Total Synthesis of the Annonaceous Acetogenins Asiminocin and Asiminecin by a Bidirectional Approach

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Received March 7, 1997[⊗]

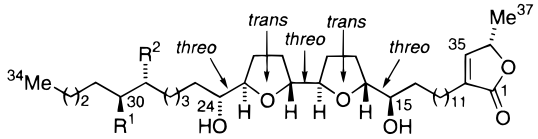
A total synthesis of the Annonaceous acetogenins asiminocin and asiminecin is described. The approach is bidirectional starting from the (*S*,*S*)-tartrate derived dialdehyde **7** and the (*R*)-α-OSEM stannane **6**. Addition of **6** to **7** in the presence of $InCl_3$ afforded the bis-adduct, *anti*-diol **8**. The derived tosylate **9** was converted to the bis-tetrahydrofuran core unit **10** upon treatment with TBAF. Selective silylation of one of the two equivalent terminal diol groupings led to the OTBS ether alcohol **11**. Oxidation to aldehyde **12** and then $InCl_3$-promoted addition of the (*S*)-allylic stannane **14** gave the *anti* adduct **15**. Removal of the OH group by reduction of the tosylate **16** with $LiBEt_3H$ yielded the SEM ether **17**. Hydrogenation of the three double bonds of **17** followed by cleavage of the terminal silyl ether and oxidation afforded aldehyde **20**. Conversion to the vinylic iodide **21** followed by Pd(0)-catalyzed coupling with the (*S*)-alkynyl butenolide **24** gave the asiminocin derivative **25**. Selective hydrogenation of the enyne moiety with diimide and cleavage of the SEM protecting groups completed the synthesis of asiminocin (**27**). Asiminecin (**41**) was prepared starting from aldehyde **12** and the OTBS allylic stannane **28**. Addition of the latter to the former in the presence of $InCl_3$ afforded the anti adduct **29** which was protected as the SEM ether **30**. Hydrogenation followed by OTBS cleavage with TBAF and selective silylation of the primary alcohol with TBSCl and Et_3N−DMAP led to the secondary alcohol **33**. Tosylation and hydrogenolysis with $LiEt_3BH$ removed the C30 OTs group affording the SEM ether **35**. The remaining steps were carried out along the lines described for asiminocin via the vinyl iodide **38** which was coupled with acetylenic butenolide **24** to afford enyne **39**. Selective reduction with diimide and SEM cleavage completed the synthesis.

In the previous paper we described a total synthesis of the Annonaceous acetogenin asimicin.[1] While those investigations were in progress, McLaughlin and coworkers published a report on the isolation and structure elucidation of asiminocin, a C37 acetogenin with nearly one billion times the cytotoxic potency of a standard reference, adriamycin, as measured against several human solid tumor cell lines. A second closely related isomer, asiminecin, also exhibits impressive antitumor activity (Table 1).[2]

Asiminocin and asiminecin are members of the asimicin subgroup of Annonaceous acetogenins and, as such, possess the same basic core bis-tetrahydrofuran *threo,trans,threo,trans,threo* stereochemistry. In view of the significant biological activity reported for asiminocin and the relative scarcity of the natural material,[3] we initiated a total synthesis along the lines described for asimicin. As will be seen the synthetic route, with minor modification, can also be used for asiminecin.

Asiminocin differs from asimicin in two obvious and important respects—the presence of a C30 (*S*) hydroxyl substituent and the absence of a C4 hydroxyl substituent. These differences require a modification of the stannane reagent and the butenolide coupling strategy used in our previous route.[1] In the present effort we hoped to incorporate a convergent rather than a linear introduction of the butenolide terminus. Specifically, the use of a shorter chain allylic stannane in the bidirectional addition would enable us to introduce a preformed butenolide segment through an appropriate coupling reaction. This strategy would also allow for the introduction of the C30 (*S*)-alcohol.

Table 1. Comparative Cytotoxicity of Asiminocin, Asiminecin, and Adriamycin Against Human Tumor Cell Lines (ED_{50} μg/mL[2])



	R^1	R^2	A-549[a]	MCF-7[b]	HT-29[c]
asiminocin	OH	H	3.1×10^{-12}	2.9×10^{-12}	$<10^{-12}$
asiminecin	H	OH	3.3×10^{-7}	2.7×10^{-9}	$<10^{-12}$
adriamycin			1.8×10^{-2}	1.3×10^{-1}	3.6×10^{-2}

[a] Lung cancer. [b] Breast cancer. [c] Colon cancer.

The requisite stannane **6** was prepared from 4-OTBS-, 1-butanol **1**[4] as outlined in eq 1.[5] This six-step process was effected in 30% overall yield and gave material of >95% ee as judged by the ^1H NMR spectra of the (*R*)- and (*S*)-*O*-methylmandelate derivatives.[6]

Dialdehyde **7**[7] was treated with the (*R*)-α-OSEM allylic stannane **6** in the presence of $InCl_3$ affording the C_2 symmetric adduct **8** in 77% yield (eq 2). The derived bis-

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1997.

(1) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989.

(2) Zhao, G.-X.; Chao, J.-F.; Zeng, L.; Rieser, M. J.; McLaughlin, J. L. *Bioorg. Med. Chem.* **1996**, *4*, 25. Zhao, G.-X.; Miesbauer, L. R.; Smith, D. L.; McLaughlin, J. L. *J. Med. Chem.* **1994**, *37*, 1971.

(3) For example, 15 kg of air-dried pulverized stem bark of *Asimina triloba* (L.) Dunal afforded only 10 mg of asiminecin after multiple partition extractions, several column chromatographies, preparative HPLC, and, finally, preparative TLC fractionation.[2]

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(5) Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, *113*, 647.

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(7) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 4247.

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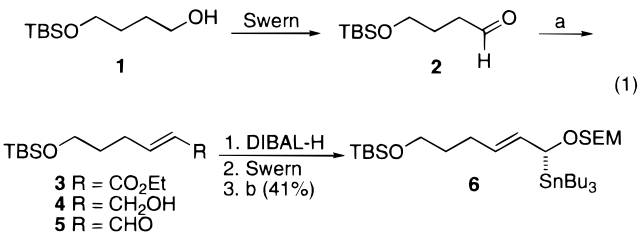
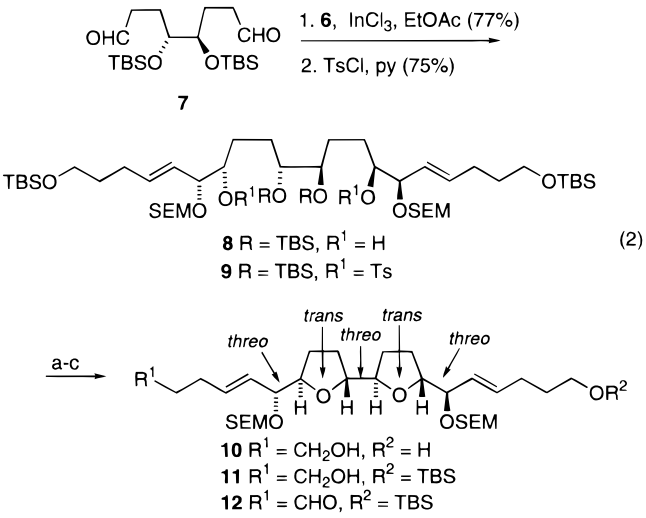


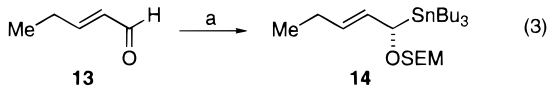
a) $(EtO)_2POCH_2CO_2Et$, NaH, THF
b) 1. Bu_3SnLi, then 1,1'-(azodicarbonyl)dipiperidine (ADD) 2. *(S)*-BINAL-H 3. SEMCl, *i*-Pr_2NEt

tosylate **9**, upon mild heating with TBAF in THF, gave the *threo,trans,threo,trans,threo* bis-THF diol **10** in 76% yield. Selective silylation[4] followed by Swern oxidation[8] yielded the aldehyde **12**. The silylation reaction gave mainly the mono OTBS derivative **11** and recovered diol **10**. Only small amounts of the bis-OTBS derivative were isolated. The three products were easily separated on silica gel with little loss of material. The apparent rate difference between mono and bis silylation may result from internal H-bonding by one of the two equivalent terminal OH functions.[1]



a) TBAF, THF (76%) b) NaH, TBSCl (79%) c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 (85%)

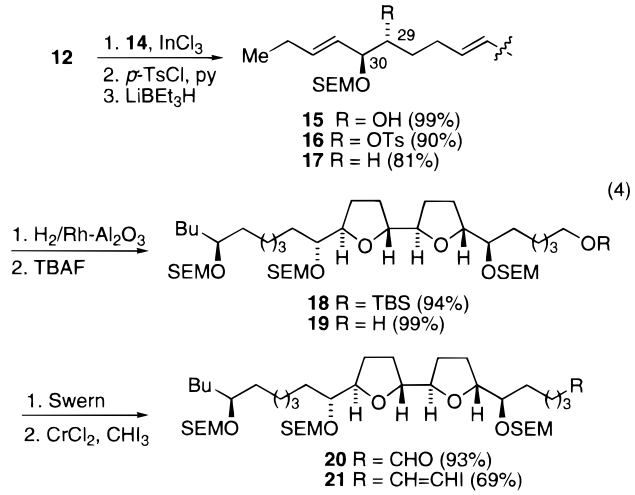
Completion of the left-hand side chain and installation of the C30 (*S*) hydroxyl substituent was effected by means of the (*S*)-stannane **14** prepared from enal **13** along the same lines as **6** (eq 3).[5]



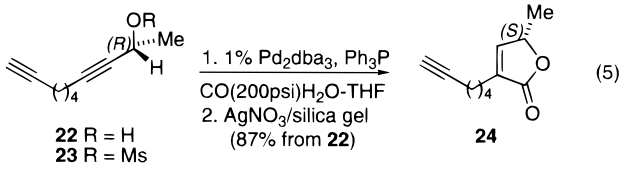
a) 1. Bu_3SnLi, then ADD 2. *(R)*-BINAL-H 3. SEMCl, *i*-Pr_2NEt

Treatment of aldehyde **12** with stannane **14** in the presence of $InCl_3$ afforded the *anti* adduct **15** in nearly quantitative yield. The ee of the C29 carbinyl center was found to be greater than 95% by ^1H NMR analysis of the (*R*)- and (*S*)-*O*-methylmandelates.[6] On the basis of this analysis, and our previous findings, we can surmize that the center at C30 is (*S*) and of equally high ee.[7] Hydrogenolysis of the C29 alcohol was effected by reduction of the tosylate **16** with $LiBEt_3H$.[9]

Hydrogenation of triene **17** over $Rh-Al_2O_3$ afforded the hexahydro derivative **18**. Cleavage of the TBS ether of **18** and oxidation of the alcohol **19** gave aldehyde **20** which was converted to the *(E)*-vinyl iodide **21** (eq 4).[10]



An appropriate butenolide coupling partner, **24**, for vinylic iodide **21** was prepared from the (*R*)-propargylic alcohol **22**[11] *via* the mesylate **23** through Pd(0)-catalyzed hydrocarbonylation[12] and subsequent treatment of the intermediate allenic acid with catalytic $AgNO_3$ on silica gel (eq 5).[13] The ee of this butenolide was found to be >95% by HPLC analysis.[14] The configuration assignment is made by analogy to previous conversions.[12]



Pd(0)-catalyzed coupling of vinylic iodide **21** with alkynylbutenolide **24** afforded the enyne **25** in 96% yield (eq 6).[15] Selective reduction with Wilkinson's catalyst in the manner of Hoye and co-workers resulted in appreciable reduction of the butenolide double bond.[16] None of the corresponding reduction product was detected when a C4 ODPS analogue of **25** was similarly hydrogenated.[17] Thus it would appear that the proximal C4 substituent retards this undesired reduction. The problem could be circumvented in the case of **25** through use of diimide, generated *in situ* from tosylhydrazine.[18]

Removal of the SEM protecting groups from the reduced product was effected with PPTS in ethanol.[1] The resulting triol, **27**, exhibited ^1H and ^{13}C NMR spectra

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(9) Brown, H. C.; Kim. S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.
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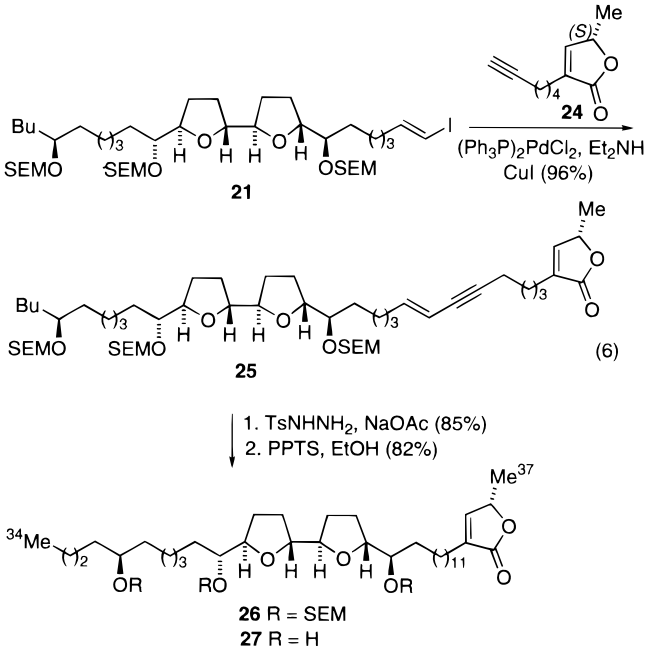
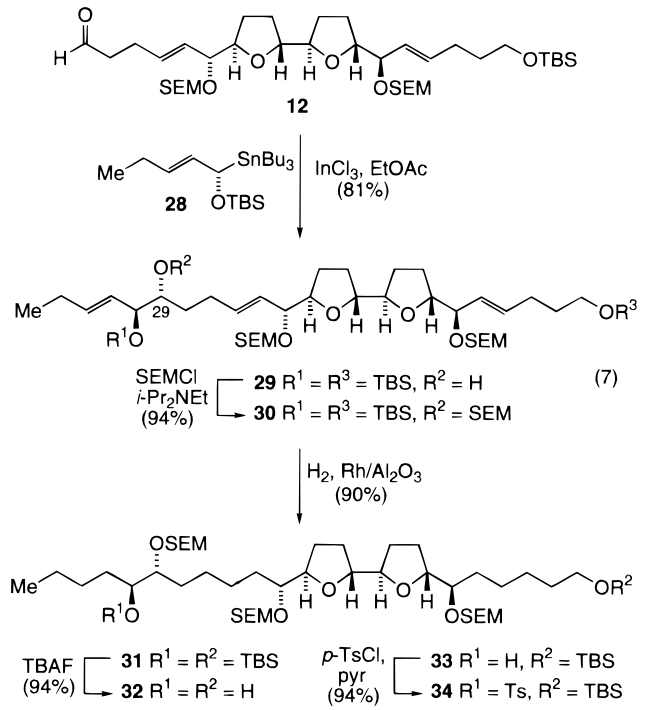
(13) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966.
(14) A Chiracel OB-H column was used with 90:10 hexanes−*i*-PrOH as the eluting solvent.
(15) *Cf.* (a) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 2.4. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
(16) Hoye, T. R.; Hanson, P. R.; Kovelsky, A. C.; Ocain, T. D.; Zhung, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369.
(17) *Cf.* Hoye, T. R.; Tan, L. *Tetrahedron Lett.* **1995**, *36*, 1995. Sinha, S. C.; Sinha, A.; Yazbak, A.; Keinan, E. *J. Org. Chem.* **1996**, *61*, 7640. Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801.
(18) Hart, D. J.; Hong, W.-P.; Hsu, L.-Y. *J. Org. Chem.* **1987**, *52*, 4665.

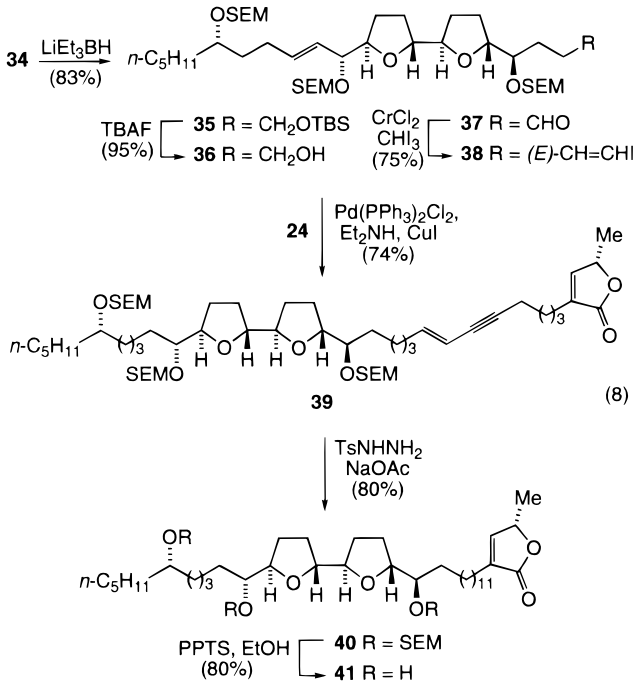


indentical to those of asiminocin. The optical rotation was also in accord with the reported value.[2]

Aldehyde **12** also served as the starting point for a synthesis of asiminecin. In this case the OTBS stannane **28**, prepared as described for the OSEM analogue **14**, was used to introduce the requisite 29(*R*) stereocenter. The $InCl_3$-promoted addition afforded the adduct **29** in 81% yield. Conversion to the SEM ether **30** followed by hydrogenation led to the hexahydro derivative **31**. The derived diol **32** gave rise to the mono-TBS derivative **33** in 84% yield by treatment with TBSCl and Et_3N, DMAP (eq 7).



The remaining steps of the synthesis parallel those employed for asiminocin. Thus hydrogenolysis of the tosylate **34** with $LiEt_3BH$ afforded the deoxy derivative **35**. Cleavage of the TBS ether followed by Swern oxidation gave aldehyde **37** in 87% yield. The derived vinyl iodide **38**[10] was coupled with the previously described acetylenic butenolide **24**,[15] and the resulting enyne **39** was selectively reduced with diimide to the hexahydro derivative **40**. No trace of product resulting from butenolide reduction could be detected. Removal of the SEM protecting groups, as before, yielded asiminecin (**41**) (eq 8). The spectral properties of this material and those of the tris Mosher ester derivative were in accord with the reported values.[2]



The foregoing syntheses of asiminocin and asiminecin, like our previous synthesis of asimicin,[1] follows a bidirectional approach. However by using a shorter chain allylic stannane in the intial bis-addition, we increase the flexibility of the route and thereby permit the introduction of an intact butenolide moiety. In the present syntheses the selective reduction of side chain unsaturation is effectively achieved by diimide. This methodology should find general usage in the synthesis of Annonaceous acetogenins.[17]

Experimental Section

Diol 8. A suspension of $InCl_3$ (440 mg, 2.0 mmol) in EtOAc (50 mL) was placed in a sonication bath for 15 min to dissolve the $InCl_3$. The solution was removed from the bath, and dialdehyde **7** (402 mg, 1.0 mmol) was added. The resulting mixture was cooled to −78 °C followed by slow addition of a solution of stannane **6** (1.65 g, 2.5 mmol) in EtOAc (10 mL) with stirring. After addition, the reaction mixture was stirred for 30 min at −78 °C and then allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated $NaHCO_3$. After separation, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, treated with Et_3N (3 mL), and concentrated. The residue was purified by flash chromatography (10% EtOAc in hexanes) to give 0.86 g (77%) of diol **8** as a colorless oil: $[\alpha]_D$ −24.5 (*c* 2.65, CH_2Cl_2); IR (neat) 3484, 2951, 1248, and 1108 cm^{-1}; ^1H NMR δ 5.72 (dt, J = 15.3 and 6.6 Hz, 2H), 5.41 (dd, J = 15.3 and 8.7 Hz, 2H), 4.71, 4.65 (ABq, J = 6.6 Hz, 4H), 3.95 (dd, J = 8.1 and 3.3 Hz, 2H), 3.76−3.49 (m, 10H), 2.25 (br s, 2H), 2.12 (q, J = 7.2 Hz, 4H), 1.91−1.20 (m, 12H), 0.96−0.87 (m, 40H), and 0.04−0.02 (m, 42H); ^{13}C NMR δ 136.4, 125.3, 92.1, 80.6, 75.9, 74.3, 65.3, 62.5, 32.3, 29.9, 28.8, 26.8, 25.9, 25.8, 18.1, 18.0, −1.4, −4.1, −4.6, and −5.3. Anal. Calcd for $C_{56}H_{122}O_{10}Si_6$: C, 59.84; H, 10.94. Found: C, 59.96; H, 10.95.

Bis-Tosylate 9. To a stirred solution of diol **8** (1.0 g, 0.89 mmol) in pyridine (10 mL) at 0 °C was added *p*-TsCl (2.4 g, 12 mmol). The resulting mixture was stirred for 30 min and then warmed to room temperature and stirred for another 18 h. EtOAc and brine were added. After separation, the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (10% EtOAc in hexanes) to give 0.95 g (75%) of bis-tosylate **8** as a colorless oil: $[\alpha]_D$ −27.2 (*c* 1.56, $CHCl_3$); IR (neat) 2951, 2855, 1466, 1370, and 1099 cm^{-1}; ^1H NMR δ 7.78 (d, J = 8.4 Hz, 4H), 7.30 (d, J = 8.4 Hz, 4H), 5.72 (dt, J = 15.6 and 6.6 Hz, 2H), 5.24 (dd, J = 15.6 and 7.8 Hz, 2H), 4.59, 4.51 (ABq, J = 6.6 Hz, 4H), 4.46 (m, 2H), 4.24 (dd, J = 7.5 and 3.0 Hz, 2H), 3.71−3.43 (m, 8H), 3.33 (br d, J = 9.0 Hz, 2H), 2.42 (s, 6H), 2.09 (m, 4H), 1.72−1.45 (m, 12H), 0.94−0.81 (m, 40H), and 0.04−0.02 (m, 42H); ^{13}C NMR δ 144.0, 136.5, 134.7, 129.5, 127.9, 125.2, 92.1, 85.5, 77.8, 75.3, 65.1, 62.4, 32.1, 28.7, 27.0, 26.4, 25.9, 25.8, 21.6, 18.3, 17.9, −1.4, −4.1, −4.7, and −5.3. Anal. Calcd for $C_{70}H_{134}O_{14}S_2Si_6$: C, 58.69; H, 9.43. Found: C, 58.78; H, 9.50.

bis-Tetrahydrofuran Diol 10. To a stirred solution of bis-tosylate **9** (3.60 g, 2.5 mmol) in THF (100 mL) at rt was added TBAF (1.0 M solution in THF, 20 mL, 20 mmol). The resulting mixture was heated to 50 °C and stirred for 12 h. After being cooled to rt, the mixture was concentrated. The residue was purified by flash chromatography (75% EtOAc in hexanes) to give 1.2 g (76%) of bis-tetrahydrofuran **10** as a colorless oil: $[\alpha]_D$ −66.2 (*c* 1.33, CH_2Cl_2); IR (neat) 3441, 2943, 1449, and 1248 cm^{-1}; ^1H NMR δ 5.71 (dt, J = 15.3 and 6.6 Hz, 2H), 5.41 (dd, J = 15.3 and 7.8 Hz, 2H), 4.70, 4.66 (ABq, J = 6.6 Hz, 4H), 4.06−3.92 (m, 6H), 3.77−3.48 (m, 8H), 2.15 (m, 4H), 1.94−1.60 (m, 12H), 0.92 (m, 4H), and 0.01 (s, 18H); ^{13}C NMR δ 134.7, 127.1, 91.8, 81.4, 81.3, 78.4, 64.8, 61.7, 31.7, 28.6, 27.8, 27.7, 17.9, and −1.6. Anal. Calcd for $C_{32}H_{62}O_8Si_2$: C, 60.91; H, 9.90. Found: C, 60.77; H, 9.87.

Mono-TBS Ether Alcohol 11. To a solution of diol **10** (290 mg, 0.46 mmol) in THF (10 mL) at rt was added NaH (95%; 20 mg, 0.79 mmol). The resulting mixture was stirred for 30 min, and TBSCl (85 mg, 0.56 mmol) was added. The reaction mixture was stirred for another 40 min. The reaction was quenched with saturated $NaHCO_3$, and Et_2O was added. After separation, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (10% EtOAc in hexanes first, then 30% EtOAc in hexanes, then 75% EtOAc in hexanes) to give 130 mg (38%) of OTBS ether **11** along with 5% of the bis-OTBS derivative and 150 mg (52%) of recovered diol **10**. **11**: $[\alpha]_D$ −53.6 (*c* 1.76, CH_2Cl_2); IR (neat) 3484, 2951, 1466, and 1248 cm^{-1}; ^1H NMR δ 5.71 (dt, J = 15.3 and 6.6 Hz, 1H), 5.70 (dt, J = 15.3 and 6.6 Hz, 1H), 5.40 (dd, J = 15.3 and 7.8 Hz, 1H), 5.35 (dd, J = 15.3 and 7.8 Hz, 1H), 4.70, 4.66 (ABq, J = 6.9 Hz, 4H), 4.07−3.93 (m, 6H), 3.78−3.48 (m, 8H), 2.12 (m, 4H), 1.94−1.54 (m, 12H), 0.92 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H), and 0.01 (s, 18H); ^{13}C NMR δ 135.0, 134.6, 127.3, 126.8, 91.9, 91.8, 81.3, 81.3, 81.3, 78.6, 78.5, 64.8, 64.8, 62.5, 62.1, 32.2, 31.9, 28.7, 28.6, 27.9, 27.8, 25.9, 18.4, 18.0, −1.5, and −5.3. Anal. Calcd for $C_{36}H_{76}O_8Si_3$: C, 61.24; H, 10.28. Found: C, 61.30; H, 10.25.

Data for bis-OTBS: $[\alpha]_D$ −50.7 (*c* 1.21, $CHCl_3$); ^1H NMR δ 5.70 (dt, J = 15.3 and 6.6 Hz, 2H), 5.35 (dd, J = 15.3 and 7.8 Hz, 2H), 4.70, 4.66 (ABq, J = 6.9 Hz, 4H), 4.06−3.93 (m, 6H), 3.79−3.48 (m, 8H), 2.10 (m, 4H), 1.96−1.54 (m, 12H), 0.92 (m, 4H), 0.89 (s, 18H), 0.04 (s, 12H), and 0.01 (s, 18H). Anal. Calcd for $C_{42}H_{90}O_8Si_4$: C, 61.48; H, 10.55. Found: C, 61.57; H, 10.61.

Aldehyde 12. To a stirred solution of oxalyl chloride (0.44 mL, 5.0 mmol) in CH_2Cl_2 (50 mL) at −78 °C was slowly added DMSO (0.71 mL, 10 mmol). The resulting mixture was stirred for 20 min. A solution of alcohol **11** (0.60 g, 0.81 mmol) in CH_2Cl_2 (10 mL) was then added. The mixture was stirred for 1 h, followed by addition of Et_3N (2.8 mL). After being stirred for an additional 5 min at −78 °C, the reaction mixture was slowly warmed to rt. The reaction was quenched with saturated NH_4Cl, and H_2O was added. After separation, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (20% EtOAc in hexanes) to give 0.51 g (85%) of aldehyde **12** as a yellow oil: $[\alpha]_D$ −58.0 (*c* 1.32, $CHCl_3$); IR (neat) 2951, 2887, 1725, and 1253 cm^{-1}; ^1H NMR δ 9.76 (br s, 1H), 5.70 (dt, J = 15.3 and 6.6 Hz, 2H), 5.43 (dd, J = 15.3 and 7.8 Hz, 1H), 5.35 (dd, J = 15.3 and 7.8 Hz, 1H), 4.70, 4.66 (ABq, J = 6.9 Hz, 2H), 4.67 (s, 2H), 4.06−3.90 (m, 6H), 3.78−3.48 (m, 6H), 2.53 (m, 2H), 2.39 (m, 2H), 2.10 (m, 2H), 1.90−1.54 (m, 10H), 0.92 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H), and 0.01 (s, 18H). Anal. Calcd for $C_{42}H_{88}O_8Si_4$: C, 61.41; H, 10.03. Found: C, 61.37; H, 9.95.

Alcohol 15. The procedure for diol **8** was followed with 0.30 g (1.4 mmol) of $InCl_3$ in 25 mL of EtOAc, 0.50 g (0.67 mmol) of aldehyde **12**, and 1.0 g (2.0 mmol) of stannane **14** in 10 mL of EtOAc. After extraction and removal of solvent, the residue was purified by flash chromatography (20% EtOAc in hexanes) to give 0.65 g (100%) of alcohol **15** as a colorless oil: $[\alpha]_D$ −17.2 (*c* 1.44, $CHCl_3$); IR (neat) 3476, 2943, 1248, and 1029 cm^{-1}; ^1H NMR δ 5.82−5.65 (m, 3H), 5.41−5.31 (m, 3H), 4.72−4.63 (m, 6H), 4.06−3.91 (m, 7H), 3.78−3.48 (m, 7H), 3.60 (t, J = 6.6 Hz, 2H), 2.31−1.50 (m, 18H), 1.00 (t, J = 7.2 Hz, 3H), 0.97−0.86 (m, 6H), 0.89 (s, 9H), 0.04 (s, 6H), 0.02 (s, 9H), and 0.01 (s, 18H); ^{13}C NMR δ 138.8, 135.1, 135.0, 127.0, 126.9, 124.2, 92.1, 91.9, 81.50, 81.46, 81.3, 80.7, 78.7, 78.6, 72.9, 65.3, 65.4, 62.5, 32.3, 31.8, 28.8, 28.7, 28.0, 27.8, 26.0, 25.4, 18.3, 18.1, 13.5, −1.4, and −5.3. Anal. Calcd for $C_{49}H_{98}O_{10}Si_4$: C, 61.33; H, 10.29. Found: C, 61.33; H, 10.36.

Tosylate 16. The procedure described for bis-tosylate **9** was employed with 0.54 g (0.56 mmol) of alcohol **15** in 10 mL of pyridine and 1.0 g (5.2 mmol) of *p*-TsCl. After extraction and removal of solvent the residue was purified by flash chromatography (15% EtOAc in hexanes) to give 0.57 g (90%) of tosylate **16** as a colorless oil: $[\alpha]_D$ −19.9 (*c* 1.63, $CHCl_3$); ^1H NMR δ 7.79 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 5.75−5.64 (m, 2H), 5.59 (dt, J = 15.3 and 6.6 Hz, 1H), 5.35 (dd, J = 15.3 and 7.8 Hz, 1H), 5.28 (dd, J = 15.3 and 7.8 Hz, 1H), 5.16 (dd, J = 15.3 and 7.8 Hz, 1H), 4.70, 4.67 (ABq, J = 6.6 Hz, 2H), 4.65 (s, 2H), 4.56, 4.46 (ABq, J = 6.9 Hz, 2H), 4.52 (m, 1H), 4.13 (dd, J = 7.5 and 3.0 Hz, 1H), 4.07−3.90 (m, 6H), 3.79−3.40 (m, 6H), 3.60 (t, J = 6.9 Hz, 2H), 2.44 (s, 3H), 2.13−1.54 (m, 18H), 0.96 (t, J = 7.5 Hz, 3H), 0.95−0.85 (m, 6H), 0.89 (s, 9H), 0.04 (s, 6H), and 0.01 (s, 27H). Anal. Calcd for $C_{56}H_{104}O_{12}SSi_4$: C, 60.39; H, 9.41. Found: C, 60.29; H, 9.35.

Triene 17. To a stirred solution of tosylate **16** (0.55 g, 0.49 mmol) in THF (5 mL) under Ar was added $LiBEt_3H$ (1.0 M in THF, 5.0 mL, 5.0 mmol). The resulting solution was stirred at 40 °C for 24 h. The reaction was quenched with saturated NH_4Cl, and Et_2O was added. After separation, the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (10% EtOAc in hexanes, then 20% EtOAc in hexanes) to give 0.38 g (81%) of hydrogenolysis product **17**, along with 50 mg (11%) of alcohol **15**: $[\alpha]_D$ −23.8 (*c* 1.31, $CHCl_3$); ^1H NMR δ 5.75−5.61 (m, 3H), 5.39−5.29 (m, 2H), 5.23 (ddd, J = 15.3, 8.1, and 1.5 Hz, 1H), 4.70, 4.66 (ABq, J = 6.9 Hz, 2H), 4.70, 4.65 (ABq, J = 6.9 Hz, 2H), 4.70, 4.57 (ABq, J = 6.9 Hz, 2H), 4.06−3.90 (m, 7H), 3.79−3.46 (m, 6H), 3.60 (t, J = 6.6 Hz, 2H), 2.13−1.23 (m, 20H), 0.99 (t, J = 7.5 Hz, 3H), 0.96−0.85 (m, 6H), 0.89 (s, 9H), 0.04 (s, 6H), 0.02 (s, 9H), and 0.01 (s, 18H). Anal. Calcd for $C_{49}H_{98}O_9Si_4$: C, 62.37; H, 10.47. Found: C, 62.47; H, 10.33.

TBS Ether 18. In a 25-mL round bottom flask was placed triene **17** (0.36 g, 0.38 mmol), EtOAc (15 mL), and 5% Rh/Al_2O_3 (103 mg, 0.05 mmol). The reaction atmosphere was flushed first with Ar and then with H_2, and then a ballon containing H_2 was affixed to the flask. After being stirred for 12 h, the reaction mixture was filtered through a Celite bed and the filtrate was concentrated. The residue was purified by flash chromatography (10% EtOAc in hexanes) to yield 0.34 g (94%) of hydrogenated product **18** as a colorless oil: $[\alpha]_D$ +29.1 (*c* 1.50, $CHCl_3$); ^1H NMR δ 4.84, 4.71 (ABq, J = 6.9 Hz, 4H), 4.68 (s, 2H), 4.09 (dt, J = 8.1 and 5.7 Hz, 2H), 3.90 (m, 2H), 3.72−3.45 (m, 11H), 1.99−1.23 (m, 32H), 0.97−0.87 (m, 9H), 0.88 (s, 9H), 0.04 (s, 6H), and 0.01 (m, 27H); ^{13}C NMR δ 94.9, 93.5, 81.7, 81.2, 79.3, 77.2, 65.2, 64.9, 63.2, 34.3, 34.2, 32.9, 31.1, 30.2, 28.1, 27.5, 26.0, 25.9, 25.8, 25.6, 25.3, 22.9, 18.3, 18.1, 14.0, −1.4, and −5.3. Anal. Calcd for $C_{49}H_{104}O_9Si_4$: C, 61.97; H, 11.04. Found: C, 62.07; H, 11.14.

Alcohol 19. To a stirred solution of TBS ether **18** (0.32 g, 0.34 mmol) in THF (10 mL) was added TBAF (1.0 M solution in THF; 1.5 mL, 1.5 mmol). The reaction mixture was stirred at rt for 12 h and then concentrated. The residue was purified by flash chromatography (30% EtOAc in hexanes) to give 0.28 g (100%) of alcohol **19** as a colorless oil: $[\alpha]_D$ +31.1 (*c* 1.30, $CHCl_3$); IR (neat) 3484, 2943, and 1055 cm^{-1}; ^1H NMR δ 4.84, 4.71 (ABq, J = 6.9 Hz, 2H), 4.83, 4.71 (ABq, J = 6.9 Hz, 2H), 4.68 (s, 2H), 4.00 (m, 2H), 3.90 (m, 2H), 3.72−3.39 (m, 11H), 1.95−1.30 (m, 32H), 0.97−0.87 (m, 9H), and 0.01 (m, 27H); ^{13}C NMR δ 94.7, 93.3, 81.6, 81.5, 81.1, 79.3, 79.1, 77.1, 65.1, 65.07, 64.9, 62.6, 34.2, 34.0, 32.6, 31.0, 30.9, 30.1, 28.1, 28.0, 27.4, 25.8, 25.7, 25.4, 25.2, 22.8, 18.0, 14.0, and −1.5. Anal. Calcd for $C_{43}H_{90}O_9Si_3$: C, 61.82; H, 10.86. Found: C, 61.77; H, 10.79.

Aldehyde 20. The procedure for aldehyde **12** was followed with oxalyl chloride (0.11 mL, 1.3 mmol) in CH_2Cl_2 (10 mL), DMSO (0.18 mL, 2.5 mmol), and alcohol **19** (0.27 g, 0.32 mmol) in CH_2Cl_2 (2 mL). The product was purified by flash chromatography (15% EtOAc in hexanes) to give 0.25 g (93%) of aldehyde **20** as a colorless oil: $[\alpha]_D$ +33.1 (*c* 1.35, $CHCl_3$); IR (neat) 2951, 1728, and 1038 cm^{-1}; ^1H NMR δ 9.76 (t, J = 1.5 Hz, 1H), 4.84, 4.71 (ABq, J = 6.9 Hz, 2H), 4.83, 4.71 (ABq, J = 6.9 Hz, 2H), 4.68 (s, 2H), 4.00 (m, 2H), 3.90 (m, 2H), 3.72−3.47 (m, 9H), 2.42 (dt, J = 7.5 and 1.5 Hz, 2H), 1.96−1.30 (m, 30H), 0.96−0.87 (m, 9H), and 0.01 (m, 27H); ^{13}C NMR δ 202.3, 94.9, 94.8, 93.4, 81.7, 81.4, 81.2, 79.3, 79.0, 77.1, 65.2, 65.1, 64.9, 43.8, 34.3, 34.0, 31.0, 30.8, 30.1, 28.1, 28.09, 28.0, 27.5, 25.7, 25.3, 22.8, 22.2, 18.0, 14.0, and −1.5. Anal. Calcd for $C_{43}H_{88}O_9Si_3$: C, 61.97; H, 10.64. Found: C, 62.06; H, 10.60.

Vinyl Iodide 21. To a stirred suspension of $CrCl_2$ (0.25 g, 1.9 mmol) in THF (6 mL) was added a solution of aldehyde **20** (0.23 g, 0.28 mmol) and iodoform (0.25g, 0.63 mmol) in 1,4-dioxane (4 mL). The resulting mixture was stirred for 12 h, and Et_2O and H_2O were added. After separation, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (5% of EtOAc in hexanes, then 10% EtOAc in hexanes) to give 0.18 g (69%) of vinyl iodide **21** as a yellow oil: $[\alpha]_D$ +27.8 (*c* 1.63, $CHCl_3$); ^1H NMR δ 6.47 (dt, J = 14.1 and 7.5 Hz, 1H), 5.95 (d, J = 14.1 Hz, 1H), 4.82, 4.68 (ABq, J = 6.9 Hz, 2H), 4.81, 4.68 (ABq, J = 6.9 Hz, 2H), 4.66 (s, 2H), 3.97 (m, 2H), 3.88 (m, 2H), 3.69−3.44 (m, 9H), 2.10−1.23 (m, 32H), 0.96−0.85 (m, 9H), and −0.01 (s, 27H); ^{13}C NMR δ 146.4, 94.8, 93.4, 81.7, 81.5, 81.2, 79.3, 79.1, 77.1, 74.4, 65.2, 65.1, 64.9, 35.9, 34.3, 34.0, 31.1, 30.8, 30.1, 28.5, 28.1, 28.0, 27.5, 25.7, 25.3, 25.0, 22.8, 18.0, 14.0, and −1.5. Anal. Calcd for $C_{44}H_{89}IO_8Si_3$: C, 55.20; H, 9.37. Found: C, 55.37; H, 9.44.

Butenolide 24. To a stirred solution of alcohol **22** (0.33 g, 2.2 mmol) in CH_2Cl_2 (30 mL) at −78 °C under N_2 was added Et_3N (0.75 mL, 5.4 mmol), followed by MsCl (0.30 mL, 3.9 mmol). The reaction mixture was stirred at −78 °C for 1.5 h, and a solution of saturated $NaHCO_3$ was added. The mixture was then warmed to rt, and Et_2O was added. After separation, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give the crude mesylate **23** as a brown oil.

In a round bottom flask under Ar were placed $Pd_2(dba)_3$ (8 mg, 0.009 mmol), PPh_3 (16 mg, 0.061 mmol), and THF (15 mL). The flask was then flushed with CO, and the mixture was stirred for 5 min. The resulting solution was transfered to a Parr reactor containing a mixture of crude mesylate obtained above, H_2O (1.5 mL), and THF (20 mL). The Parr reactor was charged with 200 psi of CO gas. After being stirred for 1 h, the reaction mixture was washed with brine. The aqueous layer was extracted with EtOAc (15 mL). The combined organic layers were dried over $MgSO_4$ and filtered.

To the above filtrate was added 10% $AgNO_3$/silica gel (0.75 g, 0.44 mmol). The resulting mixture was stirred in the dark for 12 h. The solid was removed by filtration. The filtrate was concentrated and purified by flash chromatography (15% EtOAc in hexanes) to give 0.34 g (87% overall) of butenolide **24** as a light yellow oil: $[\alpha]_D$ +43.4 (*c* 1.72, $CHCl_3$); IR (neat) 2934, 1754, and 1090 cm^{-1}; ^1H NMR δ 7.02 (br s, 1H), 5.00 (dq, J = 6.9 and 1.2 Hz, 1H), 2.29 (t, J = 6.9 Hz, 2H), 2.22 (dt, J = 6.9 and 2.4 Hz, 2H), 1.95 (t, J = 2.4 Hz, 1H), 1.74−1.51 (m, 4H), and 1.40 (d, J = 6.9 Hz, 3H). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.09; H, 7.99.

Enyne 25. To a stirred solution of iodide **21** (95 mg, 0.10 mmol) in Et_2NH (5 mL) under Ar were added $(PPh_3)_2PdCl_2$ (7 mg, 0.010 mmol), CuI (6 mg, 0.030 mmol), and butenolide **24** (mg, mmol). The resulting mixture was stirred for 2 h and concentrated. The residue was purified by column chromatography (20% EtOAc in hexanes) to give 96 mg (96%) of enyne **25** as a yellow oil: $[\alpha]_D$ +31.7 (*c* 1.33, $CHCl_3$); IR (neat) 2934, 1763, and 1029 cm^{-1}; ^1H NMR δ 7.02 (m, 1H), 6.04 (dt, J = 15.9 and 6.9 Hz, 1H), 5.44 (dt, J = 15.9 and 1.5 Hz, 1H), 5.00 (m, 1H), 4.85, 4.71 (ABq, J = 6.9 Hz, 2H), 4.84, 4.71 (ABq, J = 6.9 Hz, 2H), 4.68 (s, 2H), 4.00 (m, 2H), 3.91 (m, 2H), 3.72−3.46 (m, 9H), 2.35−2.27 (m, 4H), 2.09−1.25 (m, 36H), 1.41 (d, J = 6.9 Hz, 3H), 0.98−0.88 (m, 9H), and 0.01 (m, 27H). Anal. Calcd for $C_{55}H_{102}O_{10}Si_3$: C, 65.56; H, 10.20. Found: C, 65.30; H, 10.10.

Asiminocin (27). To a stirred solution of 94 mg (0.093 mmol) of enyne **25** and 1.2 g (6.4 mmol) of *p*-toluenesulfonyl hydrazide in 10 mL of dimethoxyethane at reflux was added a solution of 0.60 g (7.3 mmol) of NaOAc in 10 mL of H_2O over a 4-h period. The mixture was then cooled to rt, poured into H_2O, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (20% EtOAc in hexanes) to give 80 mg (85%) of hexahydro product **26** as a colorless oil: $[\alpha]_D$ +29.2 (*c* 1.21, $CHCl_3$); IR (neat) 2925, 1763, and 1064 cm^{-1}; ^1H NMR δ 6.98 (m, 1H), 4.99 (m, 1H), 4.85, 4.71 (ABq, J = 6.9 Hz, 2H), 4.84, 4.71 (ABq, J = 6.9 Hz, 2H), 4.68 (s, 2H), 4.00 (m, 2H), 3.91 (m, 2H), 3.74−3.46 (m, 9H), 2.26 (br t, J = 6.9 Hz, 2H), 1.96−1.25 (m, 49H), 0.97−0.86 (m, 9H), and 0.01 (m, 27H).

A solution of 76 mg (0.075 mmol) of the above product, PPTS (250 mg, 1.0 mmol), and EtOH (10 mL) was stirred at 75 °C for 16 h, cooled to rt, and concentrated under reduced pressure. The residue was purified by flash chromatography (2% MeOH in 7:3 EtOAc:hexanes) to give 38 mg (82%) of asiminocin **(27)** as a colorless oil: $[\alpha]_D$ +19 (*c* 0.82, $CHCl_3$) (lit.[2] +26, but measured on a 1-mg sample in 1 mL of solvent); IR (neat) 3439, 2927, 2853, and 1747 cm^{-1}; ^1H NMR δ 6.98 (q, J = 1.5 Hz, 1H), 4.99 (m, 1H), 3.84 (m, 4H), 3.57 (m, 1H), 3.38 (m, 2H), 2.25 (tt, J = 7.6 and 1.5 Hz, 2H), 1.97−1.25 (m, 46H), 1.39 (d, J = 6.9 Hz, 3H), and 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 173.9, 148.8, 134.3, 83.2, 83.1, 81.8, 77.4, 74.0, 73.9, 71.9, 37.3, 37.1, 33.4, 33.3, 29.7, 29.6, 29.5, 29.3, 29.1, 29.0, 28.3, 27.8, 27.4, 25.6, 25.5, 25.4, 25.1, 22.7, 19.2, and 14.1.

Acknowledgment. This research was supported by Research Grants GM 39998 from the National Institutes of General Medical Sciences and CHE 9220166 from the National Science Foundation. We thank Professor J. L. McLaughlin for the NMR spectra of asiminocin and asiminecin.

Supporting Information Available: Experimental procedures for compounds **2**−**6**, **14**, **22**, and **29**−**41**; ^1H NMR spectra for compounds **2**, **3**, **4**, **6**, **6** (*S*)-mandelate, **6** (*R*)-mandelate, **10**, **14**, **14** (*S*)-mandelate, **14** (*R*)-mandelate, **25**, **26**, asiminocin (**27**), authentic asiminocin, **28**, **29**, **32**, **40**, asiminecin (**41**), **41** (*S*)-MPTA ester, **41**(*R*)-MPTA ester, and authentic asiminecin; ^{13}C NMR spectra of **10**, asiminocin (**27**), authentic asiminocin, asiminecin (**41**) and authentic asiminecin (36 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.

JO970424K