Development of a Strategy for Synthesis of the Unusual Marine Alkaloid Sarain A

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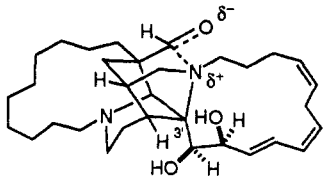
Received May 7, 1993•

An 11-step approach to tricyclic compound **42**, which contains the alkaloidal nucleus of the marine natural product sarain A (**1**), has been developed. Pivotal steps in the construction of **42** include stereospecific intramolecular dipolar [3 + 2]-cycloaddition of an azomethine ylide generated from aziridine **27** to afford bicyclic lactam **28** and a novel intramolecular allylsilane/*N*-tosyliminium ion cyclication of **41** to produce the tricycle.

Introduction

The marine sponge *Reniera sarai* produces an unusual alkaloid sarain A (**1**) which was recently isolated and characterized by Cimino and co-workers.[1] The unique structure of **1**, established by spectral methods and by



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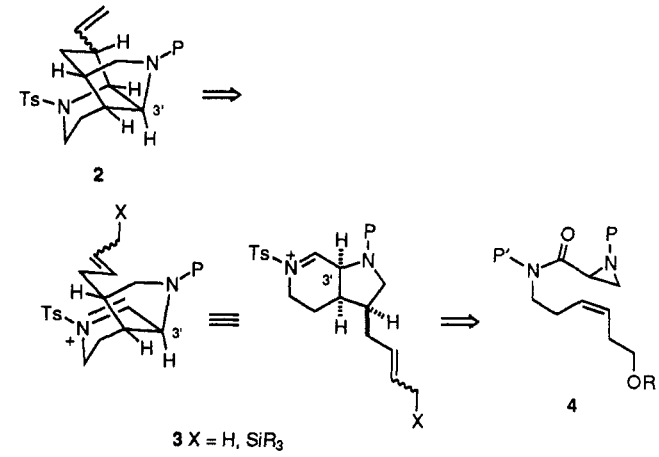
X-ray crystallography of a derivative, was found to incorporate a fused tricyclic inner core and two macrocyclic rings. Interestingly, spectral studies have shown that the molecule has a tertiary amine–aldehyde proximal interaction reminiscent of the type of transannular amino ketone interactions studied by Leonard et al. many years ago.[2]

We have been interested in assessing the feasibility of the strategy for a total synthesis of sarain A which is outlined retrosynthetically in Scheme I.[3,4] In particular, we hoped to test two key steps for construction of the tricyclic nucleus of **1**. It was our intention to prepare tricycle **2** by an ene or enelike cyclization of an *N*-sulfonyliminium compound **3** (X = H). Alternatively, an intramolecular allylsilane addition to the electrophilic sulfonyliminium complex (X = SiR_3) would afford **2**. *N*-Sulfonylimines and iminium ions, unlike *N*-alkyl- and *N*-acylimines, have not been widely used synthetically. However, there are a few reported examples of pericyclic *N*-sulfonylimine–olefin ene reactions,[5] and we have recently described some intramolecular *N*-sulfonylimine reactions with olefins which give enelike products via a

Scheme I



3 X = H, SiR_3

stepwise ionic process.[6] Moreover, some intermolecular additions of allylsilanes to *N*-sulfonylimines have been documented.[7]

A second pivotal step to be tested was preparation of the bicyclic system of **3** with its attendant stereochemistry via an intramolecular dipolar [3 + 2]-cycloaddition of an aziridine olefin like **4**. Good precedent for this transformation can be found in the studies of Takano and Ogasawara[8] and of DeShong.[9] It should be noted that, for simplicity, initial studies were conducted with a system lacking a functionalized, carbon substituent at C-3′ (vide infra).

Results and Discussion

Our initial concern with executing the route shown in Scheme I dealt with the choice of protecting groups for cycloaddition precursor **4**. In view of the work of Takano and Ogasawara[8] which utilized *p*-methoxyphenyl (PMP) protection of a side-chain oxygen,[10] we decided to use this

• Abstract published in *Advance ACS Abstracts*, August 15, 1993.

(1) Cimino, G.; Mattia, C. A.; Mazzarella, L.; Puliti, R.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *Tetrahedron* **1989**, *45*, 3863. Cimino, G.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *J. Nat. Prod.* **1990**, *53*, 1519.

(2) Leonard, N. J.; Oki, M.; Chiavarelli, S. *J. Am. Chem. Soc.* **1955**, *77*, 5234 and related papers.

(3) For a preliminary account of this work, see: Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1991**, *56*, 3210. For a recent related approach to sarain A, see: Henke, B. R.; Kouklis, A. J.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 7056.

(4) Taken in part from the Ph.D. thesis of J. Sisko, The Pennsylvania State University, 1991.

(5) Achmatowicz, O.; Pietraszkiewicz, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2680. Tschaen, D. M.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058.

(6) Melnick, M. J.; Freyer, A. J.; Weinreb, S. M. *Tetrahedron Lett.* **1988**, *29*, 3891.

(7) Ralbovsky, J. L.; Kinsella, M. A.; Sisko, J.; Weinreb, S. M. *Synth. Commun.* **1990**, *20*, 573. Shono, T.; Matsumura, Y.; Uchida, K.; Nakatani, F. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3029. Shono, T.; Matsumura, Y.; Katoh, S.; Takeuchi, K.; Sasaki, K.; Kamada, T.; Shimizu, R. *J. Am. Chem. Soc.* **1990**, *112*, 2368.

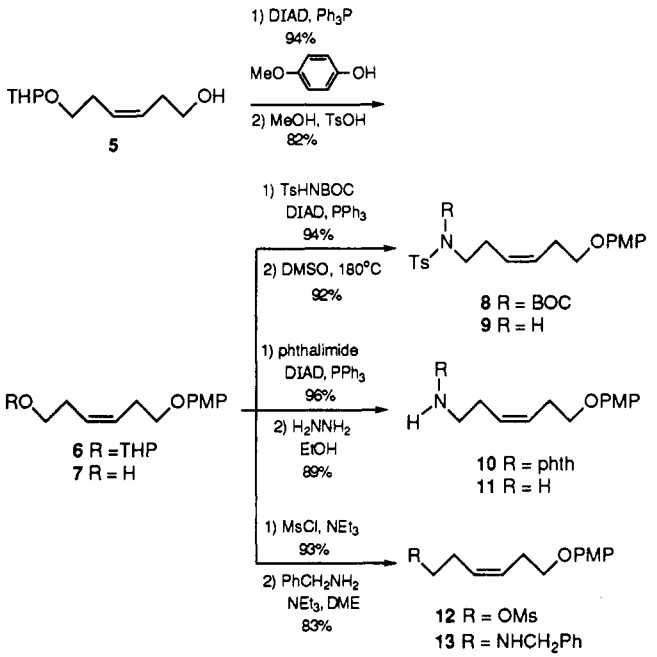
(8) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* **1987**, *109*, 5523. Takano, S.; Tomita, S.; Iwabuchi, Y.; Ogasawara, K. *Heterocycles* **1989**, *29*, 1473. Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1204.

(9) DeShong, P.; Kell, D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, *50*, 2309.

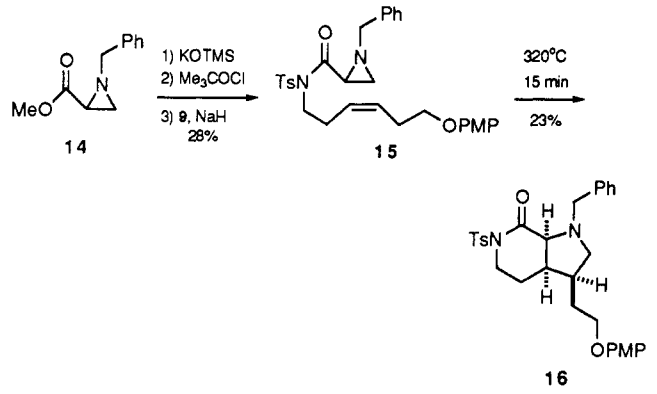
(10) Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291.

0022-3263/93/1958-4945$04.00/0

Scheme II



Scheme III

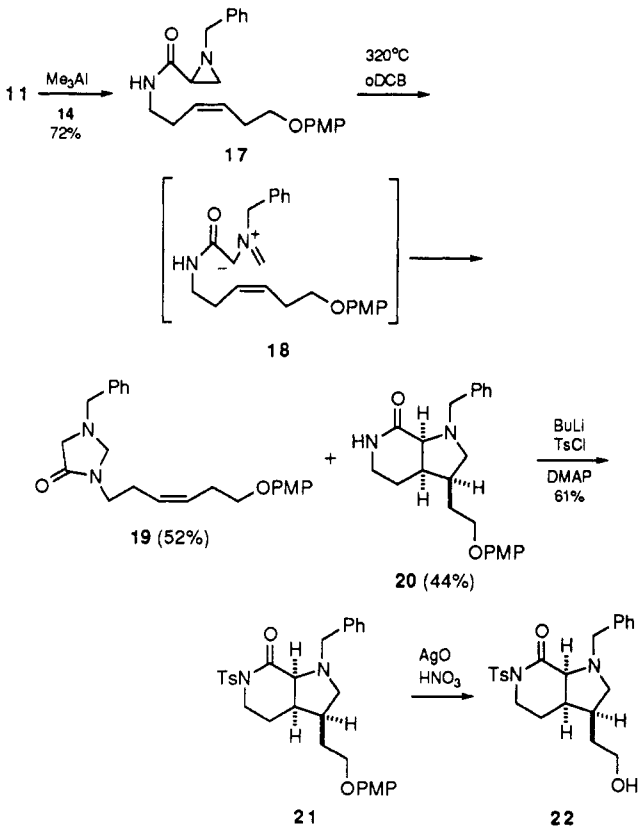


group as R in **4**. Thus, readily available alcohol **5**[11] was converted via a Mitsunobu reaction to ether **6**, followed by THP cleavage leading to **7** (Scheme II).

For our exploratory studies, three different types of nitrogen substitution were introduced into **7**. Using Mitsunobu methodology developed in these laboratories,[12] alcohol **7** was converted into *N*-BOC sulfonamide **8**. Thermal cleavage of the BOC group afforded sulfonamide **9**. Similarly, Mitsunobu reaction[13] of **7** with phthalimide yielded **10**, which was cleaved to primary amine **11**. Finally, alcohol **7** was converted to mesylate **12** and then to *N*-benzylamine **13**.

Easily prepared *N*-benzylaziridine ester **14**[9] was converted to the potassium carboxylate salt with potassium trimethylsilanolate[14] and then to the mixed anhydride with pivaloyl chloride.[15] Coupling of this anhydride with sulfonamide **9** gave acyl sulfonamide **15** in 28% yield (Scheme III). Thermolysis of **15** at 320 °C in a sealed tube gave the desired cycloaddition product **16**, but only in low yield. The major side product in this step was sulfonamide **9**. In view of the poor yields in preparing **16**, this system was abandoned and another was investigated.

Scheme IV



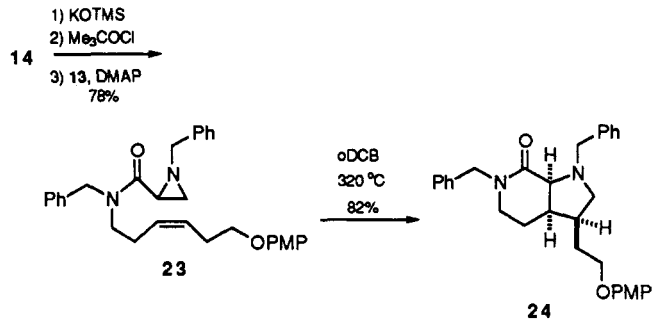
Primary amine **11** was converted to the corresponding aluminum amide reagent[16] and combined with aziridine ester **14** to afford amide **17** (Scheme IV). Thermolysis of **17** yielded a mixture of bicyclic lactam **20** (44%) along with compound **19** (52%). Imidazolone **19** is probably derived from addition of the amide nitrogen of intermediate ylide **18** to the terminal carbon. With the hope that **19** might thermally revert to the ylide, this side product was heated at 320 °C, but none of the desired cycloadduct **20** was produced. Although the yield of **20** was only mediocre, we decided to continue with the synthesis. Therefore, the lactam **20** was converted to *N*-sulfonyllactam **21**. Attempts to cleave the PMP group of **21** using the standard oxidative procedure (e.g., ceric ammonium nitrate[10]) proved unsuccessful. It was in fact possible to convert **21** to alcohol **22** with AgO via the methodology of Rapoport.[17] However, while this reaction gave a 74% yield of **22** on a 30-mg scale, on larger scales the yield dropped precipitously (<25%).

As a result of these problems, another *N*-protected system was briefly investigated. Thus, ester **14** was combined with *N*-benzylamine **13** to afford amide **23** (Scheme V). We were pleased to find that cycloaddition of **23** at 320 °C in *o*-dichlorobenzene gave bicyclic lactam **24** in 82% yield. Unfortunately, all attempts to oxidatively remove the PMP protecting group of **24** gave only unidentifiable decomposition products.

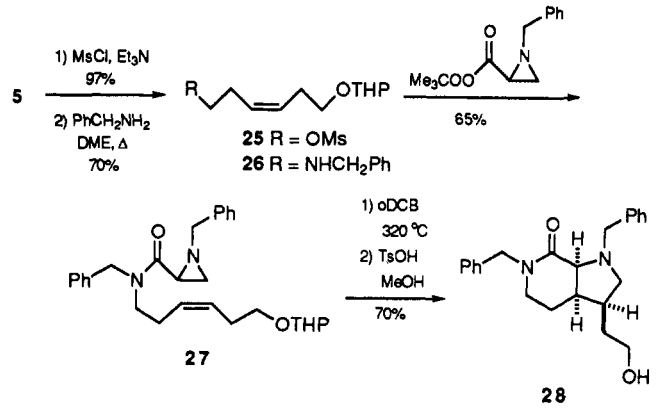
Since the PMP protecting group had proven to be unsuitable for our needs, we looked at another type of oxygen protection. Alcohol **5** was converted to mesylate **25** which was used to alkylate benzylamine to give **26** (Scheme VI). Conversion of **26** to **27** was effected as for

(11) Carvalho, J. F.; Prestwich, G. D. *J. Org. Chem.* **1984**, *49*, 1251.
(12) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.
(13) Mitsunobu, O. *Synthesis* **1981**, 1.
(14) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831.
(15) Lambert, C.; Viehe, H. G. *Tetrahedron Lett.* **1985**, *26*, 4439.
(16) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.
(17) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227.

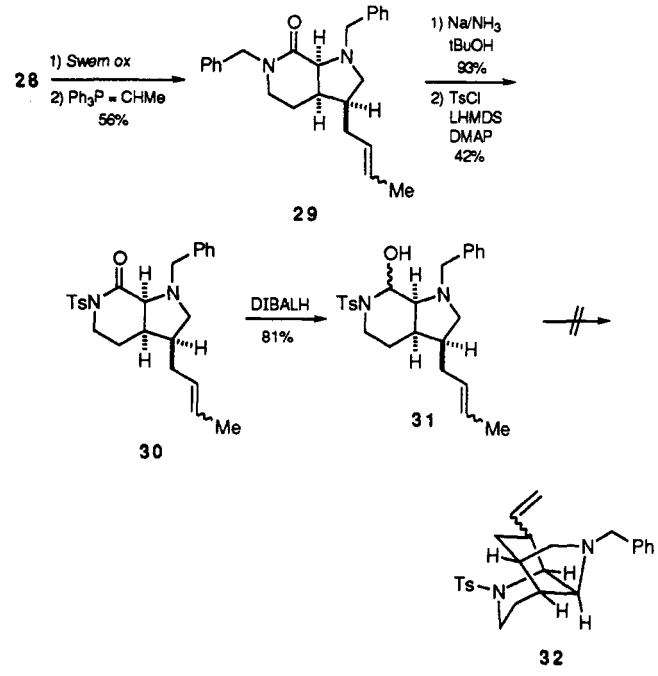
Scheme V



Scheme VI



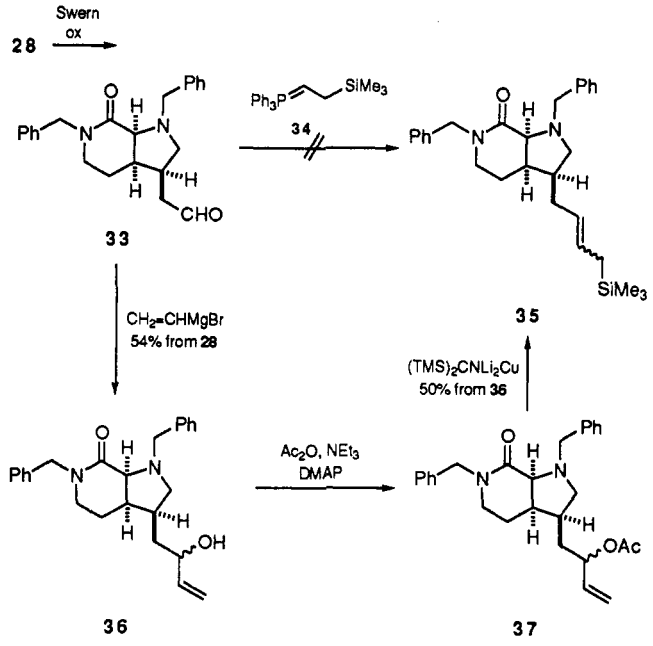
Scheme VII



23 to yield cyclization precursor **27**. Thermolysis of **27** at 320 °C, followed by brief treatment with methanolic acid, indeed afforded the desired bicyclic lactam alcohol **28** in good yield.

With substantial amounts of a bicyclic compound now available, we turned to effecting closure of the third ring of the sarain A core. One route which was tested involved enelike[6] (amidoalkylation) chemistry. Thus, alcohol **28** was oxidized to the aldehyde and converted to olefin **29** as a mixture of *E*/*Z* isomers (Scheme VII). Removal of the lactam *N*-benzyl group could be effected selectively with sodium in ammonia, and subsequent *N*-tosylation afforded the *N*-sulfonyllactam **30**. Reduction of **30** then

Scheme VIII



provided the hydroxy sulfonamide **31**. Disappointingly, treatment of **31** with Lewis acids such as BF_3·Et_2O and $FeCl_3$ afforded none of the desired tricyclic compound **32** but led only to decomposition products.

A route involving an allylsilane nucleophile ultimately proved to be successful.[7,18] Alcohol **28** was oxidized to the aldehyde **33**, but all attempts to add known ylide **34**[19] to this compound to produce allylsilane **35** failed (Scheme VIII). However, it was possible to prepare **35** utilizing chemistry described by Fleming et al.[20] Thus, vinylmagnesium bromide was added to **33** to afford a mixture of allylic alcohols **36**, which was converted to acetate **37**. Addition of a higher order[21] silyl cuprate to **37** provided allylsilane **35** as a 1:1 mixture of *E*/*Z* isomers.

Selective mono-*N*-debenzylation of **35** (Scheme IX) could be effected in high yield using Na/NH_3 in the presence of excess t-BuOH for 1 min at −78 °C.[22] If the t-BuOH was omitted, or if longer reaction times were used, the silyl group was also lost. Lactam **38** was then *N*-tosylated[23] to yield sulfonyllactam **39**, which could be cleanly reduced to hydroxy sulfonamide **40**.

Initial cyclization experiments were conducted on the acetate derivative of alcohol **40**, prepared with Ac_2O, NEt_3, and DMAP. Treatment of this compound with $TiCl_4$ (−78 °C) gave mainly decomposition products, along with a trace of tricycle **42**. Direct exposure of alcohol **40** to BF_3·Et_2O and $TiCl_4$ afforded only protodesilylation products. Finally, it was found that anhydrous $FeCl_3$ in methylene chloride induced cyclization of **40** to give **42** as a single stereoisomer in 61% isolated yield. The structure

(18) For examples of additions of allyl silanes to N-acylimines, see: Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. Gramain, J.-C.; Remuson, R. *Heterocycles* **1989**, *29*, 1263.

(19) Seyferth, D.; Wursthorn, K. R.; Lim, T. F. O.; Sepelak, D. J. *J. Organomet. Chem.* **1979**, *181*, 293. Seyferth, D.; Wursthorn, K. R.; Mammarella, R. E. *J. Org. Chem.* **1977**, *42*, 3104.

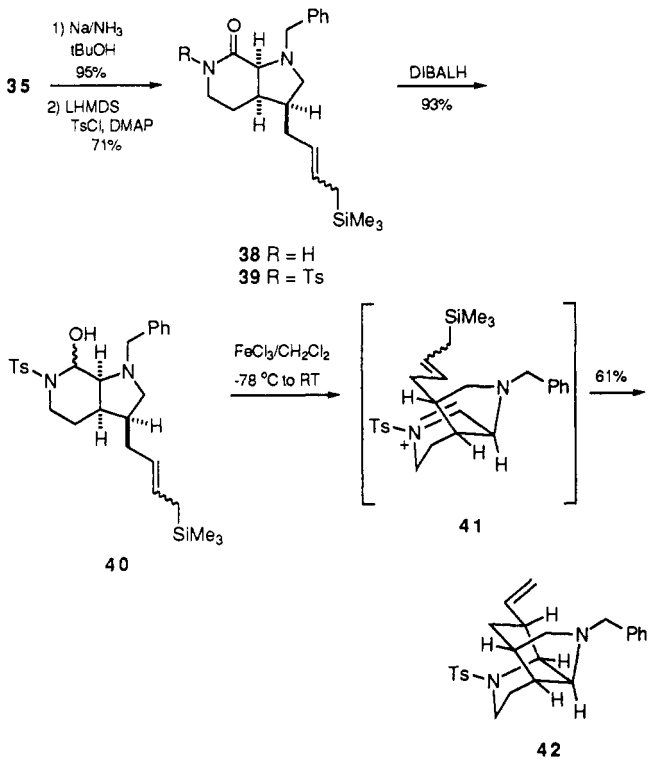
(20) Fleming, I.; Thomas, A. P. *J. Chem. Soc., Chem. Commun.* **1985**, 411. Fleming, I.; Newton, T. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1805.

(21) For a recent review on higher-order mixed organocuprates, see: Lipshutz, B. H. *Synthesis* **1987**, 325.

(22) Coughlin, D. J.; Salomon, R. G. *J. Org. Chem.* **1979**, *44*, 3784. Eaborn, C.; Jackson, R. A.; Pearce, R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 475.

(23) Cf. Somfai, P.; He, H. M.; Tanner, D. *Tetrahedron Lett.* **1991**, *32*, 283.

Scheme IX



and stereochemistry of **42** were confirmed by ^{1}H NMR NOE experiments (see Experimental Section). We believe that **42** is formed via *N*-sulfonyliminium species **41**, which cyclizes via the conformation shown.

Conclusion

We have therefore developed an efficient route to the tricyclic nucleus **42** of sarain A in approximately 11 steps from aziridine ester **14** and amine **26** utilizing a novel intramolecular allylsilane *N*-sulfonyliminium ion cyclization as a key step. The methodology has now been extended to preparation of a tricyclic compound similar to **42** bearing a carbon substituent at C-3′ (sarain A numbering).[24] Work which is now in progress on annulation of the two macrocyclic rings onto this central unit will be reported in the near future.

Experimental Section

Preparation of Alkene 6. A solution of alcohol **5**[11] (5.52 g, 27.30 mmol) and Ph_3P (8.60 g, 32.76 mmol) dissolved in 60 mL of THF was slowly added via syringe to a solution of *p*-methoxyphenol (5.42 g, 43.68 mmol) and diisopropyl azodicarboxylate (6.49 mL, 32.76 mmol) dissolved in 150 mL of THF. The resulting mixture was stirred for 24 h and concentrated in vacuo, and the product ether **6** was purified as a colorless oil (7.95 g, 94%) by flash chromatography using hexanes/ethyl acetate (4:1): IR (film) 2940, 2870, 1595 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.82 (4H, s), 5.57 (2H, t, J = 4.7 Hz), 3.89 (3H, m), 3.76 (1H, m), 3.75 (3H, s), 3.46 (2H, m), 2.54 (2H, q, J = 6.3 Hz), 2.40 (2H, q, J = 6.4 Hz), 1.74 (2H, m), 1.33 (4H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 153.6, 152.9, 128.3, 126.8, 115.4, 114.5, 98.6, 67.9, 66.8, 62.1, 55.6, 30.6, 28.0, 27.6, 25.4, 19.5.

Preparation of Alcohol 7. The alkene **6** (7.95 g, 25.78 mmol) was dissolved in 150 mL of methanol, 0.05 g (0.29 mmol) of *p*-toluenesulfonic acid was added, and the mixture was stirred at rt for 1 h. The solution was concentrated in vacuo, washed with saturated $NaHCO_3$ solution (15 mL) and brine (10 mL), extracted with ethyl acetate (100 mL), dried ($MgSO_4$), and concentrated. The alcohol **7** was obtained in 82% yield (4.75 g) as an amorphous white solid after flash chromatography using hexanes/ethyl acetate (1:1): IR (film) 3300, 1590, 825 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (4H, s), 5.58 (2H, m), 3.93 (2H, t, J = 6.5 Hz), 3.74 (3H, s), 3.66 (2H, t, J = 6.2 Hz), 2.53 (2H, q, J = 6.6 Hz), 2.35 (2H, q, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 152.8, 128.5, 128.1, 115.3, 114.5, 67.8, 61.9, 55.6, 30.7, 27.6; MS m/z (relative intensity) (M^+ + 1) 223 (5), 222 (35), 124 (100), 109 (23); exact mass calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1261.

Preparation of BOC Sulfonamide 8. To a solution of alcohol **7** (4.41 g, 19.66 mmol), Ph_3P (6.70 g, 25.56 mmol), and *N*-BOC *p*-toluenesulfonamide (6.93 g, 25.56 mmol) dissolved in 150 mL of THF was added diisopropyl azodicarboxylate (5.06 mL, 25.56 mmol) slowly via syringe. The solution was stirred overnight at rt and concentrated in vacuo. The product **8** was isolated (8.14 g, 87%) as a viscous, colorless oil by flash chromatography using hexanes/ethyl acetate (4:1): IR (film) 2970, 2860, 2830, 1715, 1590, 820 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.75 (2H, d, J = 8.3 Hz), 7.22 (2H, d, J = 8.3 Hz), 6.78 (2H, m), 5.40 (4H, m), 3.67 (3H, s), 2.52 (4H, m), 2.34 (3H, s), 1.29 (9H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 153.4, 152.7, 150.5, 143.8, 137.1, 128.9, 128.1, 127.5, 127.0, 115.1, 114.2, 83.7, 67.5, 55.2, 46.1, 28.0, 27.4, 27.3, 21.1. MS m/z (relative intensity) 475 (0.5), 375 (31), 184 (83), 155 (95), 124 (100), 91 (80), 41 (53); exact mass calcd for $C_{25}H_{33}NO_6S$ 475.2028, found 475.2032.

Preparation of Sulfonamide 9. A solution of BOC sulfonamide **8** (7.79 g, 16.31 mmol) dissolved in 50 mL of DMSO was heated at 180 °C for 2 h. After being cooled to rt, the solution was diluted with 150 mL of H_2O, extracted with ethyl acetate (3 × 100 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Sulfonamide **9** was isolated as a colorless, viscous oil in 92% yield (5.65 g) after flash chromatography using hexanes/ethyl acetate (4:1): IR (film) 3280, 3020, 2960, 2880, 1600, 820 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.73 (2H, d, J = 8.2 Hz), 7.28 (2H, d, J = 8.3 Hz), 6.83 (4H, s), 5.58 (1H, m), 5.35 (1H, m), 4.88 (1H, t, J = 5.9 Hz), 3.89 (2H, t, J = 6.4 Hz), 3.76 (3H, s), 3.01 (2H, q, J = 6.5 Hz), 2.43 (5H, m), 2.24 (2H, q, J = 6.9 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 153.8, 152.8, 143.3, 136.9, 129.6, 129.0, 127.4, 127.0, 115.5, 114.5, 67.8, 55.6, 42.6, 27.5, 27.4, 21.4; MS m/z (relative intensity) (M^+ + 2) 377 (4), (M^+ + 1) 376 (5), 375 (23), 184 (52), 155 (58), 124 (100), 109 (25), 91 (72); exact mass calcd for $C_{20}H_{25}NO_4S$ 375.1504, found 375.1514.

Preparation of Imide 10. To a solution of alcohol **7** (4.25 g, 18.95 mmol), phthalimide (3.35 g, 22.74 mmol), and Ph_3P (5.96 g, 22.74 mmol) dissolved in 150 mL of THF was added diisopropyl azodicarboxylate (4.50 mL, 22.74 mmol) dropwise via syringe, and the solution was stirred for 2.5 h at rt. After the mixture was concentrated in vacuo, the product **10** was isolated as a clear oil (6.41 g, 96%) by flash chromatography using hexanes/ethyl acetate (5:1) which crystallized on standing to give colorless crystals: mp 50–2 °C; IR (film) 3000, 2930, 1760, 1700, 1600 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (2H, m), 7.70 (2H, m), 6.77 (4H, m), 5.57 (2H, m), 3.79 (4H, m), 3.76 (3H, s), 2.49 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 153.7, 152.9, 133.9, 132.0, 128.4, 127.5, 123.2, 115.4, 114.5, 67.9, 55.7, 37.5, 27.5, 26.6; MS m/z (relative intensity) (M^+ + 1) 352 (2), 351 (10), 228 (9), 160 (100), 124 (12); exact mass calcd for $C_{21}H_{21}NO_4$ 351.1470, found 351.1476.

Preparation of Amine 11. Phthalimide **10** (14.86 g, 42.05 mmol) was dissolved in 200 mL of EtOH and gently warmed to 45–50 °C. Hydrazine monohydrate (2.45 mL, 50.45 mmol) was added via syringe, and the solution was stirred overnight. After the mixture was cooled to rt, the EtOH was removed in vacuo and the residue was dissolved in ethyl acetate (200 mL) and 15% KOH (75 mL). The organics were separated and acidified with 5–6 mL of concentrated HCl and washed with 200 mL of H_2O. The aqueous layer was basified with 50 mL of 15% KOH solution and extracted with ethyl acetate (2 × 100 mL). After drying ($MgSO_4$) and concentration of the extract, flash chromatography of the residue using ethyl acetate/methanol (1:1) provided amine **11** (8.27 g, 89%) as an amorphous white solid: IR (film) 3300 (br) cm^{-1}; ^{1}H NMR (360 MHz, CD_3OD) δ 6.71 (4H, s), 5.58 (1H, m), 5.41 (1H, m), 3.82 (2H, t, J = 6.4 Hz), 3.61 (3H, s), 2.66 (2H, t, J = 6.9 Hz), 2.42 (2H, q, J = 6.3 Hz), 2.22 (2H, q, J = 6.8 Hz); ^{13}C NMR (90 MHz, CD_3OD) δ 155.4, 154.5, 129.7, 128.9, 116.6, 115.7, 69.1, 56.1, 41.6, 29.9, 28.7; MS m/z (relative intensity) (M^+

(24) Henry, J. R.; Weinreb, S. M. Unpublished results.

+ 1) 222 (4), 221 (25), 124 (88), 109 (40), 98 (100), 81 (25), 77 (14); exact mass calcd for $C_{13}H_{19}NO_2$ 221.1416, found 221.1415.

Mesylation of Alcohol 7. Alcohol 7 (8.44 g, 37.97 mmol) was dissolved in 300 mL of CH_2Cl_2, and the mixture was cooled to 0 °C. Methanesulfonyl chloride (3.25 mL, 41.76 mmol) and Et_3N (6.35 mL, 45.56 mmol) were added sequentially via syringe, and the resulting solution was warmed to rt and stirred for 3 h. The mixture was washed with 5% HCl (40 mL), saturated $NaHCO_3$ solution (40 mL), and brine (15 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue using hexanes/ethyl acetate (2:1) provided mesylate **12** (10.65 g, 93%) as a clear oil: IR (film) 3000, 2930, 1500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (4H, d, J = 0.7 Hz), 5.67 (1H, m), 5.51 (1H, m), 4.22 (2H, t, J = 6.5 Hz), 3.93 (2H, t, J = 6.5 Hz), 3.75 (3H, s), 2.98 (3H, s), 2.53 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 152.7, 129.3, 125.4, 115.3, 114.5, 69.0, 67.5, 55.5, 37.2, 27.5, 27.3; MS m/z (relative intensity) (M^+ + 1) 301 (0.4), 300 (3), 137 (23), 124 (97), 109 (44), 81 (100), 41 (61).

Formation of Benzylamine 13 from Mesylate 12. To a solution of mesylate **12** (3.53 g, 11.75 mmol) and Et_3N (2.13 mL, 15.28 mmol) in 50 mL of DME was added benzylamine (2.57 mL, 23.50 mmol), and the mixture was heated at reflux overnight. The solution was cooled to rt, concentrated, and diluted with 100 mL of ethyl acetate. After the solution was washed with H_2O (20 mL) and brine (10 mL), the organics were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue using ethyl acetate yielded 3.01 g (83%) of amine **13** as a yellow oil: IR (film) 3300, 3000, 2900, 1500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (5H, m), 6.82 (4H, s), 5.56 (2H, m), 3.93 (2H, t, J = 6.8 Hz), 3.82 (2H, s), 3.77 (3H, s), 2.71 (2H, t, J = 7.0 Hz), 2.56 (2H, q, J = 6.6 Hz), 2.34 (2H, q, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 152.9, 140.2, 129.6, 128.3, 128.0, 127.0, 126.8, 115.4, 114.5, 67.9, 55.6, 53.8, 48.8, 27.9, 27.6; MS m/z (relative intensity) (M^+ + 1) 312 (2), 311 (9), 121 (28), 120 (100), 109 (21), 65 (21).

Preparation of Aziridine 15. To a solution of ester aziridine **14** (0.51 g, 2.67 mmol) dissolved in 50 mL of THF at rt was added 90% potassium trimethylsilanolate (0.42 g, 2.94 mmol) in one portion. After being stirred for 2 h, the solution was concentrated in vacuo. The residue was dissolved in 50 mL of CH_2Cl_2 and cooled to 0 °C, and trimethylacetyl chloride (0.40 mL, 3.20 mmol) was added via syringe. In a separate flask, a solution of sulfonamide **9** (1.00 g, 2.67 mmol) and 80% NaH in mineral oil (0.16 g, 5.34 mmol) in 10 mL of toluene was stirred for 30 min at room temperature and added via syringe to the aziridine solution. The resulting mixture was stirred overnight with gradual warming to rt. The solution was diluted with 70 mL of ethyl acetate, washed with H_2O (30 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. After flash chromatography of the residue using hexanes/ethyl acetate (4:1), 0.41 g (28%) of aziridine **15** was isolated as a yellow oil: IR (film) 3020, 2920, 1685, 1590, 820 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.76 (2H, d, J = 8.2 Hz), 7.26 (7H, m), 6.81 (4H, s), 5.58 (2H, m), 3.87 (2H, t, J = 6.8 Hz), 3.73 (3H, s), 3.71 (2H, m), 3.61 (1H, m), 3.38 (1H, m), 3.15 (1H, m), 2.43 (4H, m), 2.38 (3H, s), 2.23 (1H, m), 1.67 (1H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.6, 153.7, 153.0, 144.9, 137.7, 136.6, 129.9, 128.7, 128.4, 128.1, 127.3, 127.2, 126.9, 115.5, 115.4, 114.6, 67.9, 63.6, 55.7, 46.2, 38.5, 35.7, 27.5, 21.6; MS m/z (relative intensity) (M^+ + 1) 535 (1), 534 (3), 375 (5), 155 (11), 124 (31), 109 (15), 91 (100), 81 (18); exact mass calcd for $C_{30}H_{34}N_2O_5S$ 534.2188, found 534.2210.

Preparation of Bicyclic Lactam 16. A solution of aziridine **15** (0.125 g, 0.23 mmol) dissolved in 6 mL of *m*-xylene was degassed in a resealable tube at −78 °C. The tube was sealed and heated at 320 °C for 15 min and cooled to rt. The solvent was removed by vacuum distillation, and the product was isolated by preparative TLC using hexanes/ethyl acetate (3:1) and further purified by preparative TLC using CH_2Cl_2/acetone (99:1) to yield 29 mg (23%) of lactam **16** as a colorless oil: IR (film) 3040, 2920, 1680, 1590, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 8.2 Hz), 7.24 (5H, m), 7.09 (2H, m), 6.78 (4H, m), 4.30 (1H, dt, J = 4.9, 12.4 Hz), 4.08 (1H, d, J = 13.6 Hz), 3.92–3.72 (3H, m), 3.76 (3H, s), 3.39 (1H, d, J = 13.6 Hz), 3.29 (1H, d, J = 6.2 Hz), 2.66 (2H, m), 2.51 (1H, m), 2.36 (3H, s), 1.85 (3H, m), 1.67 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 153.8, 152.7, 144.7, 139.1, 135.9, 129.3, 128.5, 128.4, 128.1, 126.8, 115.2, 114.6, 67.8, 67.1, 58.4, 56.2, 55.7, 45.6, 40.6, 37.2, 28.7, 22.3, 21.6.

Preparation of Aziridine 17. To a solution of amine **11** (1.95 g, 8.82 mmol) in 40 mL of CH_2Cl_2 was added a 2.0 M solution of Me_3Al in hexanes (6.20 mL, 12.35 mmol), and the mixture was stirred for 15 min. A solution of aziridine **14** (1.85 g, 9.70 mmol) in 10 mL of CH_2Cl_2 was added, and the solution was stirred at rt overnight. After slow addition of 1 mL of H_2O to the mixture, the resulting aluminum salts were filtered through a pad of Celite, and the organics were washed with H_2O (50 mL) and extracted with 100 mL of ethyl acetate. After drying ($MgSO_4$) and concentration of the solution, flash chromatography of the residue using hexanes/ethyl acetate (1:2) provided **17** as a pale yellow oil (2.41 g, 72%): IR (film) 3350, 3060, 3000, 2920, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (5H, m), 6.82 (4H, m), 6.61 (1H, m), 5.59 (1H, m), 5.44 (1H, m), 3.89 (2H, t, J = 6.8 Hz), 3.76 (3H, s), 3.54 (1H, d, J = 13.4 Hz), 3.44 (1H, d, J = 13.4 Hz), 3.25 (2H, q, J = 6.6 Hz), 2.45 (2H, q, J = 6.9 Hz), 2.26 (2H, q, J = 6.8 Hz), 2.21 (1H, dd, J = 3.1, 7.0 Hz), 1.94 (1H, d, J = 3.1 Hz), 1.75 (1H, d, J = 17.1 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.2, 153.7, 152.8, 137.9, 128.4, 128.2, 127.8, 127.8, 127.3, 115.4, 114.5, 67.8, 62.9, 55.6, 39.1, 38.2, 35.1, 27.5, 27.4; MS m/z (relative intensity) (M^+ + 1) 381 (10), 380 (33), 257 (100), 243 (45), 189 (28), 55 (33); exact mass calcd for $C_{23}H_{28}N_2O_3$ 380.2100, found 380.2082.

Preparation of Bicyclic Lactam 20. A solution of aziridine **17** (75 mg, 0.20 mmol) was dissolved in 5 mL of *o*-dichlorobenzene and sealed under vacuum in a resealable tube at −78 °C. The tube was sealed and heated at 320 °C for 2 h and then cooled to rt. The solvent was removed by vacuum distillation, and the product was isolated by preparative TLC using ethyl acetate to yield 33 mg (44%) of lactam **20** as a white solid: mp 127–8 °C; IR (KBr) 3180, 3040, 2930, 1660, 1500, 1230 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.28 (5H, m), 6.79 (4H, m), 5.92 (1H, br s), 4.59 (1H, d, J = 13.8 Hz), 3.86 (2H, m), 3.77 (3H, s), 3.60 (1H, d, J = 13.8 Hz), 3.43 (1H, m), 3.31 (1H, dt, J = 3.8, 11.9 Hz), 3.25 (1H, d, J = 4.8 Hz), 2.80 (1H, t, J = 9.5 Hz), 2.69 (1H, t, J = 9.5 Hz), 2.40 (2H, m), 1.88 (2H, m), 1.72 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 153.8, 152.8, 139.9, 128.6, 128.1, 126.5, 115.2, 114.6, 67.3, 65.1, 59.4, 56.3, 55.7, 41.6, 40.5, 36.9, 28.9, 20.5; MS m/z (relative intensity) 380 (2), 322 (32), 257 (84), 172 (18), 91 (100); exact mass calcd for $C_{23}H_{28}N_2O_3$ 380.2100, found 380.2068.

The product **19** was isolated from the above reaction mixture (39 mg, 52%) as an oil: IR (film) 3000, 2920, 1690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.29 (5H, m), 6.78 (4H, m), 5.49 (2H, m), 4.03 (2H, s), 3.84 (2H, t, J = 6.8 Hz), 3.65 (3H, s), 3.62 (2H, s), 3.22 (2H, t, J = 6.7 Hz), 3.20 (2H, s), 2.46 (2H, m), 2.20 (2H, m).

Conversion of Lactam 20 to *N*-Sulfonyllactam 21. To a solution of lactam **20** (0.13 g, 0.34 mmol) in 40 mL of THF at 0 °C was added 0.26 mL of 1.6 M BuLi in hexanes (0.41 mmol), and the mixture was stirred for 15 min. *p*-Toluenesulfonyl chloride (0.089 g, 0.51 mmol) was added in one portion along with DMAP (10 mg). The solution was warmed to rt and after 40 min diluted with $NaHCO_3$ solution (5 mL) and extracted with ethyl acetate (50 mL). After drying ($MgSO_4$) and concentration of the extract, flash chromatography of the residue using hexanes/ethyl acetate (2:1) yielded 0.11 g of sulfonyllactam **21** (61%) as an oil: IR (film) 3040, 2920, 1680, 1590, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 8.2 Hz), 7.24 (5H, m), 7.09 (2H, m), 6.78 (4H, m), 4.30 (1H, dt, J = 4.9, 12.4 Hz), 4.08 (1H, d, J = 13.6 Hz), 3.92–3.72 (3H, m), 3.76 (3H, s), 3.39 (1H, d, J = 13.6 Hz), 3.29 (1H, d, J = 6.2 Hz), 2.66 (2H, m), 2.51 (1H, m), 2.36 (3H, s), 1.85 (3H, m), 1.67 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 153.8, 152.7, 144.7, 139.1, 135.9, 129.3, 128.5, 128.4, 128.1, 126.8, 115.2, 114.6, 67.8, 67.1, 58.4, 56.2, 55.7, 45.6, 40.6, 37.2, 28.7, 22.3, 21.6.

Oxidation of *p*-Methoxyphenyl Ether 21 to Alcohol 22. To a solution of ether **21** (30 mg, 0.056 mmol) in 3 mL of dioxane was added freshly prepared AgO (28 mg, 0.23 mmol). Brief sonication of the mixture formed a uniform dispersion of the oxidant. Nitric acid (6 N, 0.1 mL) was added to initiate oxidation, and the reaction was stirred for an additional 5 min. The solution was diluted with ethyl acetate (30 mL) and H_2O (20 mL), and the layers were separated. After drying ($MgSO_4$) and concentration of the organic solution, alcohol **22** (17 mg, 74%) was isolated by preparative TLC of the residue on silica gel using hexanes/ethyl acetate (1:1): IR (film) 3400, 3030, 2930, 1690, 1600, 1360, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 8.5 Hz), 7.24 (5H, m), 7.12 (2H, m), 4.30 (1H, dt, J = 4.8, 12.6 Hz), 4.11 (1H, d, J = 13.4 Hz), 3.74 (1H, dt, J = 6.7, 12.7

Hz), 3.51 (2H, m), 3.39 (1H, d, J = 13.3 Hz), 3.30 (1H, d, J = 6.9 Hz), 2.60 (2H, m), 2.40 (3H, s), 2.31 (1H, m), 1.84 (2H, m), 1.62 (2H, m), 1.48 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 144.7, 138.8, 136.0, 129.3, 128.6, 128.4, 128.1, 126.9, 67.6, 61.2, 58.6, 56.3, 45.6, 40.7, 36.7, 31.9, 22.5, 21.6; CI MS (M + 1) 429, 273, 157, 91.

Preparation of Aziridine 23. Potassium trimethylsilanolate (1.78 g, 13.87 mmol) was added in one portion to a solution of aziridine **14** (2.65 g, 13.87 mmol) in 100 mL of THF. After 1.5 h, the solution was concentrated in vacuo, and the residue was dissolved in 100 mL of CH_2Cl_2 and cooled to 0 °C. Pivaloyl chloride (1.51 mL, 12.27 mmol) was added slowly, and the resulting solution was gradually warmed to rt over 2 h. After the mixture was recooled to 0 °C, a solution of amine **13** (3.32 g, 10.67 mmol) in 10 mL of CH_2Cl_2 was added slowly followed by DMAP (0.13 g, 1.07 mmol). The solution was stirred overnight at rt, diluted with 20 mL of brine, and extracted with ethyl acetate (100 mL). After drying ($MgSO_4$) and concentration of the extract, flash chromatography of the residue using hexanes/ethyl acetate (1:2) provided aziridine **23** (3.94 g, 78%) as a yellow oil: IR (film) 3020, 2920, 2820, 1640, 1500 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.26 (10H, m), 6.82 (4H, m), 5.47 (2H, m), 4.57 (2H, m), 3.86 (2H, m), 3.74 (3H, s), 3.38 (4H, m), 2.48 (1H, q, J = 6.7 Hz), 2.35 (3H, m), 2.25 (1H, t, J = 6.6 Hz), 2.19 (1H, dd, J = 3.2, 6.2 Hz), 1.66 (1H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.1, 168.9, 153.6, 153.4, 152.7, 152.6, 138.0, 137.9, 137.1, 136.7, 128.6, 128.2, 128.2, 128.1, 127.9, 127.9, 127.7, 127.7, 127.4, 127.2, 127.0, 126.9, 126.0, 115.2, 114.3, 114.3, 67.6, 67.4, 63.8, 55.3, 50.8, 48.6, 46.4, 45.9, 36.6, 36.3, 34.2, 33.8, 27.3, 27.2, 26.7, 25.4; MS m/z (relative intensity) (M^+ + 1) 471 (8), 470 (24), 333 (100), 305 (43), 186 (46), 160 (58), 132 (78), 120 (99).

Cyclization of Aziridine 23 to Lactam 24. A solution of aziridine **23** (1.10 g, 2.34 mmol) dissolved in 13 mL of o-dichlorobenzene was degassed in a resealable tube at −78 °C. The tube was sealed and heated at 320 °C for 2 h and cooled to rt. The solvent was removed by vacuum distillation, and the product was isolated by flash chromatography using hexanes/ethyl acetate (1:1) to yield 0.90 g (82%) of lactam **24** as a yellow oil: IR (film) 3020, 2920, 1630, 1225 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (10H, m), 6.81 (4H, m), 4.93 (1H, d, J = 14.7 Hz), 4.71 (1H, d, J = 13.8 Hz), 4.38 (1H, d, J = 14.7 Hz), 3.86 (2H, m), 3.77 (3H, s), 3.62 (1H, d, J = 13.8 Hz), 3.37 (1H, d, J = 4.8 Hz), 3.28 (2H, m), 2.76 (2H, m), 2.43 (2H, m), 1.88 (2H, m), 1.72 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 153.7, 152.8, 140.2, 137.2, 128.5, 128.0, 127.8, 127.2, 126.5, 115.2, 114.5, 67.3, 65.7, 59.1, 56.4, 55.6, 49.7, 46.7, 40.7, 36.8, 28.8, 20.9; MS m/z (relative intensity) (M^+ + 1) 471 (4), 470 (13), 379 (18), 348 (32), 322 (100), 172 (19), 91 (40); exact mass calcd for $C_{30}H_{34}N_2O_3$ 470.2569, found 470.2556.

Preparation of Amine 26. To a solution of alcohol **5** in 100 mL of CH_2Cl_2 was added Et_3N (9.0 g, 0.089 mol). The solution was cooled to 0 °C, and methanesulfonyl chloride (9.2 g, 0.081 mol) was added dropwise. After 1 h, 100 mL of H_2O was added. The organic layer was washed with 20 mL of brine, dried ($MgSO_4$), and concentrated yielding suitably pure mesylate **25** (22 g, 97%) as an oil: IR (film) 2920, 1720, 1640, 1430, 1350 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (2H, m), 4.44 (1H, m), 4.07 (2H, t, J = 6.8 Hz), 3.7 (1H, m), 3.6 (1H, m), 3.3 (2H, m), 2.87 (3H, s), 2.39 (2H, q, J = 6.9 Hz), 2.22 (2H, q, J = 6.8 Hz), 1.5 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.6, 124.5, 98.3, 68.9, 66.2, 61.8, 36.8, 30.3, 30.2, 27.6, 26.9, 25.0, 19.2.

To a solution of mesylate **25** (22 g, 0.078 mol) in 100 mL of DME was added benzylamine (25 g, 0.23 mol), and the solution was refluxed for 18 h. The DME was removed in vacuo, and the residue was dissolved in 100 mL of ethyl acetate and washed with 100 mL of brine. The organics were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue using ethyl acetate yielded amine **26** (15.9 g, 70%) as a yellow oil: IR (film) 3300, 2920, 1660, 1450 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (5H, m), 5.45 (2H, m), 4.54 (1H, m), 3.70 (4H, m), 3.35 (2H, m), 2.61 (2H, t, J = 7.0 Hz), 2.25 (4H, m), 1.5 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.1, 128.8, 128.1, 127.8, 127.6, 126.6, 98.5, 66.7, 62.0, 53.6, 48.6, 30.5, 27.9, 27.7, 25.2, 19.4.

Preparation of Aziridine 27. To a solution of aziridine **14** (6.7 g, 0.035 mol) in 100 mL of THF was added potassium trimethylsilanolate (4.5 g, 0.035 mol). After 1.5 h, the solution was concentrated, the residue was dissolved in 100 mL of CH_2Cl_2, cooled to 0 °C, and pivaloyl chloride (4.0 mL, 0.032 mol) was added. After 1.5 h, a solution of amine **26** (8.5 g, 0.029 mol) and DMAP (0.17 g, 1.36 mmol) in 20 mL of CH_2Cl_2 was added to the solution of aziridine. The solution was stirred for 2 h, diluted with 20 mL of $NaHCO_3$, extracted with 100 mL of CH_2Cl_2, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue using ethyl acetate provided the aziridine **27** (4.0 g, 65%) as an oil: IR (film) 2920, 1720, 1660, 1440 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (10H, m), 5.4 (2H, m), 4.55 (2H, s), 3.75 (4H, m), 3.35 (6H, m), 2.25 (6H, m), 1.6 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 169.0, 138.0, 137.9, 136.8, 128.8, 128.6, 128.4, 128.3, 128.2, 128.0, 127.8, 127.4, 127.3, 127.2, 127.1, 127.0, 127.0, 126.3, 126.0, 98.7, 98.6, 98.5, 66.7, 66.5, 63.9, 63.9, 62.2, 62.2, 62.0, 50.8, 48.7, 46.5, 46.0, 36.6, 36.4, 34.2, 33.9, 30.4, 27.8, 27.7, 26.7, 25.4, 25.2, 25.2, 19.5, 19.4, 19.4.

Formation of Lactam 28. The aziridine **27** (2.5 g, 5.6 mmol) was dissolved in 15 mL of o-DCB and degassed in a resealable tube. The tube was sealed under vacuum and heated at 320 °C for 1.5 h. After the mixture was cooled to rt, the solvent was removed by vacuum distillation. The resulting viscous oil was dissolved in 50 mL of MeOH, and TsOH (1.1 g, 5.6 mmol) was added at rt. After being stirred for 3 h, the solution was neutralized with solid $NaHCO_3$. The MeOH was removed in vacuo, and the residue was dissolved in 50 mL of CH_2Cl_2 and washed with 20 mL of water. The organic layer was washed with 3 × 20 mL of 5% HCl. The acidic extracts were made basic with solid K_2CO_3, and extracted with 3 × 20 mL of ethyl acetate. The ethyl acetate extracts were dried ($MgSO_4$) and concentrated yielding lactam **28** (1.4 g, 70%) as an oil: IR (film) 3400, 3020, 2920, 1625 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (10H, m), 4.87 (1H, d, J = 14.7 Hz), 4.65 (1H, d, J = 13.8 Hz), 4.34 (1H, d, J = 14.8 Hz), 3.56 (1H, d, J = 14.0 Hz), 3.51 (2H, dt, J = 2.9, 6.7 Hz), 3.29 (1H, d, J = 5.3 Hz), 3.21 (2H, m), 2.65 (2H, m), 2.31 (2H, m), 1.81 (1H, dq, J = 5.6, 12.9 Hz), 1.65 (2H, m), 1.47 (1H, m); ^{13}C (75 MHz, $CDCl_3$) δ 170.2, 140.1, 137.0, 128.5, 128.0, 127.7, 127.2, 126.4, 65.6, 61.2, 59.2, 56.4, 49.6, 46.6, 40.5, 36.3, 31.9, 20.8; MS m/z (relative intensity) (M^+ + 1) 365 92), 364 (7), 216 (25), 120 (39), 91 (100); exact mass calcd for $C_{23}H_{28}N_2O_2$ 364.2151, found 364.2153.

Conversion of Alcohol 28 to Allylic Alcohol 36. Oxalyl chloride (0.93 mL, 10.65 mmol) was dissolved in 75 mL of CH_2Cl_2, and the mixture was cooled to −78 °C. DMSO (0.90 mL, 12.77 mmol) was added slowly, and after 10 min, alcohol **28** (1.55 g, 4.26 mmol) in 15 mL of CH_2Cl_2 was added. The mixture was stirred for 30 min, Et_3N (2.08 mL, 14.89 mmol) was added, and the mixture was warmed to rt over 30 min. The solution was diluted with CH_2Cl_2 (75 mL) and washed with H_2O (2 × 50 mL) and brine (25 mL). The organics were dried and concentrated to give the unstable aldehyde **33**, which was diluted with 100 mL of THF and cooled to 0 °C. Vinylmagnesium bromide (5.33 mL, 5.33 mmol) was added slowly, and the solution was stirred at rt for 1 h. After being diluted with 100 mL of Et_2O, the mixture was washed with a saturated Rochelle's salt solution (150 mL) and brine (40 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue using ethyl acetate provided alcohol **36** (0.90 g, 54%) as a yellow oil as a 1:1 mixture of diastereomers: IR (film) 3380, 3020, 2920, 1625 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (10H, m), 5.80 (1H, m), 5.16 (1H, d, J = 6.9 Hz), 5.05 (1H, m), 4.87 (1H, m), 4.65 (1H, m), 4.35 (1H, m), 3.98 (1H, m), 3.59 (1H, m), 3.31 (1H, d, J = 4.1 Hz), 3.22 (2H, m), 2.70 (2H, m), 2.34 (2H, m), 1.84 (1H, m), 1.52 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 141.3, 140.9, 140.2, 137.1, 128.5, 128.0, 127.8, 127.2, 126.5, 114.9, 114.6, 72.1, 71.7, 65.8, 65.6, 65.4, 59.2, 59.1, 56.5, 49.8, 49.7, 49.6, 49.6, 46.7, 40.8, 40.6, 36.4, 36.2, 36.1, 20.9; MS m/z (relative intensity) (M^+ + 1) 391 (41), 390 (47), 388 (37), 299 (56), 214 (77), 188 (51), 172 (72), 146 (100), 92 (94); exact mass calcd for $C_{25}H_{30}N_2O_2$ 390.2307, found 390.2315.

Acylation of Alcohol 36 to Acetate 37. Alcohol **36** (0.89 g, 2.28 mmol) was dissolved in 50 mL of CH_2Cl_2 and cooled to 0 °C. Acetic anhydride (0.27 mL, 2.85 mmol), Et_3N (0.40 mL, 2.85 mmol), and DMAP (28 mg, 0.23 mmol) were added sequentially. The mixture was stirred for 2 h at rt, diluted with CH_2Cl_2 (50 mL), and washed with H_2O (2 × 40 mL). After drying ($MgSO_4$) and concentration of the solution, the acetate **37** was used without purification. Attempts to purify **37** by flash chromatography led to extensive decomposition: IR (film) 3020, 2920, 1730, 1630 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (10H, m), 5.71 (1H, m), 5.17 (3H, m), 4.88 (1H, m), 4.64 (1H, m), 4.37 (1H, m), 3.59 (1H, m), 3.25 (3H, m), 2.69 (2H, m), 2.35 (2H, m), 2.14 (1H, m), 2.00

(3H, s), 1.86 (1H, m), 1.61 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 169.8, 140.1, 137.1, 136.0, 128.8, 128.6, 128.1, 127.9, 127.3, 126.5, 117.3, 117.2, 73.6, 65.5, 59.1, 58.9, 56.4, 56.2, 49.7, 46.6, 40.7, 40.6, 36.1, 35.9, 33.6, 21.2, 20.7; MS *m/z* (relative intensity) (M^+ + 1) 433 (0.6), 432 (2), 362 (7), 214 (11), 91 (100); exact mass calcd for $C_{27}H_{32}N_2O_3$ 432.2413, found 432.2416.

Formation of Allylsilane 35 from Acetate 37. Hexamethyldisilane (1.19 mL, 5.83 mmol) dissolved in 2 mL of HMPA was cooled to 0 °C and treated with 1.0 M MeLi (5.83 mL, 5.83 mmol).[25] After being stirred for 15 min, the solution was diluted with 6 mL of THF, and CuCN (0.26 g, 2.92 mmol) was added in one portion.[26] The resulting solution was stirred for 20 min and cooled to −25 °C, and allylic acetate **37** (0.84 g, 1.94 mmol) was added as a solution in 3 mL of THF. After 1 h, the reaction was quenched with 10 mL of saturated NH_4Cl solution and diluted with 50 mL of Et_2O. After washing with NH_4Cl solution (3 × 40 mL), H_2O (25 mL), and brine (25 mL), the organics were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue using hexanes/ethyl acetate (2:1) provided allylsilane **35** (0.45 g, 50%) as a light yellow oil as a 1:1 mixture of *E* and *Z* olefin isomers: IR (film) 3055, 3020, 2945, 2840, 1635 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (10H, m), 5.38 (1H, m), 5.16 (1H, m), 4.92 (1H, m), 4.67 (1H, m), 4.37 (1H, m), 3.62 (1H, m), 3.34 (1H, d, *J* = 5.0 Hz), 3.26 (2H, m), 2.69 (2H, m), 2.38 (1H, m), 2.23 (1H, m), 1.96 (3H, m), 1.63 (1H, m), 1.39 (2H, m), −0.021 (4.5H, s), −0.052 (4.5H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 140.1, 137.2, 129.2, 128.6, 128.5, 128.0, 127.8, 127.5, 127.2, 126.7, 126.5, 124.9, 65.8, 59.1, 56.5, 56.3, 49.7, 46.7, 40.3, 40.3, 40.0, 32.4, 26.5, 22.6, 20.8, 18.6, −1.8, −2.1; MS *m/z* (relative intensity) (M^+ + 1) 447 (9), 446 (23), 319 (22), 298 (16), 184 (19), 91 (100), 73 (29); exact mass calcd for $C_{28}H_{38}N_2OSi$ 446.2753, found 446.2719.

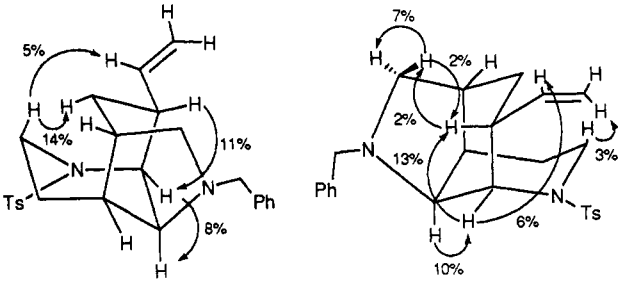
Monodebenzylation of Lactam 35 to Lactam 38. A flask containing 0.25 mL of *tert*-butyl alcohol and 3 mL of THF was cooled to −78 °C, and approximately 5 mL of NH_3 was condensed into the mixture. Sodium metal (43 mg, 1.88 g atom) was added in small portions to produce a deep blue solution. Lactam **35** (210 mg, 0.47 mmol) dissolved in 3 mL of THF was added to the flask, and the mixture was stirred for 1 min. The ice bath was removed, and the reaction was quenched with 0.5 mL of saturated NH_4Cl solution. After the NH_3 was allowed to evaporate, the solution was dissolved in 40 mL of ethyl acetate and washed with 5 mL of saturated K_2CO_3 solution and 10 mL of brine. The organics were dried ($MgSO_4$) and concentrated, and the yellow oil **38** (160 mg, 95%) was isolated as a 1:1 mixture of olefin isomers by preparative TLC using ethyl acetate/methanol (5:1): IR (film) 3200, 3000, 2940, 1650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (5H, m), 6.10 (1H, br s), 5.38 (1H, m), 5.15 (1H, m), 4.58 (1H, m), 3.60 (1H, m), 3.42 (1H, m), 3.28 (2H, m), 2.68 (2H, m), 2.28 (2H, m), 1.95 (3H, m), 1.66 (1H, m), 1.40 (2H, m), −0.021 (4.5H, m), −0.058 (4.5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 140.0, 128.6, 128.5, 127.9, 127.5, 126.7, 126.4, 125.0, 65.3, 65.2, 59.4, 56.5, 56.3, 41.6, 50.1, 32.4, 26.6, 22.6, 20.4, 20.3, 18.6, −1.8, −2.1; MS *m/z* (relative intensity) (M^+ + 1) 357 (11), 356 (39), 229 (37), 184 (31), 91 (100), 73 (41); exact mass calcd for $C_{21}H_{32}N_2OSi$ 356.2284, found 356.2290.

***N*-Sulfonation of Lactam 38 to *N*-Sulfonyllactam 39.** Lactam **38** (65 mg, 0.18 mmol) was dissolved in 10 mL of THF and cooled to 0 °C. A 0.5 M solution of lithium bis(trimethylsilyl)-amide (0.74 mL, 0.37 mmol) in THF was added dropwise via syringe, and the mixture was stirred for 15 min. *p*-Toluenesulfonyl chloride (87 mg, 0.46 mmol) and DMAP (6 mg, 0.054 mmol) were added in one portion, and the solution was slowly warmed to rt over 1 h. After dilution of the mixture with ethyl acetate (25 mL), the organics were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. Preparative TLC of the residue using hexanes/ethyl acetate (4:1) followed by elution with hexanes/ether (2:1) provided the *N*-sulfonyllactam **39** (66 mg, 71%) as a mixture of olefin isomers as a colorless oil: IR (film) 3020, 2940, 1680, 1590 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.92 (2H, d, *J* = 8.3 Hz), 7.24 (5H, m), 7.09 (2H, m), 5.37 (1H, m), 5.09 (1H, m), 4.27 (1H, m), 4.05 (1H, m), 3.75 (1H, m), 3.36 (1H, m), 3.26 (1H, d, *J* = 6.3 Hz), 2.53 (3H, m), 2.39 (3H, s), 2.15 (1H, m), 1.92 (4H, m), 1.39 (2H, m), −0.028 (4.5H, s), −0.067 (4.5H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.7, 144.6, 139.1, 136.1, 129.7, 129.3, 128.5, 128.4, 128.1, 128.0, 127.2, 126.7, 126.1, 124.6, 68.2, 68.0, 58.4, 56.5, 56.3, 45.6, 40.3, 32.4, 26.6, 22.7, 22.3, 22.2, 21.6, 18.7, −1.7, −2.0; (+)-FAB MS (M^+ + 1) 511, 510, 355.

Reduction of *N*-Sulfonyllactam 39 to α-Hydroxysulfonamide 40. To a solution of lactam **39** (15 mg, 0.029 mmol) in 5 mL of CH_2Cl_2 at −78 °C was added a 1.0 M solution of DIBALH in hexanes (0.12 mL, 0.12 mmol). The solution was slowly warmed to rt over 3 h, and 0.1 mL of H_2O was added. The solution was filtered through a pad of silica gel which was washed with ethyl acetate. The filtrate was concentrated, and the product **40** (14 mg, 93%) was isolated as a mixture of diastereomers as a clear oil by preparative TLC using hexanes/ethyl acetate (3:1): IR (film) 3350, 2940, 1590 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (2H, d, *J* = 8.3 Hz), 7.26 (5H, m), 7.15 (2H, m), 5.50 (1H, s), 5.36 (1H, m), 5.12 (1H, m), 3.84 (1H, m), 3.61 (1H, m), 3.32 (2H, m), 2.92 (1H, m), 2.71 (1H, m), 2.56 (2H, m), 2.38 (3H, s), 2.26 (2H, m), 1.91 (2H, m), 1.47 (3H, m), −0.036 (4.5H, s), −0.068 (4.5H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 139.6, 137.4, 129.6, 128.4, 128.3, 128.0, 127.4, 127.3, 126.6, 126.4, 124.9, 67.2, 67.1, 59.1, 56.5, 56.4, 40.4, 38.3, 35.9, 31.8, 25.9, 22.6, 21.5, 18.6, −1.8, −2.0; MS *m/z* (relative intensity) (M^+ − Ts) 357 (11), 211 (23), 184 (32), 103 (34), 91 (100), 73 (21); CIMS 513, 512, 495, 357, 338, 157, 91, 69.

Cyclization of α-Hydroxysulfonamide 40 to Tricycle 42. Alcohol **40** (14 mg, 0.027 mmol) was dissolved in 10 mL of CH_2Cl_2 and cooled to −78 °C. Anhydrous ferric chloride (8.9 mg, 0.055 mmol) was added in one portion, and the resulting solution was slowly warmed to 0 °C over 2.5 h. The solution was diluted with saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organics were dried ($MgSO_4$) and concentrated, and the tricyclic product **42** (7 mg, 61%) was isolated as clear oil by preparative TLC using hexanes/ethyl acetate (3:1): IR (film) 2900, 2840, 1630, 1590 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (2H, d, *J* = 7.9 Hz), 7.35 (5H, m), 7.09 (2H, d, *J* = 7.9 Hz), 5.89 (1H, ddd, *J* = 6.0, 10.7, 17.0 Hz), 5.08 (1H, d, *J* = 17.3 Hz), 5.02 (1H, d, *J* = 10.6 Hz), 3.98 (1H, t, *J* = 4.8 Hz), 3.79 (1H, d, *J* = 13.6 Hz), 3.72 (1H, d, *J* = 13.5 Hz), 3.64 (1H, dd, *J* = 7.6, 14.5 Hz), 3.23 (1H, ddd, *J* = 5.5, 12.3, 14.4 Hz), 3.03 (1H, m), 2.84 (1H, d, *J* = 9.5 Hz), 2.75 (1H, dd, *J* = 4.9, 9.0 Hz), 2.62 (1H, t, *J* = 4.8 Hz), 2.38 (3H, s), 2.35 (1H, m), 1.90 (4H, m), 1.63 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 140.3, 139.8, 139.1, 129.4, 128.3, 128.2, 126.9, 126.6, 114.3, 68.0, 60.2, 55.8, 40.2, 39.3, 37.2, 34.2, 31.8, 25.6, 23.8, 21.5; MS *m/z* (relative intensity) (M^+ + 1) 423 (5), 422 (15), 268 (15), 267 (73), 148 (13), 120 (10), 91 (100); exact mass calcd for $C_{25}H_{30}N_2O_2S$ 422.2028, found 422.2052.

NOE enhancements:



Acknowledgment. We are grateful to the National Institutes of Health (GM-32299) for financial support.

Supplementary Material Available: NMR spectra of new compounds (28 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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