Imino Diels−Alder-Based Construction of a Piperidine A-Ring Unit for Total Synthesis of the Marine Hepatotoxin Cylindrospermopsin†

Geoffrey R. Heintzelman and Steven M. Weinreb*

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

Masood Parvez‡

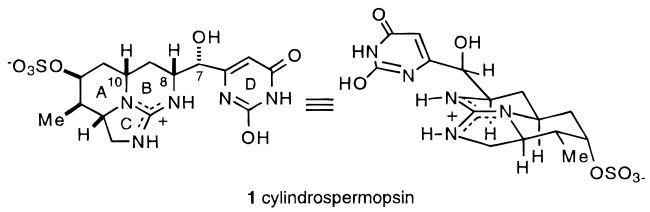
Department of Chemistry, University of Calgary, 2500 University Drive, N.W., Calgary, Alberta T2N 1N4, Canada

Received January 3, 1996⊗

The synthesis of a piperidine A-ring precursor to the alkaloid cylindrospermopsin (**1**) is described. The initial approach to the A-ring precursor focused on the imino Diels−Alder reaction of diene **8** with ethyl (*N*-tosylimino)acetate (**9**) to form the cycloadduct **10** as a single stereoisomer. However, all attempts to convert ester **10** to a requisite diene such as **5** were unsuccessful. An alternative strategy involved the Diels−Alder cycloaddition of *N*-tosylimine **9** with oxygenated diene **19** under either thermal or Lewis acid-catalyzed conditions to produce a mixture of *cis* and *trans* enones **20** and **21**. Although the undesired *cis*-enone **20** was the major product under all reaction conditions, it could be converted to the desired *trans* enone **21** by acid-catalyzed isomerization. Copper-mediated conjugate addition of vinylmagnesium bromide to *cis*-enone **20** followed by stereoselective ketone reduction with L-Selectride produced alcohol **23**, whose structure was confirmed by X-ray crystallography. Similarly, *trans*-enone **21** was converted to alcohol **25** whose structure and stereochemistry were also established by X-ray analysis. Alcohol **25** was then protected as the silyl ether **26**, which was hydroborated at the terminal olefin to produce primary alcohol ester **28** having the stereochemistry and functionality needed for cylindrospermopsin.

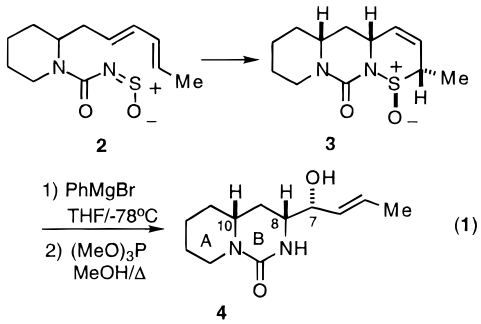
As the result of a serious outbreak of hepatoenteritis in 1979 on Palm Island (Queensland, Australia) due to contaminated drinking water, a search was undertaken to identify the agent responsible for this public health problem.[1,2] An epidemiological investigation led to the cyanobacterium (blue-green alga) *Cylindrospermopsin raciborskii*, which was found to produce a toxic substance having hepatotoxicity in mice and which is believed to be the cause of the symptoms in humans. More recently, the same toxin was isolated from the alga *Umezakia natans* collected in Lake Mikata (Fukui, Japan).[1] In 1992, Moore and co-workers[2] described the isolation of the hepatotoxin, which was named cylindrospermopsin and was found by a series of NMR experiments to have the tetracyclic structure and conformation shown in **1**. Studies by Runnegar and co-workers have demonstrated that cylindrospermopsin probably exerts its toxic effects by inhibition of synthesis of cell-reduced glutathione.[3]

To date, two approaches to synthesis of this fascinating and complex heterocyclic structure have appeared. Snider and Harvey have described an interesting biogenetically-



1 cylindrospermopsin

patterned route to an AC ring fragment of **1**.[4] We recently disclosed a strategy involving an intramolecular *N*-sulfinyl dienophile Diels−Alder cycloaddition of **2** to produce adduct **3**, which can be rearranged to model bicyclic urea **4** having the AB ring system and correct C-7,8,10 stereochemistry of cylindrospermopsin (eq 1).[5,6] In order to extend this approach to the total synthesis of



2 **3** **4** (1)

cylindrospermopsin (**1**), the piperidine-substituted diene **5** is required (eq 2). We anticipate preparing **5** from piperidine **6**, which has the appropriate functionality and

† Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

‡ Author to be contacted about X-ray crystal structure determinations.

⊗ Abstract published in *Advance ACS Abstracts,* June 1, 1996.

(1) (a) Harada, K.; Ohtani, I.; Iwamoto, K.; Suzuki, M.; Watanabe, M. F.; Watanabe, M.; Terav, K. *Toxicon* **1994**, *32*, 73. (b) Terav, K.; Ohmori, S.; Igarashi, K.; Ohtani, I.; Watanabe, M. F.; Harada, K. I.; Ito, E.; Watanabe, M. *Toxicon* **1994**, *32*, 833, and references cited therein.

(2) Ohtani, I.; Moore, R. E.; Runnegar, M. T. C. *J. Am. Chem. Soc.* **1992**, *114*, 7941. Moore, R. E.; Ohtani, I.; Moore, B. S.; DeKoning, C. B.; Yoshida, W. Y.; Runnegar, M. T. C.; Carmichael, W. W. *Gazz. Chim. Ital.* **1993**, *123*, 329.

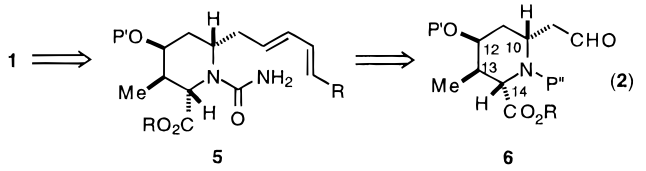
(3) Runnegar, M. T.; Kong, S.-M.; Zhong, Y.-Z.; Ge, J.-L.; Lu, S. C. *Biochem. Biophys. Res. Commun.* **1994**, *201*, 235. Runnegar, M. T.; Kong, S.-M.; Zhong, Y.-Z.; Lu, S. C. *Biochem. Pharmacol.* **1995**, *49*, 219.

(4) Snider, B. B.; Harvey, T. C. *Tetrahedron Lett.* **1995**, *36*, 4587.

(5) Heintzelman, G. R.; Parvez, M.; Weinreb, S. M. *Synlett* **1993**, 551.

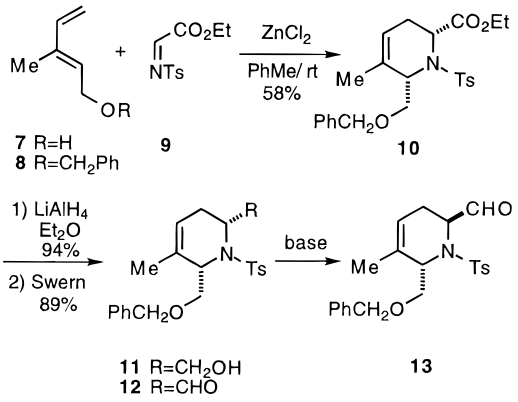
(6) For a review of *N*-sulfinyl dienophile Diels−Alder methodology, see: Weinreb, S. M. *Acc. Chem. Res.* **1988**, *21*, 313.

S0022-3263(96)00035-7 CCC: $12.00



stereochemistry at C-10,12,13,14 (cylindrospermopsin numbering). This paper outlines an entry to synthons like **6** utilizing a strategy based upon imino Diels–Alder cycloaddition methodology.[7]

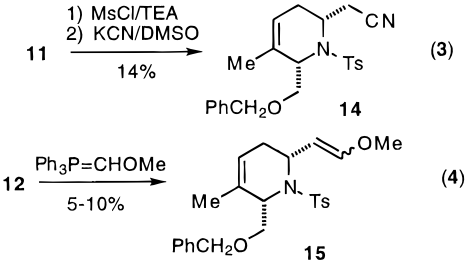
Scheme 1



Our initial foray into synthesis of a requisite piperidine utilized diene ether **8**, prepared from readily available diene alcohol **7**,[8] which reacted with ethyl (*N*-tosylimino)-acetate (**9**)[9] to afford a single stereoisomeric Diels–Alder adduct **10** (Scheme 1). The *cis*-2,6-tetrahydropyridine stereochemistry in adduct **10** was assigned by consideration of the closely analogous work of Hamada and coworkers[10] and from subsequent chemistry (*vide infra*). In order to investigate one carbon homologation of **10** (*cf.* **6**), the ester functionality was reduced to afford alcohol **11**, which could be oxidized by the Swern procedure to produce aldehyde **12**. It might be noted that this aldehyde is very easily isomerized in the presence of traces of base to the *trans*-substituted system **13**, and thus care needed to be taken in handling **12**.

Attempts were made to homologate both alcohol **11** and aldehyde **12**. Thus, alcohol **11** was converted to the mesylate, but cyanide displacement afforded nitrile **14** in only meager yield (eq 3). Similarly, Wittig homologation of aldehyde **12** provided only traces of enol ether **15** (eq 4).

An alternative homologation procedure involving an Arndt–Eistert sequence was next investigated.[11] Oxidation of aldehyde **12** successfully afforded carboxylic acid **16**, which on subjection to the standard conditions of the Arndt–Eistert homologation (oxalyl chloride; CH_2N_2/



Et_2O; Ag_2O/MeOH) afforded a poor yield of the ester **17**, surprisingly as a mixture of stereoisomers (Scheme 2). In addition, lactone **18** was also produced, confirming the *cis* stereochemistry of Diels–Alder adduct **10**. In view of these disappointing results, we turned to what proved to be a more successful and simpler strategy for imino Diels–Alder construction of the requisite piperidine derivative.

The known, easily prepared oxygenated diene **19**,[12] which is a 4/1 mixture of *Z*/*E* isomers,[12b] was found to react with glyoxylate-derived *N*-tosylimine **9** to afford, after *in situ* acidic hydrolysis, a mixture of enones **20** and **21** (Scheme 3). The yields and ratios of these cycloadducts was found to be dependent upon the specific reaction conditions employed. For example, with $AlCl_3$ as catalyst (PhMe, −78 °C, 3 h) a 53% yield of a 7/1 mixture of **20**/**21** was obtained. Using $ZnCl_2$ as catalyst under similar conditions, the ratio of **20**/**21** was 22/1 (60% total yield). The uncatalyzed condensation of diene **19** with imine **9** (PhMe, rt, 3 h) led to a 4.7/1 mixture of **20**/**21** in 51% total yield. It seems reasonable that the major *cis* product **20** arises from the *Z*-diene via a transition state having the carboxylate group of the imine **9** *endo*.[9,13] Similarly, minor *trans* adduct **21** would be derived from the *E*-diene isomer. It is possible that the variable ratios of **20**/**21** result from *E*/*Z* isomerization of the diene under the reaction conditions and/or by epimerization of the adducts upon workup and purification. In fact, if the major keto ester isomer **20** is treated with *p*-TsOH in refluxing benzene, a 4/1 mixture of **21**/**20** is produced. Similarly, acid-catalyzed isomerization of minor enone **21** provides the same 4/1 equilibrium mixture of **21**/**20**. This equilibration also allows obtention in quantity of the requisite *trans* isomer **21** from the unwanted *cis* compound **20**. However, since at this point we could not unambiguously decide which of the cycloadducts was the desired *trans* isomer, both compounds were carried through the next series of reactions. It was possible at a later stage of the synthesis to firmly establish the relative configurations of **20** and **21** (*vide infra*).

Thus, the major imino Diels–Alder cycloadduct **20** was found to undergo copper-promoted conjugate addition[14] of vinylmagnesium bromide to yield vinyl ketone **22** as a single stereoisomer (Scheme 4). This ketone was reduced with L-Selectride[14] to cleanly afford piperidine alcohol **23**.

(7) For reviews of imino Diels–Alder reactions, see: Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; Chap. 2. Weinreb, S. M. Heterodienophile Additions to Dienes. in *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 401.

(8) Burger, B. V.; du Plessis, E.; Garbers, C. F.; Pachler, K. G. R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 584.

(9) Hamley, P.; Holmes, A. B.; Kee, A.; Ladduwahetty, T.; Smith, D. F. *Synlett* **1991**, 29. See also: Weinreb, S. M.; Herr, R. J. Butyl *N*-(*p*-Toluenesulfonyl)iminoacetate. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, U.K., 1995.

(10) Hamada, T.; Sato, H.; Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1989**, *30*, 6405. Hamada, T.; Zenkoh, T.; Sato, H.; Yonemitsu, O. *Tetrahedron Lett.* **1991**, *32*, 1649.

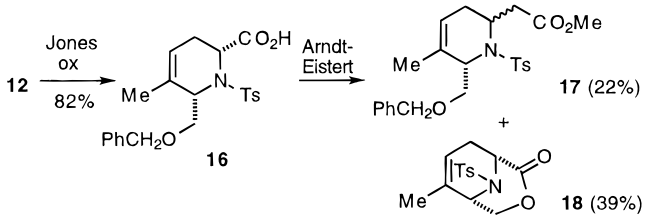
(11) *cf.* Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240.

(12) (a) Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001. (b) Harayama, T.; Cho, H.; Inubushi, Y. *Chem. Pharm. Bull.* **1978**, *26*, 1201. (c) Burger, M. T.; Still, W. C. *J. Org. Chem.* **1996**, *61*, 775.

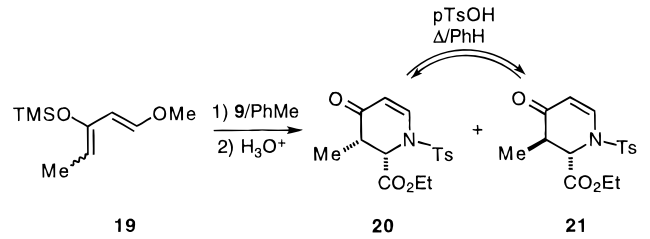
(13) McFarlane, A. K.; Thomas, G.; Whiting, A. *Tetrahedron Lett.* **1993**, *34*, 2379. These authors postulate (but do not prove) that similar cycloaddition reactions with Danishefsky's diene and glyoxylate-derived *N*-sulfonylimines proceed to form products resulting from an *exo*-carboxylate transition state.

(14) Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445.

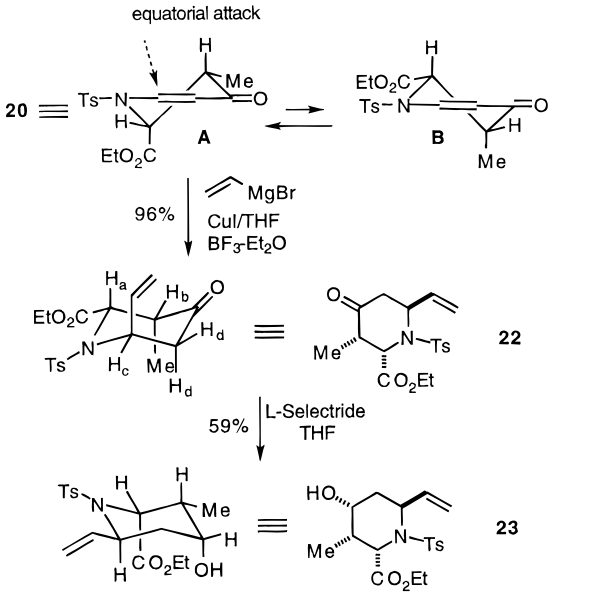
Scheme 2



Scheme 3



Scheme 4



The structure of this compound was established by X-ray crystallography.[15] The relative stereochemistry and conformation of piperidine **23** can be seen in the ORTEP plot in Figure 1. This structure also confirms the assignment of the *cis* stereochemistry to starting enone **20**.

We believe that *cis*-enone **20** has the half-chair conformation shown in **A** (Scheme 4). This conformation would minimize A-strain between the carboethoxy substitutent and the *N*-tosyl group (*cf.* **B**).[17] It is well-documented that related *N*-acylpiperidines have axial C-2 substituents for this reason.[14,16,17] It thus appears that vinyl cuprate attack on **20A** occurs from an equatorial direction,[18] perhaps to avoid 1,3-diaxial steric interactions with the ester moiety. Adduct **22** exists in the conformation indicated, as confirmed by ^{1}H NMR (J_{ab} = 6 Hz; J_{cd} = 3.6 Hz) and as expected L-Selectride reduction of the ketone functionality produced axial alcohol **23**.[19] As can be seen, piperidinol **23** does not have the required stereochemistry for cylindrospermopsin (*cf.* **6**).

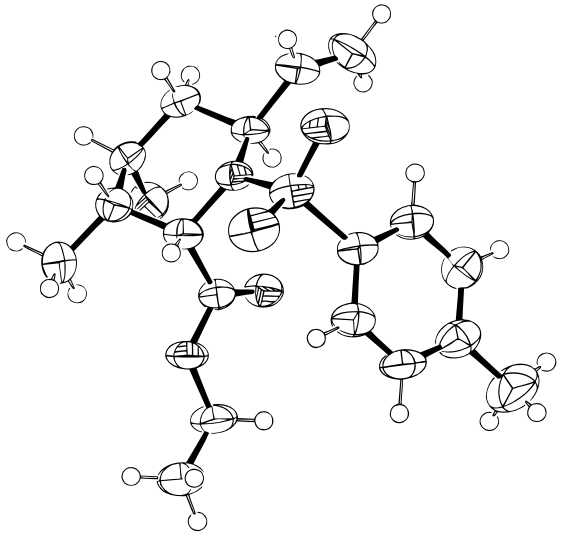
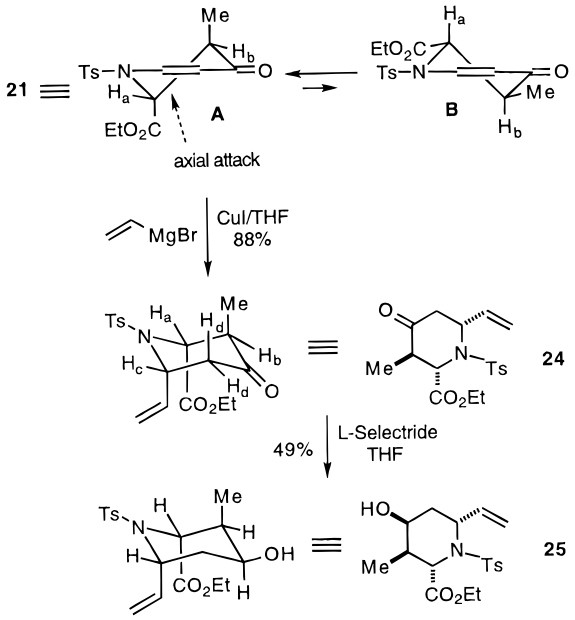


Figure 1. ORTEP plot of piperidinol **23**.

Scheme 5



The same series of reactions has been conducted on *trans*-enone **21**. Conjugate addition of a vinyl group to **21** produced a single vinyl ketone **24**, which upon L-Selectride reduction[14] yielded alcohol **25** (Scheme 5). Once again, the structure of this compound was proven by single crystal X-ray analysis.[15] Figure 2 shows an ORTEP plot of **25**. Interestingly, this piperidinol exists in a chair conformation with the C-2, 3, and 6 substituents all axial, probably to minimize A-strain[16,17] with the *N*-tosyl group.

In this case, we think starting enone **21** exists as half chair conformer **A**, again to minimize A-strain. The ^{1}H NMR spectrum of **21** shows J_{ab} = 2 Hz, which is

(15) The authors have deposited X-ray data with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(16) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(17) Beak, P.; Zajdel, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 1010 and references cited therein.

(18) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983; Chap. 6.

(19) For a general review of the stereochemistry of cyclohexanone reductions, see: Boone, J. R.; Ashby, E. C. Reduction of Cyclic and Bicyclic Ketones by Complex Metal Hydrides. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Wiley: New York, 1979; Vol. 11, p 53.

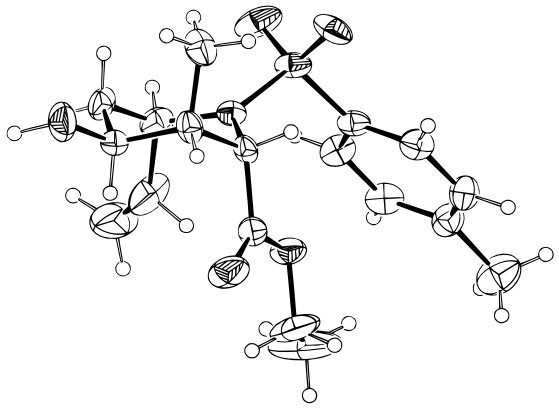
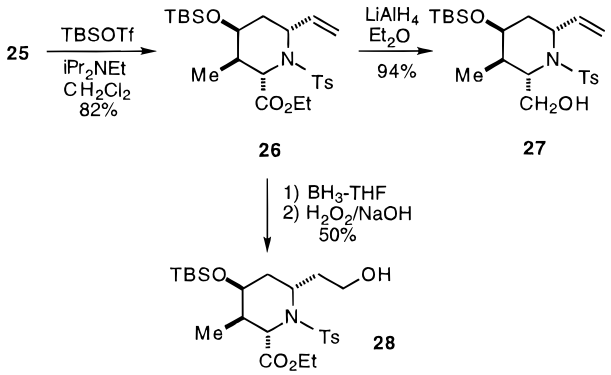


Figure 2. ORTEP plot of piperidinol **25**.

Scheme 6



consistent with conformation **A**, but not **B**. Attack of the vinyl cuprate on **21A** must thus occur from an axial direction, perhaps for a combination of stereoelectronic and steric reasons.[18] Ketone **24** exists in the all-axial conformation shown (J_{ab} = 7 Hz; J_{cd} = 4.6 Hz). L-Selectride reduction of ketone **24** leads to equatorial alcohol **25** via axial delivery of hydride.[20] Compound **25** in fact has the functionality and stereochemistry needed for our approach to **1** (*cf.* eq 2).

We have performed some additional transformations to elaborate piperidinol **25** into useful cylindrospermopsin intermediates. For example, the alcohol functionality of **25** could be protected as the silyl ether **26** (Scheme 6). Reduction of the ester moiety then provided primary alcohol **27**. In addition, it was possible to hydroborate terminal olefin **26** to produce the primary alcohol ester **28**. We anticipate that these intermediates will ultimately prove instrumental in developing a total synthesis of cylindrospermopsin (**1**), and our future work in this area will be reported in due course.

Experimental Section

Preparation of Diene Benzyl Ether 8. To a 0 °C mixture of NaH (95%, 0.735 g, 30.6 mmol) in 15 mL of THF was added 3-methyl-2,4-pentadienol[8] (**7**, 2.50 g, 25.5 mmol) in 10 mL of THF. After stirring the mixture for 1 h, benzyl bromide (4.36 g, 25.5 mmol) was added. The mixture was warmed to rt and after 48 h water was added. After extraction of the mixture with Et_2O (3 × 30 mL), the combined organics were washed with brine and dried over $MgSO_4$. The residue was purified by flash chromatography eluting with 5:95 EtOAc:hexanes to yield 2.60 g (54%) of ether diene **8**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38−7.22 (m, 5H), 6.43 (dd, 1H, J = 17, 11 Hz), 5.71 (t, 1H, J = 7 Hz), 5.22 (d, 1H, J = 11 Hz), 5.07 (d, 1H, J = 11 Hz), 4.54 (s, 2H), 1.78 (s, 3H).

Preparation of Cycloadduct 10. To a solution of ethyl glyoxylate (1.20 g, 11.8 mmol, freshly distilled from P_2O_5) in 10 mL of toluene was added *p*-toluenesulfonyl isocyanate (2.32 g, 11.8 mmol), and the solution was heated at reflux for 3 d. The solution was cooled to rt, and the diene **8** (1.10 g, 5.91 mmol) in 5 mL of toluene and $ZnCl_2$ (0.161 g, 1.18 mmol) were added. After stirring the mixture at rt for 6 d, water was added and the mixture was extracted with EtOAc (3 × 30 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography eluting with 15:85 EtOAc:hexanes to yield 1.52 g (58%) of cycloadduct **10**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.66 (d, 2H, J = 8 Hz), 7.30−7.20 (m, 7H), 5.45 (br s, 1H), 4.90 (d, 1H, J = 6 Hz), 4.42 (d, 2H, J = 2 Hz), 4.09 (br d, 1H, J = 18 Hz), 3.84 (br d, 1H, J = 17 Hz), 3.76−3.55 (m, 4H), 2.89 (br s, 1H), 2.37 (s, 3H), 1.69 (s, 3H), 0.98 (t, 3H, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 143.1, 137.6, 135.4, 130.0, 129.2, 128.0, 127.3, 127.2, 127.0, 118.7, 72.8, 67.8, 60.3, 54.7, 42.5, 41.4, 21.2, 20.0, 13.5; IR (neat) 2919, 1732, 1453 cm^{-1}; EIMS m/z (relative intensity) 443 (0.6), 322 (11), 288 (35), 91 (100); HREIMS calcd for $C_{24}H_{29}NO_5S$ m/z 443.1766, found m/z 443.1776.

Reduction of Ester 10. To a suspension of $LiAlH_4$ (0.253 g, 6.66 mmol) and 20 mL of Et_2O at 0 °C was added a solution of ester **10** (1.47 g, 3.33 mmol) in 10 mL of Et_2O. After stirring at rt for 1 h, the reaction was cooled to 0 °C and quenched by the sequential addition of 2 mL of EtOAc, 2 mL of H_2O, 2 mL of 10% NaOH, and 4 mL of saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated to yield 1.26 g (94%) of alcohol **11**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70 (d, 2H, J = 8 Hz), 7.38−7.14 (m, 7H), 5.38 (br s, 1H), 4.46 (s, 2H), 4.19 (q, 1H, J = 6 Hz), 4.07 (br d, 1H, J = 18 Hz), 3.75−3.45 (m, 5H), 2.53 (br s, 1H), 2.39 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 137.5, 137.2, 131.8, 129.6, 128.4, 127.8, 127.7, 126.9, 119.0, 73.2, 67.9, 59.8, 55.2, 41.2, 39.5, 21.0, 19.9; IR (neat) 3520, 2862, 1453, 1330 cm^{-1}; CIMS m/z (relative intensity) 402 (100), 384 (11), 370 (17), 294 (16), 280 (23), 246 (30), 157 (49), 91 (53); HREIMS calcd for $C_{22}H_{27}NO_4S$ m/z 401.1662, found m/z 401.1629.

Swern Oxidation of Alcohol 11. To a −78 °C solution of oxalyl chloride (0.269 g, 2.12 mmol) was added a solution of DMSO (0.330 g, 4.23 mmol) in 5 mL of CH_2Cl_2. After stirring the mixture for 10 min, a solution of alcohol **11** (0.283 g, 0.706 mmol) in 10 mL of CH_2Cl_2 was added slowly. After 20 min, triethylamine (0.285 g, 2.82 mmol) was added and the solution was warmed to rt. After 10 min, the solution was diluted with water, poured into 5% HCl, and extracted with CH_2Cl_2 (3 × 40 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated to yield 0.250 g (89%) of aldehyde **12**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.66 (d, 2H, J = 8 Hz), 7.40−7.12 (m, 7H), 5.37 (br s, 1H), 4.63 (d, 1H, J = 6 Hz), 4.00 (br d, 1H, J = 17 Hz), 3.75 (br d, 1H, J = 17 Hz), 3.69 (d, 2H, J = 6 Hz), 2.86 (br s, 1H), 2.40 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 143.4, 137.2, 135.6, 131.3, 129.4, 128.2, 127.6, 127.5, 127.2, 118.8, 173.0, 67.5, 61.3, 42.7, 41.4, 21.3, 20.0; IR (neat) 2862, 1731, 1453 cm^{-1}.

Preparation of Carboxylic Acid 16. To a solution of aldehyde **12** (0.120 g, 0.301 mmol) in 5 mL of acetone was added Jones reagent (0.7 M, 0.859 mL, 0.601 mmol). After 24 h, the reaction was quenched by the addition of 2-propanol. The mixture was diluted with water and extracted with Et_2O (3 × 20 mL). The combined organics were washed with water and brine, dried over $MgSO_4$, and concentrated to yield 0.103 g (82%) of acid **16**, which was used without purification: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (d, 2H, J = 8 Hz), 7.42−7.15 (m, 7H), 5.45 (br s), 4.91 (d, 1H, J = 6 Hz), 4.43 (d, 2H, J = 3 Hz), 4.04 (br d, 1H, J = 18 Hz), 3.86 (br d, 1H, J = 17 Hz), 3.67 (d, 2H, J = 6 Hz), 2.88 (br s, 1H), 2.39 (s, 3H), 1.65 (s, 3H).

(20) Addition of hydrides and other nucleophiles to *trans*-4-*tert*-butyl-2-methylcyclohexanone (axial Me) gives predominantly products of axial attack: (a) Cherest, M. *Tetrahedron* **1980**, *36*, 1593. (b) Fang, J.-M.; Sun, S.-F.; Rei, M.-H. *J. Chem. Soc., Perkin Trans. 2* **1989**, 747.

Arndt−Eistert Homologation of Acid 16. To a solution of acid **16** (0.103 g, 0.248 mmol) in 5 mL of toluene was added oxalyl chloride (0.070 g, 0.558 mmol). After stirring for 4 h, the solution was concentrated and the residue was dissolved in 5 mL of Et_2O. An excess of CH_2N_2 in Et_2O was added at 0 °C. After 15 min, the solution was warmed to rt and allowed to stand for 1 h. The solution was concentrated, and the residue was dissolved in 10 mL of MeOH. A catalytic amount of Ag_2O was added, and the mixture was stirred for 20 h. After filtration of the mixture through Celite and concentration of the filtrate, the residue was purified by preparative TLC eluting with 25:75 EtOAc:hexanes to yield 0.030 g (39%) of ester lactone **18** and 0.025 g (22%) of ester **17** as a 1:1 mixture of stereoisomers. **18**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (d, 2H, J = 8 Hz), 7.29 (d, 2H, J = 8 Hz), 5.61 (br s, 1H), 5.16 (d, 1H, J = 7 Hz), 4.32 (s, 2H), 4.03 (br d, 1H, J = 18 Hz), 3.47 (br d, 1H, J = 16 Hz), 3.00 (br s, 1H), 2.40 (s, 3H), 1.69 (s, 3H); CIMS m/z (relative intensity) 308 (73.5), 152 (100). **17**: EIMS m/z (relative intensity) 443 (0.74), 370 (3.2), 322 (10), 155 (21), 91 (100).

Thermal Formation of Cycloadducts 20 and 21. To a solution of ethyl glyoxylate (0.600 g, 5.90 mmol, freshly distilled from P_2O_5) in 5 mL of toluene was added *p*-toluenesulfonyl isocyanate (1.16 g, 5.90 mmol), and the solution was heated at reflux for 2 d. The solution was cooled to rt and a solution of diene **19**[12] (0.741 g, 3.98 mmol) in 5 mL of toluene was added. After stirring the mixture for 3 h, 5 mL of 5% HCl solution was added. After 0.5 h, the mixture was extracted with Et_2O (2 × 20 mL), and the combined organics were washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography eluting with 25:75 EtOAc:hexanes to yield 0.560 g (42%) of *cis*-adduct **20** and 0.120 (9%) of *trans*-adduct **21**. **20**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.69 (d, 2H, J = 8 Hz), 7.63 (dd, 1H, J = 8, 2 Hz), 7.31 (d, 2H, J = 8 Hz), 5.31 (d, 1H, J = 8 Hz), 4.76 (dd, 1H, J = 7, 2 Hz), 3.88−3.71 (m, 2H), 2.83 (pent, 1H, J = 7 Hz), 2.39 (s, 3H), 1.06 (t, 3H, J = 7 Hz), 1.00 (d, 3H, J = 7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.8, 166.7, 145.3, 140.9, 134.4, 130.0, 127.3, 106.6, 61.5, 61.0, 40.6, 21.4, 13.6, 10.1; IR (neat) 2960, 1735, 1665, 1590, 1355, 1160 cm^{-1}; CIMS m/z (relative intensity) 338 (100), 184 (33), 157 (32); HREIMS calcd for $C_{16}H_{19}NO_5S$ m/z 337.0984, found m/z 337.1006. **21**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75 (d, 2H, J = 8 Hz), 7.70 (dd, 1H, J = 8, 2 Hz), 7.36 (d, 2H, J = 8 Hz), 5.24 (dd, 1H, J = 8, 1 Hz), 4.58 (t, 1H, J = 2 Hz), 4.10−3.93 (m, 2H), 2.80 (q, 1H, J = 7 Hz), 2.41 (s, 3H), 1.10 (t, 3H, J = 7 Hz), 0.96 (d, 3H, J = 7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 193.4, 167.6, 145.3, 141.4, 134.5, 130.0, 129.4, 127.3, 126.1, 105.2, 62.1, 61.9, 42.2, 21.4, 21.2, 16.7, 13.7; IR (neat) 2950, 1725, 1650, 1580, 1355, 1160 cm^{-1}; EIMS m/z (relative intensity) 337 (16.6), 264 (66), 155 (67), 91 (100); HREIMS calcd for $C_{16}H_{19}NO_5S$ m/z 337.0984, found m/z 337.0972.

Lewis Acid-Catalyzed Formation of Cycloadducts 20 and 21. To a solution of ethyl glyoxylate (0.600 g, 5.90 mmol, freshly distilled from P_2O_5) in 5 mL of toluene was added *p*-toluenesulfonyl isocyanate (1.16 g, 5.90 mmol), and the solution was heated at reflux for 2 d. The solution was cooled to −78 °C, and then a solution of diene **19** (0.741 g, 3.98 mmol) in 5 mL of toluene and anhydrous $ZnCl_2$ (0.054 g, 0.40 mmol) was added. After stirring the mixture for 3 h at −78 °C, 5 mL of 5% HCl solution was added, and the mixture was warmed to rt. After 0.5 h, the mixture was extracted with Et_2O (2 × 20 mL), and the combined organics were washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography eluting with 25:75 EtOAc:hexanes to yield 0.765 g (57%) of *cis*-adduct **20** and 0.035 g (3%) of *trans*-adduct **21**.

Isomerization of *cis*-Adduct 20. To a solution of major Diels−Alder adduct **20** (1.02 g, 3.00 mmol) in 15 mL of benzene was added a few milligrams of *p*-TsOH, and the solution was heated at reflux for 4 d. Saturated $NaHCO_3$ solution was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography eluting with 25:75 EtOAc:hexanes to yield 0.140 g (14%) of *cis*-adduct **20** and 0.583 g (57%) of *trans*-adduct **21**.

Preparation of Vinyl Ketone 22. To a −20 °C mixture of CuI (0.434 g, 2.28 mmol) in 5 mL of THF was added a 1.0 M solution of vinylmagnesium bromide in THF (2.28 mL, 2.28 mmol). After 1 h, the solution was cooled to −78 °C and $BF_3{\cdot}OEt_2$ (0.323 g, 1.14 mmol) was added. After 10 min, a solution of enone **20** (0.384 g, 1.14 mmol) in 3 mL of THF was added. The reaction mixture was stirred at −78 °C for 16 h and then poured into 15 mL of 10% NH_4OH in saturated NH_4Cl solution. The mixture was extracted with Et_2O (3 × 20 mL), and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated to yield 0.400 g (96%) of ketone **22**, which was pure enough to be used without further purification: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.71 (d, 2H, J = 8 Hz), 7.27 (d, 2H, J = 8 Hz), 5.90 (ddd, 1H, J = 17, 11, 6 Hz), 5.13 (dd, 1H, J = 10, 2 Hz), 5.11 (dd, 1H, J = 18, 2 Hz), 4.88 (br s, 1H), 4.65 (d, 1H, J = 7 Hz), 3.94 (q, 2H, J = 1 Hz), 3.19 (dd, J = 18, 6 Hz), 2.98 (1H, pent, J = 7 Hz), 2.60 (dd, 1H, J = 18, 3 Hz), 2.37 (s, 3H), 1.13 (t, 3H, J = 7 Hz), 0.96 (d, 3H, J = 7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.9, 170.0, 143.7, 139.0, 136.3, 129.3, 127.3, 116.4, 61.2, 60.2, 54.6, 43.3, 43.0, 43.0, 21.2, 13.6, 10.2; IR (neat) 2980, 1720, 1345, 1160 cm^{-1}; CIMS m/z (relative intensity) 366 (88), 292 (36), 210 (100), 157 (39).

Reduction of Ketone 22. To a −78 °C solution of ketone **22** (0.375 g, 1.03 mmol) in 10 mL of THF was added a 1.0 M solution of L-Selectride in THF (1.85 mL, 1.85 mmol). After 1.5 h, 1.5 mL of 30% H_2O_2 and 2.5 mL of 10% NaOH were added, and the mixture was warmed to rt. The mixture was acidified with 5% HCl and extracted with ether (3 × 15 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography eluting with 25:75 EtOAc:hexanes to yield 0.222 g (59%, 57% from *cis*-adduct **20**) of alcohol **23** which was recrystallized from EtOAc/hexanes to yield colorless prismatic crystals (mp 91−93 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.66 (d, 2H, J = 8 Hz), 7.22 (d, 2H, J = 8 Hz), 5.89 (ddd, 1H, J = 17, 10, 7 Hz), 5.07 (d, 1H, J = 17 Hz), 5.00 (d, 1H, J = 11 Hz), 4.66 (d, 1H, J = 6 Hz), 4.46−4.36 (m, 1H), 4.17−3.92 (m, 2H), 3.78 (br s, 1H), 2.91 (br s, 1H), 2.35 (s, 3H), 2.25−2.10 (m, 1H), 2.03−1.83 (m, 1H), 1.20 (t, 3H, H = 7 Hz), 1.09 (d, 3H, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 143.2, 137.8, 129.0, 127.7, 127.5, 116.5, 67.4, 61.4, 59.3, 53.8, 39.8, 36.9, 21.4, 13.8, 13.7; IR (neat) 3500, 2960, 1720 cm^{-1}; CIMS m/z (relative intensity) 368 (100), 350 (37), 294 (74), 212 (78), 157 (47).

Preparation of Vinyl Ketone 24. To a −20 °C mixture of CuI (0.033 g, 0.17 mmol) in 5 mL of THF was added a 1.0 M solution of vinylmagnesium bromide in THF (1.74 mL, 1.74 mmol). After 1 h, the solution was cooled to −78 °C, and a solution of *trans*-enone **21** (0.390 g, 1.16 mmol) in 3 mL of THF was added. The solution was warmed to −20 °C and stirred for 20 h. The reaction mixture was poured into 15 mL of 10% NH_4OH in saturated NH_4Cl solution and extracted with Et_2O (3 × 20 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated to yield 0.373 g (88%) of vinyl ketone **24**, which was used without further purification: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.83 (d, 2H, J = 8 Hz), 7.33 (d, 2H, J = 8 Hz), 5.73 (ddd, 1H, J = 17, 11, 5 Hz), 5.32 (dd, 1H, J = 17, 2 Hz), 5.12 (dd, 1H, J = 11, 2 Hz), 4.78−4.71 (m, 1H), 4.44 (d, 1H, J = 7 Hz), 4.17 (q, 2H, J = 7 Hz), 3.04 (pent, 1H, J = 7 Hz), 2.49 (d, 1H, J = 4 Hz), 2.43 (m, 1H), 2.41 (s, 3H), 1.22 (t, 3H, J = 7 Hz), 1.17 (d, 3H, J = 7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.5, 170.6, 144.0, 136.9, 136.1, 129.6, 127.7, 117.8, 61.7, 60.7, 54.5, 44.1, 40.6, 21.4, 13.8, 13.8; IR (neat) 2960, 1720, 1345, 1155 cm^{-1}; CIMS m/z (relative intensity) 366 (100), 292 (46), 210 (75), 157 (49).

Reduction of Ketone 24. To a −78 °C solution of ketone **24** (0.373 g, 1.02 mmol) in 10 mL of THF was added a 1.0 M solution of L-Selectride in THF (2.04 mL, 2.04 mmol). After 2 h, 0.8 mL of 10% NaOH and 0.75 mL of 30% H_2O_2 were added. The mixture was warmed to rt and extracted with ether (3 × 20 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography eluting with 25:75 EtOAc:hexanes to yield 0.182 g (49%, 43% over two steps) of alcohol

25, which was recrystallized from EtOAc/hexanes to yield colorless prismatic crystals (mp 92−94 °C): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.83 (d, 2H, J = 8 Hz), 7.29 (d, 2H, J = 8 Hz), 5.65 (ddd, 1H, J = 18, 11, 5 Hz), 4.99 (dd, 1H, J = 18, 2 Hz), 4.96 (dd, 1H, J = 10, 2 Hz), 4.71 (d, 1H, J = 2 Hz), 4.60 (br s, 1H), 4.21−3.99 (m, 3H), 2.67−2.60 (m, 1H), 2.39 (s, 3H), 1.83−1.71 (m, 2H), 1.66 (br s, 1H), 1.15 (t, 3H, J = 7 Hz), 1.01 (d, 3H, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 143.2, 137.3, 136.5, 129.1, 127.6, 115.8, 62.8, 61.1, 59.2, 54.4, 34.2, 29.0, 21.2, 13.6, 10.2; IR (neat) 3500, 2910, 1725 cm^{-1}; CIMS *m*/*z* (relative intensity) 368 (78), 350 (18), 294 (33), 214 (100), 157 (81).

Preparation of Silyl Ether 26. To a 0 °C solution of alcohol **25** (0.143 g, 0.39 mmol) and diisopropylethylamine (0.101 g, 0.78 mmol) in 10 mL of CH_2Cl_2 was added *tert*-butyldimethylsilyl triflate (0.154 g, 0.58 mmol). The reaction mixture was warmed to rt and stirred for 18 h. The reaction was quenched by the addition of a few drops of MeOH and concentrated. The residue was purified by flash chromatography eluting with 15:85 EtOAc:hexanes to yield 0.154 g (82%) of silyl ether **26**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.81 (d, 2H, J = 8 Hz), 7.67 (d, 2H, J = 8 Hz), 5.68 (ddd, 1H, J = 18, 11, 5 Hz), 4.97 (dd, 1H, J = 17, 2 Hz), 4.95 (dd, 1H, J = 12, 2 Hz), 4.64 (d, 1H, J = 2 Hz), 4.53 (br s, 1H), 4.16−3.94 (m, 3H), 2.55−2.44 (m, 1H), 2.39 (s, 3H), 1.86−1.63 (m, 2H), 1.18 (t, 3H, J = 7 Hz), 0.97 (d, 3H, J = 7 Hz), 0.84 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 143.2, 137.6, 137.4, 129.3, 127.8, 115.5, 63.8, 61.2, 59.6, 54.7, 35.0, 30.1, 25.7, 21.5, 17.9, 13.9, 10.7, −4.9; IR (neat) 2955, 1732 cm^{-1}; CIMS *m*/*z* (relative intensity) 482 (70), 424 (63), 350 (66), 328 (96), 157 (55). Anal. Calcd for $C_{24}H_{39}NO_5SiS$: C, 59.84; H, 8.16. Found: C, 59.66; H, 8.19.

Reduction of Ester 26. To a 0 °C solution of ester **26** (0.072 g, 0.15 mmol) in 5 mL of Et_2O was added $LiAlH_4$ (0.011 g, 0.30 mmol). After stirring for 1 h, the reaction was quenched by the sequential addition of 1 mL of EtOAc, 1 mL of H_2O, 1 mL of 10% NaOH, and 2 mL of saturated NH_4Cl solution. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated to yield 0.062 g (94%) of alcohol **27**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74 (d, 2H, J = 8 Hz), 7.28 (d, 2H, J = 8 Hz), 5.98 (ddd, 1H, J = 18, 11, 4 Hz), 5.26 (dd, 1H, J = 18, 2 Hz), 5.18 (dd, 1H, J = 11, 2 Hz), 4.74 (br s, 1H), 4.01 (pent, 1H, J = 5 Hz), 3.91−3.72 (m, 2H), 3.60−3.52 (m, 1H), 2.40 (s, 3H), 2.23 (br s, 1H), 1.88 (pent, 1H, J = 7 Hz), 1.71−1.63 (m, 2H), 0.82 (s, 9H), 0.51 (d, 3H, J = 7 Hz), −0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 140.5, 138.0, 127.1, 115.6, 64.0, 63.5, 62.1, 54.3, 34.8, 29.8, 25.7, 21.5, 18.0, 11.3, −4.7, −4.9. Anal. Calcd for $C_{22}H_{37}NO_4SiS$: C, 60.09; H, 8.52. Found: C, 60.06; H, 8.52.

Hydroboration of Alkene 26. To a 0 °C solution of alkene **26** (0.035 g, 0.073 mmol) in 5 mL of THF was added a 1.0 M solution of BH_3·THF in THF (0.218 mL, 0.22 mmol). The reaction was warmed to rt and stirred for 16 h. The reaction was cooled to 0 °C and 1.5 mL of 10% NaOH and 1.5 mL of 30% H_2O_2 were added. After 30 min, the mixture was extracted with EtOAc (3 × 15 mL). The combined organics were washed with 2 M $Na_2S_2O_3$ and brine, and dried over $MgSO_4$. After concentration, the residue was purified by flash chromatography eluting with 25:75 EtOAc:hexanes to yield 0.018 g (50%) of alcohol **28**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (d, 2H, J = 8 Hz), 7.31 (d, 2H, J = 8 Hz), 4.47 (s, 1H), 4.34−3.82 (m, 5H), 3.57−3.45 (m, 1H), 2.50 (t, 1H, J = 7 Hz), 2.41 (s, 3H), 1.85−1.25 (m, 4H), 1.27 (t, 3H, J = 7 Hz), 0.80 (s, 9H), 0.57 (d, 3H, J = 7 Hz), −0.02 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 144.1, 138.0, 130.0, 127.7, 63.8, 61.6, 60.1, 58.8, 50.7, 36.6, 34.8, 31.5, 25.4, 21.2, 17.6, 13.6, 10.5, −5.5; IR ($CDCl_3$) 3416, 2954, 1731 cm^{-1}; CIMS *m*/*z* (relative intensity) 500 (85), 442 (39), 368 (50), 346 (74), 157 (100).

Acknowledgment. We are grateful to the National Science Foundation (CHE-94-23670) for financial support of this research.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of new compounds (12 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.

JO960035A