Synthesis of the South Unit of Cephalostatin. 7. Total Syntheses of (+)-Cephalostatin 7, (+)-Cephalostatin 12, and (+)-Ritterazine K[1]

Jae Uk Jeong, Chuangxing Guo,* and P. L. Fuchs*

Contribution from the Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

Received May 18, 1998

Abstract: Transformation of alcohol **4** to α-azidoketone **6**, a hexacyclic steroid bearing the requisite functionality and spiroketal stereochemistry of the symchiral South portion of cephalostatin 7 (**10**) is described. Reaction of a 1:1 mixture of α-azidoketones **5** and **6** with sodium hydrogen telluride is followed by cleavage of the protecting groups cephalostatin 12 (**9**), cephalostatin 7 (**10**), and ritterazine K (**11**).

Introduction

Cephalostatin 7 (**10**)[2] belongs to a family of 43 trisdecacyclic pyrazines, characterized by the groups of Pettit at Arizona State University and Fusetani at the University of Tokyo.[3] Pettit hypothesized that the pyrazine core structure was assembled via dimerization and oxidation of steroidal α-aminoketones, a well-known reaction in the laboratory.[4,5] In the preceding paper,[6] we detailed the conversion of hecogenin acetate **1** to a pair of homoallylic alcohols **3**, **4** (via key aldehyde **2**) and the conversion of the former (**3**) to the North azide **5** (Scheme 1). In this paper we describe the synthesis of the South α-azide **6** from homoallyl alcohol **4**[7] and the completion of the total syntheses of cephalostatin 7 (**10**), cephalostatin 12 (**9**), and ritterazine K (**11**).[1] The South skeleton was found to be one of the most basic assemblies in the cephalostatin/ritterazine family as it is present in 18 out of 43 members.

(1) Cephalostatin Synthesis. 15. Portions of this work have been communicated in Articles 6 and 9 of this series: Jeong, J. U.; Fuchs, P. L. *Tetrahedron Lett.* **1995**, *36*, 2431. Jeong, J. U.; Sutton, S. C.; Kim, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **1995**, *117*, 10157. For additional syntheses of cephalostatin-related pyrazines, see: (a) Pan, Y.; Merriman, R. L.; Tanzer, L. R.; Fuchs, P. L. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 967. (b) Heathcock, C. H.; Smith, S. C. *J. Org. Chem.* **1994**, *59*, 6828. (c) Kramer, A.; Ullmann, U.; Winterfeldt, E. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2865. (d) Ganesan, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 611. (e) Drogemuller, M.; Jantelat, R.; Winterfelt, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1572. (f) Guo, C.; Bhandaru, S.; Fuchs, P. L.; Boyd, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10672. (g) LaCour, T. G.; Guo, C.; Bhandaru, S.; Boyd, M. R.; Fuchs, P. L. *J. Am. Chem. Soc.* **1998**, *120*, 692. (h) Drögemüller, M.; Flessner, T.; Jaulelat, R.; Scholz, U.; Winterfeldt, E. *Eur. J. Org. Chem.* **1998**, 2811.

(2) Pettit, G. R.; Kamano, Y.; Inoue, M.; Dufresne, C.; Boyd, M. R.; Herald, C. L.; Schmidt, J. M.; Doubek, D. L.; Christie, N. D. *J. Org. Chem.* **1992**, *57*, 429.

(3) (a) Pettit, G. R.; Xu, J.-P.; Ichihara, Y.; Williams, M. D.; Boyd, M. R. *Can. J. Chem* **1994**, *72*, 2260 and references therein. (b) Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *J. Org. Chem.* **1997**, *62*, 4484 and references therein.

(4) Pettit, G. R.; Inoue, M.; Kamano, Y.; Herald, D. L.; Arm, C.; Dufresne, C.; Christie, N. D.; Schmidt, J. M.; Doubek, D. L.; Krupa, T. S. *J. Am. Chem. Soc.* **1988**, *110*, 2006.

(5) (a) Edwards, O. E.; Purushothaman, K. K. *Can. J. Chem,.* **1964**, *42*, 712. (b) Doorenbos, N. J.; Dorn, C. P. *J. Pharm. Sci.* **1965**, *54*, 1219. (c) Ohta, G.; Koshi, K. *Chem. Pharm. Bull.* **1968**, *16*, 1487. (d) Wolloch, A.; Zibiral, E. *Tetrahedron* **1976**, *32*, 1289.

(6) Kim, S.; Sutton, S. C.; Guo, C.; LaCour, T. G.; Fuchs, P. L. *J. Am. Chem. Soc.* **1999**, *121*, 2056.

(7) More than 15 g of alcohol **4**, the Stanyl allylation product from the pentacyclic aldehyde **2**, was accumulated during synthesis of the North unit. For detail, see preceding paper.

(8) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.

Table 1. Dihydroxylation of the Olefins **12** and **13**

substrate	conditions	yield (%)	C_{25} nat/epi ratio	
12	Sharpless AD-mix-α, 0 °C, 16 h[10]	40	**16*S*/16*R***	1:2
13	Sharpless AD-mix-α, 0 °C, 16 h[10]	95	**17*S*/17*R***	2.5:1
13	Sharpless AD-mix-*β*, 0 °C, 16 h[10]	95	**17*S*/17*R***	1:2
13	(*S*,*S*)-**15**,[11] −78 °C, 1 h	90	**17*S*/17*R***	1:1.8
13	(*R*,*R*)-**15**,[11] −78 °C, 1 h	90	**17*S*/17*R***	2:1
13	$(DHQ)_2$-PYR,[10] 0 °C, 16 h	90	**17*S*/17*R***	2.5:1

Osmylation of the Terminal Olefin

Deoxygenation of the C_{23} alcohol moiety of homoallyl alcohol **4** was accomplished via xanthate **12** (Scheme 2). Xanthate **12** was highly disposed toward formation of triene **14** since both the C−O and C−H bonds are allylically activated; therefore, the reaction was conducted by rapid addition of **12** and AIBN to a preheated oil bath containing the appropriate tin hydride reagent. Even under these optimized conditions, tributyltin hydride still afforded a mixture of the desired 1,5 diene **13** accompanied by inseparable triene **14**. Fortunately, utilization of the more reactive[8] triphenyltin hydride smoothly provided **13** without a trace of triene **14** (Scheme 2).

Previous studies on osmylation of (*R*)-configured C_{23} TBDPS ethers resulted in stereocontrol at C_{25} with good selectivity.[6,9,10] However, when C_{23} was substituted with (*S*)-configured xanthate **12**, or unsubstituted (**13**), the results were far less satisfactory (Scheme 3 and Table 1). Further indication of the lack of a usable diastereotopic environment without a TBDPS ether at C_{23} was that the inseparable mixture of diols **17*S*/17*R*** gave no indication of being a diastereomeric mixture when assayed by 300 MHz proton and 50 MHz carbon NMR with $CDCl_3$ as solvent. Ultimately, it was discovered that the product ratio could be assessed by 300 MHz NMR in C_6D_6 (**17*S*** = δ 1.01; **17*R*** = δ 1.03). An alternative mode of analysis was via C_6D_6 NMR of the $C_{25,26}$ diphenylsilyl acetonide derivatives **18*S*/18*R*** (Ph_2SiCl_2, Et_3N, CH_2Cl_2, 0 to 25 °C, >90% yield). In this case one proton of the C_{26} methylene AB patterns could be accurately integrated (**18*S*** = δ 3.76; **18*R*** = δ 3.74).

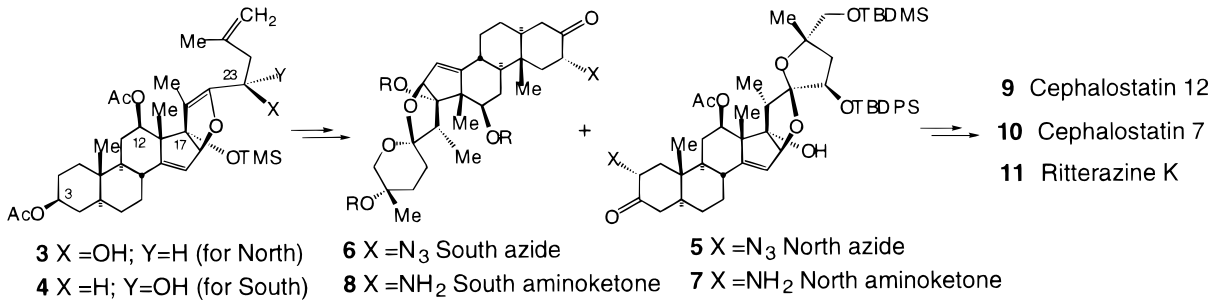
Since (*R*)-configured C_{23} TBDPS ether **19** resulted in a 4:1 ratio of stereocontrol at C_{25},[6] we also investigated osmylation

(9) Jeong, J. U.; Fuchs, P. L. *J. Am. Chem. Soc.* **1994**, *116*, 773.

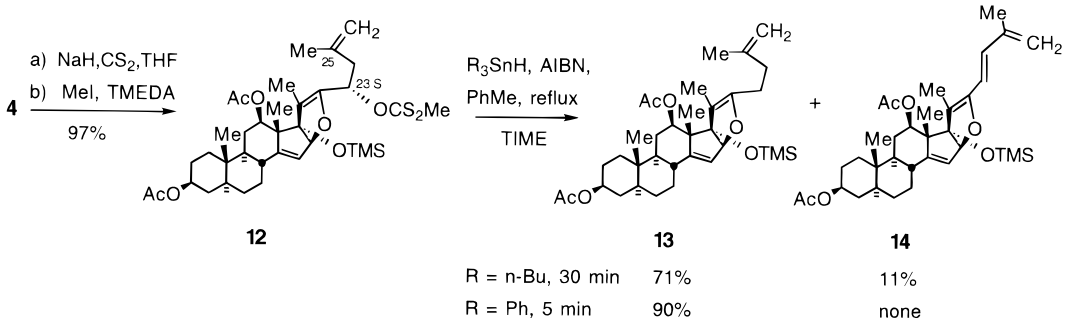
(10) (a) Crispino, G.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785. (b) Kolb, H. C.; VanNieuwenhze, M. S. *Chem. Rev.* **1994**, *94*, 2483.

10.1021/ja9817141 CCC: $18.00
Published on Web 02/24/1999

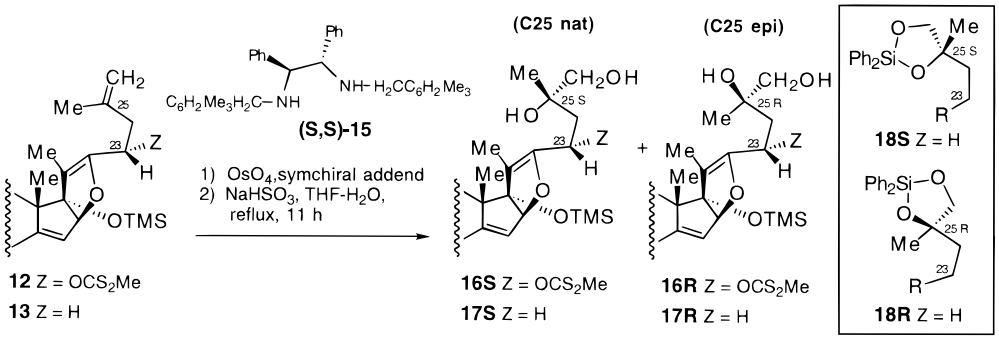
Scheme 1



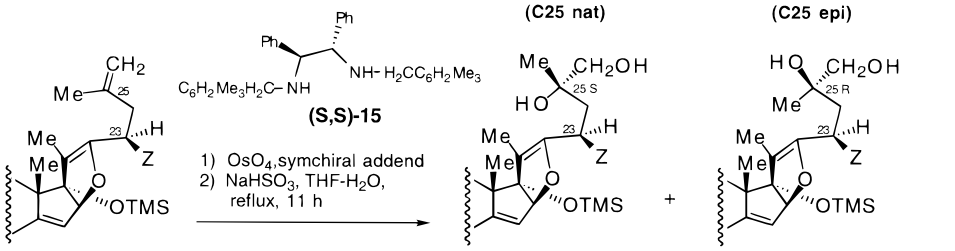
Scheme 2



Scheme 3



Scheme 4



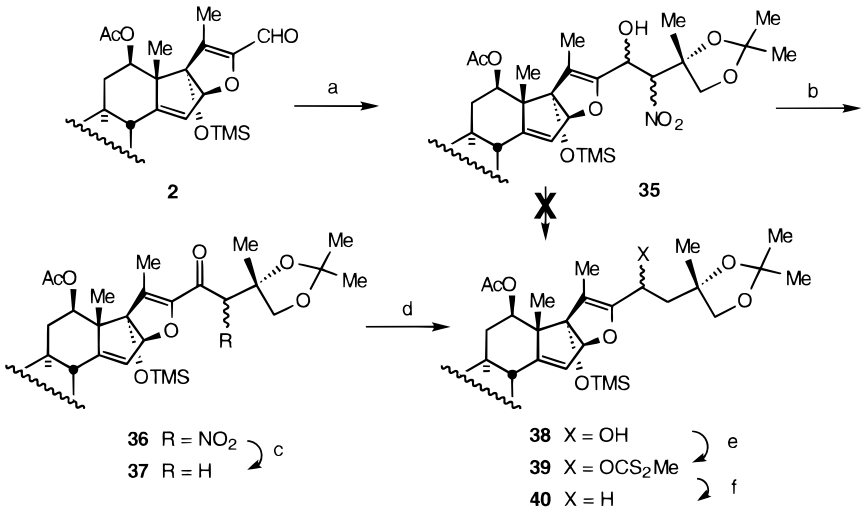
of trityl ether **21**, *p*-methoxybenzoate **23**,[11] and tri(isopropyl)-silyl ether **25**, with a view to later deoxygenation of the C_{23} position (Scheme 4 and Table 2). In the event, these substrates did not afford improved stereospecificity, necessitating consideration of other options for stereocontrol.

(11) (a) Corey, E. J.; Noe, M. C.; Guzman-Perez, A. *J. Am. Chem. Soc.* **1995**, *117*, 10817. (b) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805. (c) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *Tetrahedron Lett.* **1995**, *36*, 3481. (d) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 12109.

The Nitro Aldol Approach to C-25 Stereocontrol

In an effort to avoid the difficulty inherent in osmylation of the terminal olefin, we explored introduction of the C_{25} (*S*) stereocenter starting with optically pure nitroacetonide **34** which was derived from (*S*)-2-methylglycidol **27**.[12] Treatment of acetonide **34** and aldehyde **2** with KF[13] in *i*-PrOH at 25 °C provided an equilibrium mixture of diastereomeric β-nitro alcohols **35** (68%) along with unreacted aldehyde **2** (32%, Scheme 5). Attempts to obtain C_{23} alcohol **38** directly via

Scheme 5



(a) **34**, KF, i-PrOH, 25 °C, 12 h, 68% (32% of **2** recovered); (b) Dess-Martin periodinane, 25 °C, 30 min, quant; (c) Ph_3SnH, AIBN, benzene, reflux, 1 h, 81%; (d) $LiBH_4$, THF, 0 °C, 1 h, 87%; (e) NaH, CS_2, THF, 0 °C, 30 min, and then MeI, TMEDA, 0 °C, 1 h, quant; (f) Ph_3SnH, ACN, toluene, reflux, 20 min, 90%.

Scheme 6

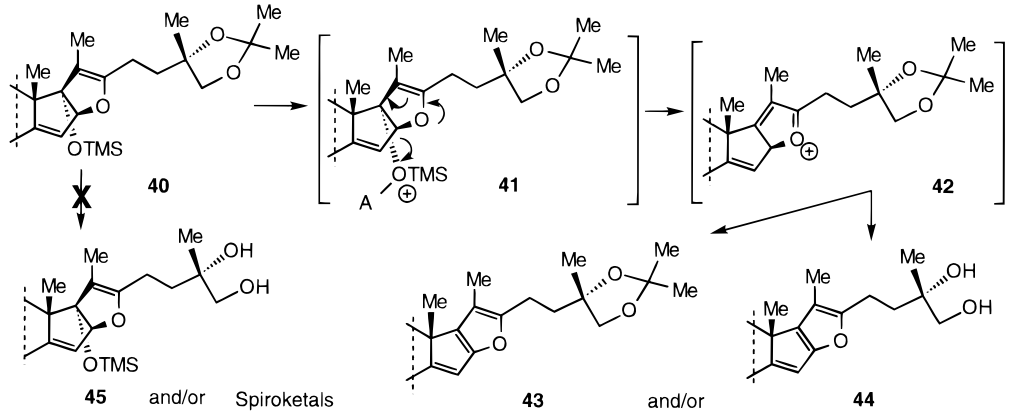


Table 2. Dihydroxylation of Substrates with C_{23} (*R*) Configuration

substrate	conditions	yield (%)	C-25 nat/epi ratio	
13	Sharpless AD-mix-α, 0 °C, 16 h[10]	95	**17*S*/17*R***	2.5:1
19	(*S*,*S*)-**15**,[11] −78 °C, 1 h	95[6]	**20*S*/20*R***	4:1
21	Sharpless AD-mix-α, 0 °C, 4 days	40	**22*S*/22*R***	2.2:1
23	Sharpless AD-mix-α, 0 °C, 16 h	95	**24*S*/24*R***	2.8:1
25	(*S*,*S*)-**15**,[11] −78 °C, 1 h	94	**26*S*/26*R***	3:1

denitration of **35** were unsuccessful, presumably due to the free hydroxy group at C_{23}, but the nitro group was easily removed from α-nitroketone **36** with Ph_3SnH in the presence of AIBN (or ACN) to give ketone **37**. α-Nitroketone **36** can be obtained from *β*-nitro alcohol mixture **35** by the Dess−Martin oxidation.[14]

The target acetonide **40** was prepared from the ketone **37** via reduction to alcohols **38**, preparation of xanthates **39**, followed by deoxygenation to acetonide **40**.

Unfortunately, all attempts to cleave acetonide **40** were uniformly unsuccessful due to the intervention of a Ferrier-type process which readily occurred even under "neutral" conditions providing aromatized furans **43** and/or **44** (Scheme 6).[15] The only reaction condition that gave evidence for diol **45** or spiroketals (not shown) derived therefrom involved DDQ oxidation, but even in that case the aromatization product **43** was the major species observed. Buffered DDQ failed to produce any improvement.

An Alternative Approach Employing *β*-Ketosulfone Chemistry

Since the nitro-aldol approach was unsuccessful, a new scheme involving *β*-ketosulfone chemistry was explored (Scheme 7). The idea was to mask the C_{25} alcohol as a ketone before the spiroketal formation and to create the C_{25} stereochemistry at a

(12) For preparation of **34**, commercially available (*S*)-2-methylglycidol **27** was protected as benzyl ether **28** followed by epoxide opening with LiOH in *t*-BuOH−H_2O at reflux to provide 1,2-diol **29**, which was converted to acetonide **30**. Cleavage of the benzyl ether of **30** by hydrogenation followed by Swern oxidation of the resultant alcohol **31** provided aldehyde **32**. Aldehyde **32** was converted to oxime **33**, which was oxidized to the desired nitroacetonide **34** by using Petrini's protocol (see: Ballini, R.; Marcantoni, E.; Petrini, M. *Tetrahedron Lett.* **1992**, 4835). For experimental procedure, see Supporting Information.

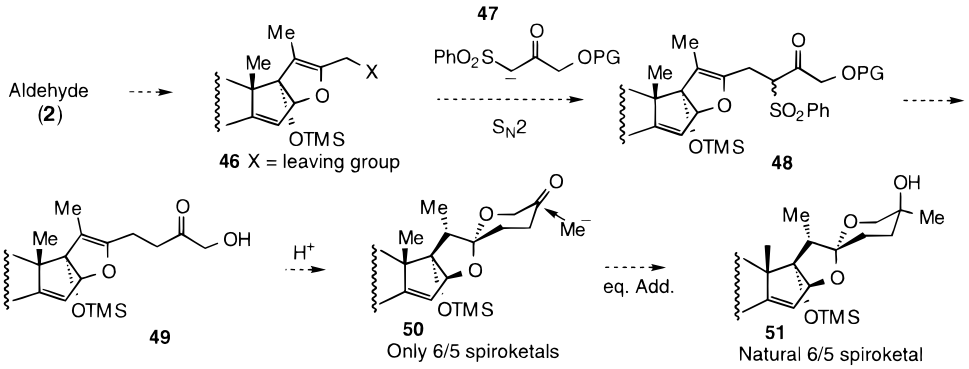
(13) (a) Stevens, R. V.; Beaulieu, N.; Chan, W. H.; Daniewski, A. R.; Takeda, T.; Waldner, A.; Willard, P. G.; Zutter, U. *J. Am. Chem. Soc*. **1986**, *108*, 1039. (b) Williams, T. M.; Mosher, H. S. *Tetrahedron Lett*. **1985**, 6269 and references therein.

(14) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155

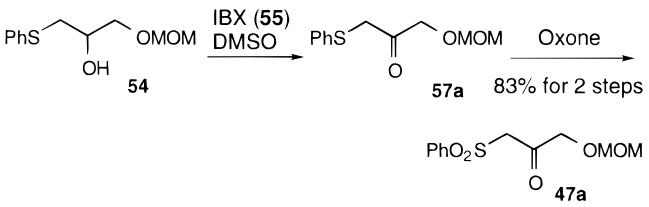
(15) Ireland, R. E.; Meissner, R. S.: Rizzacasa, M. A. *J. Am. Chem. Soc*. **1993**, *115*, 7166 and references therein.

(16) Commercially available glycidol **52** was protected as MOM ether **53**, followed by epoxide opening to give phenyl sulfide **54** (2 steps, 70%) and oxone oxidation to afford sulfone **56** (90%). In our initial attempt, oxidation of the hydroxyl in **56** was found to be problematic. For experimental procedure, see Supporting Information.

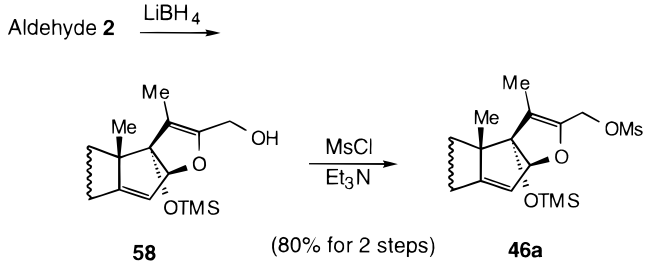
Scheme 7



Scheme 8



Scheme 9



later stage. The β-ketosulfone **47a** was prepared from glycidol **52** (Scheme 8).[16] The β-hydroxysulfide **54** was chemoselectively oxidized to β-ketosulfide **57a** upon treatment of *o*-iodoxybenzoic acid (IBX, **55**) in DMSO.[17] The desired side chain **47a** was obtained in 84% yield (for two steps) when sulfide **57a** was oxidized by oxone (3 equiv).[18] The 1,2-reduction of pentacyclic aldehyde **2** and mesylation of the resultant alcohol **58** proceeded smoothly (Scheme 9).

Attempts to install β-ketosulfone side chain **47a** by S_N2 reaction of mesylate **46a** were unsuccessful, even though the model study demonstrated that the methyl 4-methoxyacetoacetate anion **59** could add to mesylate **46a** to give the desired product **60** in 60% yield when heated in THF at reflux (Scheme 10). Mesylate **46a** was transformed to iodide **46b**. The same reaction conditions (THF/reflux) only led to faster decomposition. Since the substitution reaction was thought to be of the S_N2 type, DMSO was employed as the reaction solvent to facilitate the substitution.[19] Even though mesylate **46a** again showed no reaction, iodide **46b** smoothly reacted with β-ketosulfone anion **47a** within 30 min at room temperature to give the desired adduct **61** in 86% yield.

After the ketosulfone side chain was installed, desulfonylation was achieved by SmI_2 reduction at −78 °C (Scheme 11).[20] Significant amounts (33%) of overreduced product **63** formed when excess SmI_2 (5 equiv) was used. Attempts to remove the MOM group in **62** were fruitless because Ferrier type elimination again intervened.

Therefore, the MOM group was replaced with the benzyl group, which can be removed by hydrogenation under neutral conditions. Fortunately, the technology developed for the MOM series could be successfully employed on the benzyl protected series (Scheme 12). The benzyl ether side chain **47b** was prepared in good yield via alcohol **66** with use of the same four-step sequence. Under optimized conditions, C_{26} benzyl ether **67** was obtained from the S_N2 reaction in 91% yield. For the subsequent desulfonylation, a smaller excess of SmI_2 (3 equiv) was used, compared to the desulfonylation of MOM ether **61**. The desired benzyl ether **68** was obtained in 86% yield while the formation of over-reduced ketone **63** was substantially decreased (<10%). The key debenzylation (H_2/Pd-C) afforded the C_{26} alcohol **49** in 99% yield as expected.

Unfortunately, acid-catalyzed spiroketal formation proved to be unexpectedly problematic (Scheme 13 and Table 3).[9,21] The C_{25} ketone in **49** makes the proximate hydroxyl less nucleophilic, and increases the rigidity in the resultant six-membered ring. The best conditions employed camphor-sulfonic acid (CSA) in benzene which slowly provided the desired 6,5-spiroketal **55** in 33% yield (80% based on recovered **49**).

With the C_{25} ketone **50** in hand, the diastereoselective addition of methyl anion was tested. According to an MM2 calculation (CAChe 3.7), the most stable conformation (2.8 kcal/mol lower than the second most stable conformation) of ketone **50** is as shown in Schemes 13 and 14. Therefore, equatorial attack of methyl should give the desired stereochemistry at C_{25}. In the case of 4-*tert*-butylcyclohexanone **69**, the addition of Me_2CuLi[22] or MeLi with $LiClO_4$[23] proceeded mainly through equatorial addition providing the axial alcohol with good selectivity (>92:8). However, all the trials on C_{25} ketone **50** with different methyl anion reagents afforded predominantly the undesired equatorial alcohol (Scheme 14). The observed selectivity may be due to the directing effect of the C_{26} oxygen, which chelates with metal ion and induces axial addition of methyl anion.

Establishment of the 6,5-Spiroketal

Concurrent with the above two approaches, we moved forward with the mixture of the diastereomeric C_{25} diols **17*S*/17*R***. Treatment of the inseparable **17*S*/17*R*** mixture with

(17) (a) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272. (b) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.

(18) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.

(19) Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry*, 3rd ed.; Plenum Press, 1990; Part A, 5.5, p 284.

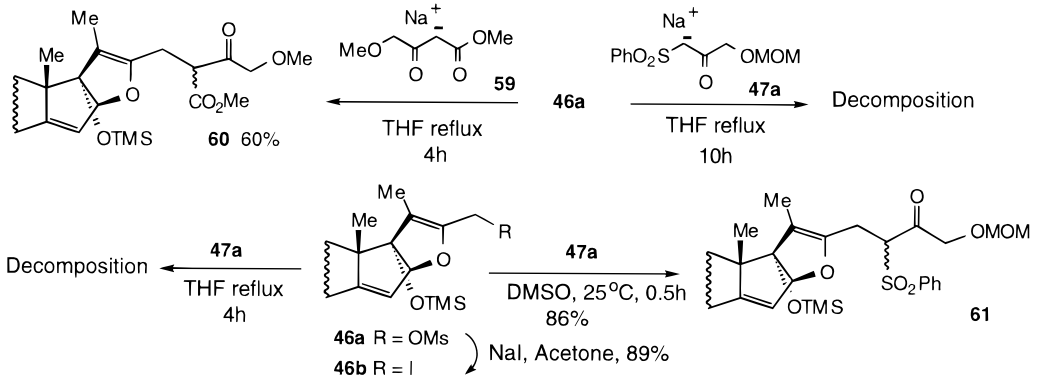
(20) (a) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135. (b) Kunzer, H.; Stahnke, M.; Sayyer, G.; Wiechert, R. *Tetrahedron Lett.* **1991**, *32*, 1949.

(21) Williams, D. R.; Jass, P. A.; Gaston, R. D. *Tetrahedron Lett.* **1993**, *34*, 3231.

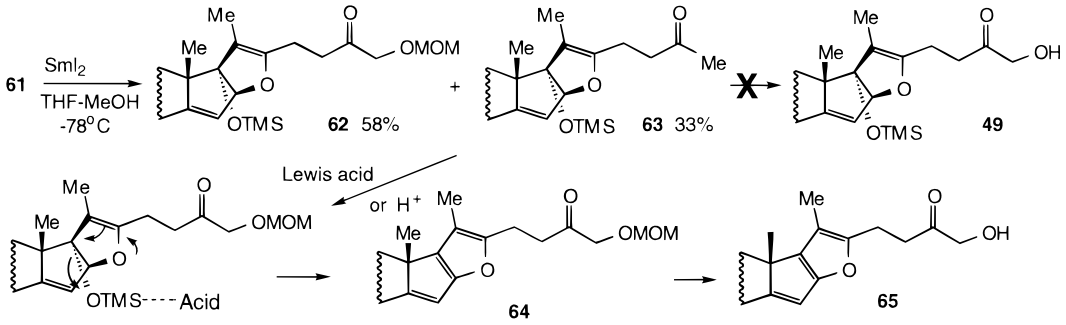
(22) Macdonald, T. L.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *97*, 5280.

(23) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4371.

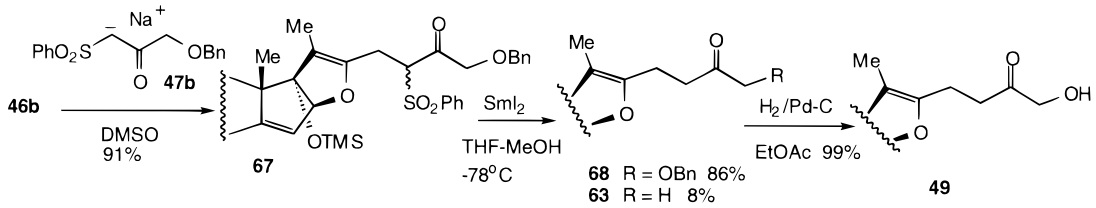
Scheme 10



Scheme 11



Scheme 12



Scheme 13

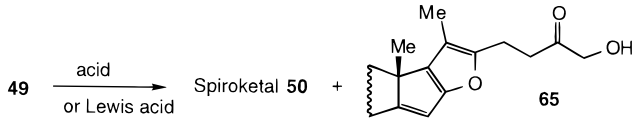


Table 3. Optimization of Spiroketal Formation

entry	reagent/conditions	result	ref
1	(+)-CSA(cat.) in CH_2Cl_2, RT, 3.5 h	**50** (30%), **65** (25%) and **49** (25%)	9
2	(+)-CSA(cat.) in Et_2O, RT, 1 h	NR	9
3	(+)-CSA(cat.) in CH_3CN, RT, 1 h	**65** (major), **49** (trace)	9
4	(+)-CSA(cat.) in THF, RT, 0.5 h	**65** (25%), **49** (70%)	9
5	(+)-CSA(cat.) in benzene, RT, 3.5 h	**50** (33%), **65** (15%) and **49** (47%)	9
6	PPTs (cat.) in benzene, RT, 2 h	NR	9, 21
7	PPTs (cat.) in MeOH, RT, 1 h	NR	9
8	silica gel in benzene, RT, 2 days	NR	
9	CF_3CO_2H (10 equiv) in Et_2O, 0 °C, 1 h	decomposition	21
10	CF_3SO_3H (cat.) in Et_2O, −78 °C, 1 h	**65** (40%), **49** (50%)	21

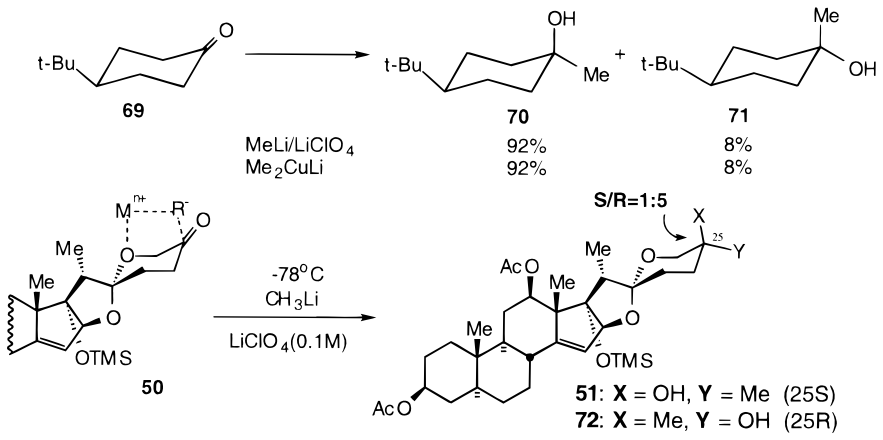
camphorsulfonic acid (CSA) in methylene chloride provided a *new inseparable mixture containing three major components* in roughly equal amounts as assayed by NMR (Scheme 15). Silylation of the new mixture with TBDMS-Cl followed by chromatography afforded a pure sample of the South spiroketal **51** (27% in three steps from **13**). Bis-deprotection of this material with TBAF in THF at reflux for 3 h yielded a sample of triol **76**, whose structure was secured by X-ray crystallography.[24] Similar deprotection of the remaining inseparable binary mixture of ***S*-74**/***R*-74** provided individual samples of triols ***S*-75** (21% for five steps from **13**) and ***R*-75** (19% in five steps from **13**) after chromatographic separation. The stereochemistry of both ***S*-75** and ***R*-75** was also unambiguously determined by X-ray analysis.[24] The resultant 1:1 ratio for the mixture of **51** and ***S*-73** is consistent with molecular mechanics calculations,[25] since these isomers are predicted to have steric energies within 0.1 kcal/mol. Similar calculations predict the formation of a 0.8 kcal/mol less stable, 6,5-spiroketal (25*R*) diastereomer of **51** (not shown). A small quantity of this minor isomer may have been lost during the chromatographic separation.

In addition to providing authentic samples of the above three spiroketals, this study revealed an interesting reversal in selectivity for acetate cleavage. As we previously observed,[6] when C_{17} is present as a TMS ether (**51**) treatment with potassium bicarbonate in 4:1 methanol/water smoothly resulted in exclusive deprotection of the less-hindered C_3 acetate moiety, giving C_3 alcohol **77** (Scheme 16). However, the fluoride-mediated cleavage reactions described above resulted in desilylation with concomitant scission of the adjacent C_{12} acetoxy moiety, yielding triol **76**. Presumably this reaction involved

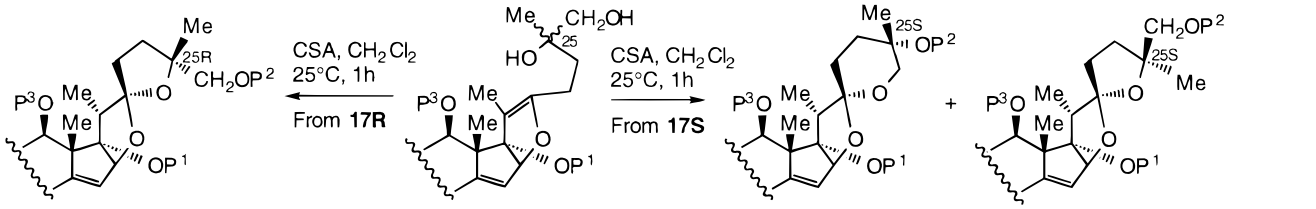
(24) X-ray structural information relating to compounds **76**, ***S*-75**, and ***R*-75** can be obtained from the Cambridge Crystallographic Data Centre.

(25) Calculations were performed using a Tektronix CAChe v3.5. For additional examples of using molecular mechanics for prediction of spiroketal thermodynamics, see ref 8.

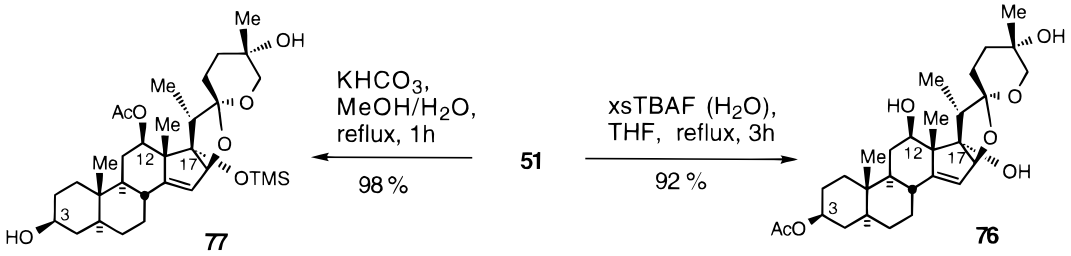
Scheme 14



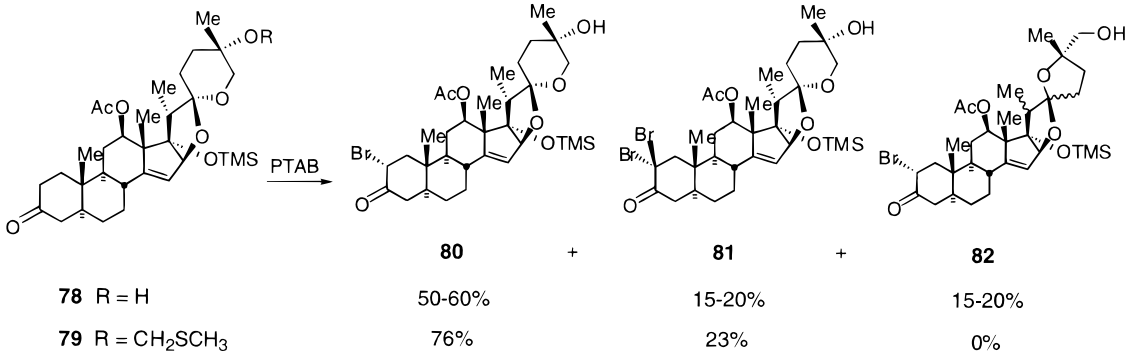
Scheme 15



Scheme 16



Scheme 17



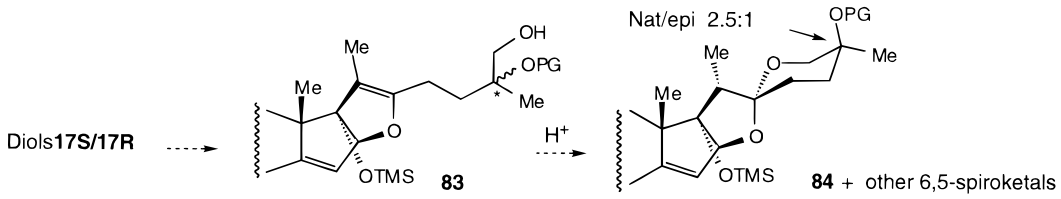
activation of the C_{12} ester via intramolecular hydrogen bonding from the proximal C_{17} alcohol followed by nucleophilic deacylation.

Oxidation of C_3 alcohol **77** by the Brown variant of the Jones oxidation[26] afforded ketone **78** in 91% yield (Scheme 17). Reaction of **78** with phenyltrimethylammonium tribromide (PTAB) in THF at 0 °C for 10 min provided C_2 bromide **80** in 50−60% yield along with the 2,2′-dibromide **81** and the C_2 bromide bearing a 5,5-spiroketal **82** resulting from acid-catalyzed rearrangement of the South 6,5-spiroketal. To prevent acid-catalyzed rearrangement, C_{25} alcohol **78** was treated with DMSO and acetic anhydride[27] at 25 °C for 19 h to provide methylthiomethyl ether **79** in quantitative yield. Bromination of ketone **79** with PTAB (1.3 equiv) in THF at 0 °C for 20 min

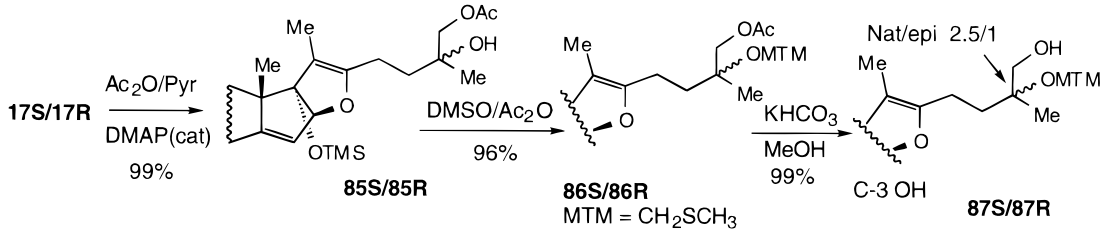
(26) Brown, H. C.; Garg, C. P.; Liu, K.-T. *J. Org. Chem.* **1971**, *36*, 387.

(27) Pojer, P. M.; Angyal, S. J. *Aust. J. Chem.* **1978**, *31*, 1031.

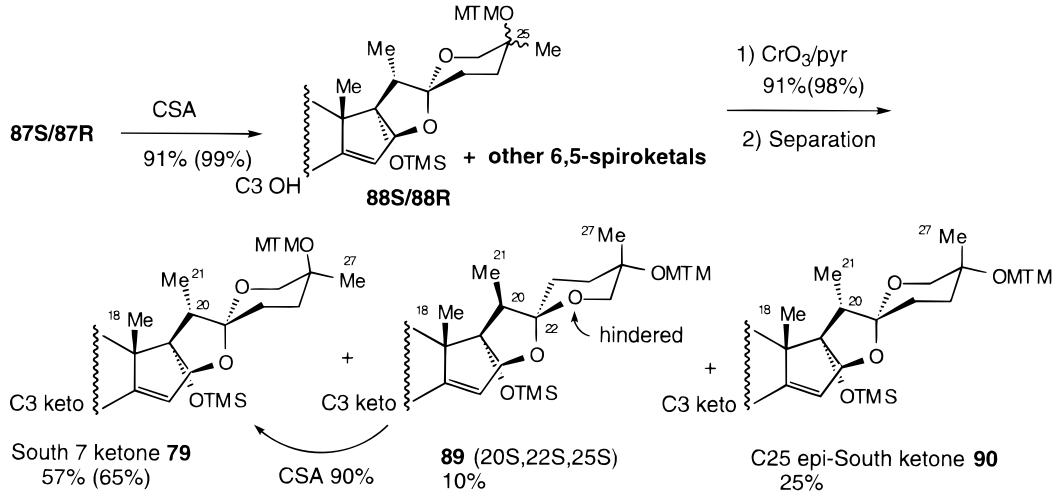
Scheme 18



Scheme 19



Scheme 20



afforded a 76% yield of South bromoketone **80**, which had suffered concomitant C_{25} deprotection without the intervention of any acid-catalyzed rearrangement to **82**.

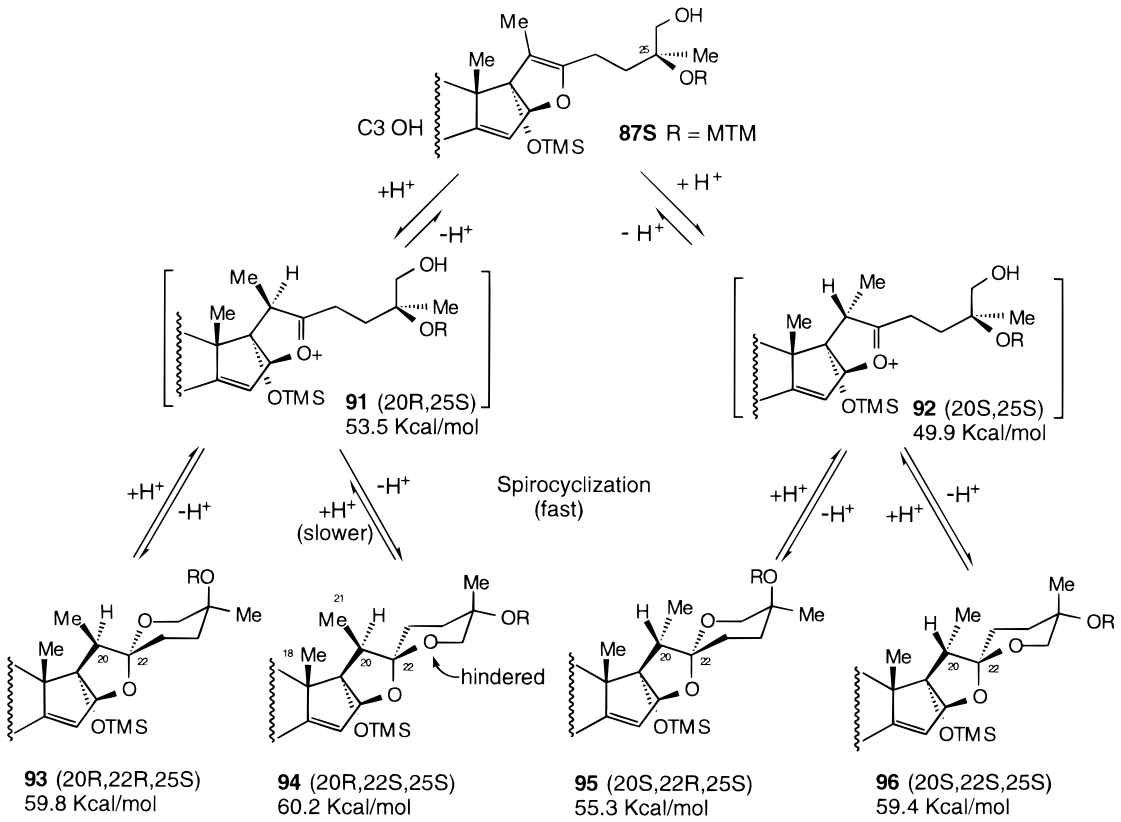
Final Optimized Scheme for Synthesis of the South Steroid Unit

After two failed attempts at improving the C_{25} stereospecificity, we focused on avoiding the undesired 5,5-spiroketal formation. The scheme started with diol mixture **17*S*/17*R*** and involved protection of the C_{25} alcohol before cyclization (Scheme 18). To mask the hindered tertiary alcohol at C_{25}, a variety of protecting groups including acetate, MTM, and silyl groups were surveyed. The MTM group could be introduced in high yield and was expected to exhibit reasonable stability in the upcoming (acidic) spiroketalization reaction (Scheme 19). Therefore, The primary C_{26} alcohol in **17*S*/17*R*** was selectively acylated in the presence of the tertiary alcohol in nearly quantitative yield. The MTM group was then affixed to the C_{25} alcohol affording **86*S*/86*R*** (97%). The C_3, C_{26} acetates were cleaved with alkali hydrolysis to give a mixture of diols **87*S*/87*R*** in 99% yield.

With the C_{25} alcohol blocked by the MTM group, only 5/6 spiroketals (mainly **88*S*/88*R***) were produced (91% yield plus 9% SM) as an inseparable mixture upon treatment of camphorsulfonic acid (CSA) in CH_2Cl_2 (1 h). Limited reaction time was given to avoid the possible complication of Ferrier type elimination at C_{17}, therefore full equilibrium between the spiroketals (**88*S*/88*R***) was not established at this stage (Scheme 20). Chemoselective oxidation of the C_3 alcohol was next investigated in hopes of separation of the spiroketals. Both Swern oxidation[28] and IBX oxidation[17] failed to achieve the desired transformation although the literature reports cases where an alcohol was oxidized in the presence of a thioether moiety. Fortunately, the C_3 alcohol could be chemoselectively oxidized to ketone in 91% yield (7% SM recovered) upon treatment with pyridine−CrO_3 for 5 min. To our surprise and delight, three different 5/6 spiroketals were successfully isolated from the mixture (C_3 ketone) by column chromatography. They are the desired South 7 spiroketal **79** (57%), the C_{25} (*R*) spiroketal **90** (25%), and spiroketal **89** (10%), which can be converted to the desired **79** in 90% yield when treated with CSA. The final yields of spiroketals **79** and **90** were 65 and 25%, respectively. The stereochemical assignment of spiroketal **90** is based on the fact that **90** is the only major isomer (25%) that cannot be converted into the natural spiroketal **79**. Thermodynamic product (**90**) should adopt the most stable configuration (optimized by MM2) of the C_{25} (*R*) epimer as shown in Scheme 22. On the other hand, the structure of spiroketal **89**, which has a natural configuration at C_{25} (*S*), was proposed by comparing the three methyl resonances (C_{18}, C_{21}, C_{27}) in the proton NMR (C_6D_6)

(28) Williams, D. R.; Klingler, F. D.; Dabral, V. *Tetrahedron Lett.* **1988**, *29*, 3415.

Scheme 21



Scheme 22

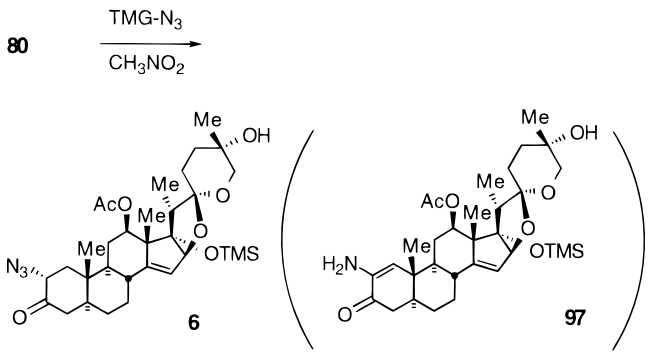


Table 4. Proton NMR Resonances in C_6D_6 (ppm)

compound	C-18 (s)	C-21 (d)	C-27 (s)
MTM ether **79** (20*S*,22*R*,25*S*)	0.77	1.11	1.12
MTM ether **90** (20*S*,22*R*,25*R*)	0.80	0.97	1.36
MTM ether **89** (20*R*,22*S*,25*S*)	1.22	0.91	1.33
alcohol **51** (20*S*,22*R*,25*S*)	1.14	1.05	1.00
alcohol **72** (20*S*,22*R*,25*R*)	1.11	1.00	1.13

of **79**, **90**, **89**, **51**, and **72** (Table 4). The chemical shift (1.22 ppm) of methyl-18 of **89** is 0.45 ppm further downfield than that of naturally configured **79** (0.77 ppm), indicating a $C_{20}\beta$ stereochemistry in **89**. A similar chemical shift change (0.62 ppm, Table 4, preceding paper) of methyl-18 was observed between the North 1 pentaol (compound **92**α, preceding paper) and its C_{20} epimer (compound **92**β, preceding paper). The chemical shift (1.33 ppm) of methyl-27 of **89** is 0.22 ppm more downfield than that of **79** (1.12 ppm), suggesting an axial methyl-27 in **89**. A similar chemical shift difference of methyl-27 can be found between **79** and **90** and between the C_{25} alcohols **51** and **72**. According to MM2 calculations, the chair conformations shown in Scheme 22 are at least 1 kcal/mol more stable than the alternative chair conformations. Therefore, the C_{22} of **89** bears an *S*-configuration if methyl-27 is axial.

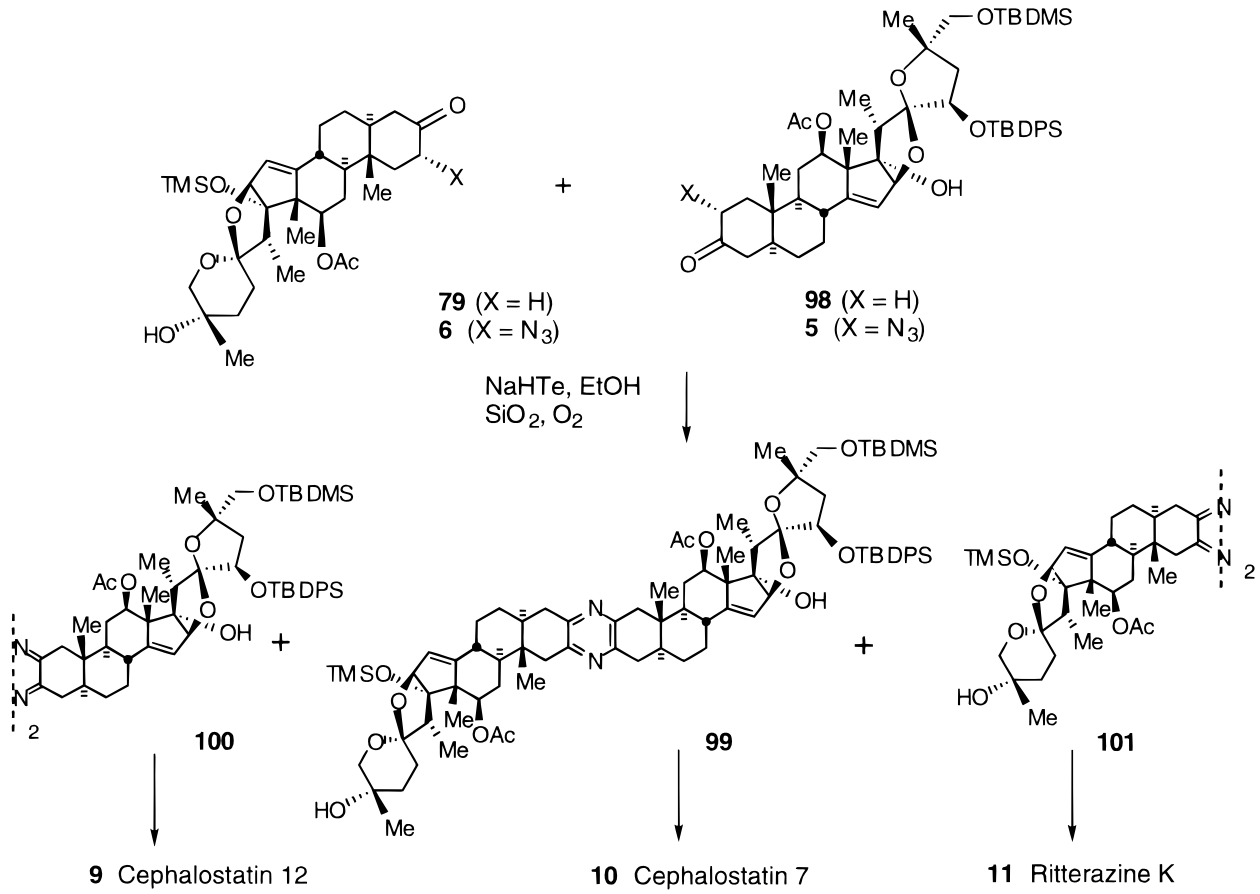
In the key acid-catalyzed spiroketal formation step (Scheme 21), protonation of $C_{20,22}$ enol ether occurs principally from the α-face, affording oxonium ion **91** (20*R*,25*S*). The kinetically unfavorable but thermodynamically more stable oxonium ion **92** (20*S*,25*S*) leads to the desired spiroketal **95** (20*S*,22*R*,25*S*) which is calculated to be 4.1 kcal/mol more stable than spiroketal **96** (20*S*,22*S*,25*S*).[29] The desired spiroketal **95** (20*S*,22*R*,25*S*) was the major product after equilibration at 25 °C for 1 h, which indicates that reversable deprotonation of C_{20} in oxonium ions **91**/**92** is facile under these conditions, and intermediates **91**/**92** readily interconvert via the enol ether **87*S***. The oxonium ion with a 21α-methyl (**92** (20*S*,25*S*)) was calculated to be favored by 3.6 kcal/mol because the 21β-methyl in **91** (20*R*,25*S*) interacts with the 18-methyl. Therefore, the natural spiroketal **95** (20*S*,20*R*,25*S*), whose energy is more than 4.1 kcal/mol lower than any other epimers at C_{20} and/or C_{22}, is the predominant product upon treatment of acid. Interestingly, the equibration process in the 17-deoxy analogues[30] requires elevated temperature (80 °C). The presence of the C_{17} TMS ether group not only makes the α-face of the $C_{20,22}$ enol ether less accessible to the attack of a proton, but more importantly, apparently inductively increases the acidity of the C_{20} methine poton in the oxonium ions (**91**/**92**).[31] The isomerization of **89** (or **94**) to form the natural **79** (or **95**) was slower than that for the other isomers. This is presumably due to steric retardation (21β-methyl) of the acid-catalyzed spiroketal opening.

(29) MM2 calculation was performed using CAChe v.3.7.

(30) Jeong, J. U.; Fuchs, P. L. *Tetrahedron Lett.* **1994**, *35*, 5385.

(31) Equilibration between kinetically favored **93**/**94** and more stable **95** involves the enol ether **87*S***. Its formation, the elimination of the C_{20} methine proton was believed to be the slowest step in the proposed mechanism.

Scheme 23



In the final improved scheme, the overall yield from diol **17*S*/17*R*** to the ketone **79** was doubled (from 25 to 54%) without adding more steps compared to the earlier synthetic route (Schemes 4, 17).

Completion of the synthesis of the South α-azidoketone **6** involved reaction of α-bromoketone **80** with 4 equiv of tetramethylguanidinium azide (TMGA) in nitromethane at 25 °C for 4 h (Scheme 22). This solvent was the key to avoiding competitive decomposition (to **97**) of the initially formed α-azidoketone **6**. In this instance, the isolated yield of **6** was 95% with nitromethane,[6,32] as compared to 30−40% along with 60−70% of α-aminoenone **97** (via base-catalyzed nitrogen elimination from **6**) when employing acetonitrile or dichloromethane as the reaction solvent.

Pyrazine Synthesis

The total synthesis of cephalostatin 7 (**10**) involved in situ reduction of α-azidoketones **5** and **6** to α-aminoketones **7** and **8** followed by statistical combination to produce cephalostatins 7 (**10**) and 12 (**9**) and ritterazine K **11** (Scheme 1). Pyrazine formation was accomplished by treating a 1:1 mixture of α-azidoketones **5**[6a] and **6**[6b] in ether with 6 equiv of ethanolic NaHTe[33] for 1 h at 25 °C, followed by adding silica gel as a mild acid catalyst and allowing the mixture to stir in ethyl acetate while exposed to the air for 18 h. Chromatography of the reaction mixture afforded the protected pyrazines **99**, **100**, and **101** in 35, 14, and 23% isolated yields, respectively. Azide-cleaved ketones **79** and **98** were recovered in 36 and 15% yields from this reaction. Individual treatment of protected **99**−**101** with TBAF (15 equiv) in THF at reflux for 3 h provided the first synthetic samples of cephalostatin 7 (**10**), cephalostatin 12 (**9**), and ritterazine K (**11**), each in approximately 80% yield (Scheme 23). Samples of each of the three synthetic materials were provided to Pettit at Arizona State, who confirmed the identity of cephalostatins 7 and 12 by direct NMR and chromatographic comparison.[34] Pyridine-d_5 proton and carbon NMR data for compound **11** are identical with those reported by Fusetani for natural ritterazine K.[35]

Conclusion

The "one pot" syntheses of cephalostatin 7 (**10**), cephalostatin 12 (**9**), and ritterazine K (**11**) were the first synthetic preparations of these materials. The sequence also provided a sufficient quantity of the steroidal units for the preparation of other cephalostatins and ritterazines. Since cephalostatin 7 (**10**) and cephalostatin 1 share the same North half, this work also paved the way to the first total synthesis of cephalostatin 1,[1f,g] the most potent member in this family.

Experimental Section

General Procedures. See the preceding paper.

C_2 Azide 6. To a solution of bromide **80** (25 mg, 0.038 mmol) in CH_3NO_2 (2 mL) was added TMGA[32] (24 mg, 0.153 mmol) at 25 °C. The reaction mixture was stirred for 4 h. After concentration, the residue

(32) (a) Li, C.; Arasappan, A.; Fuchs, P. L. *Tetrahedron Lett.* **1993**, *34*, 3535. (b) Li, C.; Shih, T.-L.; Jeong, J. U.; Arasappan, A.; Fuchs, P. L. *Tetrahedron Lett.* **1994**, *35*, 2645.

(33) Suzuki, H.; Kawaguchi, T.; Takaoka, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 665.

(34) We are extremely grateful to Professor G. R. Pettit and Dr. Jun-Ping Xu of Arizona State for comparisons of synthetic cephalostatins 7 (**10**) and 12 (**9**) with the natural materials.

(35) Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *Tetrahedron* **1995** *51*, 6707.

was purified by flash column chromatography on silica gel (1:6 EtOAc/hexanes) to provide 23 mg (96%) of azide **6**: $R_f = 0.16$ (1:3 EtOAc/hexanes); ^{1}H NMR (C_6D_6, 300 MHz) δ 0.31 (s, 9H), 0.32 (s, 3H), 0.98 (s, 3H), 1.03 (d, $J = 7.2$ Hz, 3H), 1.12 (s, 3H), 1.80 (s, 3H), 3.14−3.28 (m, 2H), 3.75 (d, $J = 11.1$, 1H), 4.78 (d, $J = 2.2$ Hz, 1H), 5.16 (dd, $J = 11.7$, 4.6 Hz, 1H), 5.33 (t, $J = 2.3$ Hz, 1H); ^{13}C NMR (C_6D_6, 75 MHz) δ 2.3*, 9.1*, 11.3*, 19.8*, 20.7*, 25.1*, 26.9, 27.4, 28.2, 28.7, 32.6, 33.9*, 36.2, 43.0, 44.2, 44.9*, 46.7*, 49.5*, 56.3, 63.0*, 65.9, 68.9, 73.3*, 89.9*, 93.2, 107.7, 117.6*, 158.2, 168.9, 202.8; MS (EI) 615 $(M)^+$; HRMS (EI) calculated for $C_{32}H_{49}N_3O_7Si$ 615.3340, found 615.3321.

Cephalostatin 12 (9), Cephalostatin 7 (10), and Ritterazine K (11). Individual samples of protected pyrazines **99**, **100**, and **101** with 15 equiv of TBAF in THF were heated at reflux for 1−3 h. After removing THF, the residue was dissolved in EtOAc. The organic layer was washed with saturated aqueous NH_4Cl (×2) and brine and dried over $MgSO_4$. After filtration and evaporation, the residue was subjected to silica gel chromatography to give cephalostatin 12 (**9**) and ritterazine K (**11**) each in approximately 80% yield. Cephalostatin 7 (**10**) was chromatographed on prep TLC (1:3 EtOAc/hexanes).

Cephalostatin 7 (10): $R_f = 0.38$ (1:10 MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 0.59 (3H, s), 0.61 (3H, s), 0.90 (3H, s), 1.00 (3H, d, $J = 6.9$ Hz), 1.03 (3H, d, $J = 6.9$ Hz), 1.18 (3H, s), 1.19 (3H, s), 1.29 (3H, s), 2.4−2.7 (2H, m), 2.85−3.2 (3H, m), 2.44 (1H, s), 3.70 (1H, d, $J = 11$ Hz), 3.76 (1H, s), 3.97 (1H, s), 4.08 (1H, dd, $J = 12.0$, 5.2 Hz), 4.48 (1H, s), 4.82 (1H, s), 4.89 (1H, s), 5.39 (1H, s), 5.46 (1H, s). MS (FAB, NBA) 929 $(M + H)^+$; HRMS (FAB, NBA) calculated for $C_{54}H_{76}N_2O_{11}$ 929.5527, found 929.5518. $[\alpha]^{23}_D$ +97 ± 10° (*c* 0.03, MeOH); lit.[2] $[\alpha]_D$ +106° (*c* 0.244, MeOH).

Cephalostatin 12 (9): $R_f = 0.36$ (1:10 MeOH/CH_2Cl_2);^{1}H NMR (300 MHz, C_5D_5N) δ 0.73 (6H, s, H_{19}), 1.33 (6H, s, H_{18}), 1.35 (6H, d, $J = 7.2$ Hz, H_{21}), 1.64 (6H, s, H_{27}), 2.35 (2H, $J = 11.4$, H_{24a}), 3.07 (2H, d, $J = 16.8$ Hz, H_{1b}), 3.71 (2H, dd, $J = 11.4$, 4.8 Hz, H_{26a}), 3.81 (2H, dd, $J = 11.2$, 4.6 Hz, H_{26b}), 4.04 (2H, dd, $J = 11.2$, 4.6 Hz, H_{12}), 4.71 (2H, br s, 12OH), 4.80 (2H, m, H_{23}), 5.24 (2H, s, H_{16}), 5.63 (2H, s, H_{15}), 6.25 (2H, s, H_{17}), 6.60 (2H, br s, H_{26}), 8.12 (2H, d, $J = 7.6$ Hz, 23OH). MS (FAB, NBA) 945 $(M + H)^+$; HRMS (FAB, NBA) calculated for $C_{54}H_{76}N_2O_{12}$ 945.5477, found 945.5411. $[\alpha]^{23}_D$ +151 ± 10° (*c* 0.025, MeOH); lit.[36] $[\alpha]_D$ +157.5° (*c* 0.40, MeOH).

Ritterazine K (11): $R_f = 0.42$ (1:10 MeOH/CH_2Cl_2);^{1}H NMR (300 MHz, C_6D_6) δ 0.61 (6H, s, H_{19}), 0.93 (6H, s, H_{27}), 1.02 (6H, d, $J = 6.9$ Hz, H_{21}), 1.19 (6H, s, H_{18}), 2.53 (2H, d, $J = 16.8$ Hz, H_{1b}), 2.62 (2H, dd, m, H_{4b}), 2.92 (2H, dd, $J = 17.8$, 5.1 Hz, H_{4a}), 3.03 (2H, br d, $J = 11.4$ Hz, H_{26b}), 3.17 (2H, d, $J = 16.8$ Hz, H_{1a}), 3.49 (2H, s, OH), 3.72 (2H, d, $J = 11.3$ Hz, H_{26a}), 3.98 (2H, s, OH), 4.07 (2H, dd, $J = 11.6$, 5.1 Hz, H_{12}), 4.91 (2H, s, H_{16}), 5.40 (2H, s, H_{15});^{13}C NMR (75 MHz, C_6D_6) δ 8.2 (C_{21}), 11.8 (C_{19}), 13.0 (C_{18}), 27.0 (C_{27}), 27.7 (C_{23}), 28.3 (C_6), 29.0 (C_7), 29.2 (C_{11}), 33.3 (C_{24}), 34.0 (C_8), 35.8 (C_4), 36.3 (C_{10}), 41.8 (C_5), 46.0 (C_1), 48.5 (C_{20}), 52.9 (C_9), 56.0 (C_{13}), 65.8 (C_{25}), 70.2 (C_{26}), 75.7 (C_{12}), 93.3 (C_{17}), 93.7 (C_{16}), 107.9 (C_{22}), 120.0 (C_{15}), 148.6 (C_2), 148.9 (C_3), 154.8 (C_{14}); MS (FAB, NBA) 913 $(M + H)^+$; HRMS (FAB, NBA) calculated for $C_{54}H_{76}N_2O_{10}$ 913.5578, found 913.5566; $[\alpha]^{23}_D$ +83 ± 10° (*c* 0.1, MeOH); lit.[35] $[\alpha]_D$ +74° (*c* 0.1, MeOH).

Xanthate 12. To a solution of alcohol **4**[37] (700 mg, 1.17 mmol) in CS_2 (3 mL) and THF (3 mL) at 0 °C was added hexane-washed NaH (140 mg, 5.85 mmol). 20 min later, MeI (0.3 mL, 4.82 mmol) and TMEDA (0.8 mL) were added to the reaction mixture. After being stirred for 1 h at 0 °C, the reaction mixture was concentrated, and the residue was dissolved in EtOAc and H_2O. The mixture was extracted with EtOAc and dried over $MgSO_4$. After concentration, the residue was purified by flash column chromatography on silica gel (1:20 EtOAc/hexanes) to provide 785 mg (97%) of xanthate **12**: $R_f = 0.29$ (1:8 EtOAc/Hex); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.62 (s, 9H, OTMS), 0.84 (s, 3H), 0.97 (s, 3H), 1.71 (s, 3H), 1.77 (s, 3H), 1.99 (s, 3H), 2.01 (s, 3H), 2.52 (s, 3H, SCH_3), 2.77 (dd, $J = 14.6$, 8.8 Hz, 1H), 4.83 (brs, 2H), 4.98−5.03 (m, 2H), 5.39 (t, $J = 2.3$ Hz, 1H), 6.38 (dd, $J = 8.7$, 5.7 Hz, 1H); ^{13}C NMR (C_6D_6, 75 MHz) δ 1.6*, 9.2*, 11.3*, 18.1*, 18.66*, 20.8*, 20.9*, 22.3*, 26.8, 27.4, 27.6, 29.2, 33.9, 34.1*, 35.2, 35.9, 39.1, 43.3*, 50.1*, 58.3, 72.8*, 73.3*, 75.8*, 94.0*, 98.4, 113.9, 117.2*, 140.2, 149.7, 160.0, 168.7, 169.2; MS (CI) 583 $(M + H - HOCS_2CH_3)^+$; HRMS (FAB, NBA) calculated for $C_{34}H_{51}O_6Si$ 583.3455, found 583.3413.

Olefin 13. A solution of xanthate **12** (66 mg, 0.10 mmol), Ph_3SnH (195 mg, 0.56 mmol), and a catalytic amount of AIBN (1.6 mg, 0.01 mmol) in toluene (100 mL) was heated at reflux with a preheated oil bath. After 5 min, the solution was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by flash column chromatography (2% EtOAc/hexanes to 8% EtOAc/Hex) on silica gel to provide 50 mg (90%) of the product **13**: $R_f = 0.57$ (1:6 EtOAc/Hex); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.61 (s, 9H), 0.85 (s, 3H), 1.05 (s, 3H), 1.58 (s, 3H), 1.73 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 4.62−4.75 (m, 3H), 4.96 (d, $J = 2.1$ Hz, 1H), 5.03 (dd, $J = 11.7$, 4.7 Hz, 1H), 5.37 (t, $J = 2.3$ Hz, 1H); ^{13}C NMR (C_6D_6, 50 MHz) δ 2.3*, 9.9*, 12.1*, 18.6*, 21.5*, 21.8*, 22.9*, 26.0, 27.9, 28.1, 28.5, 30.0, 34.6, 34.8*, 35.2, 36.0, 36.7, 44.1*, 51.0*, 59.1, 73.6*, 74.4*, 94.4*, 99.6, 107.0, 111.1, 118.6*, 145.5, 155.1, 159.4, 169.4, 170.0; MS (CI) 585 $(M+H)^+$; HRMS (CI, isobutane) calculated for $C_{34}H_{52}O_6Si$ 585.3611, found 585.3572.

Diols 17*S*/*R*. AD-mix-α (200 mg) was dissolved in *t*-BuOH (0.6 mL) and H_2O (0.6 mL) at 25 °C. The clear orange solution was cooled to 0 °C and olefin **13** (30 mg, 0.05 mmol) was added. After being stirred for 16 h at 0 °C, the reaction mixture was quenched with Na_2SO_3 (220 mg) and H_2O (2 mL) and then stirred for 1 h at 25 °C. The mixture was extracted with CH_2Cl_2. The combined extract was washed with brine followed by drying over $MgSO_4$. After concentration, the residue was purified by flash column chromatography on silica gel (1:6 EtOAc/hexanes to 1:3 EtOAc/hexanes) to provide 30 mg (95%) of inseparable diastereomeric diols **17*S*** and **17*R*** (ratio; 2.5:1, based on ^{1}H NMR integration of C26 methyl): $R_f = 0.06$ (1:3 EtOAc/hexanes); ^{1}H NMR of a mixture of diastereomeric diols **17*S*** and **17*R*** (C_6D_6, 300 MHz) δ 0.23 (s, 9H), 0.50 (s, 3H), 1.01 (*R* at C26) and 1.03 (*S* at C26) (two s (ratio: **1:2.5**), 3H), 1.24 (s, 3H), 1.69 (s, 3H), 1.88 (s, 3H), 3.13−3.24 (m, 2H), 4.64−4.78 (m, 1H), 5.19 (d, $J = 2.5$ Hz, 1H), 5.35−5.41 (m, 2H); ^{13}C NMR (C_6D_6, 50 MHz) δ 2.3*, 9.8*, 12.1*, 18.6*, 21.5*, 21.8*, 21.9, 23.9*, 27.8, 28.1, 28.5, 30.0, 34.6, 34.8*, 36.0, 36.6, 44.0*, 51.0*, 59.1, 70.5, 72.5, 73.6*, 74.4*, 94.5*, 99.5, 107.2, 118.3*, 155.4, 159.8, 159.9, 169.5, 170.1; MS (CI) 619 $(M + H)^+$; HRMS (CI, isobutane) calcd for $C_{34}H_{54}O_8Si$ 619.3666, found 619.3665.

Diastereomeric β-Nitro Alcohols 35. To a solution of aldehyde **2** (31 mg, 0.057 mmol) and nitro compound **34** (25 mg, 0.143 mmol)[38] in *i*-PrOH (1 mL) was added KF (6.6 mg, 0.114 mmol) at 25 °C. After being stirred for 12−24 h, the solution was concentrated and the residue was subjected to flash column chromatography on silica gel (1:12 to 1:6 EtOAc/hexanes) to provide 28 mg (68%) of diastereomeric β-nitro alcohols **35** along with 10 mg (32%) of recovered aldehyde **2** and 13 mg of nitro compound **34**: $R_f = 0.42$ (1:3 EtOAc/hexanes); ^{1}H NMR of one of the diastereomers ($CDCl_3$, 300 MHz) δ 0.08 (s, 9H), 0.85 (s, 3H), 1.04 (s, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.52 (s, 3H), 1.71 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 3.23 (d, $J = 10.9$ Hz, 1H), 3.80 and 4.37 (two d, $J_{AB} = 9.5$ Hz, 1H each), 4.63−4.77 (m, 1H), 4.78 (d, $J = 3.2$ Hz, 1H), 4.83 (dd, $J = 11.0$, 3.1 Hz, 1H), 4.97 (d, $J = 1.9$ Hz, 1H), 4.97−5.03 (m, 1H), 5.32 (br t, $J = 1.8$ Hz, 1H); MS (EI) 719 $(M)^+$; HRMS (EI) calculated for $C_{37}H_{57}NO_{11}Si$ 719.3701, found 719.3715.

Diastereomeric α-Nitro Ketones 36. To a solution of α-nitro alcohols **35** (375 mg, 0.52 mmol) in CH_2Cl_2 (25 mL) was added Dess−Martin periodinane (553 mg, 1.30 mmol)[14] at 25 °C. After 30 min, the solution was concentrated, and the residue was dissolved in EtOAc followed by washing with cold 5% aqueous NaOH solution and brine. After drying over $MgSO_4$ and concentration, column chromatography on silica gel (1:8 EtOAc/Hex) provided 373 mg (quant) of **36**: $R_f = 0.51$ (1:3 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.08 (s, 9H), 0.86 (s, 3H), 1.05 (s, 3H), 1.41 (s, 3H), 1.44 (s, 3H), 1.50 (s, 3H), 2.00 (s, 3H), 2.01 (s, 3H), 2.02 (s, 3H), 3.97 and 4.07 (two d, $J_{AB} = 9.7$ Hz, 1H each), 5.02 (dd, $J = 11.6$, 4.7 Hz, 1H), 5.13 (d, $J = 2.6$ Hz, 1H), 5.42 (t, $J = 2.2$ Hz, 1H), 5.56 (s, 1H); MS (CI) 718 $(M+H)^+$.

(36) Pettit, G. R.; Ichihara, Y.; Xu, J.-P.; Boyd, M. R.; Williams, M. D. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1507.

(37) For the preparation of **4**, see the preceding paper.

(38) See Supporting Information for the preparation of nitro compounds **34**, **47a**, and **47b**.

Ketone 37. A solution of α-nitro ketone **36** (79 mg, 0.11 mmol) and Ph_3SnH (77 mg, 0.22 mmol) in degassed benzene (5 mL) was heated at reflux for 1 h in the presence of AIBN. After concentration, flash column chromatography on silica gel (4% to 10% EtOAc/hexanes) provided 60 mg (81%) of ketone **37**: $R_f = 0.30$ (1:6 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.07 (s, 9H), 0.86 (s, 3H), 1.05 (s, 3H), 1.36 (s, 6H), 1.40 (s, 3H), 1.95 (s, 3H), 2.02 (s, 6H), 2.79 and 3.15 (two d, $J = 17.2$ Hz, 1H each), 3.89 and 3.98 (two d, $J_{AB} = 8.8$ Hz, 1H each), 4.62−4.77 (m, 1H), 5.03 (dd, $J = 11.6$, 4.3 Hz, 1H), 5.11 (br s, 1H), 5.42 (br s, 1H); ^{13}C NMR (C_6D_6, 75 MHz) δ 1.3*, 11.1*, 11.3*, 11.7*, 20.7*, 20.9*, 25.1*, 26.9, 27.3*, 27.4, 27.7, 29.3, 33.8, 34.2*, 35.2, 35.9, 43.3*, 49.6, 50.2*, 58.7, 72.8*, 73.1*, 73.9, 79.4, 93.8*, 98.5, 108.6, 117.2*, 123.6, 149.3, 159.7, 168.6, 169.3, 194.1.

Diastereomeric Alcohols 38. To a solution of ketone **37** (53 mg, 0.079 mmol) in THF (2 mL) was added 2 M $LiBH_4$ in THF (0.05 mL, 0.095 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C and quenched with H_2O followed by extraction with EtOAc. After drying over $MgSO_4$ and concentration, flash column chromatography on silica gel (1:6 EtOAc/hexanes) provided 46 mg (87%) of diastereomeric alcohols **38**: $R_f = 0.32$ and 0.36 (1:3 EtOAc/hexanes); ^{1}H NMR of one of the diastereomers ($CDCl_3$, 300 MHz) δ 0.10 (s, 9H), 0.85 (s, 3H), 1.04 (s, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.44 (s, 3H), 1.67 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 3.60 (br s, 1H), 3.79 and 3.87 (two d, $J_{AB} = 8.5$ Hz, 1H each), 4.63−4.75 (m, 2H), 5.00−5.08 (m, 2H), 5.39 (br t, $J = 2.0$ Hz, 1H).

Acetonide 40. To a solution of diastereomeric alcohols **38** (209 mg, 0.31 mmol) in CS_2 (3 mL) and THF (3 mL) was added NaH (60% dispersion in mineral oil, 50 mg, 1.2 mmol) at 0 °C. 30 min later, TMEDA (1 mL) and MeI (0.5 mL, 8 mmol) were added at 0 °C. After being stirred for 2 h at 0 °C, the mixture was concentrated and the residue was dissolved in EtOAc and H_2O. The mixture was extracted with EtOAc, and then dried over $MgSO_4$. After concentration, flash column chromatography on silica gel (1:18 EtOAc/hexanes) provided 220 mg of inseparable diastereomeric xanthates **39** (91%): ^{1}H NMR (partial) of a mixture of two diastereomeric xanthates ($CDCl_3$, 300 MHz) δ 0.028 and 0.033 (2 s, TMS), 2.54 and 2.55 (2 s, SMe), 3.68 (dd, $J = 18.4$, 8.6 Hz), 3.86 (dd, $J = 8.6$, 6.2 Hz), 4.60−4.78 (m, 1H), 4.95−5.05 (m, 1H), 6.30−6.44 (m, 1H).

A solution of xanthates **39** (155 mg, 0.20 mmol), Ph_3SnH (470 mg, 1.34 mmol) and 2,2′-azobiscyclohexylnitrile (3 mg, 0.01 mmol) in toluene was heated at reflux (the oil bath was preheated at 135 °C). After 20 min, the solution was cooled to 25 °C and concentrated under reduced pressure. Flash column chromatography (2% to 8% EtOAc/hexanes) on silica gel provided 119 mg (90%) of the desired product **40**: $R_f = 0.50$ (1:3 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.06 (s, 9H), 0.85 (s, 3H), 1.05 (s, 3H), 1.28 (s, 3H), 1.40 (s, 3H), 1.58 (s, 3H), 1.73 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 3.71 and 3.81 (two d, $J_{AB} = 8.4$ Hz, 1H each), 4.61−4.73 (m, 1H), 4.96 (d, $J = 2.0$ Hz, 1H), 5.03 (dd, $J = 11.6$, 4.7 Hz, 1H), 5.37 (br t, $J = 1.9$ Hz, 1H); ^{13}C NMR (C_6D_6, 75 MHz) δ 1.5*, 9.1*, 11.4*, 17.8*, 20.8*, 21.0*, 21.8, 24.3*, 27.1*, 27.1, 27.2*, 27.4, 27.8, 29.3, 33.9, 34.1*, 35.3, 35.9, 36.6, 43.4*, 50.3*, 58.4, 72.8*, 73.7*, 74.0, 80.3, 93.7*, 98.9, 106.0, 108.9, 117.8*, 154.7, 158.7, 168.7, 169.2; MS (CI) 659 $(M + H)^+$; HRMS (EI) calculated for $C_{37}H_{58}O_8Si$ 658.3901, found 658.3894.

C_{26} Iodide 46b. To aldehyde **2** (280 mg, 0.51 mmol) in THF (10 mL) was added slowly at −25 °C $LiBH_4$ (0.51 mmol) in THF (0.26 mL, 2 M). After 5 min, the reaction was quenched by addition of saturated NH_4Cl solution (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL), dried over $MgSO_4$, and concentrated. The crude product **58** (∼300 mg) was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C and Et_3N (95 μL, 0.68 mmol) and MsCl (32 μL, 0.41 mmol) were added. After being stirred for 10 min, ice-cold saturated $NaHCO_3$ solution (10 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL) and concentrated. The residue was passed through a short pad of silica gel (deactivated by Et_3N, 10% EtOAc/hexanes) to give 260 mg (80% for two steps) of the desired mesylate **46a** (slowly decomposed at 25 °C). To the mesylate **46a** (21 mg, 0.32 mmol) in acetone (20 mL) at 0 °C was added NaI (58 mg, 0.38 mmol). After 30 min, the solution was concentrated and purified by column chromatography (10% EtOAc/hexanes; silica gel was treated with Et_3N) to give 196 mg (89%) of iodide **46b**, stable at 25 °C.

Mesylate 46a: $R_f = 0.28$ (25% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.39 (1H, br t), 5.09 (1H, d), 5.01 (1H, dd), 4.74 (2H, s), 4.68 (1H, m), 3.03 (3H, s), 2.03 (3H, s), 2.00 (3H, s), 1.72 (3H, s), 1.07 (3H, s), 0.84 (3H, s), 0.07 (9H, s).

Iodide 46b: $R_f = 0.22$ (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.39 (1H, br t), 5.05 (1H, d), 4.99 (1H, dd), 4.66 (1H, m), 3.80 (2H, s), 2.00 (3H, s), 1.98 (3H, dd), 1.57 (3H, s), 1.02 (3H, s), 0.83 (3H, s), 0.07 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 169.7, 159.7, 149.6, 117.2, 111.3, 98.1, 93.8, 73.8, 58.6, 50.5, 44.0, 36.6, 35.9, 34.4, 33.9, 29.5, 28.1, 27.3, 26.8, 21.6, 21.5, 17.6, 12.0, 9.6, 1.9; MS (FAB, DTT/DTE) 567 (M + H − HOTMS); HRMS (FAB, DTT/DTE) calcd for $C_{27}H_{46}IO_5$ 567.1608, found 567.1619.

C_{26} Alcohol 49. To an EtOAc (3 mL) solution of C_{26} benzyl ether **68** (18 mg, 0.026 mmol) was added Pd/C (5 mg (10%), ∼3% w/w). The solution was stirred under hydrogen (1 atm) for 30 min, then filtered through Celite. The filtrate was concentrated and purified by column chromatography (35% EtOAc/hexanes) affording 16 mg (quant) of C_{26} alcohol **49**. $R_f = 0.20$ (35% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34 (1H, br t), 5.01 (1H, dd), 4.94 (1H, d, $J = 2.4$ Hz), 4.68 (1H, m), 4.23 (2H, s), 3.03 (1H, br s), 2.58 (2H, m), 2.48 (2H, m), 2.02 (2H, s), 2.00 (3H, s), 1.59 (3H, s), 1.02 (3H, s), 0.85 (3H, s), 0.04 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.8, 170.7, 169.8, 159.3, 151.6, 117.3, 108.1, 98.4, 93.5, 73.9, 73.4, 68.3, 58.2, 50.6, 44.1, 36.6, 35.9, 34.8, 34.3, 33.9, 29.8, 29.5, 28.1, 27.4, 27.0, 21.6, 21.5, 20.7, 17.9, 12.0, 9.1, 1.7. MS (EI) 602 (M^+, base peak); MS (CI) 603 (M + H), 513 (M + H − HOTMS, base peak); HRMS (EI) calcd for $C_{33}H_{50}O_8Si$ 602.3275, found 602.3247.

6,5-Spiroketal 50. To a benzene (1 mL) solution of C_{26} alcohol **49** (8.6 mg, 0.014 mmol) was added CSA (0.6 mg, 0.026 mmol). After the mixture was stirred for 4.5 h, Na_2CO_3 (solid, 10 mg) was added. Benzene was evaporated to give a yellow residue, which was purified by column chromatography (20% EtOAc/hexanes) affording 2.8 mg (33%) of desired spiroketal **50** as a single diastereomer and 4 mg (47%) of starting material. $R_f = 0.31$ (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (1H, br t), 4.95 (1H, dd), 4.70 (1H, m), 4.69 (1H, d), 4.19 (1H, d), 3.92 (1H, d), 2.70 (1H, m), 2.49 (1H, m), 2.27 (1H, m), 2.02 (3H, s), 1.97 (3H, s), 1.15 (3H, s), 0.89 (3H, d), 0.86 (3H, s), 0.09 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.0, 170.7, 169.9, 160.7, 116.4, 107.8, 93.0, 90.5, 74.0, 73.4, 67.3, 56.4, 50.6, 46.5, 44.0, 36.8, 35.8, 35.0, 34.9, 33.9, 31.4, 30.4, 29.8, 29.5, 28.1, 27.4, 26.5, 21.5, 21.4, 20.3, 12.0, 9.2, 2.3; MS (EI) 602 (M^+), 544 ($M - CO_2CH_2$); MS (CI) 603 (M + H), 453 (M + H − HOAc − HOTMS, base peak); HRMS (EI) calcd for $C_{33}H_{50}O_8Si$ 602.3275, found 602.3287.

Alcohols 51 and 72 from Ketone 50. To a Et_2O (0.5 mL) solution of $LiClO_4$ (0.1 M) at −78 °C was added in one portion C_{25} ketone (2.8 mg, 0.0046 mmol), followed by MeLi in ether (8.7 μL (0.8 M), 0.0070 mmol). The solution was stirred for 10 min, then quenched by addition of saturated NH_4Cl solution (1 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated. Column chromatography (25% EtOAc in hexanes) afforded 1.5 mg (52%) of undesired C_{25} (*R*) alcohol **72**, 0.3 mg (10%) of desired C_{25} (*S*) alcohol **51**, and 0.9 mg (32%) of starting material **50**.

Desired C_{25} (*S*) alcohol **51** (less polar): identical to that obtained from the CSA catalyzed cyclization of the diols **17*S*/*R***.

Undesired C_{25} (*R*) alcohol **72** (more polar): $R_f = 0.20$ (25% EtOAc/hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 5.32 (1H, br s), 5.17 (1H, dd, $J = 11.2$, 4.7 Hz), 4.77 (1H, br s), 4.66 (1H, m), 3.72 (1H, d, $J = 11$ Hz), 3.19 (1H, m), 2.32 (1H, q, $J = 6.4$ Hz), 1.75 (3H, s), 1.70 (3H, s), 1.15 (3H, s), 1.12 (3H, s), 1.00 (3H, d, $J = 6.5$ Hz), 0.48 (3H, s), 0.28 (9H, s).

Adduct 61. To a DMSO (6.4 mL) solution of MOM-protected β-ketosulfone **47a** (165 mg, 0.64 mmol)[38] was added NaH (60% in mineral oil, 26 mg, 0.64 mmol) in one portion. The mixture was stirred for 15 min, then iodide **46b** (105 mg, 0.16 mmol) was added. After 0.5 h, the reaction was quenched by addition of ice-cold H_2O (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL) and H_2O (30 mL), dried over $MgSO_4$, and concentrated. Column chroma-

tography (20% EtOAc/hexanes) gave 5.6 mg (5%) of recovered iodide **46b** and 107 mg (86%) of desired adduct **61** (two diastereomers). R_f = 0.28 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) (selected peaks) δ 7.9−7.5 (phenyl H's, m), 5.32 and 5.27 (H-15, two br s), 4.91 and 4.85 (H-16, two d), 4.64−4.60 (CH_2 (MOM), two s), 3.40 and 3.37 (Me (MOM), two s), 2.73 (23-CH_2, m), 2.01 (3H, s), 1.98 (3H, two s), 1.53 and 1.50 (21-Me, two s), 0.02 and −0.02 (TMS, two s); MS (FAB, DTT/DTE) 786 (M^+).

MOM Ether 62. To a THF solution of SmI_2 (7.5 mL (0.1 M), 0.75 mmol) at −78 °C, was added dropwise β-ketosulfone **61** (107 mg, 0.14 mmol) in 1:1 THF/MeOH (degassed, 0.5 mL). After 5 min at −78 °C, the solution was poured into saturated $NaHCO_3$ (20 mL) solution. The mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were then washed with saturated $NaHCO_3$ (2 × 25 mL), dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (20% EtOAc/hexanes) to give 51 mg (58%) of desired desulfonylation product **62** and 26 mg (33%) of overreduction product **63**.

MOM ether 62: R_f = 0.33 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (1H, br s), 5.00 (1H, dd), 4.93 (1H, br d), 4.68 (2H, s), 4.68 (1H, m), 4.18 (2H, s), 3.39 (3H, s), 2.60 (2H, m), 2.40 (2H, m), 2.00 (3H, s), 1.99 (3H, s), 1.59 (3H, s), 1.01 (3H, s), 0.82 (3H, s), 0.04 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 170.7, 169.8, 159.2, 152.2, 117.4, 107.7, 98.4, 96.5, 93.5, 73.9, 73.4, 72.2, 58.2, 55.8, 50.6, 44.1, 36.6, 35.8, 35.4, 34.3, 33.9, 29.5, 28.1, 27.3, 26.9, 21.6, 21.5, 20.3, 17.8, 12.0, 9.1, 1.7; MS (FAB, DTT/DTE) 646 (M^+); HRMS (FAB, DTT/DTE) calcd for $C_{35}H_{54}O_9Si$ 646.3537, found 646.3524.

Compound 63: R_f = 0.47 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (1H, br s), 5.00 (1H, dd), 4.93 (1H, br s), 4.69 (1H, m), 2.60 (2H, t), 2.13 (3H, s), 2.01 (3H, s), 1.99 (3H, s), 1.60 (3H, s), 1.02 (3H, s), 0.83 (3H, s), 0.03 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 170.7, 169.8, 159.2, 152.2, 117.4, 107.5, 98.4, 93.5, 73.9, 73.4, 58.2, 50.6, 44.1, 39.9, 36.6, 35.9, 34.3, 33.9, 30.0, 29.5, 28.1, 27.4, 27.0, 21.6, 21.5, 20.8, 17.9, 12.0, 9.1, 1.7; MS (FAB, DTT/DTE) calcd for $C_{33}H_{50}O_7Si$ 586.3326, found 586.3313.

Ketosulfone 67. Following the procedure for making **61**, adduct **67** was obtained in 91% yield and 40% β-ketosulfone **47b**[38] was recovered. Benzyl sulfone **67** (two diastereomers): R_f = 0.30 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) (selected peaks) δ 8.0−7.5 (5H, m), 7.37 (5H, m), 5.20 (H-15, br t), 4.88 and 4.80 (H-16, two d), 2.80 (2H, t), 2.63 (2H, br t), 2.01 (3H, two s), 1.98 (3H, two s), 1.53 and 1.48 (21-Me, two s), 0.98 and 0.89 (18-Me, two s), 0.83 and 0.79 (19-Me, two s), 0.02 and −0.03 (TMS, two s); MS (FAB, DTT/DTE) 833 (M^+ + H).

Ketone 68. To a THF (1 mL) suspension of Sm (Aldrich, 27 mg, 0.22 mmol) was added in one portion at 25 °C 1,2-diiodoethane (31 mg, 0.11 mmol). After 1 h, the suspension turned into a deep blue solution, which was cooled to −78 °C. β-Ketosulfone **67** (30 mg, 0.036 mmol) in 1:1 THF/MeOH (degassed, 0.5 mL) solution was added dropwise. After 1 min, the solution was poured into saturated $NaHCO_3$ (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2 × 25 mL), dried over $MgSO_4$, and concentrated. Column chromatography (20% EtOAc/hexanes) gave 21.5 mg (86%) of desired desulfonylation product **68** and 2.5 mg (8%) of overreduction product **63**. Benzyl ether **68**: R_f = 0.30 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (5H, m), 5.33 (1H, t, J = 2 Hz), 5.03 (1H, dd, J = 11.4, 4.5 Hz), 4.93 (1H, J = 2 Hz), 4.68 (1H, m), 4.58 (2H, s), 4.06 (2H, s), 2.63 (2H, m), 2.41 (2H, m), 2.02 (3H, s), 2.00 (3H, s), 1.59 (3H, s), 1.02 (3H, s), 0.85 (3H, s), 0.04 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 170.7, 169.8, 159.1, 152.2, 137.2, 128.6*, 128.1*, 127.9*, 117.4*, 107.6, 98.4, 93.4*, 75.0, 73.9*, 73.4(2, o), 58.2, 50.5*, 44.0*, 36.5, 35.8, 35.4, 34.2*, 33.8, 29.5, 28.1, 27.3, 26.9, 21.6*, 21.5*, 20.3, 17.8*, 11.9*, 9.1*, 1.7*; MS (FAB, DTT/DTE) 692 (M^+); HRMS (FAB, DTT/DTE) calcd for $C_{40}H_{57}O_8Si$ 693.3823, found 693.3816.

Spiroketals 51, *S*-73, and *R*-73. To a solution of the mixture of diols **17S/*R*** (618 mg, 1.0 mmol) in CH_2Cl_2 was added (+)-CSA (23 mg, 0.1 mmol) at 25 °C. The mixture was stirred for 1 h at 25 °C and quenched with solid Na_2CO_3 (1 g). After filtration and concentration, flash column chromatography on silica gel (1:6 EtOAc/hexanes) provided 555 mg (90%) of inseparable major spiroketals **51**, ***S*-73**, and ***R*-73**: R_f = 0.38 (1:3 EtOAc/hexanes); ^{1}H NMR of a mixture of major spiroketals **51**, ***S*-73**, and ***R*-73** (C_6D_6, 300 MHz) δ 0.34 (s), 0.52 (s), 0.99 (s), 1.14 (s), 1.75 (s), 1.80 (s), 3.20−3.50 (m), 4.60−4.78 (m), 4.70, 4.79, and 4.80 (three brs), 5.10−5.41 (m, 2H).

Isolation of 6,5-Spiroketal 51 from a Mixture of Spiroketals 51/*S*-73/*R*-73. To a solution of spiroketals **51**, ***S*-73**, and ***R*-73** (555 mg, 0.9 mmol) in dry DMF (9 mL) were added TBDMSCl (677 mg, 4.5 mmol) and imidazole (1.06 g, 6.28 mmol) at 25 °C. The mixture was stirred for 10 h at 25 °C, followed by addition of ether (50 mL). The solution was washed with 5% aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine and dried over $MgSO_4$. After evaporation, flash column chromatography on silica gel (1:16 to 1:6 EtOAc/hexanes) provided 180 mg (32%) of 6,5-spiroketal **51** along with a mixture of 5,5-spiroketals ***S*-74** and ***R*-74** (0.5 g) which have a C_{26} TBDMS ether: Compound **51**: R_f = 0.38 (1:3 EtOAc/hexanes); ^{1}H NMR (C_6D_6, 300 MHz) δ 0.35 (s, 9H), 0.52 (s, 3H), 0.99 (s, 3H), 1.05 (d, J = 7.2 Hz, 3H), 1.14, (s, 3H), 1.75 (s, 3H), 1.80 (s, 3H), 3.25 (dd, J = 11.4, 2.3 Hz, 1H), 3.76 (d, J = 11.3 Hz, 1H), 4.65−4.78 (m, 1H), 4.80 (d, J = 2.0 Hz, 1H), 5.22 (dd, J = 11.6, 4.6 Hz, 1H), 5.39 (t, J = 2.1 Hz, 1H); MS (CI) 619 (M + H)$^+$; HRMS (EI) calculated for $C_{34}H_{54}O_8Si$ 618.3588, found 618.3600.

Preparation of Crystals of 76, *S*-75, and *R*-75 for X-ray Determination. General Procedure: Individual samples of spiroketals **51** or the mixture of ***S*-74** and ***R*-74** with 15 equiv of TBAF in THF were heated at reflux for 2−4 h. After concentration, the residue was dissolved in EtOAc. The organic layer was washed with saturated aqueous NH_4Cl (2×) and brine, and dried over $MgSO_4$. After filtration and evaporation, silica gel chromatography gave **76** (1:3 EtOAc/hexanes), ***S*-75** (1:30 THF/CH_2Cl_2), and ***R*-75** (1:30 THF/CH_2Cl_2) each in 80−90%. All three alcohols **76**, ***S*-75**, and ***R*-75** were separately crystallized from a CH_2Cl_2/hexanes solution (started at 1:2 (v/v), and slowly evaporated).

Compound 76: R_f = 0.18 (1:1 EtOAc/hexanes); ^{1}H NMR (C_5D_5N, 300 MHz) δ 0.75 (s, 3H), 1.22 (s, 3H), 1.27 (d, J = 7.3 Hz, 3H), 1.30 (s, 3H), 2.03 (s, 3H), 2.54 (dt, J = 11.7, 1.6 Hz, 1H), 4.00 (d, J = 12.2 Hz, 1H), 4.12 (dd, J = 8.4, 2.1 Hz, 1H), 4.64 (s, 1H, OH), 4.79 (m, 1H), 5.06 (s, 1H, OH), 5.14 (s, 1H), 5.58 (s, 1H), 5.71 (s, 1H, OH); mp 186−187 °C dec.

Compound *S*-75: R_f = 0.36 (1:10 THF/CH_2Cl_2);^{1}H NMR (C_6D_6, 300 MHz) δ 0.59 (s, 3H), 0.83 (s, 3H), 0.89 (d, J = 6.8 Hz, 3H), 1.18 (s, 3H), 1.75 (s, 3H), 3.27 (brs, 1H), 3.37 and 3.51 (two d, JAB = 11.2 Hz, 1H), 3.85−4.00 (m, 1H), 4.70−4.83 (m, 1H), 4.84 (s, 1H), 5.21 (s, 1H); mp 203−204 °C dec.

Compound *R*-75: R_f = 0.25 (1:10 THF/CH_2Cl_2); ^{1}H NMR (C_6D_6, 300 MHz) δ 0 60 (s, 3H), 0.98 (d, J = 6.9 Hz, 3H), 1.21 (s, 3H), 1.31 (s, 3H), 1.74 (s, 3H), 3.15−3.23 (m, 2H), 3.62 (brs, 1H), 4.02−4.07 (m, 1H), 4.75−4.81 (m, 1H), 4.97 (s, 1H), 5.38 (s, 1H); mp 215−216 °C dec.

C_3 Alcohol 77. A solution of diacetate **51** (102 mg, 0.165 mmol) and $KHCO_3$ (41 mg, 0.412 mmol) in MeOH (1.6 mL) and H_2O (0.4 mL) was heated at reflux for 1 h. After the MeOH was removed, the mixture was neutralized with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The combined extract was washed with H_2O and brine and dried over $MgSO_4$. After evaporation, flash column chromatography on silica gel (1:6 EtOAc/hexanes) provided 95 mg (quant) of alcohol **77**: R_f = 0.12 (1:3 EtOAc/hexanes); ^{1}H NMR (C_6D_6, 300 MHz) δ 0.32 (s, 9H), 0.55 (s, 3H), 0.99 (s, 3H), 1.04 (d, J = 7.2 Hz, 3H), 1.16, (s, 3H), 1.80 (s, 3H), 1.80 (s, 3H), 3.20−3.30 (m, 2H), 3.75 (d, J = 11.3 Hz, 1H), 3.75 (d, J = 11.3 Hz, 1H), 4.79 (d, J = 2.2 Hz, 1H), 5.23 (dd, J = 11.6, 4.6 Hz, 1H), 5.40 (t, J = 2.3 Hz, 1H); ^{13}C NMR (C_6D_6, 75 MHz) δ 2.3*, 9.2*, 11.7*, 19.9*, 20.8*, 25.4*, 26.7, 28.2, 29.6, 31.5, 32.6, 34.8*, 35.5, 36.7, 38.0, 44.0*, 46.6*, 50.9*, 56.3, 66.1, 68.8, 70.3*, 70.9*, 74.0*, 89.9*, 93.2, 107.8, 117.1*, 159.5, 169.2.

C_3 Keto Alcohol 78. To a solution of alcohol **77** (95 mg, 0.165 mmol) in ether (5 mL) was added chromic acid solution (0.3 mL, 0.18 mmol). After the solution was stirred for 30 min at 25 °C, H_2O and ether were added and the mixture was extracted with ether. The combined extract was washed with saturated aqueous $NaHCO_3$ solution and brine and dried over $MgSO_4$. After evaporation, flash column chromatography on silica gel (1:6 EtOAc/hexanes) provided 86 mg (91%) of ketone **78**: R_f = 0.20 (1:3 EtOAc/hexanes); ^{1}H NMR (C_6D_6,

300 MHz) δ 0.32 (s, 9H), 0.46 (s, 3H), 0.98 (s, 3H), 1.04 (d, J = 7.2 Hz, 3H), 1.14, (s, 3H), 1.80 (s, 3H), 2.23 (q, J = 7.0 Hz, 1H), 3.24 (dd, J = 11.3, 2.6 Hz, 1H), 3.75 (d, J = 11.3 Hz, 1H), 4.78 (d, J = 2.1 Hz, 1H), 5.18 (dd, J = 11.6, 4.6 Hz, 1H), 5.36 (t, J = 2.3 Hz, 1H); ^{13}C NMR (C_6D_6, 75 MHz) δ 2.3*, 9.2*, 10.4*, 19.9*, 20.8*, 25.3*, 26.8, 28.0, 28.2, 29.0, 32.6, 34.5*, 35.2, 37.5, 44.0, 44.8*, 46.6*, 50.1*, 56.3, 66.0, 68.8, 73.6*, 89.9*, 93.1, 107.8, 117.4*, 158.8, 169.0, 208.2; MS (CI) 575 (M + H)$^+$; HRMS (EI) calculated for $C_{32}H_{50}O_7Si$ 574.3326, found 574.3320.

MTM Ether 79. To a solution of keto alcohol **78** (25 mg, 0.0435 mmol) in DMSO (0.25 mL) was added Ac_2O (0.18 mL) at 25 °C. After 19 h at 25 °C, the mixture was poured into cold saturated aqueous $NaHCO_3$ solution and extracted with ether. The combined extract was washed with saturated aqueous $NaHCO_3$ solution, H_2O, and brine. After drying over $MgSO_4$ and concentration, flash column chromatography on silica gel (1:7 EtOAc/hexanes) provided 28 mg (quant) of MTM ether **79**: R_f = 0.22 (1% THF/CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 5.39 (1H, t, J = 2.3 Hz), 5.19 (1H, dd, J = 11.7, 4.6 Hz), 4.82 (1H, d, J = 2.3 Hz), 4.44 and 4.36 (1H each, two d, J_{AB}=10.5 Hz), 3.63 (1H, dd, J = 12.2, 2.2 Hz), 3.56 (1H, d, J = 12.2 Hz), 2.10 (3H, s), 1.80 (3H, s), 1.17 (3H, s), 1.09 (3H, d, J = 7.2 Hz), 0.82 (3H, s), 0.46 (3H, s), 0.33 (9H, s); ^{13}C NMR (75 MHz, C_6D_6) δ 207.6, 168.9, 158.8, 117.5, 107.8, 93.2, 89.8, 73.6, 71.6, 66.9, 64.5, 56.3, 50.2, 46.6, 44.8, 44.0, 37.5, 37.5, 35.2, 34.5, 31.3, 29.0, 28.0, 26.8, 21.2, 20.8, 19.9, 13.9, 10.4, 9.2, 2.3; MS (EI) 634 (M$^+$); MS(CI) 635 (M + H, base peak), 545 (M + H − HOTMS); HRMS (EI) calcd for $C_{34}H_{54}O_7SSi$ 634.3360; found 634.3347.

Bromide 80. To a solution of MTM ether **79** (32 mg, 0.05 mmol) in THF (2 mL) was added phenyltrimethylammonium tribromide (PTAB, 24 mg, 0.064 mmol) at 0 °C. After being stirred for 20 min at 0 °C, the mixture was quenched with brine and extracted with ether. The combined extract was washed with saturated aqueous $NaHCO_3$ solution and brine and dried over $MgSO_4$. After evaporation, flash column chromatography on silica gel (1:8 EtOAc/hexanes) provided 25 mg (82%) of bromide **80**: R_f = 0.16 (1:3 EtOAc/hexanes); ^{1}H NMR (C_6D_6, 300 MHz) δ 0.31 (s, 9H), 0.31 (s, 3H), 0.98 (s, 3H), 1.03 (d, J = 7.2 Hz, 3H), 1.10 (s, 3H), 1.80 (s, 3H), 2.23 (dd, J = 12.6, 6.2 Hz, 1H), 2.33 (q, J = 7.1 Hz, 1H), 3.24 (dd, J = 11.3, 2.6 Hz, 1H), 3.74 (d, J = 11.3 Hz, 1H), 4.10 (dd, J = 13.4, 6.2 Hz, 1H), 4.77 (d, J = 2.4 Hz, 1H), 5.15 (dd, J = 11.6, 4.6 Hz, 1H), 5.32 (t, J = 2.3 Hz, 1H); ^{13}C NMR (C_6D_6, 75 MHz) δ 2.3*, 9.1*, 10.8*, 19.8*, 20.7*, 25.1*, 26.8, 27.4, 28.2, 28.6, 32.6, 34.0*, 38.3, 43.2, 45.0*, 46.7*, 49.5*, 50.0, 53.6*, 56.2, 65.9, 68.9, 73.2*, 89.9*, 89.9*, 93.1, 107.7, 158.2, 168.8, 197.9; MS (EI) 652/654 (M)$^+$; HRMS (EI) calculated for $C_{32}H_{49}BrO_7Si$ 652.2431, found 652.2464.

C_{26} Acetates 85*S*/*R* from Diols 17*S*/*R*. To a pyridine/CH_2Cl_2 (2 mL, 1:2) solution of diols **17*S*/*R*** (100 mg, 0.16 mmol) at 0 °C was added DMAP (1 mg), followed by Ac_2O (0.25 mL). After 20 min, the solution was diluted with CH_2Cl_2 (20 mL), washed with saturated $NaHCO_3$ (3 × 10 mL), dried over $MgSO_4$, and concentrated. Column chromatography (15% EtOAc/hexanes) afforded 107 mg (quant) of C_{26} acetates **85*S*/*R***, with nearly identical spectra. R_f = 0.21 (15% EtOAc/hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 5.34 (1H, br s), 5.32 (1H, dd), 5.13 (1H, d), 4.65 (1H, m), 3.87 (2H, s), 1.83 (3H, s), 1.68 (3H, s), 1.64 (3H, s), 1.58 (3H, s), 1.19 (3H, s), 0.96 (3H, s), 0.45 (3H, s), 0.18 (9H, s); ^{13}C NMR (75 MHz, C_6D_6) δ 169.9, 169, 168.7, 159.0, 154.4, 117.6*, 106.5, 98.8, 73.7*, 72.9*, 70.7, 58.4, 50.3*, 43.4*, 36.0, 35.6, 35.3, 34.1*, 33.9, 29,3, 27.8, 27.4, 27.1, 23.8*, 21.0*, 21.0, 20.8*, 20.0*, 17.9*, 11.4*, 9.1*, 1.6*.

C_{25} MTM Ethers 86*S*/*R*. To a DMSO (4 mL) solution of C_{25} alcohol **85*S*/*R*** (450 mg, 0.68 mmol) was added Ac_2O (2 mL). After 15 h at 25 °C, the solution was diluted with Et_2O (100 mL), washed with saturated $NaHCO_3$ solution (2 × 35 mL) and brine (40 mL), dried over $MgSO_4$, and concentrated. Column chromatography (10% EtOAc/hexanes) gave 470 mg (96%) of MTM ethers **86*S*/*R***. R_f = 0.23 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 5.39 (1H, br t), 5.35 (1H, dd), 5.17 (1H, br d), 4.65 (1H, m), 4.36 (2H, s), 3.99 (2H, AB), 1.91 (3H, s), 1.84 (3H, s), 1.66 (3H, s), 1.63 (3H, s), 1.61 and 1.60 (3H, two s (2.5:1)), 1.21 (3H, s), 0.94 (3H, s), 0.44 (3H, s), 0.19 (9H, s); ^{13}C NMR (75 MHz, C_6D_6) δ 169.4, 169.3, 168.7, 158.8, 154.5, 117.8*, 106.2, 98.8, 93.7*, 76.5, 73.7*, 72.8*, 67.3, 67.2, 58.3, 50.3*, 43.4*, 35.9, 35.3, 34.1*, 33.9, 33.0, 29.3, 27.8, 27.4, 27.1, 21.0*, 20.8*, 20.2*, 20.1, 17.9*, 13.9*, 11.3*, 9.1*, 1.6*.

$C_{3,26}$ Diols 87*S*/*R*. To an aqueous MeOH (32 mL, 12% H_2O) solution of MTM ethers **86*S*/*R*** (460 mg, 0.64 mmol) was added in one portion $KHCO_3$ (160 mg, 1.6 mmol). The solution was heated at reflux for 2 h, then cooled to 25 °C. The suspension was concentrated and extracted with CH_2Cl_2 (3 × 35 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over $MgSO_4$, and concentrated. Filtration through a short pad (3 in) of silica gel (40% EtOAc/hexanes) gave 404 mg (quant) of desired diols **87*S*/*R***. R_f = 0.18 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 5.38 (1H, br t), 5.32 (1H, dd), 5.13 (1H, br d), 4.32 (2H, AB), 3.34 (2H, s), 3.29 (1H, m), 2.63 (1H, br s), 2.21 (2H, t), 1.84 (3H, s), 1.82 (3H, s), 1.63 (3H, s), 1.19 (3H, s), 0.97 (3H, s), 0.54 (3H, s), 0.17 (9H, s); ^{13}C NMR (75 MHz, C_6D_6) δ 168.9, 159.0, 154.7, 117.7*, 106.2, 98.8, 93.7*, 78.8, 73.9*, 70.5*, 66.9, 66.4, 58.4, 50.6*, 43.9*, 38.0, 36.5, 35.5, 34.2*, 32.4, 31.5, 29.5, 28.1, 27.2, 21.1*, 21.0, 19.9*, 19.8*, 17.9*, 11.6*, 9.2*, 1,6*.

6,5-Spiroketals 88*S*/*R*. To a CH_2Cl_2 (20 mL) solution of diols **87*S*/*R*** (285 mg, 0.29 mmol) was added CSA (6.8 mg, 0.0291 mmol). The solution was stirred for 1 h at 25 °C, then quenched by addition of Na_2CO_3 (30 mg), and CH_2Cl_2 was removed by evaporation. Column chromatography (30% EtOAc/hexanes) afforded 258 mg (91%) of 6,5-spiroketals **88*S*/*R*** and 25 mg (9%) of starting materials **87*S*/*R***. R_f = 0.21 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 5.42, 5.38 and 5.34 (H-15, three br t), 5.2−5.0 (H-12, m), 4.85 and 4.76 (H-16, two br s), 4.36, 4.35, and 4.35 (CH_2 (MTM), one br s and two AB), 4.1−2.8 (26-CH_2, m), 2.04, 2.00, and 1.90 (Me (MTM), three s), 1.77 (12-OAc, three s), 0.57 (19-Me, two s), 0.20 (TMS, 3 s); ^{13}C NMR (75 MHz, C_6D_6, major spiroketal) δ 171.0, 159.4, 117.1, 107.8, 89.9, 73.9, 71.6, 70.3, 66.9, 64.5, 56.3, 50.9, 46.7, 38.0, 36.6, 35.4, 34.8, 31.5, 31.3, 29.6, 28.1, 28.0, 26.8, 21.2, 20.0, 11.7, 9.3, 2.3; MS (FAB, DTT/DTE) 637 (M + H); HRMS (FAB, DTT/DTE) calcd for $C_{34}H_{57}O_7SSi$ 637.3594, found 637.3581.

C_3 Ketones (79/89/90). To a pyridine/CH_2Cl_2 (0.8 mL/2 mL) solution was added in one portion CrO_3 (53 mg, 0.53 mmol). After 20 min, the C_3 alcohol (75 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The suspension was stirred for 2.5 min, then quenched with ice-cold saturated Na_2SO_3 (5 mL). The mixture was diluted with Et_2O (100 mL), washed with brine (2 × 30 mL), dried over $MgSO_4$, and concentrated. Column chromatography (20% EtOAc/hexanes) gave 58 mg (77%) of C_3 ketones **79/89/90** and 11 mg (15%) of starting materials **88*S*/*R***. C_3 ketones (mixture of **79/89/90**) R_f = 0.30 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, C_6D_6) (selected peaks) δ 5.33 and 5.26 (H-15, two br t), 4.84, 4.76, and 4.74 (H-16, three br s), 2.02, 2.00, and 1.89 (Me of MTM, three s), 1.79 (OAc, two s), 0.21 (TMS, three s).

Equilibration and Separation of Spiroketals 79/89/90. A mixture of 6,5-spiroketals **79/89/90** (255 mg, 0.40 mmol) was subjected to column chromatography (CH_2Cl_2/THF: 200:1 to 100:1) to give 90 mg of pure desired (20*S*,22*R*,25*S*) spiroketal **79** and 155 mg of other spiroketals, which were treated with CSA (10 mol %) in CH_2Cl_2 (15 mL) for 1 h. The resulting crude spiroketals were purified by column chromatography (CH_2Cl_2/THF: 200:1 to 100:1) to give 56 mg of (20*S*, 22*R*,25*S*) spiroketal **79**, 65 mg of (20*S*,22*R*,25*R*) spiroketal **90**, and 25 mg of (20*R*,22*S*,25*S*) spiroketal **89**. Compound **89** could be converted into **79** (20 mg) upon another treatment with CSA in CH_2Cl_2. Therefore, the (20*S*,22*R*,25*S*) spiroketal **79** (166 mg) and its C_{25} epimer **90** (65 mg) were obtained in 65 and 25% yield, respectively (ca 2.5:1).

Compound 79: Identical to **79** prepared from **78**.

Compound 89: R_f = 0.18 (1% THF/CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 5.25 (1H, s), 5.01 (1H, dd), 4.85 (1H, br s), 4.38 (2H, s), 4.12 (1H, d), 3.38 (1H, d), 2.82 (1H, q), 1.91 (3H, s), 1.77 (3H, s), 1.34 (3H, s), 1.22 (3H, s), 0.91 (3H, d), 0.40 (3H, s), 0.22 (9H, s); ^{13}C NMR (125 MHz, C_6D_6) δ 207.9, 169.3, 155.1, 119.9, 109.2, 95.0, 91.2, 75.2, 72.9, 69.0, 66.9, 56.5, 51.1, 48.5, 45.4, 44.3, 37.8, 35.6, 34.3, 31.2, 30.4, 29.0, 28.6, 28.3, 27.5, 21.2, 20.4, 18.0, 14.1, 11.7, 10.7, 2.3; MS (EI) 634 (M$^+$); MS(CI) 635 (M + H, base peak), 545 (M + H − HOTMS); HRMS (EI) calcd for $C_{34}H_{54}O_7SSi$ 634.3360, found 634.3340.

Compound 90: R_f = 0.20 (1% THF/CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 5.32 (1H, br t), 5.03 (1H, dd), 4.86 (1H, br s), 4.37 (2H, AB), 3.74 (1H, d), 3.62 (1H, br dd), 2.88 (1H, q), 2.00 (3H, s), 1.75 (3H, s), 1.34 (3H, s), 0.96 (3H, d), 0.60 (3H, s), 0.39 (3H, s), 0.22 (9H, s); ^{13}C

NMR (125 MHz, C_6D_6) δ 207.6, 169.1, 155.3, 119.5, 109.2, 94.6, 90.5, 74.8, 71.9, 66.9, 66.6, 56.3, 50.8, 48.4, 45.2, 44.1, 37.6, 37.4, 35.4, 34.2, 30.8, 28.8, 28.0, 27.2, 25.8, 21.2, 20.9, 17.9, 13.9, 11.1, 10.4, 2.2; MS (EI) 634 (M^+); MS (CI) 635 (M + H, base peak), 545 (M + H − HOTMS); HRMS (EI) calcd for $C_{34}H_{54}O_7SSi$ 634.3360, found 634.3353.

Protected Pyrazines 99, 100, and 101. A solution of metallic tellurium (42 mg, 0.30 mmol) and $NaBH_4$ (29 mg, 0.76 mmol) in absolute ethanol (1 mL) was heated at reflux under argon for 1 h. After being cooled to 25 °C, 0.28 mL (0.083 mmol) of the resultant dark red solution (NaHTe)[33] was added to a solution of azido ketones **5** (12.6 mg, 0.014 mmol) and **6** (8.5 mg, 0.014 mmol) in ether (1 mL) at 25 °C. The dark red solution instantly turned black with evolution of nitrogen. After 1 h, the reaction mixture was exposed to air and stirred for 1 h. Silica gel (230−400 mesh, 30 mg) and EtOAc (3 mL) were added and the mixture was stirred for 18 h. After removal of the solvents by evaporation, silica gel chromatography (1:15 to 1:3 EtOAc/hexanes) gave protected pyrazines **100** (3.5 mg, 14%), **99** (7.0 mg, 35%), and **101** (3.6 mg, 23%) separately. Azido-cleaved ketones **98** (4.3 mg, 36%) and **79** (1.2 mg, 15%) were also obtained.

Protected Cephalostatin 12 (100): R_f = 0.20 (1:3 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.15 and −0.14 (two s, 12H), 0.74 (s, 18H), 0.85 (s, 6H, H-19), 1.00 (s, 18H), 1.11 (s, 6H, H-18), 1.12 (d, J = 7.1 Hz, 6H, H-21), 1.24 (s, 6H, H-27), 2.00 (s, 6H), 2.44−2.63 (m, 6H), 2.81 (dd, J = 18.0, 5.3 Hz, 2H, H-4a), 2.85 (d, J = 17.0 Hz, 2H, H-1b), 2.97 (d, J = 10.0 Hz, 2H, H-26b), 3.10 (d, J = 10.0 Hz, 2H, H-26a), 3.96 (s, 2H, OH), 4.30 (dd, J = 9.6, 7.2 Hz, 2H, H-23), 4.95 (br s, 2H, H-16), 5.06 (dd, J = 11.0, 4.8 Hz, 2H, H-12), 5.56 (br s, 2H, H-15), 7.36−7.76 (m, 4H), 7.84−7.87 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.7, −5.6, 8.8, 11.7, 13.5, 18.2, 19.2, 21.3, 25.7, 25.9 (3C), 26.6 (3C), 27.3, 27.9, 28.3, 33.6, 35.2, 36.0, 37.5, 41.5, 44.3, 45.5, 52.6, 53.3, 69.2, 73.9, 74.6, 81.8, 89.4, 93.3, 116.5, 122.4, 127.6 (2C), 128.0 (2C), 129.8, 130.2, 132.7, 133.7, 135.5 (2C), 136.0 (2C), 148.3, 148.5, 151.5, 170.1; MS (FAB, NBA) 1734.8 $(M + H)^+$. Protected cephalostatin 7 (**99**): R_f = 0.08 (1:3 EtOAc/hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ −0.11 (s, 3H), −0.09 (s, 3H), 0.34 (s, 9H), 0.55 (s, 3H, H-19′), 0.85 (s, 9H), 1.81 (s, 3H), 2.02 (s, 3H), 2.47−2.68 (m, 4H), 2.85−3.20 (m, 5H), 3.20−3.28 (m, 2H), 3.76 (d, J = 11.3, 1H, H-26′b), 4.37 (s, OH), 4.65 (dd, J = 10.4, 8.1 Hz, 1H, H-23), 4.81 (d, J = 2.3 Hz, 1H, H-16′), 5.28−5.35 (m, 2H, H-16 and H-12′), 5.39−5.45 (m, 2H, H-12 and H-15′), 5.59 (s, 1H, H-15); MS (FAB, NBA) 1439 $(M + H)^+$.

Protected Ritterazine K (101): R_f = 0.61 (1:1 EtOAc/hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 0.35 (s, 18H, OTMS), 0.55 (s, 6H, H-19), 0.99 (s, 6H, H-18), 1.06 (d, J = 7.1 Hz, 6H, H-21), 1.15 (s, 6H, H-27), 1.82 (s, 6H, OAc), 2.50−2.63 (m, 4H, H-1a and H-4b), 2.88 (dd, J = 18.2, 5.1 Hz, 2H, H-4a), 3.15 (d, J = 16.7 Hz, 2H, H-1b), 3.25 (dd, J = 11.3, 2.4 Hz, 2H, H-26a), 3.77 (d, J = 11.3 Hz, 2H, H-26b), 4.82 (d, J = 2.3 Hz, 2H, H-16), 5.31 (dd, J = 11.6, 4.6 Hz, 2H, H-12), 5.43 (t, J = 2.1 Hz, 2H, H-15); ^{13}C NMR (C_6D_6) δ 2.3 (OTMS), 9.2 (C21), 11.4 (C19), 19.9 (C18), 20.8 (***C***H_3CO_2), 25.1 (C27), 26.8 (C23), 27.7 (C6), 28.2 (C7), 29.1 (C11), 32.6 (C24), 34.5 (C8), 35.3 (C4), 35.5 (C10), 40.5 (C5), 45.6 (C1), 46.6 (C20), 50.3 (C9), 56.3 (C13), 66.0 (C25), 68.8 (C26), 73.6 (C12), 89.9 (C16), 93.2 (C17), 107.8 (C22), 117.5 (C15), 148.2 (C2), 148.6 (C3), 159.1 (C14), 169.0 (CH_3***C***O_2); MS (FAB, DDT/DTE) 1141 $(M + H)^+$; HRMS (FAB, DDT/DTE) calculated for $C_{64}H_{96}N_2O_{12}Si_2$ 1141.6580, found 1141.6470.

Acknowledgment. We thank the National Institutes of Health (CA 60548) for support of this work. Special thanks are due to Mr. Lawrence Knox, Mr. Lei Jiang, and Mr. Patrick Crouse for conversion of hecogenin acetate to advanced synthetic intermediates. We are grateful to Arlene Rothwell for supplying mass spectral data and Dr. P. Fanwick for providing X-ray structures.

Supporting Information Available: Experimental procedures as well as a characterization check list and NMR spectra (PDF). This material is available free of charge via the Intenet at http://pubs.acs.org.

JA9817141