz), 4.65 (1H, d, J = 13.8 Hz), 4.40 (1H, d, J = 14.9 Hz), 4.26 (1H, dd, J = 5.0, 6.4 Hz), 4.07 (1H, d, J = 8.4 Hz), 3.76 (1H, d, J = 13.8 Hz), 3.46 (1H, d, J = 8.4 Hz), 3.39 (3H, s), 3.29 (3H, s), 3.28 (2H, m), 3.27 (3H, s), 2.71 (1H, t, J = 8.9 Hz), 2.64 (1H, t, J = 8.9 Hz), 2.54 (2H, m), 1.73 (3H, m), 1.53 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 141.6, 137.7, 128.7, 128.2, 128.0, 127.3, 126.5, 104.0, 72.5, 69.0, 59.6, 56.1, 53.6, 53.4, 53.1, 50.5, 46.5, 42.4, 34.0, 32.7, 21.9; FABMS m/z (relative intensity) (M^+ + 1) 454 (14), 453 (44), 452 (28), 421 (22), 406 (28), 407 (100), 357 (12).

Preparation of Aziridine Amide 19. To a solution of amine **18**[3b] (0.75 g, 3.4 mmol) in 50 mL of CH_2Cl_2 was added a 2.0 M solution of trimethylaluminum in hexanes (2.6 mL, 5.1 mmol). After 20 min, aziridine **17**,[6] dissolved in 5 mL of CH_2Cl_2, was slowly added at room temperature, and the resulting solution was stirred overnight. The reaction was quenched with 10 mL of 5% HCl, filtered through Celite, washed with 20 mL of brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue using ethyl acetate yielded aziridine **19** as a yellow oil (0.73 g, 52%): IR (film) 3345, 2920, 1650, 1500, 1440 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33 (5H, m), 6.31 (4H, m), 5.50 (2H, m), 4.39 (1H, d, J = 14.8 Hz), 4.10 (1H, d, J = 10.0 Hz), 3.85 (2H, m), 3.74 (3H, s), 3.62 (1H, d, J = 14.8 Hz), 3.30 (6H, m), 2.49 (2H, m), 2.24 (2H, m), 1.95 (1H, s), 1.72 (1H, s).

Conversion of Aziridine Amide 19 to *N*-Benzyl Amide 20. Aziridine amide **19** (0.12 g, 0.28 mmol) was dissolved in 10 mL of THF and cooled to 0 °C. A 0.5 M solution of lithium bis(trimethylsilyl)amide in THF (0.84 mL, 0.42 mmol) was added dropwise via syringe, and the resulting mixture was stirred for 15 min. Benzyl bromide (96 mg, 0.56 mmol) was added rapidly, and the solution was warmed to room temperature over 2 h. The solution was diluted with ethyl acetate and washed with 10 mL of water and 10 mL of brine, and the organic extracts were dried ($MgSO_4$) and concentrated. Preparative TLC of the residue using hexanes/ethyl acetate (2:1) yielded the *N*-benzyl amide **20** (73 mg, 52%) as a yellow oil: IR (film) 2940, 1640, 1520, 1460, 1245 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.21 (10H, m), 6.74 (4H, m), 5.43 (2H, m), 4.89 (1H, m), 4.34 (2H, m), 3.71 (6H, m), 3.14 (5H, m), 2.30 (5H, m), 1.71 (3H, m).

Cycloaddition of Aziridine 20 to Lactam 21. The aziridine **20** (39 mg, 0.076 mmol) was dissolved in 3 mL of *o*-DCB and degassed in a resealable tube. The tube was sealed under vacuum and heated at 320 °C for 2.5 h. After the mixture cooled to room temperature, the solvent was removed by vacuum distillation, and the product **20** (23 mg, 59%) was isolated as a yellow oil by preparative TLC using hexanes/ethyl acetate (2:1): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (10H, m), 6.78 (4H, m), 4.90 (1H, d, J = 15.0 Hz), 4.64 (1H, d, J = 13.9 Hz), 4.38 (1H, d, J = 15.0 Hz), 4.06 (1H, d, J = 8.5 Hz), 3.79 (5H, m), 3.46 (1H, d, J = 8.5 Hz), 3.29 (4H, m), 2.64 (4H, m), 1.65 (6H, m).

Mono-Debenzylation of Lactam 16 to Lactam 22. To a solution of sodium metal (905 mg, 39.33 g atm) in 70 mL of ammonia at −78 °C was added a solution of lactam **16** (3.56 g, 7.87 mmol) in 25 mL of THF and 1 mL of *t*BuOH. After 5 min, the cold bath was removed, and the reaction was quenched with 10 mL of saturated NH_4Cl solution. The NH_3 was allowed to evaporate, the solution was extracted with ether (3 × 80 mL), and the organic extract was washed with brine (100 mL). The organic phase was dried ($MgSO_4$) and concentrated to give colorless prismatic crystals of **22**, which were further purified by recrystallization using ethyl acetate/hexane (2.15 g, 75%): mp 150−1 °C; IR (CH_2Cl_2) 3405, 2935, 2830, 1660, 1495, 1455, 1255 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (5H, m), 5.86 (1H, br s), 4.46 (1H, d, J = 13.8 Hz), 4.28 (1H, dd, J = 6.4, 5.0 Hz), 3.98 (1H, d, J = 8.4 Hz), 3.78 (1H, d, J = 13.8 Hz), 3.42 (1H, d, J = 8.4 Hz), 3.37 (3H, s), 3.31 (2H, m), 3.30 (3H, s), 3.29 (3H, s), 2.71 (1H, t, J = 8.5 Hz), 2.61 (1H, t, J = 8.5 Hz), 2.56 (2H, m), 1.73 (3H, m), 1.55 (1H, ddd, J = 13.4, 8.2, 5.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 141.3, 128.0, 127.8, 126.3, 103.8, 72.4, 68.3, 59.3, 55.9, 53.5, 53.1, 52.9, 42.0, 40.9, 33.9, 32.5, 21.8; FABMS *m*/*z* (relative intensity) (M^+ + 1) 363 (76), 362 (12), 361 (38), 331 (24), 317 (100), 285 (8); HRMS calcd for $C_{20}H_{31}N_2O_4$ (M^+ + 1) 363.2284, found 363.2254.

Conversion of Lactam 22 to *N*-Sulfonyllactam 23. A 1.98 M solution of *n*BuLi in hexane (0.52 mL, 1.04 mmol) was added to a solution of bis(trimethylsilyl)amine (0.22 mL, 1.04 mmol) in 3 mL of THF at 0 °C. After 20 min, lactam **22** (250 mg, 0.69 mmol) in 3 mL of THF was added at 0 °C. The solution was stirred for 1 h at 0 °C, and *p*-toluenesulfonyl chloride (197 mg, 1.04 mmol) was added in one portion. The mixture was stirred for 1 h at room temperature, diluted with 10 mL of saturated $NaHCO_3$ solution, and extracted with 2 × 15 mL of ethyl acetate. The organics were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue eluting with hexanes/ethyl acetate (1:1) provided sulfonyl lactam **23** (290 mg, 83%) as colorless crystals, which were recrystalized from ethyl acetate to give colorless prisms: mp 132−3 °C; IR (CH_2Cl_2) 2930, 2835, 1690, 1595, 1455, 1170 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (2H, d, J = 8.3 Hz), 7.26 (2H, d, J = 8.3 Hz), 7.18 (3H, m), 6.97 (2H, m), 4.25 (1H, m), 4.23 (1H, dd, J = 6.5, 4.9 Hz), 4.02 (1H, d, J = 13.8 Hz), 3.73 (1H, d, J = 8.4 Hz), 3.67 (1H, m), 3.54 (1H, d, J = 13.8 Hz), 3.34 (1H, d, J = 8.4 Hz), 3.27 (3H, s), 3.25 (3H, s), 3.12 (3H, s), 2.66 (1H, t, J = 8.5 Hz), 2.52 (2H, m), 2.51 (1H, t, J = 8.5 Hz), 2.38 (3H, s), 1.80 (2H, m), 1.70 (1H, dt, J = 13.8, 5.9 Hz); 1.51 (1H, ddd, J = 13.4, 8.5, 4.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 144.5, 140.4, 136.4, 129.3, 128.7, 128.2, 128.0, 126.6, 103.9, 72.6, 71.2, 59.2, 56.0, 53.3, 53.1, 52.8, 45.6, 42.8, 34.0, 32.3, 23.1, 21.7; FABMS *m*/*z* (relative intensity) (M^+ + 1) 517 (68), 515 (28), 485 (42), 417 (67), 361 (100); HRMS calcd for $C_{27}H_{37}N_2O_6S$ (M^+ + 1) 517.2372, found 517.2361.

Preparation of Aldehyde 24. Palladium hydroxide on carbon (410 mg) was added to a solution of benzylamine **23** (4.09 g, 7.91 mmol) in 40 mL of methanol and 40 mL of CH_2Cl_2. The mixture was stirred overnight under 1 atm of hydrogen at room temperature and was filtered through a pad of Celite which was further washed with CH_2Cl_2. The filtrate was concentrated to produce the secondary amine (3.37 g) as a colorless amorphous solid suitable for use in the next step without purification: IR (CH_2Cl_2) 3355, 2935, 1685, 1595, 1355, 1275, 1170 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.10 (2H, d, J = 8.1 Hz), 7.37 (2H, d, J = 8.1 Hz), 4.39 (2H, m), 3.77 (2H, s), 3.59 (2H, m), 3.41 (3H, s), 3.36 (1H, m), 3.37 (3H, s), 3.07 (3H, s), 2.94 (1H, t, J = 9.3 Hz), 2.81 (1H, m), 2.73 (1H, m), 2.47 (3H, s), 2.12 (1H, br d, J = 10.8 Hz), 1.74 (3H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.7, 145.8, 134.8, 129.7, 129.0, 104.2, 74.7, 72.5, 59.4, 54.5, 54.2, 48.5, 45.7, 43.1, 36.4, 31.1, 23.5, 22.0; CIMS *m*/*z* (relative intensity) (M^+ + 1) 427 (100), 396 (98), 271 (48), 241 (50), 157 (80).

To methyl chloroformate (3.42 mL, 44.22 mmol) was slowly added a solution of the above amine (3.37 g, 7.91 mmol) in 30 mL of pyridine at 0 °C. The solution was stirred for 4 h at room temperature. The pyridine was removed in vacuo, and to the residue were added 30 mL of CH_2Cl_2 and 30 mL of H_2O. The mixture was extracted with 20 mL of CH_2Cl_2 and washed with 5% HCl solution (2 × 30 mL) and brine (30 mL). The organic extract was dried ($MgSO_4$) and concentrated to give the crude methyl carbamate as a colorless amorphous solid: IR (CH_2Cl_2) 2955, 1700, 1450, 1370, 1170 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.83 (2H, d, J = 8.1 Hz), 7.23 (2H, d, J = 8.1 Hz), 4.27 (1H, t, J = 5.4 Hz), 4.02 (1H, m), 3.78 (2H, m), 3.55 (2H, m), 3.46 (3H, s), 3.26 (6H, s), 3.23 (3H, s), 2.97 (1H, t, J = 9.3 Hz), 2.62 (2H, m), 2.35 (3H, s), 1.88 (1H, m), 1.63 (3H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.4, 154.7, 145.0, 136.5, 129.8, 129.0, 104.2, 72.9, 70.4, 59.8, 53.9, 52.9, 45.3, 44.3, 35.3, 33.0, 25.2, 22.0; CIMS *m*/*z* (relative intensity) (M^+ + 1) 453 (100), 393 (10), 331 (15), 267 (35), 157 (90).

To a solution of the above carbamate in 50 mL of THF and 50 mL of H_2O was added *p*-toluenesulfonic acid (150 mg, 0.79 mol), and the mixture was heated at reflux overnight. The solution was cooled to room temperature, extracted with ethyl acetate (2 × 50 mL), and washed with brine (50 mL). The organics were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue eluting with ethyl acetate yielded 3.12 g (86%) of aldehyde **24** as a colorless amorphous solid: IR (CH_2Cl_2) 3050, 2955, 1725, 1700, 1595, 1450, 1370, 1170 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (1H, s), 7.81 (2H, d, J = 8.3 Hz), 7.24 (2H, d, J = 8.3 Hz), 4.04 (1H, m), 3.82 (1H, dd, J = 9.3, 7.7 Hz), 3.75 (1H, d, J = 10.1 Hz), 3.66 (1H, d, J = 10.1 Hz), 3.51 (1H, m), 3.47 (3H, s), 3.22 (3H, s), 3.02 (2H, m), 2.74 (1H, m), 2.54 (2H, d, J = 6.2 Hz), 2.34 (3H, s), 1.73 (1H, br d, J = 14.6 Hz), 1.53 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 169.9, 154.2, 144.8, 136.0, 129.4, 128.4, 72.8, 70.1, 59.4, 52.9, 52.5, 44.8, 43.6, 43.2, 33.0, 24.9, 21.6; FABMS *m*/*z* (relative intensity) (M^+ + 1) 439 (18), 393 (16), 317 (7), 283 (8); HRMS calcd for $C_{20}H_{27}N_2O_7S$ (M^+ + 1) 439.1539, found 439.1508.

Formation of Acetate 26. Cerium chloride heptahydrate (1.70 g, 4.57 mmol) was dried at 140 °C for 2 h in vacuo, 20 mL of THF was added at 0 °C, and the mixture was stirred overnight at room temperature. To this suspension was added a solution of aldehyde **24** (1.18 g, 2.69 mmol) in 10 mL of THF at 0 °C, and the mixture was stirred for 30 min. To the resulting solution was added 1.0 M vinylmagnesium bromide in THF (2.96 mL, 2.96 mmol) at 0 °C. After being stirred for 2 h at the same temperature, the mixture was diluted with 30 mL of saturated NH_4Cl solution and 20 mL of ethyl acetate. The suspension was filtered through a pad of Celite which was washed with ethyl acetate. The filtrate was extracted with 20 mL of ethyl acetate, washed with 40 mL of brine, and dried ($MgSO_4$). The organic extract was concentrated to produce allylic alcohol **25** (912 mg) as a colorless amorphous solid which was a mixture of diastereomers suitable for use in the next step without purification: IR (CH_2Cl_2) 3610, 2955, 1725, 1700, 1450, 1370, 1170 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.94 (2H, d, J = 8.1 Hz), 7.48 (2H, d, J = 8.1 Hz), 6.04 (1H, ddd, J = 17.1, 10.4, 6.5 Hz), 5.42 (1H, dd, J = 17.1, 1.1 Hz), 5.31 (1H, d, J = 10.4 Hz), 4.30 (2H, m), 4.02 (2H, m), 3.78 (3H, m), 3.71 (3H, s), 3.47 (3H, s), 3.27 (1H, q, J = 11.1 Hz), 3.00 (1H, m), 2.60 (3H, s), 1.83 (2H, m), 1.44 (3H, m); CIMS *m*/*z* (relative intensity) (M^+ + 1) 467 (100), 440 (58), 313 (25), 285 (20); HRMS calcd for $C_{24}H_{33}N_2O_8S$ (M^+ + 1) 509.1958, found 509.1963.

The above alcohol **25** (912 mg) was dissolved in 20 mL of CH_2Cl_2, and the mixture was cooled to 0 °C. Acetic anhydride (0.22 mL, 2.35 mmol), NEt_3 (0.35 mL, 2.54 mmol), and DMAP (22 mg, 0.20 mmol) were added sequentially. The mixture was

stirred for 3 h at room temperature, diluted with CH_2Cl_2 (20 mL), and washed with H_2O (20 mL) and brine (30 mL). After drying ($MgSO_4$) and concentration of the solution, the acetate **26** (840 mg, 84%) was purified by flash chromatography eluting with hexanes/ethyl acetate (2:1) to give a colorless amorphous solid as a mixture of diastereomers: IR ($CDCl_3$) 2955, 1735, 1695, 1450, 1375, 1235, 1170 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.02 (2H, d, J = 8.1 Hz), 7.43 (2H, d, J = 8.1 Hz), 6.13 (1H, ddd, J = 17.6, 10.4, 6.7 Hz), 5.66 (1H, d, J = 17.6 Hz), 5.37 (1H, d, J = 10.4 Hz), 5.36 (1H, m), 4.28 (1H, m), 3.91 (3H, m), 3.81 (1H, m), 3.68 (3H, s), 3.40 (3H, s), 3.33 (1H, m), 2.79 (2H, m), 2.55 (3H, s), 2.18 (3H, s), 2.09 (1H, m), 1.84 (3H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.4, 170.3, 154.6, 145.1, 136.5, 136.1, 135.9, 129.8, 128.9, 118.2, 118.0, 73.8, 73.8, 59.8, 52.9, 45.3, 45.1, 44.3, 44.1, 35.9, 35.5, 34.0, 33.9, 25.0, 24.9, 22.0, 21.5; FABMS m/z (relative intensity) (M^+ + 1) 509 (3), 507 (1), 495 (1).

Preparation of Allylsilane 27 from Acetate 26. Hexamethyldisilane (2.74 mL, 12.65 mmol) dissolved in 5 mL of HMPA was cooled to 0 °C and treated with a solution of 1.32 M MeLi in ether (8.52 mL, 11.25 mmol). After being stirred for 15 min, the solution was diluted with 15 mL of THF, and CuCN (509 mg, 5.62 mmol) was added in one portion. The resulting solution was stirred for 40 min and cooled to −25 °C, and allylic acetate **26** (1.43 g, 2.81 mmol) was added as a solution in 10 mL of THF. After 1 h, the reaction was quenched with 20 mL of saturated NH_4Cl solution. The resulting solution was filtered through a pad of Celite which was washed with ether (40 mL). After being washed with saturated NH_4Cl solution (40 mL), the organic extract was dried ($MgSO_4$) and concentrated. Flash chromatography of the residue eluting with hexanes/ethyl acetate (2:1) provided colorless amorphous allysilane **27** (0.94 g, 64%) as a 1:1 mixture of *E* and *Z* olefin isomers: IR (CH_2Cl_2) 2955, 1720, 1700, 1560, 1450, 1370, 1170 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.90 (2H, d, J = 8.1 Hz), 7.30 (2H, d, J = 8.1 Hz), 5.45 (1H, m), 5.16 (1H, m), 4.13 (1H, d, J = 10.0 Hz), 3.82 (1H, d, J = 10.0 Hz), 3.75 (1H, m), 3.64 (2H, m), 3.51 (3H, s), 3.28 (3H, s), 3.04 (1H, q, J = 7.9 Hz), 2.67 (2H, m), 2.41 (3H, s), 2.08 (2H, m), 2.02 (1H, m), 1.63 (1H, m), 1.45 (1H, dd, J = 7.9, 3.5 Hz), 1.40 (1H, d, J = 7.9 Hz), 0.00 (4.5H, s), −0.03 (4.5H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.9, 156.1, 146.4, 138.0, 131.2, 130.4, 130.3, 129.5, 127.0, 125.4, 74.5, 72.2, 61.1, 55.4, 54.2, 46.8, 45.2, 41.2, 34.1, 28.3, 26.3, 26.2, 24.5, 23.4, 20.6, −0.2, −0.3; EIMS m/z (relative intensity) (M^+) 522 (4), 507 (5), 477 (11), 367 (7), 335(6); HRMS calcd for $C_{25}H_{39}N_2O_6SSi$ (M^+ + 1) 523.2297, found 523.2298.

Cyclization of Allylsilane 27 to Tricycle 28. To a solution of lactam **27** (476 mg, 0.91 mmol) in 10 mL of CH_2Cl_2 at −78 °C was added a 1.0 M solution of DIBALH in hexane (2.73 mL, 2.73 mmol). After the mixture was stirred for 35 min, 2.5 mL of saturated NH_4Cl solution was added. The mixture was stirred for 1 h at room temperature and filtered through a pad of Celite which was washed with CH_2Cl_2. The filtrate was concentrated to give the colorless amorphous aminal as a mixture of diastereomers: IR (film) 3405, 2955, 1685, 1450, 1250, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (2H, d, J = 8.1 Hz), 7.31 (2H, d, J = 8.1 Hz), 5.69 (1H, br d, J = 3.5 Hz), 5.45 (1H, m), 5.22 (1H, m), 3.99 (1H, d, J = 10.0 Hz), 3.73 (1H, d, J = 10.0 Hz), 3.70 (3H, s), 3.66 (3H, m), 3.32 (3H, s), 3.31 (1H, q, J = 7.9 Hz), 3.02 (2H, m), 2.57 (2H, m), 2.42 (3H, s), 2.22 (1H, m), 2.02 (2H, m), 1.66 (1H, m), 1.45 (1H, m), 0.07 (4.5H, s), 0.00 (4.5H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 145.2, 137.4, 131.3, 131.1, 129.6, 129.4, 129.0, 128.8, 127.8, 126.3, 79.7, 75.8, 72.8, 61.1, 60.9, 54.3, 54.1, 53.9, 44.3, 42.9, 40.1, 39.2, 27.6, 24.5, 23.3, 20.4, 20.1, 0.0, −0.3; FABMS m/z (relative intensity) (M^+ − OH) 509 (30), 508 (38), 507 (80), 449 (100), 435(28).

The above aminal was dissolved in 10 mL of CH_2Cl_2 and cooled to −78 °C. Anhydrous ferric chloride (427 mg, 2.63 mmol) was added in one portion, and the resulting solution was warmed to room temperature. After 10 min, the solution was diluted with 10% NaOH solution (2.5 mL) and stirred for 1 h. The mixture was extracted with CH_2Cl_2 (2 × 30 mL), washed with brine (30 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue eluting with hexanes/ethyl acetate (1:1) gave the tricyclic product **28** (342 mg, 86%) as a colorless amorphous solid which was a 3:2 mixture of diastereomers at C-3: IR (CH_2Cl_2) 2935, 1695, 1450, 1265, 1160 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.63 (2H, d, J = 8.1 Hz), 7.27 (0.8H, d, J = 8.1 Hz), 7.25 (1.2H, d, J = 8.1 Hz), 5.54 (1H, m), 4.92 (0.6H, d, J = 17.3 Hz), 4.85 (0.6H, d, J = 9.6 Hz), 4.79 (0.4H, d, J = 9.0 Hz), 4.75 (0.4H, d, J = 17.4 Hz), 4.31 (2H, m), 3.74 (1H, m), 3.71 (1.8H, s), 3.67 (1.2H, m), 3.32 (1.8H, s), 3.27 (3H, m), 3.22 (1.2H, s), 2.40 (3H, s), 2.33 (2H, br s), 1.95 (5H, m), 1.60 (1H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 155.6, 154.7, 143.4, 142.0, 138.9, 130.1, 129.7, 127.5, 115.4, 113.1, 70.2, 68.8, 63.7, 62.6, 59.6, 59.5, 57.9, 56.4, 55.7, 54.5, 54.3, 53.6, 52.4, 52.1, 40.3, 39.8, 39.0, 38.6, 38.4, 36.8, 36.4, 35.5, 32.5, 30.9, 22.5, 21.8; EIMS m/z (relative intensity) (M^+) 434 (12), 389 (70), 351 (4), 279 (70), 247 (30); HRMS calcd for $C_{22}H_{30}N_2O_5S$ (M^+) 434.1875, found 434.1899.

Preparation of Nitrile 31. A solution of tricyclic olefin **28** (290 mg, 0.67 mmol) in 10 mL of CH_2Cl_2 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 (0.49 mL, 6.67 mmol) was added, and the resulting solution was gradually warmed to room temperature. After being stirred overnight, the solution was diluted with 20 mL of H_2O, extracted with CH_2Cl_2 (2 × 40 mL), and washed with brine (30 mL). The organics were dried ($MgSO_4$) and concentrated to produce the colorless amorphous aldehyde **29** as a 1:1 mixture of diastereomers: IR (CH_2Cl_2) 2955, 2730, 1725, 1690, 1450, 1380, 1160 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.73 (0.5H, s), 9.60 (0.5H, s), 8.13 (2H, d, J = 8.1 Hz), 7.91 (1H, d, J = 8.1 Hz), 7.87 (1H, d, J = 8.1 Hz), 5.25 (0.5H, br s), 5.08 (0.5H, br s), 4.51 (0.5H, br s), 4.36 (0.5H, br d, J = 10.5 Hz), 4.03 (2.5H, m), 3.93 (1.5H, s), 3.84 (1.5H, s), 3.68 (0.5H, m), 3.54 (1.5H, s), 3.48 (2.5H, m), 3.42 (1.5H, s), 3.05 (0.5H, m), 2.64 (3H, s), 2.59 (3H, m), 2.41 (0.5H, m), 2.14 (1H, dd, J = 14.8, 4.8 Hz), 2.05 (1H, dd, J = 14.8, 4.8 Hz), 1.82 (0.5H, dd, J = 14.7, 7.7 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 201.6, 199.4, 144.4, 130.5, 130.2, 127.5, 127.2, 68.2, 63.3, 59.6, 59.5, 54.5, 53.3, 52.6, 50.7, 48.5, 40.3, 36.1, 35.4, 26.6, 22.5, 22.3, 21.9; CIMS m/z (relative intensity) (M^+ + 1) 437 (70), 423 (12), 405 (25), 283 (36), 281 (40).

To a solution of the above aldehyde **29** in 6 mL of CH_2Cl_2 was added pyridine (0.21 mL, 2.67 mmol) and hydroxylamine hydrochloride (93 mg, 1.33 mmol) at room temperature. After being stirred for 16 h at the same temperature, the mixture was diluted with 20 mL of H_2O and extracted with CH_2Cl_2 (2 × 40 mL). After being washed with brine (30 mL), the organics were dried ($MgSO_4$) and concentrated to give the colorless amorphous oxime **30** as a 1:3 mixture of syn /anti oxime isomers and a mixture of C-3 isomers: IR (CH_2Cl_2) 3350, 2930, 1695, 1450, 1335, 1200, 1160 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.80 (0.25H, br s), 8.57 (0.75H, br s), 7.57 (2H, d, J = 8.1 Hz), 7.22 (1H, d, J = 8.1 Hz), 7.18 (0.75H, m), 6.32 (1H, m), 4.45 (2H, m), 3.67 (0.75H, s), 3.62 (2H, m), 3.55 (2.25H, s), 3.25 (2.25H, s), 3.21 (3H, m), 3.14 (0.75H, s), 3.00 (0.5H, m), 2.73 (0.5H, m), 2.32 (1.5H, s), 2.31 (1.5H, s), 2.78 (2H, br s), 2.13 (2H, m), 2.04 (1H, m), 1.80 (1.5H, m), 1.60 (0.5H, dd, J = 14.2, 7.3 Hz); CIMS m/z (relative intensity) (M^+ + 1) 452 (100), 434 (30), 421 (20), 402 (14), 296 (25).

To a solution of the above oxime **30** in 6 mL of CH_3CN was added a triphosgene (1.07 g, 3.97 mmol). The mixture was stirred for 24 h at room temperature, and CH_3CN was removed in vacuo. To the residue was added 40 mL of CH_2Cl_2 and 20 mL of H_2O. The mixture was extracted with CH_2Cl_2 (2 × 30 mL) and washed with brine (30 mL). The organics were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue eluting with hexanes/ethyl acetate (1:2) gave the colorless amorphous nitrile **31** (277 mg, 96%) as a 1:1 mixture of C-3 diastereomers: IR (CH_2Cl_2) 2930, 2445, 1700, 1450, 1380, 1275, 1160 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.76 (1H, d, J = 8.1 Hz), 7.68 (1H, d, J = 8.1 Hz), 7.36 (1H, d, J = 8.1 Hz), 7.28 (1H, d, J = 8.1 Hz), 4.75 (1H, m), 4.27 (1H, m), 3.79 (2H, m), 3.72 (3H, s), 3.47 (2H, m), 3.31 (1.5H, s), 3.27 (1.5H, s), 3.12 (1H, m), 2.45−2.14 (5H, m), 2.40 (3H, 2 s), 2.06 (1H, m), 1.86 (1H, dd, J = 15.0, 3.7 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 154.9, 144.8, 135.9, 130.7, 130.0, 127.9, 127.5,

121.0, 68.4, 62.5, 59.7, 59.6, 54.0, 53.6, 52.8, 52.4, 39.5, 36.0, 34.6, 31.1, 28.4, 25.8, 22.0, 21.8, 21.4, 14.6; CIMS *m/z* (relative intensity) ($M^+ + 1$) 434 (100), 419 (15), 402 (82), 338 (50), 307 (100).

Alkylation of Nitrile 31 to Nitrile 42. To a solution of nitrile **31** (301 mg, 0.69 mmol) in 5 mL of THF at −78 °C was added a 0.5 M solution of KHMDS in hexane (3.47 mL, 1.74 mmol). After the mixture was stirred for 30 min at 0 °C, a solution of mesylate **41** (285 mg, 1.74 mmol) in 2 mL of THF at −78 °C was added. After 30 min of stirring at room temperature, 18-Crown-6 (50.9 mg, 0.21 mmol) was added, and the resulting mixture was warmed to 70 °C. The solution was stirred overnight at the same temperature, and 20 mL of saturated NH_4Cl solution was added at 0 °C. After extraction with ethyl acetate (2 × 30 mL), the organics were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue eluting with hexanes/ethyl acetate (1:1) gave the nitrile **42** (245 mg, 70%) as a colorless oil and eluting with ethyl acetate afforded the starting nitrile **31** (43 mg, 14%) as a colorless oil. **42**: IR (CH_2Cl_2) 2930, 2360, 1700, 1370, 1160 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.59 (2H, d, J = 8.1 Hz), 7.24 (2H, d, J = 8.1 Hz), 6.56 (1H, br s), 5.68 (1H, ddt, J = 17.1, 10.2, 6.6 Hz), 4.94 (1H, dd, J = 17.1, 1.5 Hz), 4.92 (1H, d, J = 10.2 Hz), 4.17 (1H, m), 3.59 (3H, s), 3.51 (2H, m), 3.29 (3H, s), 3.29 (1H, m), 3.19 (1H, m), 3.04 (3H, m), 2.47 (2H, m), 2.39 (3H, s), 2.29 (1H, m), 2.21 (1H, m), 1.97 (2H, q, J = 7.1 Hz), 1.59 (3H, m), 1.18 (1H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 155.6, 143.8, 137.7, 137.1, 130.2, 127.5, 118.2, 115.9, 70.7, 68.9, 62.9, 59.7, 55.5, 52.7, 48.2, 47.2, 41.2, 33.1, 32.2, 31.2, 28.2, 24.3, 22.6, 21.9; CIMS *m/z* (relative intensity) ($M^+ + 1$) 502 (6), 470 (5), 348 (8), 316 (4), 251 (4).

Conversion of Nitrile 42 to Benzyl Ether 43. To a solution of nitrile **42** (263 mg, 0.52 mmol) in 10 mL of CH_2Cl_2 at −78 °C was added a 1.0 M solution of DIBALH in hexane (0.89 mL, 0.89 mmol). After the mixture was stirred for 35 min, 5 mL of a 5% HCl solution and 10 mL of ether were added. The mixture was stirred for 2 h at room temperature, extracted with ether (2 × 20 mL), and washed with brine (20 mL). The organics were dried ($MgSO_4$) and concentrated to give the aldehyde as a colorless oil: IR (film) 2930, 2815, 1680, 1445, 1360, 1340, 1155 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.35 (1H, s), 7.57 (2H, d, J = 8.1 Hz), 7.22 (2H, d, J = 8.1 Hz), 6.73 (1H, br s), 5.66 (1H, ddt, J = 17.1, 10.2, 6.6 Hz), 4.92 (1H, dd, J = 17.1, 1.5 Hz), 4.90 (1H, d, J = 10.2 Hz), 4.32 (1H, br s), 3.56 (3H, s), 3.53 (2H, m), 3.32 (3H, s), 3.25 (2H, m), 2.99 (4H, m), 2.37 (1H, m), 2.34 (3H, s), 2.30 (2H, m), 1.94 (2H, q, J = 6.3 Hz), 1.56 (3H, m), 1.17 (1H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 199.3, 155.7, 143.7, 137.7, 137.0, 130.2, 127.4, 115.8, 70.9, 63.5, 59.6, 55.8, 52.5, 48.1, 47.3, 42.1, 31.9, 28.2, 27.6, 24.5, 21.8, 21.4, 14.6; CIMS *m/z* (relative intensity) ($M^+ + 1$) 505 (100), 490 (22), 474 (64), 349 (50), 252 (70).

To a solution of the above the aldehyde in 6 mL of methanol was added sodium borohydride (19.5 mg, 0.52 mmol) at 0 °C. After being stirred for 10 min at the same temperature, the mixture was diluted with 10 mL of H_2O and 1 mL of acetone. Methanol and excess acetone were removed in vacuo, and to the residue were added 30 mL of CH_2Cl_2 and 20 mL of H_2O. The mixture was extracted with CH_2Cl_2 (2 × 20 mL). After being washed with brine (30 mL), the organics were dried ($MgSO_4$) and concentrated to give the alcohol as a colorless oil: IR (film) 3450, 2930, 1695, 1450, 1365, 1335, 1155 cm^{-1}; ^1HNMR (360 MHz, $CDCl_3$) δ 7.59 (2H, d, J = 8.1 Hz), 7.22 (2H, d, J = 8.1 Hz), 5.66 (1H, ddt, J = 17.1, 10.2, 6.6 Hz), 5.61 (1H, br s), 4.93 (1H, dd, J = 17.1, 1.5 Hz), 4.90 (1H, d, J = 10.2 Hz), 4.34 (1H, br d, J = 7.7 Hz), 3.88 (2H, s), 3.54 (3H, s), 3.47 (1H, m), 3.28 (1H, d, J = 10.4 Hz), 3.29 (3H, s), 3.14 (1H, m), 3.03 (2H, m), 2.34 (3H, s), 2.32 (2H, m), 2.14 (2H, m), 1.97 (3H, m), 1.56 (3H, m), 1.18 (1H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 155.7, 143.6, 137.8, 137.2, 130.1, 127.5, 115.7, 77.7, 71.0, 63.6, 59.5, 55.4, 52.2, 48.2, 47.5, 41.3, 32.3, 31.7, 31.2, 28.2, 24.9, 21.8, 14.6; FABMS *m/z* (relative intensity) ($M^+ + 1$) 507 (2), 489 (3), 391 (2), 341 (2).

The above alcohol was dissolved in 5 mL of THF and cooled to 0 °C. Benzyl bromide (0.09 mL, 0.79 mmol), 60% sodium hydride dispersion in mineral oil (39.7 mg, 0.99 mmol), and tetrabutylammonium iodide (14.7 mg, 0.04 mmol) were added sequentially. The mixture was stirred overnight at room temperature, diluted with saturated NH_4Cl solution (20 mL), and washed with ethyl acetate (2 × 30 mL). After drying ($MgSO_4$) and concentration of the solution, the benzyl ether **43** (203 mg, 65%) was isolated as a colorless amorphous solid by flash chromatography eluting with hexanes/ethyl acetate (1:2): IR (film) 2925, 1700, 1455, 1360, 1340, 1155 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.59 (2H, d, J = 8.1 Hz), 7.26 (5H, m), 7.19 (2H, d, J = 8.1 Hz), 5.65 (1H, ddt, J = 17.1, 10.2, 6.6 Hz), 5.65 (1H, br s), 4.91 (1H, dd, J = 17.1, 1.5 Hz), 4.88 (1H, d, J = 10.2 Hz), 4.34 (2H, s), 4.32 (1H, br s), 3.78 (1H, d, J = 12.3 Hz), 3.74 (1H, d, J = 12.3 Hz), 3.54 (3H, s), 3.47 (1H, ddd, J = 10.6, 5.0, 2.2 Hz), 3.34 (1H, d, J = 10.6 Hz), 3.33 (3H, s), 3.18 (2H, m), 3.02 (3H, m), 2.32 (3H, s), 2.28 (2H, m), 2.14 (1H, m), 1.98 (1H, m), 1.95 (2H, q, J = 7.1 Hz), 1.55 (3H, m), 1.30 (1H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 155.7, 143.5, 137.9, 137.8, 137.3, 130.0, 128.8, 128.1, 128.8, 127.5, 115.7, 77.9, 77.5, 73.2, 72.4, 71.0, 63.7, 59.5, 55.4, 52.2, 48.1, 47.5, 41.3, 32.4, 32.2, 31.2, 28.2, 24.8, 21.9; FABMS *m/z* (relative intensity) ($M^+ + 1$) 597 (7), 566 (4), 489 (25), 307 (22).

Preparation of Amide 44. To a solution of naphthalene (260 mg, 4.20 mmol) in 4 mL of THF was added sodium metal (100 mg, 4.40 g atm) at room temperature. After 2 h of stirring, part of the mixture (3 mL) was added to a solution of amide **43** (22.0 mg, 0.04 mmol) in 2 mL of THF at −78 °C. After 5 min, 5 mL of saturated NH_4Cl solution was added. The mixture was extracted with ethyl acetate (2 × 30 mL). The organic extract was dried (K_2CO_3) and concentrated. Flash chromatography of the residue eluting with ethyl acetate gave the secondary amine (14.7 mg, 90%) as a brown oil: IR (film) 3330, 2930, 1700, 1455, 1360, 1130, 1065 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.35 (5H, m), 5.86 (1H, ddt, J = 17.1, 10.2, 6.6 Hz), 5.79 (1H, br s), 5.06 (1H, dd, J = 17.1, 1.5 Hz), 5.01 (1H, d, J = 10.2 Hz), 4.50 (1H, m), 4.47 (2H, s), 3.93 (1H, d, J = 12.3 Hz), 3.88 (1H, d, J = 12.3 Hz), 3.68 (3H, s), 3.63 (1H, m), 3.47 (1H, d, J = 10.6 Hz), 3.44 (3H, s), 3.36 (1H, m), 2.71 (4H, m), 2.41 (4H, m), 2.15 (3H, m), 2.13 (3H, m), 1.31 (1H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 155.7, 138.7, 138.5, 128.8, 128.1, 128.0, 115.1, 77.8, 77.5, 73.2, 72.2, 70.8, 63.8, 59.6, 55.4, 52.2, 49.7, 49.0, 41.7, 32.9, 32.3, 31.9, 29.4, 26.0; CIMS *m/z* (relative intensity) ($M^+ + 1$) 443 (14), 442 (34), 351 (4), 335 (12).

The above amine (62.0 mg, 0.15 mmol) was dissolved in 3 mL of CH_2Cl_2, and the mixture was cooled to 0 °C. NEt_3 (0.41 mL, 0.29 mmol), a solution of 6-heptenoyl chloride (110 mg, 0.73 mmol) in 3 mL of CH_2Cl_2, and DMAP (1.8 mg, 14.60 μmol) were sequentially added at 0 °C. The resulting solution was stirred overnight at room temperature, and 10 mL of saturated $NaHCO_3$ solution was added. The mixture was extracted with CH_2Cl_2 (2 × 30 mL) and washed with saturated $NaHCO_3$ solution (30 mL). The organic extract was dried ($MgSO_4$) and concentrated. Flash chromatography of the residue eluting with hexanes/ethyl acetate (1:1) afforded the amide **44** (64.0 mg, 81%) as a yellow oil: IR (film) 2930, 1700, 1640, 1455, 1360, 1110, 1065 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.53 (5H, m), 6.00 (3H, m), 5.28 (1H, dd, J = 17.1, 1.5 Hz), 5.24 (2H, m), 5.17 (1H, d, J = 10.2 Hz), 4.66 (1H, m), 4.64 (2H, s), 4.08 (2H, s), 3.85 (3H, s), 3.82 (1H, m), 3.67 (1H, d, J = 10.3 Hz), 3.62 (3H, s), 3.52 (3H, m), 3.44 (2H, t, J = 7.7 Hz), 2.71 (1H, m), 2.50 (2H, m), 2.36 (1H, m), 2.28 (5H, m), 1.88 (6H, m), 1.65 (3H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.0, 172.7, 155.7, 139.0, 138.9, 138.6, 138.3, 128.8, 128.1, 128.0, 116.1, 115.3, 114.9, 77.7, 77.5, 73.2, 72.3, 70.9, 63.8, 59.6, 55.4, 52.2, 47.4, 45.8, 44.6, 33.7, 33.4, 32.7, 32.3, 31.5, 31.2, 29.2, 29.1, 28.5, 27.3, 25.3, 23.7; CIMS *m/z* (relative intensity) ($M^+ + 1$) 553 (1), 445 (2), 415 (1), 303 (1); HRMS calcd for $C_{33}H_{49}N_2O_5$ ($M^+ + 1$) 553.3641, found 553.3643.

Ring-Closing Olefin Methathesis of Diene 44 to Macrocyclic Lactam 46. A solution of diene **44** (16.4 mg, 29.70 μmol) in CH_2Cl_2 was added $Cl_2(PCy_3)_2Ru{=}CHPh$ (**45**, 5.2 mg, 5.94 μmol) in a drybox. The reaction mixture was refluxed for 2 d under an argon atomsphere. The CH_2Cl_2 was evaporated under reduced pressure, and flash chromatography of the residue eluting with hexanes/ethyl acetate (1:2) produced the starting diene **44** (1.1 mg, 7%) as a yellow oil. Elution with

hexanes/ethyl acetate (1:4) gave macrocyclic lactam **46** (7.7 mg, 49%, colorless oil) as a mixture of cis and trans isomers, and elution with ethyl acetate afforded the macrocyclic dimer (6.1 mg, 39%) as a colorless oil.

46: IR (film) 2925, 1700, 1635, 1445, 1360, 1200, 1110, 1065 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.27 (5H, m), 5.66 (1H, br s), 5.30 (2H, m), 4.38 (1H, m), 4.34 (2H, s), 3.79 (2H, s), 3.56 (3H, s), 3.36 (2H, d, J = 10.6 Hz), 3.31 (3H, s), 3.26 (3H, m), 2.41 (3H, m), 2.06 (6H, m), 1.54 (6H, m), 1.18 (5H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.7, 173.6, 172.9, 155.5, 138.6, 138.4, 137.3, 136.9, 133.5, 128.8, 128.1, 77.6, 77.4, 73.3, 72.3, 70.9, 63.8, 59.6, 55.4, 52.2, 45.3, 41.5, 34.1, 32.7, 32.3, 31.8, 30.6, 30.1, 27.3, 26.2, 25.7, 25.0, 23.7, 22.9; FABMS *m*/*z* (relative intensity) ($M^+ + 1$) 525 (4), 417 (5), 375 (3), 315 (4); HRMS calcd for $C_{31}H_{45}N_2O_5$ ($M^+ + 1$) 525.3328, found 525.3300.

Dimer: IR (film) 2925, 1700, 1640, 1445, 1360, 1200, 1110, 1065 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.27 (10H, m), 5.65 (2H, br s), 5.32 (4H, m), 4.38 (2H, m), 4.34 (4H, s), 3.78 (4H, s), 3.55 (6H, s), 3.52 (2H, m), 3.34 (4H, d, J = 10.6 Hz), 3.32 (6H, s), 3.37 (6H, m), 2.66 (4H, m), 2.42 (6H, m), 2.22 (12H, m), 1.94 (2H, m), 1.60 (12H, m), 1.51 (4H, m); FABMS *m*/*z* (relative intensity) ($M^+ + 1$) 1050 (5), 1017 (2), 942 (10), 449 (10), 297 (100).

Hydrogenation of Lactam Benzyl Ether 46 to Lactam Alcohol 47. Ten percent palladium on activated carbon (4.0 mg) was added to a solution of lactam olefin **46** (11.3 mg, 21.5 μmol) in 3 mL of methanol. The mixture was stirred overnight under 1 atm of hydrogen at 55 °C and was filtered through a pad of Celite which was washed with methanol. The filtrate was concentrated, and flash chromatography of the residue eluting with ethyl acetate/methanol (10:1) afforded the macrocyclic lactam **47** (8.1 mg, 86%) as a yellow oil: IR (film) 3415, 2925, 1695, 1620, 1445, 1375, 1195, 1110 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.17 (1H, m), 3.63 (2H, s), 3.59 (3H, s), 3.41 (4H, m), 3.28 (2H, s), 3.28 (3H, s), 3.22 (2H, m), 2.45 (1H, m), 2.31 (1H, m), 1.98 (2H, m), 1.61 (11H, m), 1.31 (8H, m); FABMS *m*/*z* (relative intensity) ($M^+ + 1$) 437 (24), 419 (50), 387 (19), 330 (20), 182 (100); HRMS calcd for $C_{24}H_{41}N_2O_5$ ($M^+ + 1$) 437.3015, found 437.2998.

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Supporting Information Available: Copies of proton and carbon NMR spectra of new compounds (49 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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