Synthesis of the North 1 Unit of the Cephalostatin Family from Hecogenin Acetate[1]

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Abstract: Hecogenin acetate (**1**) was converted to North 1 azidoketone **5** involving several key transformations: (1) conversion of cyclic sulfate **33b** to allylic alcohol **40** via Reich iodoso olefination; (2) E-ring annulation via intermolecular oxygen alkylation of highly functionalized secondary alcohol **40** using rhodium-catalyzed decomposition of an α-diazophosphonoacetate to provide α-alkoxyphosphonoacetate **52**, with subsequent intramolecular Wadsworth−Emmons reaction to provide alkoxydihydrofuran **53**; and (3) establishment of the C20 stereochemistry by chromium(II) reduction of tertiary bromide **86** to a 9:1 mixture of diastereomeric spiroketals **90**α/**90**β**,** separated as silyl ethers **91**α/**91**β. Conversion of **91**α to α-azidoketone **5** was uneventful.

Introduction

Cephalostatin 7 (**10**)[2] is a potent member of a family of 45 trisdecacyclic pyrazines, characterized by the groups of Pettit at Arizona State University and Fusetani at the University of Tokyo.[3] These materials were isolated from the marine tube worm *Cephalodiscus gilchristi,* and more recently from the tunicate *Ritterella tokioka.* In particular, cephalostatin 7 (**10**) exhibits extreme potency with GI_{50} (growth inhibition concentration) of 0.1−1 nM against a number of cancer cell lines (e.g., non-small cell lung HOP62, small cell lung DMS-273, renal RXF-393, brain U-251 and SF-295, and leukemia CCRF-CEM, HL-60, and RPM1-8226).[2] In his seminal contribution detailing the structure of cephalostatin 1, 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 context of the total synthesis of cephalostatin 7 (**10**), a biomimetic approach involved conversion of appropriately protected α-azidoketones **5** and **6** to α-aminoketones **7** and **8** followed by statistical combination to cephalostatins 12[6] (**9**) and 7 (**10**) and ritterazine K (**11**).[3b] The specific synthetic strategy involved conversion of hecogenin acetate **1** to the pentacyclic dihydrofuran−aldehyde **2** which served as the common intermediate for preparation of both hemispheres (**3** and **4**) of the target pyrazines (Scheme 1). Recent SAR studies on cephalostatins and their analogues reveal that the North part is not only the most common unit in the cephalostatin family but is also strongly associated with the most potent antitumor activity.[1g,7]

Conversion of Hecogenin Acetate 1 to Aldehyde 2[8]

Reduction of **1** with DIBAL at low temperature followed by acylation provides rockogenin diacetate **12** in 88% overall yield (Scheme 2). Isolation of **12** by recrystallization removed the hexane-soluble minor C12 α-acetate as well as tigogenin acetate (as **1** in Scheme 2 but X = H, H) present in the starting material.[9] By use of a procedure similar to Dauben's,[10] diacetate **12** was converted to pseudorockogenin triacetate **13** in 79% yield by pyridinium hydrochloride catalyzed reaction with acetic anhydride, and thence into keto ester **14** by oxidation with chromium trioxide in acetic acid. Treatment of **14** in benzene with basic alumina effected β-elimination of the pentanoate side chain, thereby providing the desired enone **15** in 71% yield from **13** on a large scale.

Allylic bromination of enone **15** with NBS[11] stereoselectively yielded bromo enone **16** (Scheme 3). Three typical solvents for

(1) Cephalostatin synthesis. 13. Portions of this work have been communicated in Article 9 of this series: 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.; Jautelat, 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. (b) Pettit, G. R.; Tan, R.; Xu, J.-p.; Ichihara, Y.; Williams, M. D.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 955 and references therein. (c) Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *Tetrahedron* **1995** *51*, 6707 and references therein. (d) Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *J. Org. Chem.* **1997**, *62*, 4484

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

(7) Guo, C.; LaCour, T. G.; Fuchs, P. L. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 419.

(8) For a preliminary account of this phase of the work see: Kim, S.; Fuchs, P. L. *Tetrahedron Lett.* **1994**, *35*, 7163.

(9) Tigogenin acetate comprises ∼5% of commercial **1**. We have subsequently found that reduction at 0 °C with $NaBH_4/CeCl_3$ (Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454), acetylation, and recrystallization provides **12** (90%) in an operationally more convenient manner.

(10) Ring opening of spiroketal **11** is based upon the general method of Micovic and Diatak (see: *Synthesis* **1990**, 591) and Dauben and Fonken (Dauben, W. G.; Fonken, G. J. *J. Am. Chem. Soc.* **1954**, *76*, 4618).

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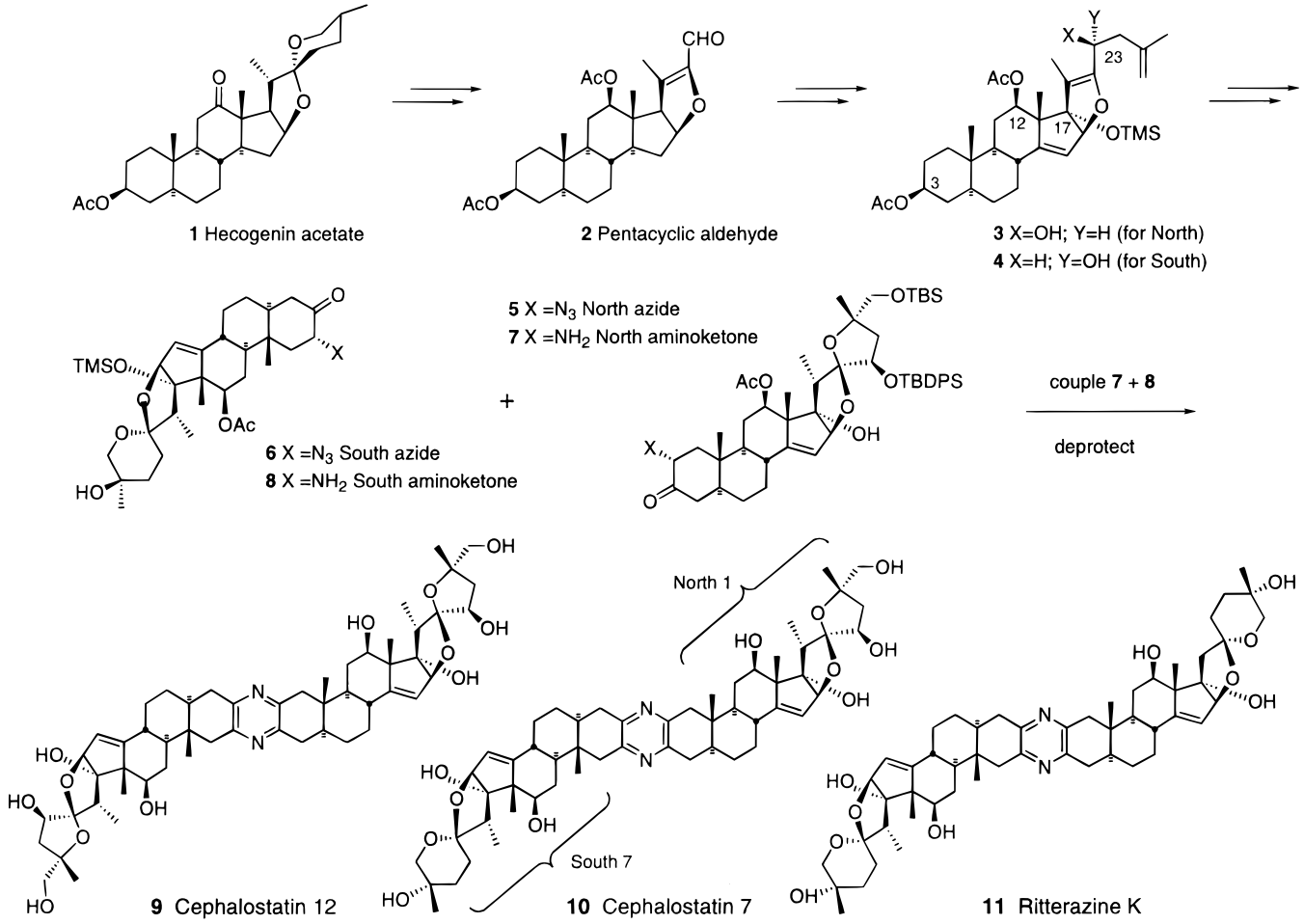
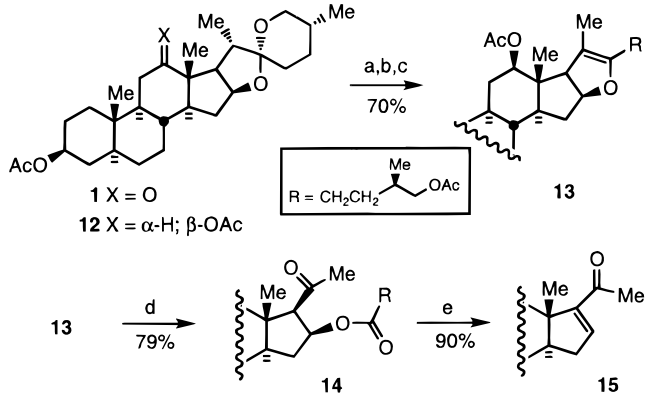
Scheme 1



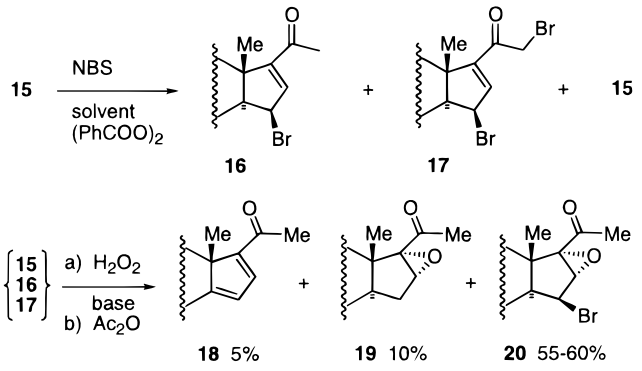
free radical reactions, CCl_4, benzene, and cyclohexane, were tested on both small and large scales. All small scale reactions produced **16** in good yield (75−85%). However, the yield in benzene decreased significantly upon scale-up. In both CCl_4 and cyclohexane, the reaction could be performed on a 10−20 g scale and at higher concentrations (0.02−0.03 M) without significant reduction in the yield of **16**, thereby imparting a significant preparative advantage. Cyclohexane was the preferred solvent due to the cost and toxicity associated with CCl_4. The reaction also returned 15% of unreacted enone **15**. Extended reaction time (2 h) or increased amounts of NBS (1.2 equiv) simply increased the proportion of unwanted dibromide **17**.

Scheme 2



a. DIBAL/-78°C, β/α = 9:1; b. Ac_2O/pyr, hexane recryst.; c. Ac_2O/pyr•HCl/Δ; d. CrO_3/HOAc; e. Al_2O_3/benzene

Scheme 3

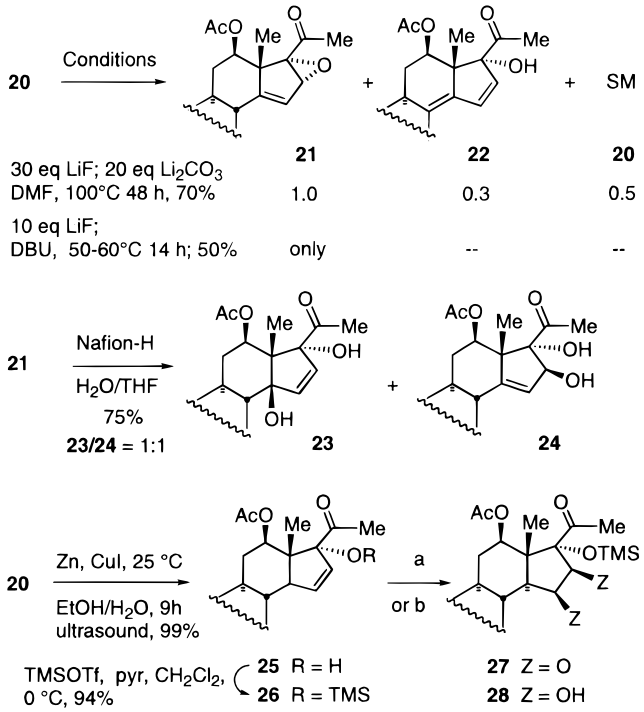


Because of separation difficulties, the crude mixture of **15**/**16**/**17** was epoxidized with alkaline hydrogen peroxide.[12] After treatment with acetic anhydride to reacetylate some C3 alcohol that arose in the epoxidation step, a mixture of three products was isolated. The reaction afforded dienone **18** (5−10%) that likely resulted from elimination of **16**, epoxide **19** (10%) from oxidation of enone **15**, and the desired epoxyketone **20** (55−60%) as a single stereoisomer. Products derived from dibromide **17** did not survive the reaction.

Although the D-ring oxidation state was secured, completion of the D-ring functionality proved extremely challenging. Elimination of bromoepoxide **20** to vinyl epoxide **21** was only

(11) Templeton, J. F.; Yan, Y. *Org. Prep. Proced. Int.* **1992**, *24*, 159.
(12) Julian, P. L.; Meyer, E. W.; Karpel, W. J.; Waller, I. R. *J. Am. Chem. Soc.* **1950**, *72*, 5145.

Scheme 4



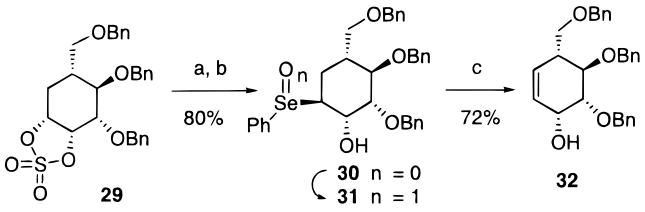
a) xs DMDO,10d, 25 °C, 30%; b) OsO_4 /Pyr; $NaHSO_3$, 25 °C, 5h, 96%

marginally successful even after substantial optimization, yielding a mixture of starting material **20**, desired product **21**, and dienylic alcohol **22** (resulting from further transformation of **21**) (Scheme 4). Many attempts were made to suppress the second elimination. After much experimentation it was found that warming **20** in neat DBU with LiF (10 equiv) provided complete conversion to **21** without any evidence for formation of **22**, although the low yield (50%) was troublesome.

This route was rapidly abandoned after finding that hydrolysis of vinyl epoxide **21** yielded an unacceptable 1:1 mixture of 1,4-diol **23** and target diol **24**. The low yield of **21** in conjunction with the failure to effect regiospecific epoxide opening necessitated reformulation of the synthetic plan.

The revised plan involved establishment of the trans C16,17 oxygenation pattern prior to introduction of the C14,15 double bond. Reductive cleavage of bromoepoxide **20** with ultrasonicated zinc/copper couple[13] proved highly effective at generating tertiary allylic alcohol **25**, which was then protected as its TMS ether **26**.[14] While the wisdom of selecting a TMS protecting group was open to serious question, the issue was settled on a pragmatic basis. Since it proved impossible to even introduce

Scheme 5



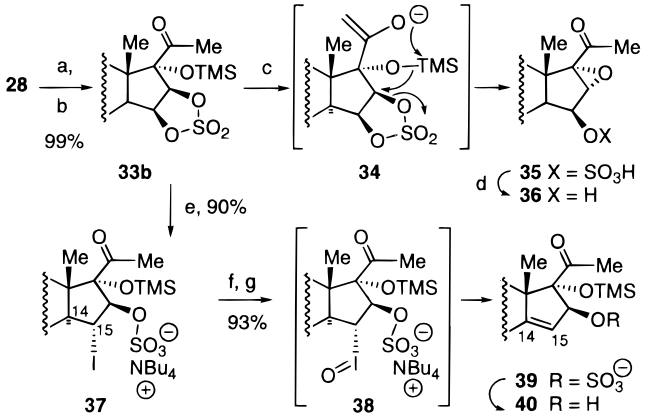
a) NaSePh; b) H^+; c) 1. mCPBA; 2. 80 °C

a TES ether with the same silyl triflate technology, the TMS series was carried forward. This approach presumably succeeded because of the sterically confined nature of the silicon moiety.[15] When olefin **26** was exposed to mCPBA in CH_2Cl_2 for extended periods, the starting material was recovered in over 90% yield. The olefin was also unreactive to mCPBA even at higher reaction temperatures.[16] The low reactivity of the olefin **26** was again apparent when repeated infusions of an excess of the highly reactive oxidant dimethyldioxirane[17] required 10 days to effect epoxidation of **26**, affording **27** in a meager 30% yield (60% recovered **26**). Fortunately, osmylation[18] of olefin **26** stereospecifically generated diol **28** in nearly quantitative yield (Scheme 4). Attempts to use catalytic OsO_4 were fruitless.

Cyclic sulfates[19] have been known for a number of years and have been exploited as electrophilic epoxide equivalents. An excellent review by Lohray[19d] explains the features that distinguish cyclic sulfates from epoxides. Although they are less strained (~5 vs ~27 kcal/mol), five-membered cyclic sulfates contain a better leaving group. They occasionally show complementary regioselectivity to epoxides in nucleophilic ring-opening reactions and appear more reactive than the corresponding epoxides. Sharpless[19a] recently developed a facile conversion of 1,2-diols into cyclic sulfates that has resulted in ready availability of this class of compounds. In 1993, Shing[19c] described the reaction of cyclic sulfate **29** with selenide anion to generate *trans*-diaxial seleno alcohol **30** after hydrolysis of the sulfate salt (Scheme 5). Regiospecific oxidative elimination of selenoxide **31** led to allylic alcohol **32** in good yield.

Two variants of the above strategy were next attempted for synthesis of the key allylic alcohol **40**. As anticipated, conversion of diol **28** to cyclic sulfate **33b** through cyclic sulfite **33a** (not shown) occurred smoothly with use of the Sharpless protocol (Scheme 6).[19a] However, attempts to introduce the requisite olefin functionality with base-catalyzed elimination of

Scheme 6



a) $SOCl_2/Et_3N$, CH_2Cl_2, 0 °C, 2 h; b) $NaIO_4$/ $RuCl_3$, aq. CH_3CN, 0.5 h; c) Base or NaSePh; d) H^+; e) 7 eq Bu_4NI, $PhCH_3$, 110 °C , 15 h; f) 3 eq mCPBA, CH_2Cl_2, 25 °C, 2.5 h; g) cat. H_2SO_4, 5 eq H_2O, THF, 25 °C

(13) (a) Nicolaou, K. C.; Duggan, M. E.; Ladduwahetty, T. *Tetrahedron Lett.* **1984**, *25*, 2069. (b) Sarandeses, L. A.; Mourino, A.; Luche, J. L. *J. Chem. Soc. Chem. Commun.* **1991**, 818.

(14) Smith, A. B., III; Lupo, A. T., Jr.; Ohba, M.; Chen, K. *J. Am. Chem. Soc.* **1989**, *111*, 6648.

(15) A similar example can be found in Paul Wender's total synthesis of (+)-resiniferatoxin. A hindered TMS ether survived HF treatment. Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976.

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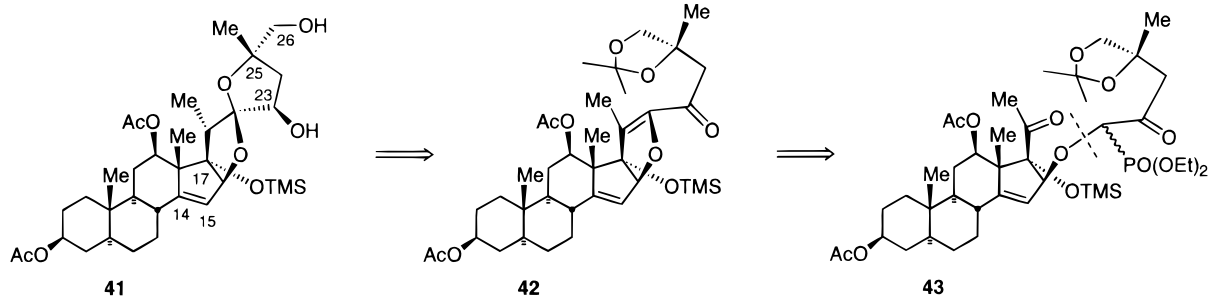
(17) (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) For review, see: Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205.

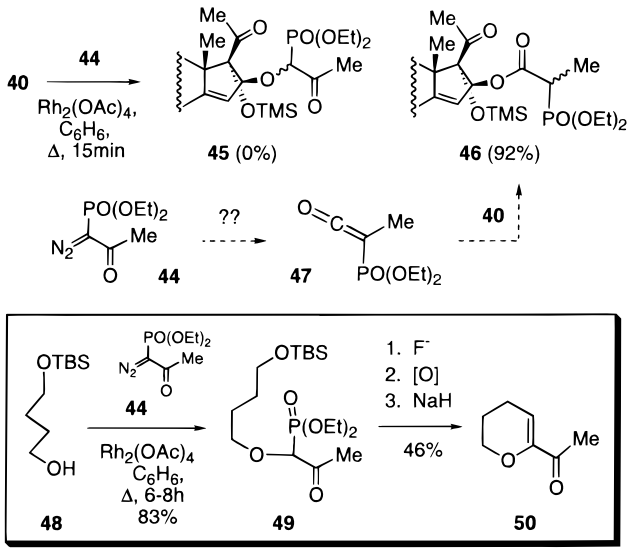
(18) Allen, W. S.; Bernstein, S. *J. Am. Chem. Soc.* **1956**, *78*, 1909.

(19) (a) Sharpless, K. B.; Gao, Y. *J. Am. Chem. Soc.* **1988**, *110*, 7538. (b) Ramaswamy, S.; Prasad, K.; Repic, O. *J. Org. Chem.* **1992**, *57*, 6344. (c) Shing, T. K. M.; Tai, V. W. F. *J. Chem. Soc. Chem. Commun.* **1993**, 995. (d) For review, see: Lohray, B. B. *Synthesis* **1992**, 1035.

Scheme 7



Scheme 8



sulfate **33b** were completely unrewarding. The only product isolated from these reactions was epoxy alcohol **36**, which may have arisen by intramolecular oxygen silylation of the ketone enolate (i.e. via **34**). No attempts were made to detect the putative silyl enol ether intermediate since an acidic workup was necessary to hydrolyze sulfate monoester **35**. Compound **36** also resulted from the action of NaSePh on sulfate **33b**.

To avoid the base lability problem, we investigated the S_N2 chemistry of substrate **33b** with iodide ion to introduce the C14,15 olefin. Treatment of sulfate **33b** with excess TBAI (tetrabutylammonium iodide) in toluene at reflux afforded iodo ammonium sulfate **37** in 90% yield (Scheme 6). Oxidation of **37** with mCPBA in CH_2Cl_2 provided key intermediate allylic alcohol **40** after protonolysis of ammonium sulfate **39**. This reaction is thought to proceed via syn-elimination of hypoiodous acid from iodoso intermediate **37**, a reaction originally developed by Reich[20] that is vastly under-exploited in complex synthesis[21,22] relative to the standard sulfoxide and selenoxide protocols. Also remarkable is that selective *protonolytic cleavage of ammonium sulfate **39** to alcohol **40** can be effected without concomitant hydrolysis of the TMS ether moiety*.

Having established the D-ring oxidation pattern, efforts were next focused upon synthesis of the E-ring present in the North 1 segment of the cephalostatins. Based on the retrosynthetic analysis (Scheme 7), α-alkoxy phosphonate ester **43** was required for E-ring annulation via an intramolecular Wadsworth−Emmons reaction. Previously published model studies[23] had indicated difficulty with the specificity of olefin osmylation as a means of establishing the C25,26 diol. Therefore, we envisaged construction of intermediate **42**, bearing an appropriately configured acetonide in an effort to avoid osmylation of a remote C25,26 olefin.[24] The appealing feature of this plan was the potential (ultimately not realized) for incorporation of the 25*S* stereocenter via reuse of the previously excised side chain or adoption of an appropriate "chiral pool" starting material. Establishment of the requisite C−O bond of compound **43** (see dashes, Scheme 7) was projected to occur via OH insertion into the rhodium carbenoid derived from an α-diazoketophosphonate with methodology developed by Moody.[25]

Since Moody has shown that unhindered primary alcohol **48** reacts slowly with α-diazoketophosphonate **44** to afford α-alkoxyketophosphonate **49**,[25] we investigated the reaction of secondary neopentyl alcohol **40** with **44** before proceeding with construction of the optically active α-diazoketophosphonate required for synthesis of **43** (Scheme 8). Surprisingly, reaction of **44** with **40** in the presence of dirhodium tetraacetate was faster by a factor of 20 than reaction with the simple alcohol **48**. Unfortunately, the product was not the desired α-alkoxyketophosphonate **45**, but was rather phosphonate-ester **46**, formed as a ∼1:1 mixture of diastereomers in 92% yield. While this product is formally in accord with a mechanism involving Wolff rearrangement[26] of **44** to ketene **47** with trapping by **40**, the fact that the slower-reacting Moody substrate **48** does not also form ketene adducts akin to **46** poses an interesting problem for future mechanistic study.[27]

From the failure of the model study above, it became apparent that assembling α-diazoketophosphonate **43** would be extremely difficult. To overcome this problem, the insertion reactions of α-diazophosphonate-ester **51** were explored (Scheme 9). It has been shown that the ester moiety is less prone to rearrange than the keto group in the rhodium(II) catalyzed diazophosphonate reaction with alcohols[28] and we were pleased to see that reaction

(20) Reich, H. J.; Peake, S. L. *J. Am. Chem. Soc*. **1978**, *100*, 4888.

(21) For additional examples of the synthetic potential of this strategy, see: (a) Macdonald, T. L.; Narasimhan, N.; Burka, L. T. *J. Am. Chem. Soc*. **1980**, *102*, 7760. (b) McCabe, P. H.; deJenga, C. I.; Stewart, A. *Tetrahedron Lett.* **1981**, *22*, 3679. (c) Zefirov, N. S.; Zhdankin, V. V.; Makhon'kova, G. V.; Dan'kov, Y. V.; Koz'min, A. S. *J. Org. Chem.* **1985**, *50*, 1872. (d) Citterio, A.; Gandolfi, M.; Giordano, C.; Castaldi, G. *Tetrahedron Lett.* **1985**, *26*, 1665. (e) Holmes, C. P.; Bartlett, P. A. *J. Org. Chem.* **1989**, *54*, 98. (f) Knapp, S.; Naughton, A. B. J.; Dhar, T. G. M. *Tetrahedron Lett.* **1992**, *33*, 1025; see also ref 19.

(22) For an improved procedure for oxidation of iodides to iodoso intermediates with dimethyldioxirane see: Mahadevan, A.; Fuchs, P. L. *J. Am. Chem. Soc*. **1995**, *117*, 3272.

(23) (a) Jeong, J. U.; Fuchs, P. L. *J. Am. Chem. Soc*. **1994**, *116*, 773. (b) Jeong, J. U.; Fuchs, P. L. *Tetrahedron Lett.* **1994**, *35*, 5385.

(24) See following article: Jeong, J. U.; Guo, C.; Fuchs, P. L. *J. Am. Chem. Soc*. **1999**, *121*, 2071.

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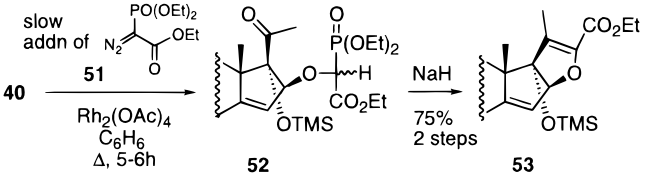
(26) (a) Corbel, B.; Hernot, D.; Haelters, J.-P.; Sturtz, G. *Tetrahedron Lett.* **1987**, *28*, 6605. (b) Cossy, J.; Belotti, D.; Thellend, A.; Pete, J. P. *Synthesis* **1988**, 720. (c) Andriamiadanarivo, R.; Pujol, B.; Chantegrel, B.; Deshayes, C.; Doutheau, A. *Tetrahedron Lett.* **1993**, *34*, 7923.

(27) It seems possible that a bidentate ligating effect of the β-hydroxy ketone is responsible for enhancement of the Wolff reaction or its operational equivalent.

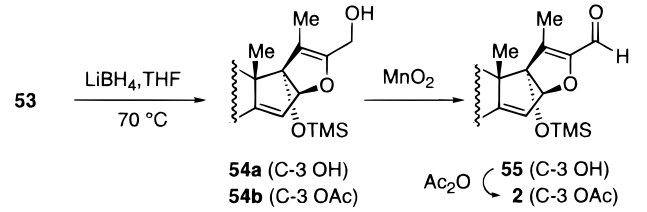
Scheme 9



of **51** with allylic alcohol **40** provided the desired insertion product **52** as a 1:1 mixture of diastereomers. Although this substrate represented the most highly functionalized alcohol which had been transformed to an α-alkoxyphosphonate at the time, subsequent studies from our group have revealed that the Moody protocol is a highly versatile strategy for the construction of complex targets.[1f,29] Due to the difficulty associated with isolation and separation,[30] **52** was carried through the intramolecular Wadsworth−Emmons reaction without additional purification. Treatment of the crude **52** with sodium hydride in THF for 10 min at 0 °C smoothly afforded the five-membered intramolecular Wadsworth−Emmons product **53** in 75% yield for the two-step procedure. The facile transformation of **40** to alkoxydihydrofuran-ester **53** was surprising, since the assembly of the densely functionalized E-ring was initially judged to be one of the most difficult tasks of the synthesis.

Completion of the synthesis of key intermediate **2** was uneventful (Scheme 10). Lithium borohydride reduction[31] of **53** provided a mixture of allylic alcohols **54a**/**54b** which only differ in that **54a** suffered acetate cleavage at C3 during borohydride treatment. This mixture was selectively reoxidized to a corresponding mixture of aldehydes **55**/**2** with MnO_2. A final acetic anhydride treatment was employed on the crude aldehydes **55**/**2** to convert the minor amount of **55** to the key pentacyclic aldehyde **2**. The overall yield for these three steps was 61%, resulting in an overall 9% yield of **2**. Subsquent studies on larger scales have resulted in 7−8% yields for the 20-step sequence from hecogenin acetate **1** to aldehyde **2**.

Scheme 10



Synthesis of the North 1 Spiroketal[32]

Various procedures examined for addition of methallylstannane to aldehyde **2** (Scheme 11) are summarized in Table 1. The more polar major adduct **3** was hydrolyzed to the C3,12,-17,23 tetraol **57** and the C23 stereochemistry was secured by X-ray crystallography.[33] The best methallyl stannane reaction involved 5 M $LiClO_4$ in ether,[34] affording a 1.3:1 mixture of **3**

Scheme 11

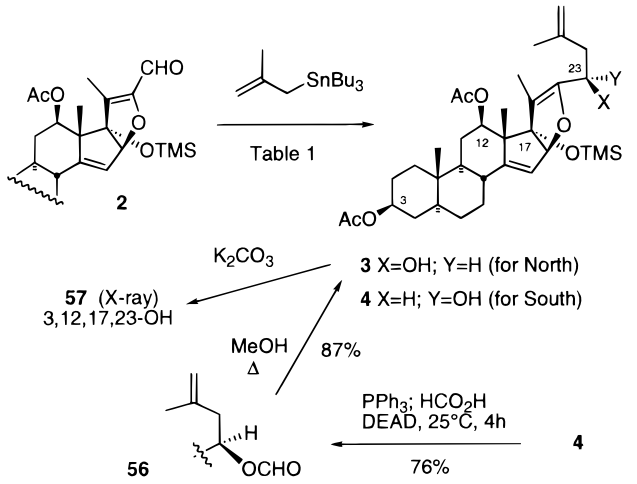


Table 1

entry	reagents	conditions	yield (ratio **3**:**4**)
1	methallyl stannane	BF_3·Et_2O, CH_2Cl_2, −78 °C, 1 h	80% (1.6:1.0)[a]
2	methallyl stannane	5.0 M $LiClO_4$,[34] Et_2O, 25 °C, 1 h	>95% (1.3:1.0)
3	methallyl-(−)-IPc_2B[35]	THF, −78 °C, 1 h	69% (1.7:1.0)[b]
4	methallyl stannane	(−)-Binaphthol, MS $Ti(O\text{-}iPr)_4$, CH_2Cl_2	NR[c,36]
5	methallyl stannane	(+)-Binaphthol, MS $Ti(O\text{-}iPr)_4$, CH_2Cl_2	NR[c]

[a] In large scale reactions the yields dropped below 50% due to the acid lability of **2**. [b] The 3-Ac was also cleaved during workup. [c] Even at 25 °C, no reaction was observed after 2 d.

and **4** in nearly quantitative yield. Asymmetric methallylation technology was also explored with the hope that double diastereoselection would be possible. Use of Brown's chiral methallyl boron reagent[35] gave a slightly better ratio of diastereomeric homoallyl alcohols (1.7:1), but the chemical yields were disappointingly low (65−75%) due in part to concomitant cleavage of the C3 acetate. Unfortunately, no reaction was observed under Keck's conditions[36] (Table 1, entries 4, 5). Since the unnatural diastereomer **4** served as progenitor of the South portion of cephalostatin 7 (**10**) via deoxygenation,[37] the readily separable mixture of alcohols **3** and **4** was perfectly acceptable at this juncture. Further stocks of "North" alcohol **3** could be secured via Mitsunobu inversion.[38] Reaction of **4** with formic acid and triphenylphosphine in the presence of diethyl azodicarboxylate smoothly afforded formate **56** in 76% yield. Heating this material in methanol at reflux provided natural alcohol **3** in 87% yield.

(28) Georgian, V.; Boyer, S. K.; Edwards, B. *J. Org. Chem.* **1980**, *45*, 1686.

(29) Bhandaru, S.; Fuchs, P. L. *Tetrahedron Lett.* **1995**, *36*, 8347.

(30) The R_f value of compound **52** is almost the same as that of diazophosphonate **51** which was used in excess, so the mixture was used directly in the Wadsworth−Emmons reaction.

(31) (a) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *J. Org. Chem.* **1982**, *47*, 4702. (b) Brown, H. C.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 1606.

(32) For a preliminary account of this phase of the work, see: Kim, S.; Sutton S. C.; Fuchs, P. L. *Tetrahedron Lett.* **1995**, *36*, 2427.

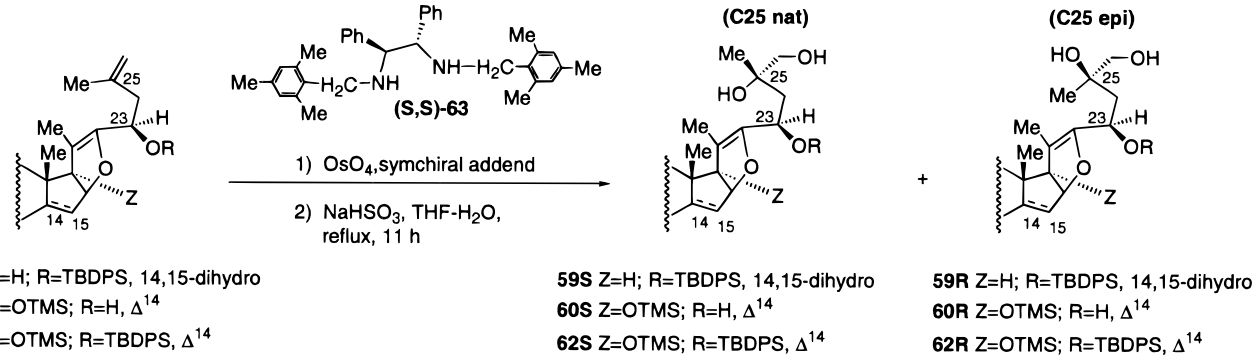
(33) X-ray structural information relating to compounds **57**, **72**, and **82** can be obtained from the Cambridge Crystallographic Data Centre.

(34) Henry, K. J., Jr.; Grieco, P. A.; Jagoe, C. T. *Tetrahedron Lett.* **1992**, *33*, 1817.

(35) (a) Racherla, U. S.; Liao, Y.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 6614. (b) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535. (c) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 320. (d) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem. 1986*, **51**, 432. (e) Brown, H. C.; Jadhav, P. K.; Perumal, P. T. *Tetrahedron Lett.* **1984**, *25*, 5111. (f) Brown, H. C.; Jadhav, P. K. *J. Org. Chem.* **1984**, *49*, 4091. (g) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.

(36) (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (b) Keck, G. E.; Krishnamurthy, D.; Grier, M. *J. Org. Chem.* **1993**, *58*, 6543. (c) Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827. (d) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Ronchi, A. U. *J. Am. Chem. Soc.* **1993**, *115*, 7001.

Scheme 12



58 Z=H; R=TBDPS, 14,15-dihydro
3 Z=OTMS; R=H, Δ^{14}
61 Z=OTMS; R=TBDPS, Δ^{14}

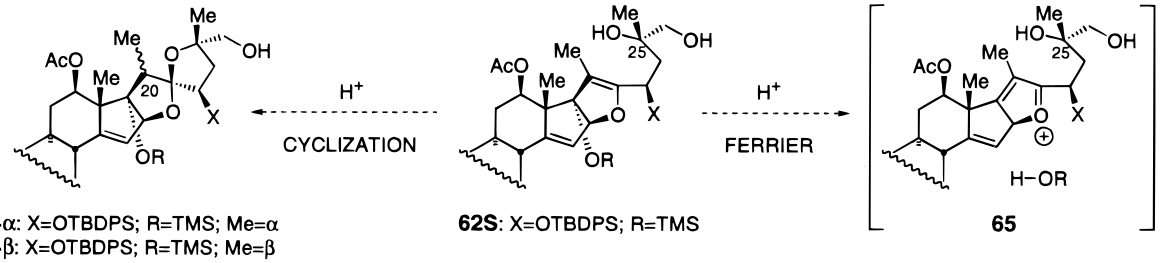
59S Z=H; R=TBDPS, 14,15-dihydro
60S Z=OTMS; R=H, Δ^{14}
62S Z=OTMS; R=TBDPS, Δ^{14}

59R Z=H; R=TBDPS, 14,15-dihydro
60R Z=OTMS; R=H, Δ^{14}
62R Z=OTMS; R=TBDPS, Δ^{14}

Table 2. Asymmetric Dihydroxylation of Terminal Alkenes

entry	substrate	conditions	yield (%)	ratio	C25 nat/epi
1	**58**	(*S,S*)-**63**, −100 °C, 0.5h[a,23]	98%	**59*S*/59*R***	8:1
2	**3**	(*S,S*)-**63**, −95 °C, 1 h	95%	**60*S*/60*R***	2:1
3	**3**	Sharpless AD-mix-α, 25 °C, 24 h	∼25% conv	**60*S*/60*R***	2:1
4	**3**	Sharpless AD-mix-*β*, 25 °C, 24 h	∼25% conv	**60*S*/60*R***	1:4
5	**61**	Sharpless AD-mix-α, 25 °C, 24 h	∼30% conv	**62*S*/62*R***	1:2
6	**61**	(*S,S*)-**63**, −95 °C, 1 h	95%	**62*S*/62*R***	4:1

Scheme 13



64α: X=OTBDPS; R=TMS; Me=α
64β: X=OTBDPS; R=TMS; Me=β

62S: X=OTBDPS; R=TMS

65

67α: X=OH; R=H; Me=α; 3-OH
67β: X=OH; R=H; Me=β; 3-OH

66S: X=OH; R=H; 3-OH

Having unambiguously determined the C23 stereochemistry of the homoallylic alcohol **57**, attention was turned toward establishment of the C25,26 diol functionality. With the acid-sensitive, electron-rich dihydrofuran moiety making most electrophilic methods (epoxidation, halohydroxylation)[39] doubtful, it seemed prudent to employ osmylation.

An osmylation model study[23a] (Scheme 12 and Table 2, entry 1) with 17-deoxy-14,15-dihydro olefin **58** required symchiral Corey ligand **63**[40] to provide reasonable diastereoselection (**59*S***/**59*R*** ∼ 8:1). Consequently, we first examined reaction of alcohol **3** using these conditions. While neither this reaction nor the Sharpless AD procedure[41] was acceptable for alcohol **3** (Table 2, entries 2−4), ligand **63** provided a usable 4:1 ratio of inseparable diols **62*S***/**62*R*** when the reaction was conducted on *tert*-butyldiphenylsilyl ether **61** (98% from **3** by the method of Hardinger,[42] Table 2, entry 6).

With the inseparable 4:1 mixture of diols **62*S***/**62*R*** as well as the corresponding mixture of tetraols **66*S***/**66*R*** (prepared via desilylation of the C17,23 diol mixture **62*S***/**62*R***) in hand, the stage was set to study acid-catalyzed spiroketal formation. A serious concern was the possibility of ionization of the C17 oxygen substituent via a Ferrier-type process[43] that could result in unwanted side products via intermediate **65** (Scheme 13).

In a model study[23a] lacking the $\Delta^{14,15}$ unsaturation and the C17 oxygen moiety, cyclization of diol **59S** (Scheme 12) under acidic conditions was unproductive. However, model triol **68S** underwent cyclization at 25 °C to provide an 8:1 mixture of spiroketals **69***β* and **70***β* both bearing the unnatural *β*-methyl configuration at C20 (Scheme 14). Brief heating of the reaction mixture at 80 °C provided **69***β* in near quantitative yield. It was hoped that in the real system, the tertiary C17 TMS ether might prevent protonation from the α-face of the molecule, thereby giving the natural α-methyl configuration at C20 (**64**α or **67**α).

Initial acid-mediated cyclization studies were conducted on the inseparable mixture of TBDPS protected diols **62*S***/**62*R***. When mild acids (pyridinium *p*-toluenesulfonate = PPTs or lutidinium *p*-toluenesulfonate) were employed, there was no reaction as expected due to the combined steric and inductive effects of the C17 and C26 oxygens. When the PPTs reaction was heated at reflux at 80 °C, or when stronger acids (Nafion-

(37) Jeong, J. U.; Fuchs, P. L. *Tetrahedron Lett.* **1995**, *36*, 2431. See also ref 24.

(38) (a) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234. (b) Caine, D.; Kotian, P. L. *J. Org. Chem.* **1992**, *57*, 6587. (c) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487.

(39) (a) Johnson, W. S.; Chan, M. F. *J. Org. Chem.* **1985**, *50*, 2598. (b) Ichikawa, Y.; Isobe, M.; Bai, D. L.; Goto, T. *Tetrahedron* **1987**, *43*, 4737.

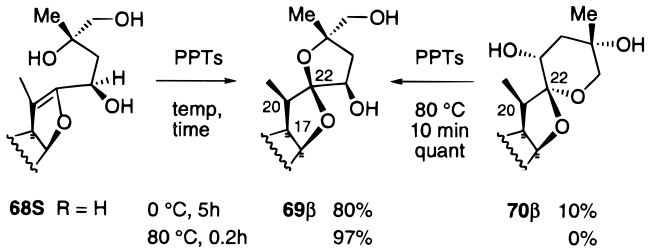
(40) Corey, E. J.; Jardine, P. D.; Virgil, S.; Yuen, P. W.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243.

(41) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768

(42) Hardinger, S. A.; Wijaya, N. *Tetrahedron Lett.* **1993**, *34*, 3821.

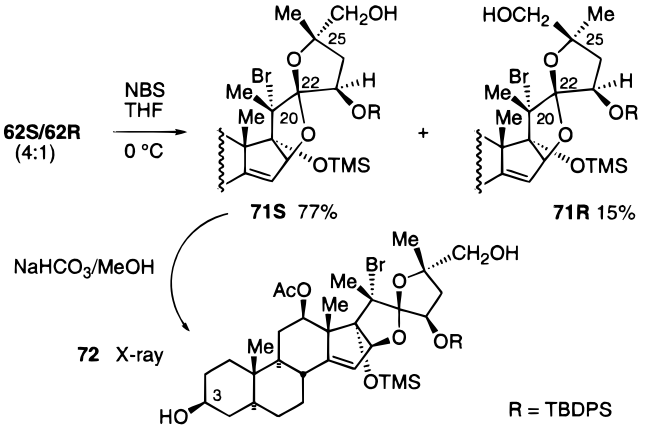
(43) Ireland, R. E.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7166 and references therein.

Scheme 14



H, TfOH, $HClO_4$, BF_3·2HOAc) were employed, complex mixtures resulted. The proton NMR spectra of these mixtures contained signals for the desired spiroketal **64**α, albeit in very low yield (<10%). Due to the complexity of the product mixture as well as the poor yield of the desired product, this approach was not synthetically viable. Cyclization of a 4:1 diastereomeric mixture of tetraols **66*S***/**66*R*** prepared via desilylation of the 4:1 **62*S***/**62*R*** mixture was also unfruitful. Further acid-catalyzed cyclizations were not attempted.

Scheme 15



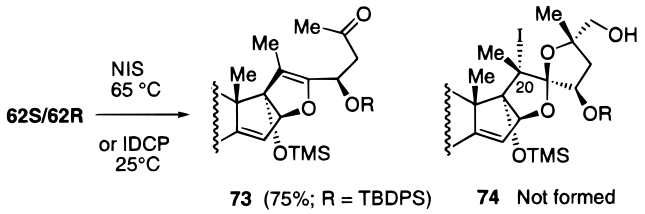
While reaction of the 4:1 **62*S***/**62*R*** diol mixture with a variety of acids was unrewarding, NBS-mediated spirocyclization[23a] cleanly afforded the C20 brominated 5/5 spiroketal **71*S*** (77%), chromatographically separable from its diastereomer **71*R*** (15%) which resulted from cyclization of the minor diol **62*R*** (Scheme 15). The structure of **71*S*** was confirmed by X-ray of alcohol **72**[33] obtained by methanolysis of the C3 acetate.

Attempts to incorporate iodide at C20 by using either NIS[44] or the highly reactive IDCP (Iodonium di-Collidine Perchlorate)[45] were not successful (Scheme 16). Presumably these reactions were unsuccessful due to the bulkiness of the reagents which retarded reaction at the enol ether moiety, thereby leading to the unwanted ketone **73** via oxidative fragmentation[46] of the C25,26 diol (Scheme 16).

Stereoselective Reduction of Hindered Bromides

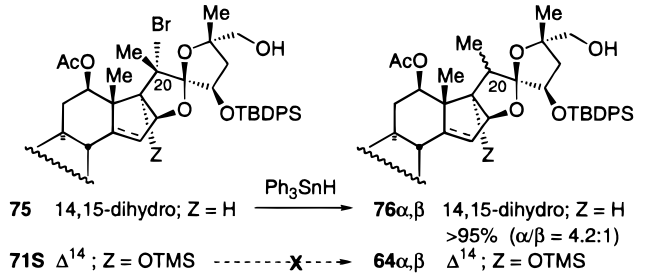
Stereoselective reductive cleavage of the tertiary C20 bromide **71*S*** provided the most severe challenge of the entire synthesis. To obtain the natural α-methyl configuration at C20, we wished to debrominate **71*S*** to **64**α as shown in Scheme 17. To this end, triphenyltin hydride reduction of bromide **71*S*** was initially

Scheme 16



attempted. Unfortunately, only complex mixtures were isolated without any sign of the debrominated products **64**α,*β*. This was surprising since tin hydride cleavage of model compound **75** to spiroketals **76**α,*β* was an excellent reaction.[23a]

Scheme 17



A number of other methods were investigated, including photochemical protocols[47−51] (Scheme 18, Table 3). It is known that alkyl halides can be reduced by irradiation in an appropriate solvent with or without reducing additives. Electron transfer within the initial radical pair cage is postulated to afford carbenium ion intermediates responsible for alkene and nucleophilically substituted sideproducts. Irradiation of **71*S*** at 254 nm in alcoholic solvent provided olefin **77** as the only product (65%), without a trace of the desired **64**. Another attempt in the presence of tin hydride[52] at 350 nm gave the same result.

Reductions via cationic intermediates under various conditions such as $NaCNBH_3$/ $ZnCl_2$[53] or $SnCl_2$[53] and Et_3SiH/Lewis acids[54] were next attempted. Unfortunately, **71*S*** was inert to these conditions. Reduction under basic conditions was also explored. However, these methods (including Birch reduction,[55] transmetalation by *t*-BuLi, Zn/Cu alloy, and lithium biphenylide) showed either no reaction or decomposition.

Since the bulky α-face silyl ether at C17 might have been responsible for retarding the reduction of the α-face C20 bromide, deprotection of the TMS group was explored (Scheme 19). Surprisingly, the C23 TBDPS group was also cleaved under mild conditions (TBAF/0 °C). Careful examination via TLC showed that deprotection of both silicon groups occurred essentially simultaneously. The resultant bromo-triol **78** was too unstable for further manipulation. When a large excess of TBAF

(44) (a) Konradsson, P.; Mootoo, D. R.; Mcdevitt, R. E.; Reid, B. F. *J. Chem. Soc. Chem. Commun.* **1990**, 270. (b) Veeneman, G. H.; Van Leeuwe, S. H.; Van Boom, J. H. *Tetrahedron Lett*. **1990**, *31*, 1331. (c) Merritt, J. R.; Reid, B. F. *J. Am. Chem. Soc*. **1992**, *114*, 8334. (d) Olah, G. A.; Wang, Q.; Sandford, G.; Prakash, G. K. S. *J. Org. Chem.* **1993**, *58*, 3194.

(45) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem*. **1965**, *43*, 2190.

(46) Beebe, T. R. *J. Org. Chem*. **1981**, *46*, 1927.

(47) Kropp, P. *Acc. Chem. Res*. **1984**, *17*, 131.

(48) Shibata, I.; Nakamura, K.; Baba, A.; Matsuda, H. *Tetrahedron Lett.* **1992**, *33*, 5709.

(49) Vedejs, E.; Duncan, S. M.; Haight, A. R. *J. Org. Chem*. **1993**, *58*, 3043.

(50) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Synlett* **1991**, 435.

(51) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1992**, *33*, 5709.

(52) Kahne, D.; Yang, D.; Lim, J. J.; Miller, R.; Paguaga, E. *J. Am. Chem. Soc*. **1988**, *110*, 8716.

(53) (a) Kim, S.; Kim, Y.; Ahn, K. H. *Tetrahedron Lett*. **1983**, *24*, 3369. (b) Kim, S.; Ko, J. S. *Synth. Commun*. **1985**, *15*, 603.

(54) Doyle, M. P.; Mcoster, C. C.; West, C. T. *J. Org. Chem.* **1976**, *41*, 1393.

(55) Berkowitz, D. B. *Synlett* **1990**, 649.

Scheme 18

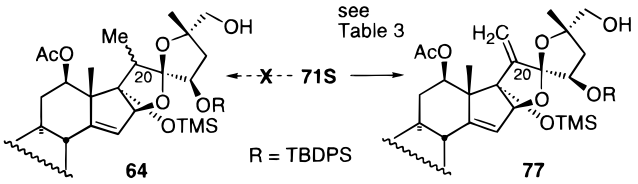
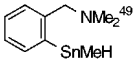
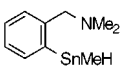


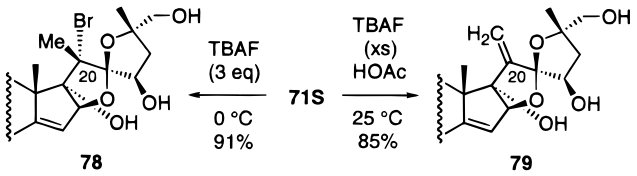
Table 3. Initial Debromination Experiments with Bromide **71S**

entry	reagents	conditions	results
1	Bu_3SnH	AIBN, 80 °C	complex
2	Bu_3SnH	Rayonet (350 nm), RT, 1 h	**77** 65%
3	Ph_3SnH	AIBN, 50 °C	**71S** recov
4	Ph_3SnH	AIBN, 80 °C	complex
5	Bu_2SnH_2[48]	AIBN, 80 °C	complex
6	 [49]	AIBN, 80 °C	complex
7		Rayonet (350 nm), RT,1 h	**77** 60%
8	$PhSiH_3$[50]	AIBN, 80 °C	**71S** recov
9	H_3PO_2/Et_3N[51]	AIBN, 110 °C	complex

was used in the presence of acid, elimination of bromide **71*S*** occurred to give olefinic triol **79** in good yield.

Although hydrogenation of olefin **79** might be expected to produce **64**β bearing the unnatural β-methyl configuration at C20, several protocols were attempted with **79**, including H_2/

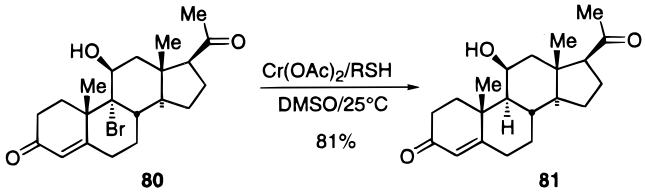
Scheme 19



Pd/60psi,[56] diimide,[57] and $[Ir(cod)(Pcy_3)Py]PF_6/H_2$.[58] Unfortunately, no **64** was observed.

In 1966, Barton reported that bromohydrin **80** could be reduced to alcohol **81** with retention of stereochemistry by using chromium acetate in the presence of a hydrogen atom transfer agent (Scheme 20).[59] In another example of chromium(II) de-

Scheme 20



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(57) Vedejs, E.; Buchanan, R. A. *J. Am. Chem. Soc.* **1989**, *111*, 8426.
(58) (a) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655. (b) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072.
(59) (a) Barton, D. H. R.; Basu, N. K.; Hesse, R. H.; Morehouse, F. S.; Pechet, M. M. *J. Am. Chem. Soc.* **1966**, *88*, 3016. (b) Barton, D. H. R.; Basu, N. K. *Tetrahedron Lett.* **1964**, *43*, 3151.
(60) (a) Bachi, M. D.; Epstein, J. W.; Minzly, Y.; Loewenthal, H. E. *J. Org. Chem.* **1969**, *34*, 126. (b) House, H. O.; Zaiko, E. *J. Org. Chem.* **1977**, *42*, 3780. (c) Hook, J. M.; Mander, L. N.; Urech, R. *J. Am. Chem. Soc.* **1980**, *102*, 6628. (d) Hook, J. M.; Mander, L. N.; Urech, R. *J. Org. Chem.* **1984**, *49*, 3250.
(61) (a) Hanson, J. R.; Premuzic, E. *Angew. Chem., Int. Ed. Engl.* **1968**, 247. (b) Hanson, J. *Synthesis* **1974**, 1.
(62) Kochi, J. K.; Mocadlo, P. E. *J. Am. Chem. Soc.* **1966**, *88*, 4094.

Scheme 21

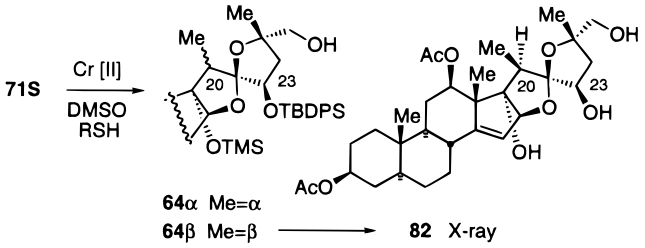


Table 4. Reduction of **71S** in DMSO

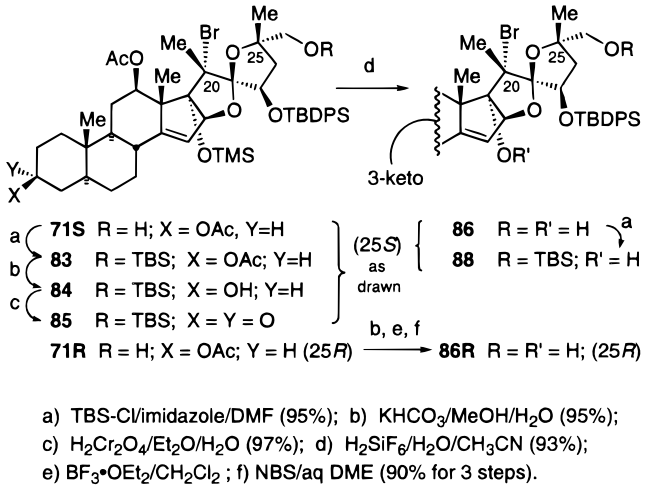
entry	**71S** + reagents and H donor[a]	temp (°C)	time	results
1	20 equiv $Cr(OAc)_2$; 80 equiv *n*−PrSH	50	48 h	**64**β (30%)
2	4 equiv $Cr(OAc)_2$; 40 equiv ED[b]	25	5 min	**77** (99%)
3	4 equiv $CrCl_2$; 10 equiv *n*−PrSH	25	24 h	no reaction
4	4 equiv $CrCl_2$; 100 equiv *n*−PrSH	25	5 h	**64** [α/β = 1:7] (80%)
5	4 equiv $CrCl_2$; 10 equiv Ph_3SnH	25	30 min	**64** [α/β = 1:2] (30%)
6	5 equiv $CrCl_2$; 100 equiv *t*−BuSH	25	6 h	**77** (50%) + **64**β (5%)

[a] DMSO was degassed by Ar which was pretreated with basic pyrogallol solution. [b] ED = ethylenediamine.

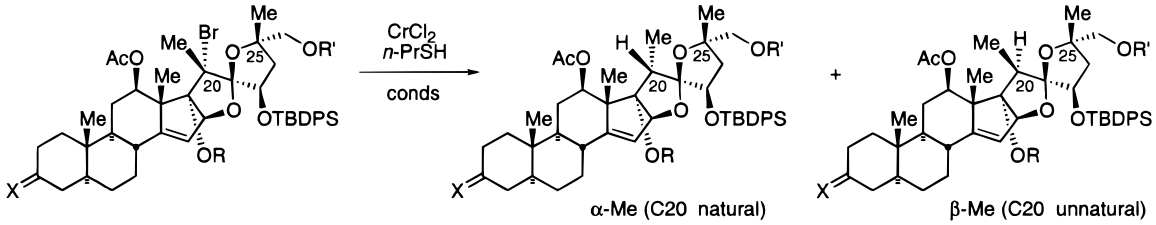
halogenation, inversion was observed.[60] It is generally held that the stereochemistry of such reductions is strongly influenced by thermodynamics at the stage of the radical intermediate.[61] This reaction signaled the beginning of the explosive growth of radical technology pioneered by the Barton school. Interestingly, with the advent of the now standard tin hydride protocols, chromium(II) mediated reductions have seen few applications in recent years. Of particular interest with reference to dehalogenation of **71*S*** was the prospect of generating the tris-β-alkoxy radical at lower reaction temperatures than via the tin hydride procedures.

Bromide **71*S*** was treated with excess $Cr(OAc)_2$ in the presence of *n*-propyl mercaptan (Scheme 21, Table 5, entry 1). While the reaction was unacceptably slow, it was extremely rewarding to isolate a C20 reduction product for the first time (30% yield) in addition to recovered starting material (60%). While the C20 stereochemistry (**64**α or **64**β) was initially indeterminate, nOe studies indicated a proximal relationship between the C23 methine and the C20 methine, which suggested

Scheme 22



Scheme 23



87 X = β-OAc, R = H, R' = H

89α X = β-OAc, R = H, R' = H (a)
92α X = β-OAc, R = H, R' = TBDMS

89β X = β-OAc, R = H, R' = H (a)
92β X = β-OAc, R = H, R' = TBDMS

86 X = O, R = H, R' = H
88 X = O, R = H, R' = TBDMS

90α X = O, R = H, R' = H (a)
91α X = O, R = H, R' = TBDMS

90β X = O, R = H, R' = H (a)
91β X = O, R = H, R' = TBDMS

86R X = O, R = H, R' = H (25*R*)

93α X = O, R = H, R' = H (25*R*)

93β X = O, R = H, R' = H (25*R*)

(a) TBDMSCl/imidazole/DMF, 25 °C, 6h (quantitative).

Table 5. Dependence of Stereoselectivity on Substrate Structure and Conditions

entry	SM	R	R′	X	no. of equiv of *n*-PrSH	solvent, temp	time (h)	products [ratio][a](yield)
1	**71*S***	TMS	H	β-OAc	100	DMSO, 25 °C	6	**64** [α/β = 1:7] (80%)
2	**87**	H	H	β-OAc	100	DMSO, 25 °C	0.5	**89** [α/β = 3.5:1] (90%)
3	**86**	H	H	O	100	DMSO, 25 °C	0.5	**90** [α/β = 3.6:1] (87%)
4	**86**	H	H	O	200	DMF, −15 °C	2.5	**90** [α/β = 9:1] (84%) (recov 13% **86**)
5	**86**	H	H	O	200	DMF, −40 °C	6	**90** [α/β = 6:1] (80%) (recov 15% **86**)
6	**88**	H	TBS	O	200	DMSO, 25 °C	12	**91**α (60%) + **91**β (15%) (+10% **88**)
7	**86*R***	H	H	O	200	DMF, −15 °C	2	NR
8	**86*R***	H	H	O	200	DMF, 25 °C	6	**93** [α/β = 5.5:1] (90%)
9	**85**	TMS	TBS	O	100	DMSO, 25 °C	12	NR

[a] Ratio for inseparable diastereomers estimated by NMR.

that the product had the unnatural β-methyl configuration **64**β. This assignment was ultimately secured by single-crystal X-ray analysis of bis-desilylated triol diacetate **82**.[33]

Although β-face quenching with thiol would give **64**α bearing the more stable natural α-methyl configuration at C20, the α-configured radical from bromide **71*S*** may have been quenched by excess thiol to give **64**β before equilibration to the more stable β-configured radical precursor of **64**α.

In an effort to mediate the selectivity of the chromium(II) system, a number of experiments were undertaken. The reactivity of $Cr(OAc)_2$ was greatly improved by adding ethylenediamine,[62] but the product was olefin **77** (Table 4, entry 2). Attempts involving $CrCl_2$ were initially disappointing as no reaction occurred (entry 3). Finally, we noted that reduction proceeded smoothly (80%) *provided that a large excess of thiol was employed* (entry 4). These observations indicated that the thiol might act not only as a hydrogen atom donor but also as a ligand, thereby enhancing the reducing power of chromium(II). The NMR spectra of the products revealed a disappointing 1:7 ratio of the long sought **64**α in addition to its inseparable diastereomer **64**β. Repeating the reaction with more sterically demanding H-atom donors was unsatisfactory (entries 5,6).

Faced with an apparently impossible separation of the C20 diastereomers, it seemed prudent to delay bromide reduction until after introduction of the ketone at C3. Accordingly, the C26 hydroxyl of **71*S*** was converted to C26 TBDMS ether **83**, followed by cleavage of the C3 acetate which afforded alcohol **84** (Scheme 22). Oxidation to ketone **85** followed by selective bis-desilylation with H_2SiF_6[63] provided diol **86** in 83% overall yield for the four-step procedure. Further reduction substrates were generated by mono-desilylation of **71*S*** to give **87** (17-OH, 94% from **71*S*** via H_2SiF_6[63] cleavage, see Scheme 23), reprotection of the C26−OH of **86** to afford **88**, and conversion of **71*R*** to **86*R***. In this case, it was found that prior protection of the C26−OH was unnecessary, as NBS-mediated oxidation[64] of the 3,17,26-triol derived from **71*R*** proceeded smoothly at C3 to give diol **86*R*** in high yield.

The breakthrough to achieve the correct C20 stereochemistry involved *conducting the chromium-mediated reductive cleavage on the C17 alcohol* (Scheme 23 and Table 6). For example, while reduction of **71*S*** (17-OTMS) generated a 1:7 mixture of **64**α and **64**β (Table 4, entry 4 = Table 5, entry 1), reaction of **87** afforded a 3.5:1 ratio of **89**α to **89**β in 90% yield (Table 5, entry 2). This structural feature carried over to the C3-keto series, with essentially identical results being obtained for dehalogenation of ketone **86** (17-OH) to **90**α and **90**β (entry 3). Furthermore, a substantially improved ratio of 9:1 for the C20 diastereomers **90**α,β was attained simply by carrying out the reduction in DMF at −15 °C (entry 4), although even lower temperature gave sluggish reaction with diminished selectivity (entry 5). While the ketodiols **90**α/**90**β were not readily separable, protection of the C26 neopentyl alcohols as TBS ethers enabled surprisingly facile isolation of the pure keto-alcohols **91**α and **91**β (Scheme 23, R = H, R′ = TBDMS, X = O) in 76% and 8% overall yields from **86**, respectively. The C3 acetates **89**α/**89**β could be likewise separated as their 26-OTBS ethers **92**α and **92**β (70% and 20%, respectively, from **87**).

Substantial effects on reduction rate were apparent for the silyloxy groups at both C17 and C26. Reaction of **87** (17-OH) proceeded far more quickly than had that of **71S** (17-OTMS). Reduction of **86** (17α,26α diol) was much faster than that of **88** (17α-OH, 26α-OTBDMS), although no change in selectivity was evident (both gave a ∼3.5:1 C20α/β ratio, entries 2 and 5). Interestingly, **86*R*** (17α,26β diol, the 25*R* epimer of **86**) also exhibited a slower rate than did **86** (entries 6 and 7), raising

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Scheme 24

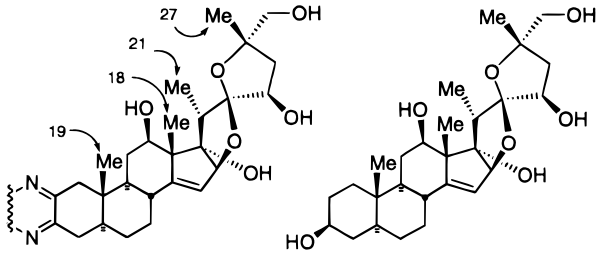


Table 6. Proton NMR Resonances in Pyridine-d_5

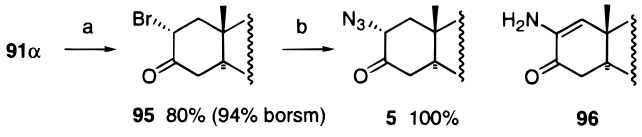
compd	C-19 (s)	C-18 (s)	C-21 (d)	C-27 (s)
CSTAT 7 (**10**)[2]	0.75	1.31	1.33	1.61
CSTAT 12 (**9**)[6]	0.73	1.33	1.35	1.63
94α	0.78	1.31	1.34	1.63
94*β*	0.80	**1.93**	**1.65**	1.63

the possibility that the 26α-OH facilitates the reaction by coordinating with the reagents. Finally, the combination of silyloxy groups at both C17α and C26α appeared to completely block access to C20 since reduction of **85** is impossibly slow (entry 8). While a more complete understanding of the mechanistic implications of these observations awaits further refinement,[65] it is apparent that a free alcohol moiety at C17 appears to be an absolute structural requirement for production of the desired stereochemistry.

While the stereochemical assignment of all of the hexacyclic compounds ultimately rested on the X-ray of **82** (desilylated **64***β*), the four methyl resonances in the proton NMR (pyridine-d_5) of pentaols **94**α and **94***β* (from deprotection of **92**α and **92***β*, respectively) were particularly informative when compared to the published data from natural products cephalostatin 7 (**10**)[2] and the "North dimer" cephalostatin 12 (**9**, Scheme 24). As can be seen in Table 6, the methyl resonances of **94**α, assigned the natural configuration at C20, had essentially identical chemical shifts to the North segments of the two reference cephalostatins. Furthermore, compound **91**α was used to complete the synthesis of both cephalostatins 7 (**10**) and 12[6] (**9**), thus removing any ambiguity about the structure of the spiroketal array.[1]

Completion of the synthesis of α-azidoketone **5** simply involved treatment of ketone **91**α with phenyltrimethylammonium perbromide (PTAB) in THF for short reaction times to afford α-bromoketone **95** (80%, 94% based on recovered **91**α) which was subjected to reaction with tetramethylguanidinium azide (TMGA) in nitromethane[66] (Scheme 25). This protocol

Scheme 25



smoothly generated α-azidoketone **5** in 75−85% yield (nearly quantitative on small scales). This can be contrasted with other azide reactions such as sodium azide in DMF that produced **5** along with up to 25% of α-aminoenone **96** resulting from competitive enolization and fragmentation[67] of azidoketone **5**.

Experimental Section

General Methods. All reactions were performed under a positive pressure of argon at 25 °C with magnetic stirring unless otherwise noted.Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl; benzene, toluene, CH_2Cl_2, dimethyl sulfoxide (DMSO), and dimethylformamide (DMF) were distilled from calcium hydride. Acetonitrile (CH_3CN), chloroform ($CHCl_3$), and methanol (CH_3OH) were spectra-grade. Ethyl acetate (EA) was reagent grade. Hexane (Hex) was distilled (95% hexanes). Thin-layer chromatography (TLC) was performed on silica gel 60 F-254 plates (EM reagents, 0.25 mm). Preparative column chromatography (sgc) was performed with 230−400 mesh silica gel. NMR spectra were determined in chloroform-d_1 ($CDCl_3$) at 300 (proton) and 75 MHz (carbon) unless otherwise noted [benzene-d_6 (C_6D_6), pyridine-d_5 (C_5D_5N), methanol-d_4 (CD_3OD), or deuterium oxide (D_2O) were alternate solvents] and are reported in parts per million (ppm, δ) referenced to internal $CHCl_3$ (7.26 and 77.00 ppm), C_6D_5H (7.15 ppm), CD_2HOD (3.30 and 49.00 ppm), C_5D_4HN (8.71 and 149.5 ppm), or HOD (4.65 ppm). Peak multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad), ap (apparent), and ABq (AB quartet). In APT spectral lists, chemical shifts of carbons with one or three attached hydrogens are marked with an asterisk; the unmarked chemical shifts represent carbons with zero or two attached hydrogen atoms. Mass spectra were run by the Purdue Campus-wide Mass Spectrometry Facility; peaks are reported as *m/z*. Microanalyses were performed by the Purdue Chemistry Department Microanalytical Laboratory.

Bromo Epoxide 20. A mixture of enone **15** (15 g, 36 mmol, from **1** via modification of the method of Dauben and Micovic[8,10,68]), NBS (7.4 g, 41 mmol), and a catalytic amount of benzoyl peroxide (0.40 g, 1.8 mmol) in cyclohexane (1.8 L) was heated at reflux for 3 h and then cooled. Succinimide was removed by filtration and the solvent evaporated under reduced pressure. The resulting oil was composed (by NMR) of unreacted starting enone **15** (∼15%), γ-bromo enone **16** (∼75%), and dibromide **17** (<5%). This ternary mixture was dissolved in 400 mL of methanol, cooled to 0 °C, and treated with 4 N NaOH (0.6 mL) and then immediately with a 30% H_2O_2 solution (0.65 mL). The mixture was then stirred at 0 °C for 24 h. The reaction was acidified with 5% HCl to pH 3, extracted into EA, and evaporated to give a pale brownish oil. The residue was reacetylated (Ac_2O/pyr), and sgc (25% EA in Hex) afforded bromo epoxide **20** (10.5 g, 57%), epoxy ketone **19** (10%), and ketone **18** (5%). Compound **20**: ^{1}H NMR δ 4.79 (1H, dd), 4.66 (1H, m), 4.3 (1H, d, J = 5.4 Hz), 3.85 (1H, s), 2.01 (3H, s), 2.00 (3H, s), 2.0 (3H, s), 1.45 (3H, s), 0.9 (3H, s), 2.0−0.9 (remaining H, m); ^{13}C NMR (50 MHz) δ 204.1, 171.7, 171.1, 74.2*, 73.7*, 71.9, 63.7*, 53.2*, 49.6*, 47.9*, 47.5, 45.2*, 36.86, 36.2, 34.1, 31.6*, 31.0, 28.6, 27.7, 27.1 27.0*, 22.0*, 21.7*, 13.8*, 12.5*; MS (FAB) 451 (M − HOAc, base); HRMS (FAB) calcd for $C_{25}H_{35}O_6$-Br 451.1484, found 451.1465; $[\alpha]^{23}_D$ −40.5° ($CHCl_3$, *c* 8); mp 185−187 °C.

17: ^{1}H NMR δ 6.66 (1H, d), 4.91 (1H, dd), 4.87 (1H, m), 4.68 (1H, m), 4.14 (2H, AB, two d), 2.00 (3H, s), 2.02 (3H, s), 1.41 (3H, s), 0.93 (3H, s), 2.2−0.8 (remaining H's, m).

18: ^{1}H NMR δ 7.21 (1H, d), 6.03 (1H, b, s), 4.62 (1H, m), 4.23 (1H, dd), 2.22 (3H, s), 1.96 (3H, s), 1.21 (3H, s), 0.92 (3H, s), 2.4−0.6 (remaining H's, m); ^{13}C NMR δ 193.2, 170.8, 170.6, 167.8, 153.3, 143.8, 120.9, 75.2, 73.2, 58.1, 52.0, 44.2, 37.0, 35.9, 34.8, 33.8, 29.1, 28.0, 27.8, 27.3, 27.2, 21.5, 21.4, 14.5, 12.2; MS (EI) 414 (M), 354 (M − HOAc, base), (CI) 415 (M + H, base), 355 (M + H − HOAc); HRMS (EI) calcd for $C_{25}H_{34}O_5$ 414.2406, found 414.2400.

19: ^{1}H NMR δ 4.87 (1H, dd), 4.63 (1H, m), 3.49 (1H, s), 2.01 (3H, s), 1.98 (3H, s), 1.97 (3H, s), 1.21 (3H, s), 0.82 (3H, s), 2.3−0.6 (remaining H's, m).

(65) A study of factors influencing the course of the chromium(II) mediated reduction is in progress and will be the subject of a future report.

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Vinyl Epoxide 21 and Dienyl Alcohol 22. A solution of bromo epoxide **20** (73 mg, 0.14 mmol) was stirred with LiF (109 mg) and Li_2CO_3 (207 mg) in DMF at 100 °C for 48 h. The reaction mixture was cooled and diluted with EA. The organic layer was washed with H_2O, dried, and concentrated to give pale yellow oil; sgc (EA/Hex) afforded **21** and **22** as well as SM **20** (**20**:**21**:**22** = 0.5:1.0:0.3). Vinyl epoxide **21**: ^{1}H NMR δ 5.68 (1H, brd, J = 0.9 Hz), 4.91 (1H, dd), 4.66 (1H, m), 3.98 (1H, s), 2.04 (3H, s), 2.03 (3H, s), 2.02 (3H, s), 1.43 (3H, s), 0.86 (3H, s), 2.2−0.6 (remaining H, m); ^{13}C NMR (50 MHz) δ 204.9, 171.1, 170.1, 161.8, 119.6*, 74.5*, 73.7*, 71.4, 65.1*, 54.1, 50.4*, 44.3*, 37.1, 36.2, 34.3*, 34.2, 29.5, 28.2, 27.7, 27.2*, 26.9, 21.9*, 21.7*, 16.4*, 12.3*; MS (EI) 430 (M), 387 (M − $COCH_3$, base), (CI) 431 (M + H), 371 (M + H − HOAc, base); HRMS (EI) calcd for $C_{25}H_{34}O_6$ 430.2355, found 430.2339.

22: ^{1}H NMR (200 MHz) δ 6.70 (1H, d, J = 5.7 Hz), 5.95 (1H, d, J = 6.0 Hz), 5.46 (1H, dd), 4.72 (1H, m), 3.50 (1H, s), 2.62 (1H, s), 2.30 (3H, s), 2.07 (3H, s), 2.02 (3H, s), 1.08 (3H, s), 0.81 (3H, s), 2.2−0.6 (remaining H, m); ^{13}C NMR (50 MHz) δ 211.4, 171.9, 171.1, 140.1, 134.8*, 133.2, 132.7*, 91.2, 73.6*, 71.3*, 51.5, 50.3*, 44.3*, 38.0, 36.5, 34.3, 30.1, 29.0, 28.8*, 27.8, 25.6, 21.9*, 21.8*, 19.0*, 13.4*; MS (EI) 387 (M − $COCH_3$), 327 (M − $COCH_3$−HOAc, base), (CI) 431 (M + H), 413 (M + H − H_2O), 353 (M + H − H_2O − HOAc, base).

Tertiary Allylic Alcohol 25. Zinc dust (253 mg, 3.87 mmol) and CuI (270 mg, 1.4 mmol) were sonicated in 50% EtOH (10 mL). After formation of a black suspension (0.5 h), a solution of bromo epoxide **20** (221 mg, 0.43 mmol) in a minimum of THF was added and sonication was continued until TLC indicated consumption of **20** (∼15 h). Addition of saturated NH_4Cl, filtration, extraction with EA, and sgc afforded **25** (183 mg, 99%). ^{1}H NMR δ 6.25 (1H, dd, J = 5.9, 1.7 Hz), 5.91 (1H, dd, J = 5.7, 3.3 Hz), 5.42 (1H, dd), 4.68 (1H, m), 3.70 (1H, s), 2.45(1H, m), 2.25 (3H, s), 2.1 (3H, s), 2.05 (3H, s), 0.9 (3H, s), 0.85 (3H, s), 2.0−1.0 (remaining H, m); ^{13}C NMR (50 MHz) δ 211.5, 172.4, 171.1, 138.1*, 132.1*, 90.6, 73.7*, 72.7*, 55.3*, 55.1, 53.8*, 45.1*, 36.8, 36.1, 34.2, 31.9, 31.5*, 28.8*, 28.7, 27.7, 27.2, 21.9*, 21.7*, 13.3*, 12.6*; MS (EI) 432 (M), 269 (M − $COCH_3$ − 2HOAc, base), (CI) 433 (M + H), 415 (M + H − H_2O, base); HRMS (EI) calcd for $C_{25}H_{36}O_6$ 432.2511, found 432.2494. Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.05; H, 8.74. $[\alpha]^{25}_D$ − 50.6° ($CHCl_3$, *c* 12); mp 70−73 °C (foam).

TMS Ether 26. To a solution of alcohol **25** (270 mg, 1.4 mmol) in pyridine at 0 °C was added TMSOTf (0.86 mL, 4.4 mmol). The mixture was stirred for 1 h, then partitioned between EA and saturated $NaHCO_3$. The organic layer was washed with saturated $CuSO_4$, dried (Na_2SO_4), and evaporated, and sgc (10% EA in Hex) afforded **26** as a white foam (1.41 g, 94%). ^{1}H NMR δ 6.04 (1H, dd, J = 6.0, 1.5 Hz), 5.87 (1H, dd, J = 6.0, 3.6 Hz), 5.40 (1H, dd), 4.67 (1H, m), 2.35 (1H, m), 2.19 (3H, s), 2.01 (3H, s), 1.98 (3H, s), 0.81 (3H, s), 0.71 (3H, s), 0.15 (9H, s), 2.0−0.8 (remaining H, m); ^{13}C NMR (50 MHz) δ 212.0, 172.0, 170.0, 136.2*, 134.1*, 94.0, 73.9*, 73.8*, 56.2*, 56.0, 53.8*, 45.0*, 30.5, 36.0, 34.0, 32.0, 31.9*, 29.0, 28.0, 27.0, 26.5*, 22.0*, 12.5*, 2.0*; MS (EI) 461 (M − $COCH_3$, base), (CI) 505 (M + H), 415 (M + H − H_2O − TMS, base); HRMS (CI) calcd for $C_{28}H_{44}O_6Si$ 504.2906, found 504.2888.

Epoxide 27. To a solution of allyl TMS ether **26** (10 mg, 0.02 mmol) in CH_2Cl_2 was added an excess of 0.1 M dimethyldioxirane in acetone. The mixture was stirred during 10 d with fresh DMDO added repeatedly. The solvent was evaporated, and sgc gave **27** (3 mg, 30%) and **26** (6 mg, 60%). ^{1}H NMR δ 5.12 (1H, dd), 4.65 (1H, m), 3.45 (2H, m), 2.25 (3H, s), 2.05 (3H, s), 1.98 (3H, s), 1.01 (3H, s), 0.85 (3H, s), 0.17 (9H, s), 2.0−0.8 (remaining H, m); ^{13}C NMR (50 MHz) δ 209.7, 171.2, 170.3, 89.4, 74.1*, 73.8*, 57.4*, 53.9*, 53.5*, 52.7*, 47.0, 45.1*, 36.7, 36.3, 34.2, 31.9, 31.3*, 28.7, 27.9*, 27.7, 27.4, 21.9*, 21.8*, 14.7*, 12.5*, 2.2*.

Diol 28. To a solution of olefin **26** (1.39 g, 2.75 mmol) in pyridine was added OsO_4 (840 mg, 3.3 mmol). The mixture was stirred for 10 h, then hydrolyzed with saturated $NaHSO_3$ for 5 h. CH_2Cl_2 was added, and the precipitate was collected by filtration (Celite) and washed with warm CH_2Cl_2. The combined filtrates were washed twice with saturated $CuSO_4$, dried (Na_2SO_4), and concentrated; sgc (35% EA in Hex) provided **28** (1.43 g, 96%) as a white foam. ^{1}H NMR δ 5.82 (1H, d, J = 4.5 Hz, D_2O exchangeable), 5.08 (1H, d), 4.7 (1H, m), 4.24 (1H, dd, J = 6.0, 4.5 Hz), 4.14 (1H, m), 3.0 (1H, brd, J = 1.5 Hz), 2.2 (3H, s), 2.0 (3H, s), 1.98 (3H, s), 0.98 (3H, s), 0.85 (3H, s), 0.2 (9H, s), 2.1−0.9 (remaining H, m); ^{13}C NMR (50 MHz) δ 218.3, 171.1, 170.1, 89.5, 82.9*, 74.3*, 73.9*, 71.0*, 53.7, 52.7*, 52.5*, 45.0*, 36.9, 36.1, 34.2, 31.7, 31.0*, 28.7, 28.5*, 27.7, 27.0, 21.9*, 21.8*, 12.7*, 12.5*, 1.9*; MS (EI) 538 (M), 435 (M − $COCH_3$ − HOAc, base), (CI) 539 (M + H), 479 (M + H − HOAc − H_2O, base); HRMS (EI) calcd for $C_{28}H_{46}O_8Si$ 538.2961, found 538.2955. Anal. Calcd for $C_{28}H_{46}O_8Si$: C, 62.42; H, 8.61; Si, 5.21. Found: C, 62.16; H, 8.94; Si, 4.87. $[\alpha]^{23}_D$ − 22.0° in CH_2Cl_2 (*c* 11).

Cyclic Sulfate 33. To a well-stirred solution of diol **28** (0.20 g, 0.37 mmol) in pyridine at 0 °C was added $SOCl_2$ (0.8 mL) dropwise over 5 min. The ice bath was removed and the mixture was stirred for 30 min, diluted with EA, and washed with saturated $CuSO_4$, then passed through silica to give **33a**. The sulfite **33a** was dissolved in CH_3CN and cooled to 0 °C, and $NaIO_4$ (120 mg, 0.56 mmol) was added followed by a catalytic amount (5%) of $RuCl_3$ hydrate and 10 mL of H_2O. After 10 min, the mixture was diluted with CH_2Cl_2 and worked up to afford **33b** (219 mg, 99%) as a white solid. ^{1}H NMR δ 5.23 (1H, brt, J = 5.7, 5.4 Hz), 4.96 (1H, dd), 4.78 (1H, d, J = 5.7 Hz), 4.67 (1H, m), 2.4 (3H, s), 2.01 (3H, s), 1.92 (3H, s), 1.26 (3H, s), 0.87 (3H, s), 0.12 (9H, s), 2.0−0.9 (remaining H, m); ^{13}C NMR (50 MHz) δ 204.3, 171.0, 170.1, 89.7, 87.4*, 84.2*, 73.6*, 73.0*, 53.2, 52.4*, 52.0*, 44.9*, 36.8, 36.2, 34.1, 31.3*, 31.0, 30.8*, 28.4, 27.6, 26.5, 21.8*, 21.2*, 12.5*, 12.2*, 2.3*; MS (EI) 557 (M − $COCH_3$), 497 (M − $COCH_3$ − HOAc), (CI) 601 (M + H); HRMS (EI) calcd for $C_{28}H_{44}O_{10}S_1Si$ 600.2425, found 600.2404. Anal. Calcd for $C_{28}H_{44}O_{10}S_1Si$: C, 55.98; H, 7.4; S, 5.34; Si, 4.67. Found: C, 56.10; H, 7.55; S, 5.23; Si, 4.45. $[\alpha]^{23}_D$ − 54.0° in CH_2Cl_2 (*c* 12); mp: 202−204 °C.

33a (a pair of diastereomers): ^{1}H NMR δ 5.43 and 5.08 (H-15, brt), 5.01 and 4.59 (H-16, d), 4.98 (H-12, dd), 4.69 (H-3, m), 2.42 and 2.38 (Me-21, s), 2.01 (C-3 OAc, s), 1.92 (C-12 OAc, s), 1.42 and 1.09 (Me-18, s), 0.87 (Me-19, s), 0.15 and 0.12 (OTMS, s)

Hydroxy Epoxide 36. To a CH_2Cl_2 solution of cyclic sulfate **33** (6 mg, 0.01 mmol) was added DBU (4 mg, 0.03 mmol). After 10 h, the mixture was poured into ice-cold sulfuric acid solution (1 N) and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over $MgSO_4$. After evaporation of solvent, crude epoxide **36** (5.5 mg) was obtained as an oil. ^{1}H NMR δ 4.82 (1H, dd), 4.81 (1H, d), 4.18 (1H, s), 3.63 (1H, br, s), 2.02 (3H, s), 1.99 (3H, s), 1.97 (3H, s), 1.40 (3H, s), 0.83 (3H, s).

Allylic Alcohol 40. To a solution of cyclic sulfate **33** (0.24 g, 0.39 mmol) in toluene (∼0.01 M) was added tetrabutylammonium iodide (1.1 g, ∼7 equiv). The mixture was stirred for 15 h at reflux and then cooled. Precipitated TBAI was removed by filtration and washed twice with toluene. The combined organic filtrates were evaporated in vacuo. The residue was dissolved in CH_2Cl_2, and 60% mCPBA (336 mg, ∼3 equiv) was added. After 3 h, the mixture was poured into cold H_2O. The organic layer was washed successively with saturated $NaHCO_3$ and dried (Na_2SO_4). After concentration under reduced pressure, the yellowish residue was dissolved in THF (10 mL) to which H_2O (0.1 mL) had been added. The clear solution was carefully acidified to pH 3 with concentrated H_2SO_4 and stirred for 2 h (until TLC analysis indicated all the ammonium salt had been hydrolyzed), then diluted with EA, washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated to afford a yellow oil in which only **40** was observed by ^{1}H NMR analysis. Sgc (15% EA in Hex) gave **40** (81%) as a white foam. ^{1}H NMR δ 5.46 (1H, dd, J = 2.1, 2.1 Hz), 5.26 (1H, dd), 5.13 (1H, brd, J = 2.7 Hz), 4.69 (2H, m), 2.26 (3H, s), 2.02 (3H, s), 2.01 (3H, s), 1.12 (3H, s), 0.85 (3H, s), 0.16 (9H, s), 2.1−0.9 (remaining H, m); ^{13}C NMR (50 MHz) δ 217.5, 171.1, 170.0, 155.6, 122.2*, 88.4, 83.5*, 73.7*, 73.3*, 57.7, 50.5*, 44.3*, 37.0, 36.1, 35.0*, 34.2, 30.0, 28.5*, 28.4, 27.7, 27.1, 21.9*, 21.9*, 17.3*, 12.3*, 2.2*; MS (EI) 520 (M), 477 (M − $COCH_3$), (CI) 521 (M + H), 503 (M + H − H_2O, base); HRMS (EI) calcd for $C_{28}H_{44}O_7Si$ 520.2856, found 520.2882. Anal. Calcd for $C_{28}H_{44}O_7Si$: C, 64.58; H, 8.52; Si, 5.39. Found: C, 64.81; H, 8.73; Si, 5.13; $[\alpha]^{23}_D$ +9.60° in CH_2Cl_2 (*c* 9).

Iodide 37: ^{1}H NMR δ 5.03 (1H, brs), 4.94 (1H, dd), 4.69 (1H, m), 4.12 (1H, dd), 2.86 (8H, m), 2.43 (3H, s), 2.01 (3H, s), 1.88 (3H, s), 1.24 (3H, s), 0.82 (3H, s), 0.21 (9H, s).

Sulfate 39: ^{1}H NMR δ 5.83 (1H, brs), 5.28 (1H, brs), 5.12 (1H, dd), 4.69 (1H, m), 3.57 (8H, m), 2.28 (3H, s), 2.02 (3H, s), 1.99 (3H, s), 1.18 (3H, s), 0.82 (3H, s), 0.18 (9H, s).

α-Phosphonate Esters 46. A solution of the diazophosphonate ketone **44** (16 mg, 0.075 mmol) in benzene was added to a mixture of a catalytic amount of $Rh_2(OAc)_4$ and the allylic alcohol **40** (13 mg, 0.025 mmol) in benzene at reflux over 15 min. The solvent was removed by evaporation, and sgc yielded α-phosphonate esters **46** (17 mg, >98%) as a diastereomeric mixture. ^{1}H NMR δ 5.60 (2H, d, J = 2.4 Hz), 5.32 (2H, brt), 5.22 (2H, dd), 4.69 (2H, m), 4.13 (4H, m), 3.05 (2H, m), 2.15 (3H, s), 2.14 (3H, s), 2.02 (6H, s), 2.0 (6H, s), 1.56 (6H, two dd), 1.31 (6H, m), 1.14 (3H, s), 1.12 (3H, s), 0.85 (6H, s), 0.19 (9H, s), 2.0−0.8 (remaining H, m); ^{13}C NMR (50 MHz) δ 209.3, 208.5, 171.1, 170.4, 170.1, 170.1, 169.4, 169.3, 159.7, 159.6, 117.4*, 117.4*, 89.6, 89.4, 83.8*, 83.6*, 73.7*, 73.1*, 63.3, 63.1, 63.0, 58.4, 58.2, 50.7*, 44.4*, 41.9*, 41.1*, 39.3*, 38.4*, 37.0, 36.2, 35.1*, 34.2, 29.8, 29.2*, 29.2*, 28.3, 27.7, 26.9, 21.9*, 21.8*, 17.3*, 16.9*, 16.8*, 16.8*, 12.3*, 12.2*, 12.1*, 11.9*, 11.8*, 2.8*.

Dihydrofuran Ester 53. A solution of the diazophosphonate ester **51** (645 mg, 2.58 mmol) in benzene was added dropwise via syringe drive over 5 to 6 h to a mixture of a catalytic amount (3−4%) of $Rh_2(OAc)_4$ and the allylic alcohol **40** (450 mg, 0.86 mmol) in benzene at reflux. The solvent was removed by evaporation, and sgc of a portion of the residue for analytical purposes provided **52** as a diastereomeric mixture. The crude product **52** was used directly for the synthesis of **53** by slow addition of NaH (155 mg, 1.5 equiv) in THF at 0 °C. After 30 min, EA and H_2O were added, the aqueous layer was extracted with EA, and the combined organic layers were washed with brine and dried. Solvent removal and sgc (10% EA in Hex) gave **53** (380 mg, 75%). ^{1}H NMR δ 5.45 (1H, app t, J = 2.4 Hz), 5.14 (1H, d, J = 2.4 Hz), 5.04 (1H, dd), 4.68 (1H, m), 4.29 (2H, q), 2.02 (6H, s), 1.98 (3H, s), 1.35 (3H, t), 1.07 (3H, s), 0.86 (3H, s), 0.09 (9H, s), 2.04−0.9 (remaining H, m); ^{13}C NMR (50 MHz) δ 171.1, 170.0, 161.7, 160.2, 142.8, 126.8, 117.6*, 98.5, 93.9*, 73.9*, 73.7*, 61.5, 58.9, 50.8*, 44.4*, 37.0, 36.2, 34.8*, 34.2, 29.9, 28.4, 27.7, 27.2, 21.9*, 21.9*, 18.2*, 14.7*, 12.4*, 11.2*, 2.0*; MS (EI) 588 (M), 528 (M − HOAc); HRMS (EI) calcd for $C_{32}H_{48}O_8Si$ 588.3118, found 588.3097. Anal. Calcd for $C_{55}H_{55}O_5Si$: C, 65.28; H, 8.22; Si, 4.77. Found: C, 65.61; H, 8.57; Si, 4.51. $[\alpha]^{24}_D$ −57.5° in CH_2Cl_2 (*c* 10) mp 90−94 °C (typically used as the crude foam).

52: ^{1}H NMR δ 5.58 (1H, brs), 5.06 (1H, two dd), 4.69 (2H, m), 4.54 (1H, brs), 4.4−4.1 (6H, m), 2.30 (3H, two s), 2.01 (6H, four s), 1.21 and 1.18 (3H, two s), 1.82 (3H, s), 0.17 (9H, s).

Dihydrofuran Aldehyde 2. A mixture of dihydrofuran ester **53** (0.41 g, 0.70 mmol) and 2.0 M $LiBH_4$ (1.3 mL, 2.6 mmol) in THF was stirred at reflux for 5 h. The solution was quenched with cold H_2O and the water layer was extracted twice with EA. The combined organic layers were washed with brine, dried (Na_2SO_4), passed through silica gel, and evaporated. The residual oil (**54a**/**54b**) was redissolved in EA and MnO_2 (1.21 g) was added. Vigorous stirring was continued for 3 h. The mixture was filtered (Celite) and the filtrate was evaporated and acetylated (Ac_2O/Et_3N/DMAP) to afford pentacyclic aldehyde **2** (232 mg, 61%) as a white foam. ^{1}H NMR δ 9.69 (1H, s), 5.45 (1H, dd, J = 2.4, 2.1 Hz), 5.15 (1H, d, J = 2.4 Hz), 5.03 (1H, dd), 4.67 (1H, m), 2.04 (3H, s), 2.01 (3H, s), 2.01 (3H, s), 1.07 (3H, s), 0.85 (3H, s), 0.09 (9H, s), 2.04−0.9 (remaining H's, m); ^{13}C NMR (50 MHz) δ 182.4*, 171.1, 170.0, 160.2, 150.1, 132.5, 117.5*, 98.3, 94.0*, 73.7*, 73.7*, 58.9, 50.8*, 44.4*, 37.0, 36.2, 34.8*, 34.2, 30.0, 28.4, 27.7, 27.1, 21.9*, 18.1*, 12.4*, 9.4*, 2.1*; MS (EI) 544 (M), 515 (M − CHO), (CI) 545 (M + H), 395 (M + H − 2HOAc − HCOH, base); HRMS (EI) calcd for $C_{30}H_{44}O_7Si$ 544.2856, found 544.2850; $[\alpha]^{23}_D$ − 50.3° in CH_2Cl_2 (*c* 6).

54a: ^{1}H NMR δ 5.40 (1H, br, t), 5.07 (1H, d, J = 2.4 Hz), 5.03 (1H, dd), 4.17 (2H, d), 3.60 (1H, m), 2.01 (3H, s), 1.65 (3H, s), 1.08 (3H, s), 0.85 (3H, s), 0.09 (9H, s), 2.1−0.8 (remaining H's, m); MS (EI) 504 (M, base), 444 (M − HOAc), (CI) 504, 415 (M + H − HOTMS, base); HRMS (EI) calcd for $C_{28}H_{44}O_6Si$ 504.2907, found 504.2917.

54b: ^{1}H NMR δ 5.40 (1H, br, t), 5.07 (1H, d, J = 2.4 Hz), 5.03 (1H, dd), 4.69 (1H, m), 4.18 (2H, br, d), 2.04 (3H, s), 2.01 (3H, s), 1.65 (3H, s), 1.08 (3H, s), 0.85 (3H, s), 0.09 (9H, s), 2.1−0.9 (remaining H's, m); MS (EI) 546 (M, base), 486 (M − HOAc), (CI) 546 (M), 457 (M + H − HOTMS, base); HRMS (EI) calcd for $C_{30}H_{46}O_7Si$ 546.3013, found 546.3018.

Homoallylic Alcohols 3 and 4 (from 2). A solution of aldehyde **2** (0.21 g, 0.39 mmol) in 5.0 M LPDE (lithium perchlorate diethyl ether) was treated with methallylstannane (0.27 g, 0.78 mmol). After 1 h, the mixture was poured into cold water and EA. The aqueous layer was extracted twice with EA. The combined organic layers were washed with brine, dried, and evaporated to give an oil (1.3:1 **3**:**4** by ^{1}H NMR), and sgc (1% THF/CH_2Cl_2) afforded **3** (126 mg) and **4** (100 mg). Compound **3**: ^{1}H NMR (C_6D_6) δ 5.35 (1H, brs), 5.29 (1H, dd), 5.14 (1H, brd, J = 2.4 Hz), 4.78 (1H, brs), 4.76 (1H, brs), 4.64 (1H, m), 4.47 (1H, m), 2.45 (2H, m), 1.8 (3H, s), 1.68 (3H, s), 1.66 (3H, s), 1.59 (3H, s), 1.14 (3H, s), 0.44 (3H, s), 0.19 (9H, s), 2.04−0.5 (remaining H, m); ^{13}C NMR (C_6D_6) δ 169.3, 168.7, 159.1, 154.0, 141.6, 117.5*, 113.2, 108.0, 98.9, 93.7*, 73.6*, 72.8,*, 65.0*, 58.2, 50.3*, 43.6, 43.4*, 35.9, 35.3, 34.1*, 33.9, 29.3, 27.8, 27.4, 27.1, 22.4*, 21.0*, 20.8*, 17.8*, 11.4*, 8.8*, 1.6*; MS (EI) 600 (M), 545 (M − C_4H_7); HRMS (EI) calcd for $C_{34}H_{52}O_7Si$ 600.3482, found 600.3458; $[\alpha]^{23}_D$ − 24.4° (CH_2Cl_2, *c* 6).

4: ^{1}H NMR (C_6D_6) δ 5.41 (1H, brt), 5.32 (1H, dd), 5.15 (1H, brd, J = 2.4 Hz), 4.80 (1H, brs), 4.86 (1H, brs), 4.67 (1H, m), 4.54 (1H, m), 2.55 (2H, m), 1.85 (3H, s), 1.74 (3H, s), 1.73 (3H, s), 1.70 (3H, s), 1.23 (3H, s), 0.51 (3H, s), 0.19 (9H, s), 2.04−0.5 (remaining H, m); ^{13}C NMR (C_6D_6) δ 169.4, 168.7, 159.6, 154.1, 141.8, 117.4*, 113.4, 108.1, 98.8, 93.6*, 73.5*, 72.9*, 65.1*, 58.4, 50.2*, 43.4*, 43.1, 36.0, 35.3, 34.2*, 33.9, 29.3, 27.8, 27.4, 27.0, 22.3*, 21.0*, 20.8*, 17.8*, 11.4*, 8.7*, 1.6*; MS (EI) 600 (M), 485 (M − C_4H_7 − HOAc, base), (CI) 601 (M + H), 511 (M + H − HOTMS, base); HRMS (EI) calcd for $C_{34}H_{52}O_7Si$ 600.3482, found 600.3494; $[\alpha]^{22}_D$ −39.6° (CH_2Cl_2, *c* 0.5).

Alcohol 3 (from 56). Formate **56** (40 mg, 0.064 mmol) in MeOH (10 mL) was heated at reflux for 15 h, then cooled and concentrated. Sgc gave **3** (33 mg, 87%).

Formate 56 (from 4). A toluene (0.8 mL) solution of alcohol **4** (50 mg, 0.083 mmol), PPh_3 (109 mg, 0.417 mmol), and formic acid (19 mg, 0.42 mmol) was treated with diethyl azodicarboxylate (DEAD, 73 mg, 0.42 mmol). After 2 h, concentration and sgc (10% EA/Hex) gave 40 mg (77%) of formate **56**. ^{1}H NMR δ 8.07 (1H, s), 5.78 (1H, t), 5.39 (1H, brs), 5.02 (1H, s), 5.00 (1H, dd), 4.80 (1H, s), 4.73 (1H, s), 4.70 (1H, m), 2.48 (2H, m), 2.01 (3H, s), 1.99 (3H, s), 1.74 (3H, s), 1.71 (3H, s), 1.02 (3H, s), 0.83 (3H, s), 0.02 (9H, s), 2.2−0.8 (remaining H's, m); ^{13}C NMR δ 170.7, 169.7, 160.1, 159.1, 149.4, 139.8, 117.3, 114.1, 111.9, 98.0, 93.6, 73.8, 73.4, 65.6, 58.2, 50.6, 44.1, 39.6, 36.6, 35.9, 34.3, 33.9, 29.5, 28.1, 27.3, 26.9, 22.6, 21.6, 21.5, 17.8, 12.0, 8.8, 1.6; MS (EI) 628 (M, base), 583 (M − OCHO), (CI) 629 (M + H), 583 (M + H − HOCHO, base); HRMS (EI) calcd for $C_{35}H_{52}O_8Si$ 628.3431, found 628.3443.

Tetraol 57. Alcohol **3** and K_2CO_3 in MeOH was refluxed for 5 h to afford **57**, which was crystallized from MeOH/Hex (1:3.5). ^{1}H NMR (CD_3OD) δ 5.33 (1H, brt), 4.69 (1H, brs), 4.65 (1H, brs), 4.41 (1H, app t, J = 7.3 Hz), 3.84 (1H, dd), 3.5 (1H, m), 2.30 (2H, brd), 2.13 (1H, s), 1.68 (3H, s), 1.66 (3H, s), 1.00 (3H, s), 0.87 (3H, s), 2.1−0.7 (remaining H, m); MS (FAB, NBA matrix) 467 (M + Na); HRMS (FAB, KIPEG/NBA/NaI matrix) calcd for $C_{27}H_{40}O_5$ + Na 467.2773, found 467.2759; mp 160 °C dec.

TBDPS Ether 61. To a solution of $AgNO_3$ (30 mg, 2 equiv) and alcohol **3** (53 mg, 0.089 mmol) in DMF was added TBDPSCl (47 μL, 2 equiv). A white precipitate formed immediately. After 15 min, the mixture was diluted with EA and H_2O. The organic layer was dried, and sgc provided pure **61** (73 mg, 98%) as a colorless oil. ^{1}H NMR δ 7.72 (4H, m), 7.38 (6H, m), 5.40 (1H, brt), 5.0 (1H, brd, J = 2.4 Hz), 4.96 (1H, dd), 4.68 (1H, m), 4.53 (1H, brs), 4.51 (1H, brs), 4.42 (1H, dd), 2.02 (3H, s), 2.00 (3H, s), 1.36 (3H, s), 1.07 (3H, s), 1.05 (9H, s), 0.94 (3H, s), 0.84 (3H, s), 0.03 (9H, s), 2.4−0.7 (remaining H, m); ^{13}C NMR (50 MHz, C_6D_6) δ 170.0, 170.0, 159.8, 154.6, 141.5, 136.9*, 136.9*, 134.8, 134.5, 130.5*, 130.5*, 118.4*, 114.3, 109.4, 99.5, 93.5*, 74.4*, 73.5*, 67.7*, 59.2, 51.0*, 44.5, 44.1*, 36.7, 36.0, 34.8*, 34.6, 30.0, 28.5, 28.1, 27.7*, 22.8*, 21.7*, 21.5*, 20.1, 18.5*, 12.1*, 9.6*, 2.6*; MS (FAB, DTT/DTE matrix) 839 (M); HRMS (FAB, KIPEG/DTT/DTE matrix) calcd for $C_{50}H_{70}O_7Si_2$ 839.4738, found 839.4657.

Diols 62*S*/62*R*. To a solution of [*S*,*S*] Corey ligand **63** (310 mg, 1.3 equiv) in CH_2Cl_2 (0.03 M) at −78 °C was added OsO_4 (1 equiv) in one portion. After 30 min, the mixture was cooled to −98 °C and a precooled solution of TBDPS ether **61** (420 mg, 0.50 mmol) in CH_2Cl_2 was added by cannula over 5 min. After 1 h, powdered $NaHSO_3$ was added, the reaction was warmed, and the solvent was removed in vacuo. The residue was taken up in aqueous THF and refluxed for 11 h. The solids were filtered off and washed with EA, and the combined filtrates were washed with brine and dried. The inseparable mixture of crude diols **62*S*/62*R*** (*S*−C25:*R*-C25 = 4:1) was purified by sgc (414 mg, 95%). ^{1}H NMR δ 7.8 (4H, m), 7.4 (6H, m), 5.43 (1H, brs), 4.95 (H-12, two dd), 4.87 (1H, s), 4.65 (2H, m), 3.35 (1H, s), 3.15 (2H, m), 2.02 and 2.00 (3H, two s (1:4)), 1.95 (3H, two s), 1.65 (3H, s), 1.24 (3H, s), 1.05 (9H, two s), 0.96 (3H, s), 0.82 (3H, s), 0.02 and 0.03 (OTMS, two s (1:4)); ^{13}C NMR, the peaks at δ 162, 118, 111, 98, 72, 71, 23, 18, 8 all show the same 1:4 ratio; MS (FAB, DTT/DTE matrix) 872 (M); HRMS (FAB, KIPEG/DTT/DTE matrix) calcd for $C_{50}H_{72}O_9Si_2$ 873.4792, found 873.4727.

Tetraols 66*S*/66*R*. To a solution of **62*S*/62*R*** (40 mg, 0.046 mmol) in THF was added TBAF (0.18 mL, 4 equiv) in THF. After 2 h, the solution was poured into saturated NH_4Cl and extracted with EA. The organic layer was washed with brine and dried, and sgc (20% MeOH in CH_2Cl_2) afforded tetraols **66*S*/66*R*** (24 mg, 93%). ^{1}H NMR (CD_3OD) δ 5.43 (1H, br, s), 5.12 (1H, dd), 4.68 (3H, m), 3.42 (1H, br, s), 3.35 (1H, br, s), 2.00 (3H, s), 1.99 (3H, s), 1.70 (3H, s), 1.22 (3H, s), 0.87 (3H, s); ^{13}C NMR δ 171.4, 170.8, 159.9, 153.9, 148.3, 117.8, 107.9, 95.6, 95.0, 73.4, 72.9, 70.8, 63.7, 57.0, 52.2, 50.2, 44.0, 42.8, 36.7, 35.8, 34.4, 33.8, 29.6, 28.0, 27.3, 25.2, 24.7, 21.6, 21.6, 21.5, 20.3, 18.6, 18.5, 13.7, 12.0, 8.0; MS (FAB, NBA matrix) 585 (M + Na); HRMS (FAB, NBA matrix) calcd for $C_{31}H_{46}O_9$ + Na 585.3040, found 585.3046.

Bromospiroketals 71S and 71R. To a solution of diols **62*S*/62*R*** (4:1 ratio; 100 mg, 0.114 mmol) in THF at −78 °C was added NBS (31 mg, 1.5 equiv) in one portion, followed by warming to 0 °C. After 1 h, saturated $Na_2S_2O_3$ and saturated $NaHCO_3$ were added, the aqueous layer was extracted with EA, and the combined organic layers were dried (Na_2SO_4). Evaporation and sgc afforded bromospiroketal **71*S*** (83.5 mg, 77%). ^{1}H NMR δ 7.93 (4H, m), 7.4 (6H, m), 5.54 (1H, brt), 5.41 (1H, dd,), 4.83 (1H, brd, J = 1.8 Hz), 4.71 (1H, m), 4.71 (1H, dd), 3.04 and 3.11 (2H, AB, two d, J = 11.4 Hz), 2.03 (3H, s), 2.01 (3H, s), 1.90 (3H, s), 1.53 (3H, s), 1.09 (3H, s), 1.05 (9H, s), 0.85 (3H, s), 0.20 (9H, s), 2.2−0.8 (remaining H's, m); ^{13}C NMR (50 MHz) δ 171.1, 170.1, 162.7, 136.6*, 136.3*, 135.6, 134.1, 130.2*, 130.0*, 128.1*, 127.8*, 117.0*, 114.8, 96.0, 86.4*, 83.0, 81.6, 80.0*, 73.8*, 73.8*, 69.9, 58.9, 49.6*, 44.5*, 40.5, 37.3, 36.0, 34.6*, 34.3, 29.8, 28.5, 27.8, 27.5*, 27.0*, 26.7, 25.5*, 22.0*, 21.9*, 19.9, 18.4*, 12.1*, 3.8*; MS (FAB, DTT/DTE matrix) 871 (M + H − HBr); HRMS (FAB, KIPEG/DTT/DTE matrix) calcd for $C_{50}H_{71}O_9Si_2$ 871.4637, found 871.4621; $[\alpha]^{25}_D$ − 11.2° in CH_2Cl_2 (*c* 5); mp 145−146 °C.

Further elution provided **71*R*** (16.5 mg, 15%): ^{1}H NMR δ 7.82 (4H, m), 7.41 (6H, m), 5.51 (1H, brt), 5.39 (1H, dd, J = 11.4, 4.6 Hz), 4.82 (1H, d, J = 1.8 Hz), 4.71 (1H, m), 4.69 (1H, dd), 3.28 (1H, d), 3.04 (1H, t), 2.73 (1H, d), 2.27 (1H, t), 2.03 (3H, s), 2.01 (3H, s), 1.90 (3H, s), 1.47 (3H, s), 1.04 (9H, s), 0.87 (3H, s), 0.84 (3H, s), 0.19 (3H, s); ^{13}C NMR δ 170.6, 169.6, 162.7, 136.2, 135.9, 134.8, 133,7, 129.9, 129.6, 127.7, 127.5, 116.3, 114.0, 95.6, 86.3, 82.0, 81.9, 79.3, 73.4, 73.4, 67.9, 58.5, 49.2, 44.1, 36.7, 35.7, 34.2, 33.9, 29.4, 29.3, 28.1,27.4, 27.1 (3C), 26.6, 26.2, 24.4, 21.6, 21.5, 19.5, 18.1, 11.7, 3.4; MS (FAB, DTT/DTE) 871 (M + H − HBr); HRMS (FAB, DTT/DTE) calcd for $C_{50}H_{71}O_9Si_2$ 871.4637, found 871.4641.

Bromospiroketal Diol 72. Selective monodeacetylation of **71*S*** was performed by our standard protocol[1g] to afford **72**. ^{1}H NMR δ 7.85 (4H, m), 7.41(6H, m), 5.53 (1H, brs), 5.40 (1H, dd), 4.82 (1H, brd, J = 2.7 Hz), 4.70 (1H, app q), 3.68 (1H, m), 3.06 (2H, AB, brq), 2.02 (3H, s), 1.91 (3H, s), 1.53 (3H, s), 1.09 (3H, s), 1.05 (9H, s), 0.84 (3H, s), 0.20 (9H, s), 2.2−0.8 (remaining H, m).

Ketone 73. To a solution of **62*S*/62*R*** (4:1 ratio; 10 mg, 0.011 mmol) in CH_3CN was added IDCP (iodonium dicollidine perchlorate, 18 mg, 3 equiv) in one portion. After 3 h, saturated $Na_2S_2O_3$ and $NaHCO_3$ were added, the aqueous layer was extracted with EA, and the combined organic layers were dried (Na_2SO_4). Evaporation and sgc afforded **73** (6.5 mg, 75%). ^{1}H NMR δ 4.05 (1H, brt), 4.95 (1H, dd), 4.90 (1H, brd), 4.89 (1H, app t), 4.71 (1H, m), 2.69 (2H, m), 2.09 (3H, s), 1.98 (3H, s), 1.97 (3H, s), 1.25 (3H, s), 1.01 (9H, s), 0.95 (3H, s), 0.91 (3H, s), −0.09 (9H, s), 2.2−0.8 (remaining H, m); ^{13}C NMR (50 MHz) δ 206.3, 171.1, 170.1, 160.4, 152.5, 136.7*, 136.4*, 133.9, 133.5, 130.4*, 130.2*, 128.1*, 128.1*, 128.1*, 117.6*, 109.9, 98.3, 92.7*, 74.1*, 73.8*, 64.7*, 58.7, 50.7*, 49.5, 44.4*, 36.9, 36.2, 34.8*, 34.3, 31.5*, 30.0, 28.5, 27.7, 27.4*, 27.1, 21.9*, 19.8, 18.4*, 12.3*, 8.7*, 2.2*; MS (FAB, NBA) 840 (M); HRMS (FAB, NBA) calcd for $C_{49}H_{67}O_8Si_2$ 840.4453, found 840.4497.

Olefin 77. *Procedure 1*: A solution of bromide **71*S*** (10 mg, 0.01 mmol) in a quartz tube containing excess $NaHCO_3$ in *i*-PrOH was irradiated at 254 nm for 1 h (Rayonet reactor). The mixture was concentrated and sgc afforded **77** (65%). ***Procedure 2*:** (**Note**: Argon was carefully deoxygenated by passing through a basic pyrogallol solution followed by drying.) To a solution of bromoketal **71*S*** (45 mg, 0.050 mmol) in dimethyl sulfoxide (3 mL, redistilled) containing ethylenediamine (0.11 mL, 1.9 mmol) was added $Cr(OAc)_2$ (89 mg, 0.47 mmol). After 30 min, the mixture was poured into ice water and extracted into EA. Concentration and sgc provided **77** (40 mg, 99%). ^{1}H NMR δ 7.76−7.34 (10H, m), 5.41 (1H, brs), 5.18 (1H, s), 5.12 (1H, s), 4.99 (1H, dd), 4.95 (1H, d, J = 2.1 Hz), 4.68 (1H, m), 4.26 (1H, dd), 3.05 and 2.93 (2H, AB, two d, J = 11.1 Hz), 2.01 (6H, s), 1.57 (3H, s, overlap with H_2O), 1.13 (3H, s), 1.06 (9H, s), 0.84 (3H, s), 0.10 (9H, s), 2.0−0.8 (remaining H, m); ^{13}C NMR δ 2.4, 11.9, 14.2, 17.9, 19.1, 21.4, 21.5, 25.5, 28.0, 29.4, 33.8, 34.4, 35.8, 36.5, 40.2, 44.1, 50.8, 56.5, 60.4, 69.7, 73.4, 74.3, 75.4, 80.3, 91.3, 92.4, 110.9, 111.4, 119.9, 127.5, 129.8, 133.5, 134.0, 135.9, 136.1, 151.5, 155.1, 169.7, 170.6; MS (FAB, NBA) 871.8 (M); HRMS (FAB, NBA) calcd for $C_{50}H_{70}O_9Si_2$ 871.4637, found 871.4625.

General Procedure for Cr(II) Mediated Reductions. NB: Argon was deoxygenated by passing through a basic pyrogallol solution followed by drying. Failure to follow this precaution resulted in little or no reduction. The substrate in DMSO or DMF was deoxygenated by purging with argon for 40 min. Propanethiol was added, and the chromous salt was added in one portion. The reaction was partitioned between water and EA, dried (Na_2SO_4), concentrated, and (if needed) purified by sgc.

Debrominated Spiroketals 64α/64*β*. Bromospiroketal **71*S*** (50 mg, 0.053 mmol) in DMSO (2 mL, redistilled) containing propanethiol (0.50 mL, 5.3 mmol) was reduced with $CrCl_2$ (27 mg, 0.21 mmol) according to the general procedure to afford **64** (β/α = 7:1 by NMR) as a colorless oil (80%, 37 mg). ^{1}H NMR (major peaks only) δ 7.8−7.4 (10H, m), 5.4 (1H, brt), 5.05 (1H, dd), 4.7 (1H, d, J = 2.4 Hz), 4.7 (1H, m), 4.03 (1H, dd), 3.13, 3.01 (2H, AB, two d, J = 11.1 Hz), 2.74 (1H, q), 2.05 (3H, s), 2.01 (3H, s), 1.41 (3H, s), 1.15 (3H, s), 1.1 (9H, s), 0.97 (3H, d, J = 7.5 Hz), 0.83 (3H, s), 0.06 (9H, s), 2.1−0.8 (remaining H, m); ^{13}C NMR (50 MHz, C_6D_6; major peaks only) δ 170.1, 169.6, 159.8, 136.8*, 136.5*, 135.3, 134.9, 130.6*, 119.3*, 113.9, 95.9, 91.5*, 81.5, 75.5*, 75.4*, 75.4*, 73.6*, 70.3, 58.2, 50.9*, 50.1*, 44.1*, 40.2, 36.8, 36.0, 34.6, 34.5*, 30.1, 28.6, 28.1, 28.0*, 26.9, 26.2*, 21.7*, 21.5*, 20.1, 17.3*, 12.0*, 9.3*, 3.4*; MS (FAB, DTT/DTE matrix) 872.5 (M, weak), 813 (M − HOAc); HRMS (FAB, DTT/DTE matrix) calcd for $C_{50}H_{72}O_9Si_2$ − HOAc 813.4582, found 813.4565.

Bromotriol 78. Deprotection of the 17-OTMS of **71*S*** (10 mg, 0.011 mmol) was performed as for **66** except 3 equiv of TBAF at 0 °C for 15 min sufficed; sgc afforded **78** (6.1 mg, 91%). ^{1}H NMR (C_6D_6) δ 5.24 (1H, brt), 5.09 (1H, brs), 5.05 (1H, dd), 4.95 (1H, dd), 4.70 (1H, m), 4.5 (1H, brs), 3.3, 3.1 (2H, AB, two d), 2.3 (2H, m), 2.1 (3H, s), 1.78 (3H, s), 1.71 (3H, s), 1.41 (3H, s), 1.2 (3H, s), 0.45 (3H, s), 2.0−0.2 (remaining H, m). This compound was too unstable for further characterization.

Olefinic Triol 79. TBAF (0.3 mL, 10 equiv) in THF was added to a solution of **71*S*** (27 mg, 0.028 mmol) in THF containing 4 equiv of AcOH. After 24 h, the mixture was poured into saturated NH_4Cl and extracted with EA. The organic layer was washed with saturated NaCl and dried (Na_2SO_4), and sgc (20% MeOH in CH_2Cl_2) afforded **79** (14.3 mg, 85%). ^{1}H NMR (CD_3OD) δ 5.54 (1H, brs), 5.41 (1H, brt), 5.32 (1H, brs), 4.65 (1H, m), 4.49 (1H, d, J = 2.4 Hz), 4.29 (1H, dd), 3.40 (2H, AB, two d, overlap with MeOH), 2.31 (1H, dd), 2.01 (3H, s), 2.00 (3H, s), 1.12 (3H, s), 1.10 (3H, s), 0.87 (3H, s), 2.12−0.9

(remaining H, m); ^{13}C NMR (50 MHz, CD_3OD) δ 172.8, 172.6, 160.0, 155.4, 119.8*, 114.8, 114.0, 93.8*, 89.1, 83.7, 80.3*, 76.0*, 75.2*, 70.0, 56.6, 52.3*, 45.6*, 40.6, 38.0, 37.1, 36.4*, 35.2, 31.0, 29.5, 28.7, 27.7, 26.4*, 21.8*, 21.5*, 19.8*, 12.5*; MS (FAB, NBA) 583 (M + Na); HRMS (FAB, NBA) calcd for $C_{31}H_{42}O_9$ + Na 583.2883, found 583.2894.

Spiroketal Triol 82. Exhaustive desilylation of spiroketals **64** (7:1β/α, 25 mg, 0.029 mmol) was performed as for **66** to provide **82** (13 mg, 81%), which was subjected to single-crystal X-ray analysis. ^{1}H NMR (CD_3OD) δ 5.36 (1H, brt), 5.15 (1H, dd), 4.63 (1H, m), 4.30 (1H, d, J = 2.4 Hz), 3.90 (1H, dd), 3.30, 3.22 (2H, AB, two d, J = 11.1 Hz), 2.83 (1H, m), 2.67 (1H, q), 2.17 (2H, m), 2.02 (3H, s), 1.97 (3H, s), 1.44 (3H, s), 1.20 (3H, s), 1.13 (3H, d, J = 7.5 Hz), 0.87 (3H, s), 2.0−0.8 (remaining H, m); MS (FAB, DTT/DTE matrix) 585 (M + Na); HRMS (FAB, DTT/DTE matrix) calcd for $C_{31}H_{46}O_9$ + Na 585.3040, found 585.3009; mp 196−199 °C.

TBS Ether 83. To a solution of **71*S*** (170 mg, 0.178 mmol) in DMF (3 mL) was added imidazole (42 mg, 0.62 mmol) and *tert*-butyldimethylsilyl chloride (67 mg, 0.45 mmol). After 5 h, the reaction was cooled to 0 °C and water was added followed by Et_2O. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with water and dried, and sgc (10% EA/Hex) afforded **83** (180 mg, 95%) as a white foam. ^{1}H NMR δ −0.12 (s, 6H), 0.19 (s, 9H), 0.79 (s, 9H), 0.85 (s, 3H), 1.00 (s, 3H), 1.05 (s, 9H), 1.54 (s, 3H), 1.90 (s, 3H), 2.01 (s, 3H), 2.02 (s, 3H), 3.01 (d, J = 9.9 Hz, 1H), 3.16 (d, J = 9.9 Hz, 1H), 4.68−4.76 (m, 1H), 4.82 (d, J = 2.7 Hz, 1H), 4.86 (dd, J = 18, 8.1 Hz, 1H), 5.43 (dd, J = 12, 4.5 Hz, 1H), 5.54 (t, J = 2.0 Hz, 1H), 7.36−7.41 (m, 6H), 7.80−7.83 (m, 2H), 7.90−7.93 (m, 2H), 0.5−2.2 (remaining H, m); ^{13}C NMR: δ −5.7 (2C), 3.3 (3C), 11.6, 17.8, 18.2, 19.5, 21.4, 21.5, 25.5, 25.7, 25.9 (3C), 26.2, 26.4, 27.0 (3C), 27.3, 28.1, 29.3, 33.8, 34.1, 35.5, 36.8, 39.8, 44.0, 49.1, 58.4, 69.3, 73.4, 79.8, 81.5, 83.4, 85.6, 95.6, 114.5, 116.6, 127.3 (2C), 127.6 (2C), 129.2, 129.6, 134.0, 135.5, 135.8 (2C), 136.2 (2C), 162.0, 169.6, 170.6; MS (FAB, NBA) 985 (M + H − HBr); HRMS (FAB, NBA) calcd for $C_{56}H_{85}O_9Si_3$ 985.5501, found 985.5471.

Alcohol 84. Selective monodeacetylation of **83** (170 mg, 0.159 mmol) as per our standard protocol[1g] provided **84** (155 mg, 95%) as a white foam. ^{1}H NMR δ −0.12 (s, 6H), 0.19 (s, 9H), 0.79 (s, 9H), 0.84 (s, 3H), 1.01 (s, 3H), 1.05 (s, 9H), 1.54 (s, 3H), 1.91 (s, 3H), 2.01 (s, 3H), 3.01 (d, J = 9.9 Hz, 1H), 3.16 (d, J = 9.9 Hz, 1H), 4.82 (d, J = 2.7 Hz, 1H), 4.86 (dd, J = 10, 8.1 Hz, 1H), 5.42 (dd, J = 12, 4.3 Hz, 1H), 5.54 (t, J = 1.9 Hz, 1H), 7.34−7.40 (m, 6H), 7.80−7.83 (m, 2H), 7.90−7.93 (m, 2H), 0.8−2.2 (remaining H, m); ^{13}C NMR δ −5.7 (2C) 3.3 (3C), 11.7, 17.7, 18.1, 19.4, 21.5, 25.5, 25.9 (3C), 26.1, 26.4, 27.0 (3C), 28.2, 29.4, 31.2, 34.1, 35.5, 37.0, 37.7, 39.8, 44.2, 49.2, 58.4, 69.2, 70.9, 73.5, 79.8, 81.4, 83.4, 85.6, 95.5, 114.5, 116.5, 127.2 (2C), 127.6 (2C), 129.2, 129.5, 134.0, 135.5, 135.7 (2C), 136.1 (2C), 162.0, 169.7; MS (FAB, NBA) 943 (M + H − HBr); HRMS (FAB, NBA) calcd for $C_{54}H_{83}O_8Si_3$ 943.5396, found 943.5388.

Ketone 85. To a solution of **84** (140 mg, 0.137 mmol) in Et_2O (3.6 mL) and CH_2Cl_2 (1.0 mL) at 0 °C was added an aqueous solution of chromic acid (0.32 mL of 1.3 M, 0.41 mmol). After 15 min, water and Et_2O were added. The aqueous layer was extracted with Et_2O and the combined organic layers were dried and filtered through a 1-in. pad of silica gel. Concentration gave **85** (136 mg, 97%) as a white foam. ^{1}H NMR δ −0.12 (s, 6H), 0.18 (s, 9H), 0.79 (s, 9H), 1.01 (s, 3H), 1.04 (s,9H), 1.56 (s, 3H), 1.91 (s, 3H), 2.02 (s, 3H), 3.01 (d, J = 9.9 Hz, 1H), 3.16 (d, J = 9.9 Hz, 1H), 4.82 (d, J = 2.7 Hz, 1H), 4.86 (dd, J = 10, 8.1 Hz, 1H), 5.44 (dd, J = 12, 4.4 Hz, 1H), 5.57 (t, J = 2.3 Hz, 1H), 7.36−7.42 (m, 6H), 7.79−7.82 (m, 2H), 7.89−7.92 (m, 2H), 0.8−2.4 (remaining H); ^{13}C NMR δ −5.7 (2C), 3.8 (3C), 11.5, 18.3, 18.7, 20.0, 22.0, 26.1(3C), 26.4, 26.9, 27.5 (3C), 28.9, 29.6, 34.6, 36.2, 38.4, 38.8, 40.3, 44.9, 46.3, 49.3, 58.9, 69.8, 73.7, 79.8, 80.3, 82.0, 83.8, 86.0, 96.1, 115.1, 117.5, 127.8 (2C), 128.2 (2C), 129.7, 130.1, 134.5, 136.0, 136.3 (2C), 136.7 (2C), 161.9, 170.2, 211.7; MS (FAB, NBA) 1023 (M + H); HRMS (FAB, NBA) calcd for $C_{54}H_{81}BrO_8Si_3$ 1021.4501, found 1021.4640.

Ketodiol 86. To a solution of ketotrisilyl ether **85** (160 mg, 0.156 mmol) in CH_3CN (13 mL) was added a solution of H_2SiF_6 in CH_3CN (2.5 mL of 0.063 M, 0.16 mmol). (Note: Direct application of commercially available 25% aqueous H_2SiF_6 for this reaction gave inferior results and led to decomposition of the diol product. The solution used here was prepared 8 days in advance and stored in a polypropylene bottle). The reaction was allowed to stir for 1.5 h while monitoring by ^{1}H NMR, then was quenched by addition of saturated $NaHCO_3$ solution. The CH_3CN was removed in vacuo and the yellow oil was dissolved in Et_2O (75 mL). The Et_2O layer was washed with brine and dried (Na_2SO_4). Sgc (30% to 40% EA/Hex) afforded 121 mg (93%) of **86** as a white foam. ^{1}H NMR δ 1.01 (s, 9H), 1.06 (s, 3H), 1.09 (s, 3H), 1.56 (s, 3H), 1.97 (s, 3H), 2.01 (s, 3H), 2.92 (dd, J = 12, 8.9 Hz, 1H), 3.16 (dd, J = 12, 5.1 Hz, 1H), 4.92 (dd, J = 11, 5.1 Hz, 1H), 5.01 (dd, J = 11, 8.1 Hz, 1H), 5.11 (d, J = 1.5 Hz, 1H), 5.53 (brs, 1H), 5.64 (s, 1H), 7.40−7.49 (m, 6H), 7.81−7.84 (m, 2H), 7.87−7.90 (m, 2H), 0.8−2.2 (remaining H, m); ^{13}C NMR δ 11.5, 13.2, 19.6, 21.9, 25.3, 26.8 (3C), 27.3, 27.6, 27.8, 28.5, 28.6, 34.3, 36.5, 38.1, 38.2, 39.6, 44.7, 46.5, 53.6, 54.1, 69.6, 77.8 (2C), 82.0, 90.2 (2C), 115.3, 121.2, 128.1 (2C), 128.3 (2C), 130.3, 130.7, 132.2, 133.6, 135.9 (2C), 136.2 (2C), 154.1, 170.5, 211.4; MS (FAB, NBA) 835 (M + H); HRMS (FAB, NBA) calcd for $C_{45}H_{60}BrO_8Si$ 835.3241, found 835.3267; $[\alpha]^{24}_D$ +44.5° in CH_2Cl_2 (*c* 20).

Ketodiol 86R. The minor diastereomer **71*R*** (0.320 g, 0.336 mmol, collected from several NBS mediated spiroketalizations of **62*S*/62*R***) was hydrolyzed as per **84**. The 3,26-diol product (0.300 g, 0.330 mmol) was dissolved in 10% aqueous DME (7 mL) and treated with NBS (0.117 g, 0.66 mmol, 2 equiv) for 4 h, then diluted with EtOAC, washed with water, dried (Na_2SO_4), and concentrated to give crude 3-keto,26-OH,17-OTMS ether. To a solution of this silyl ether (0.295 g, 0.325 mmol) in CH_2Cl_2 (6.5 mL) was added $BF_3{\cdot}OEt_2$ (49 μL, 0.39 mmol, 1.2 equiv) dropwise over 2 min. After 1.5 h, the mixture was diluted with EtOAC, washed with aqueous $NaHSO_3$, dried (Na_2SO_4), and concentrated. Sgc (50:1 to 20:1 CH_2Cl_2/THF) afforded 0.250 g (90%) of **86*R*** as offwhite solids. ^{1}H NMR δ 0.76 (s, 3H), 1.01 (s, 9H), 1.06 (s, 3H), 1.09 (s, 3H), 1.55 (s, 3H), 1.93 (s, 3H), 2.01 (s, 3H), 2.70 (dd, J = 10.5, 1.5 Hz, 1H), 3.02 (apt, J = 11 Hz, 1H), 3.30 (dd, J = 11.3, 1.5 Hz, 1H), 4.83 (dd, J = 11.5, 7.3 Hz, 1H), 4.94 (dd, J = 10.7, 5.1 Hz, 1H), 5.06 (d, J = 1.5 Hz, 1H), 5.48 (brs, 1H), 5.64 (s, 1H), 7.40−7.51 (m, 6H), 7.80−7.85 (m, 2H); ^{13}C NMR δ 11.1 (q), 12.8 (q), 19.1 (s), 21.4 (q), 23.6 (q), 26.3 (q, 3C), 26.9 (q), 27.3 (t), 28.0 (t), 28.1 (t), 33.8 (d), 35.6 (t), 36.0 (s), 37.66 (t), 37.75 (t), 44.2 (t), 46.0 (d), 53.1 (d), 53.7 (s), 67.4 (t), 75.2 (s), 75.8 (d), 77.0 (d), 81.6 (s), 89.7 (d), 90.4 (s), 114.5 (s), 120.5 (d), 127.7 (d, 2C), 127.9 (d, 2C), 130.0 (d), 130.3 (d), 131.5 (s), 132.5 (s), 135.5 (d, 2C), 135.7 (d, 2C), 154.2 (s), 170.0 (s), 210.8 (s); MS (CI) 757/759 (M + H − HBr), (FAB, NBA) 835 (M + H); HRMS (FAB, NBA) calcd for $C_{45}H_{60}BrO_8Si$ 835.3241, found 835.3256.

Diol 87. Following the procedure for desilylation of **85**, diol **87** was obtained from **71*S*** in 94% yield. ^{1}H NMR δ 7.86 (4H, m), 7.73 (6H, m), 5.61 (1H, s), 5.52 (1H, s), 5.12 (1H, s), 5.02 (1H, dd), 4.91 (1H, dd), 4.68 (1H, m), 3.17 (1H, dd), 2.94 (1H, br, t), 2.04 (3H, s), 2.02 (3H, s), 1.98 (3H, s), 1.52 (3H, s), 1.08 (9H, s), 0.86 (3H, s); ^{13}C NMR δ 171.0, 170.5, 154.6, 136.3, 135.9, 133.7, 132.3, 130.7, 130.3, 128.4, 128.1, 120.9, 115.4, 90.3, 90.2, 82.1, 77.9, 73.6, 69.7, 54.2, 54.1, 44.7, 39.7, 36.6, 36.5, 34.4, 34.1, 32.0, 28.8, 28.4, 27.7, 26.8, 25.3, 23.0, 21.9, 21.8, 19.6, 14.5, 13.3, 12.3.

26-OTBS Ether 88. Following the procedure for silylation of **83**, **86** was converted to **88** in 96% yield. ^{1}H NMR δ −0.12 (s, 6H), 0.79 (s, 9H), 1.01 (s, 9H), 1.06 (s, 3H), 1.09 (s, 3H), 1.56 (s, 3H), 1.97 (s, 3H), 2.01 (s, 3H), 2.62 (s, 1H), 2.65 (dd, 1H), 3.03 (dd, J = 12, 8.9 Hz, 1H), 4.87−5.0 (m, 2H), 5.06 (d, J = 1.5 Hz, 1H), 5.53 (brs, 1H), 5.57 (s, 1H), 7.40−7.49 (m, 6H), 7.81−7.84 (m, 2H), 7.87−7.90 (m, 2H), 0.8−2.2 (remaining H, m).

C20 Debrominated Diastereomers 89α/89β. Reduction of **87** (0.11 g, 0.13 mmol) in DMSO (2 mL) with 1-propanethiol (1.2 mL, 13 mmol) and $CrCl_2$ (79 mg, 0.64 mmol) according to the general procedure and sgc (35% to 40% EA/Hex) afforded 90 mg (87%) of the inseparable **89α/β** mixture (3.6:1). ^{1}H NMR δ 7.80 (4H, m), 7.42 (6H, s), 5.53 (1H, s), 5.27 and 5.03 (H-12, two dd (1:3.5)), 4.93 and 4.57 (H-16, two brd (3.5:1)), 4.19 and 3.83 (H-23, two dd (3.5: 1)), 3.90 and 3.68 (1H, two s (3.5:1)), 3.05 (1H, m), 2.93 (1H, m), 2.02 (3H, s), 1.99 (3H, s), 1.07 (3H, d, J = 7.2 Hz), 1.01 (9H, s), 0.88 and 0.85 (3H, two s (3.5:1)).

C20 Debrominated Diastereomers 90α/90*β*. Reduction of **86** (750 mg, 0.90 mmol) in DMF (9 mL) at −25 °C with 1-propanethiol (16 mL, 170 mmol) and $CrCl_2$ (551 mg, 4.49 mmol) according to the general procedure gave **90α,*β*** (9:1 ratio by NMR). Sgc as for **89** afforded 570 mg (84%) of **90α,*β*** (inseparable) and 100 mg (13%) of starting material **86**. **90**α: ^{1}H NMR δ 1.06 (s, 3H), 1.08 (d, J = 9.0 Hz, 3H), 1.16 (s, 3H), 1.24 (s, 3H), 2.00 (s, 3H), 2.48 (q, J = 7.1 Hz, 1H), 2.93 (d, J = 11 Hz, 1H), 3.06 (d, J = 11 Hz, 1H), 3.92 (s, 1H), 4.20 (dd, J = 11, 7.8 Hz, 1H), 4.94 (brs, 1H), 5.04 (dd, J = 11, 5.0 Hz, 1H), 5.56 (brs, 1H), 7.38−7.47 (m, 6H), 7.74−7.76 (m, 2H), 7.81−7.84 (m, 2H), 0.8−2.4 (remaining H, m); MS (FAB, NBA) 757 (M + H); HRMS (FAB, NBA) calcd for $C_{45}H_{61}O_8Si$ 757.4136, found 757.4080. **90*β***: ^{1}H NMR δ 5.28 (1H, dd), 4.55 (1H, d), 3.84 (1H, dd).

C26 TBS Ethers 91α/91*β*. Ketodiols **90α,*β*** (1.01 g, 1.33 mmol) were silylated with TBSCl as per **83** to afford, after sgc (15% to 25% EA/Hex) 1.05 g (90%) of **91**α and 0.12 g (10%) of **91*β*** as white foams. Identical products were obtained by reduction of **88** as per the general procedure. **91**α: R_f = 0.35 (25% EA/Hex); ^{1}H NMR δ −0.15 (s, 3H), −0.14 (s, 3H), 0.74 (s, 9H), 1.00 (s, 9H), 1.06 (s, 3H), 1.10 (s, 3H), 1.11 (d, J = 7.1 Hz, 3H), 1.24 (s, 3H), 1.99 (s, 3H), 2.46 (q, J = 7.1 Hz, 1H), 2.97 (d, J = 10 Hz, 1H), 3.10 (d, J = 10 Hz, 1H), 3.98 (s, 1H), 4.31 (dd, J = 11, 8.0 Hz, 1H), 4.94 (brs, 1H), 5.03 (dd, J = 11, 5.2 Hz, 1H), 5.55 (brs, 1H), 7.35−7.44 (m, 6H), 7.72−7.75 (m, 2H), 7.83−7.87 (m, 2H), 0.8−2.4 (remaining H, m); ^{13}C NMR δ −5.8, −5.6, 8.6, 11.2, 13.6, 18.2, 19.2, 21.4, 25.6, 25.9 (3C), 26.6 (3C), 27.4, 28.3 (2C), 33.6, 36.1, 37.5, 37.9 (2C), 44.2, 44.4, 46.1, 52.6, 53.3, 69.1, 73.9, 74.5, 81.8, 89.2, 93.2, 116.4, 122.3, 127.6 (2C), 127.9 (2C), 129.8, 130.1, 132.6, 133.6, 135.5 (2C), 135.9 (2C), 151.2, 170.2, 211.2; MS (FAB, NBA) 871 (M + H); HRMS (FAB, NBA) calcd for $C_{51}H_{75}O_8Si_2$ 871.5001, found 871.5010; $[\alpha]^{24}_D$ +47.6° in CH_2Cl_2 (*c* 0.5).

91*β*: R_f = 0.30 (25% EA in Hex); ^{1}H NMR δ −0.14 (s, 3H), −0.13 (s, 3H), 0.69 (d, J = 7.8 Hz, 3H), 0.74 (s, 9H), 1.04 (s, 3H), 1.08 (s, 9H), 1.16 (s, 3H), 1.38 (s, 3H), 2.07 (s, 3H), 2.45 (q, J = 7.8 Hz, 1H), 3.09 (d, J = 10 Hz, 1H), 3.15 (d, J = 10 Hz, 1H), 3.38 (s, 1H), 3.98 (apparent t, J = 8.2 Hz, 1H), 4.50 (d, J = 2.4 Hz, 1H), 5.28 (dd, J = 12, 5.0 Hz, 1H), 5.54 (brs, 1H), 7.34−7.45 (m, 6H), 7.70−7.73 (m, 4H), 0.8−2.4 (remaining H, m); ^{13}C NMR δ 211.3, 172.1, 159.0, 136.1, 134.1, 133.7, 129.9, 129.7, 127.9, 127.6, 119.2, 114.0, 91.5, 90.5, 81.8, 75.2, 74.4, 69.6, 56.6, 49.5, 48.1, 45.8, 44.5, 38.5, 38.3, 38.0, 35.7, 33.9, 29.1, 28.4, 27.4, 27.2, 26.1, 26.0, 21.9, 19.4, 18.3, 16.3, 11.2, 7.8, −5.5, −5.6; MS (FAB, DTT/DTE) 871 (M + H); HRMS (FAB, DTT/DTE) calcd for $C_{51}H_{75}O_8Si_2$ 871.5001, found 871.4992.

C26 TBDMS Ethers 92α and 92*β*. Silylation of **89** and sgc as for **91**α/*β* gave **92**α (77%) and **92*β*** (20%). **91**α: R_f = 0.39 (25% EA/Hex); ^{1}H NMR δ 7.85 (2H, m), 7.73 (2H, m), 7.41 (6H, m), 5.51 (1H, s), 5.00 (1H, dd, J = 11.2, 5.1 Hz), 4.93 (1H, s), 4.66 (1H, m), 4.28 (1H, dd, J = 10.5, 7.9 Hz), 3.94 (1H, s), 3.02 (2H, AB), 2.45 (1H, q, J = 7.0 Hz), 2.00 (3H, s), 1.97 (3H, s), 1.20 (3H, s), 1.09 (3H, s), 1.09 (3H, d, J = 6.9 Hz), 1.00 (9H, s), 0.87 (3H, s), 0.74 (9H, s), −0.15 (3H, s), −0.16 (3H, s); ^{13}C NMR δ 170.6, 170.2, 151.6, 135.9, 135.5, 133.6, 132.6, 130.1, 129.8, 127.9, 127.6, 122.0, 116.4, 93.3, 89.3, 81.8, 74.7, 73.8, 73.3, 69.1, 52.3, 52.9, 44.3, 37.5, 36.3 36.0, 33.7, 28.6, 28.0, 27.2, 26.6, 25.9, 25.6, 21.4, 19.1, 18.2, 13.6, 11.9, 8.7, −3.6, −5.6, −5.8. **91*β***: R_f = 0.32 (25% EA/Hex); ^{1}H NMR δ 7.71 (4H, m), 7.40 (6H, m), 5.52 (1H, br, t), 5.27 (1H, dd, J = 11.5, 4.6 Hz), 4.69 (1H, m), 4.50 (1H, d, J = 2.5 Hz), 3.96 (1H, dd, J = 10.3, 7.9 Hz), 3.50 (1H, s), 2.06 (3H, s), 2.03 (3H, s), 1.39 (3H, s), 1.18 (3H, s), 1.05 (9H, s), 0.88 (3H, s), 0.78 (9H, s), 0.9 (3H, d), −0.15 (3H s), −0.16 (3H, s).

Debrominated 25*R* Epimers 93α/*β*. Reduction of bromide **86*R*** (40 mg, 0.048 mmol) was performed as for the 25*S* epimer **86**, except the reaction was maintained at 25 °C and required a second charge of $CrCl_2$ after 2.5 h to bring the reaction to completion. Workup and sgc gave **93**α/*β* (33 mg, 90%; 5.5:1 ratio by NMR). ^{1}H NMR δ 0.76 (s, 3H), 1.02 (s, 9H), 1.06 (d, J = 7.3 Hz, 3H), 1.24 (s, 3H), 1.25 (s, 3H), 2.00 (s, 3H), 2.46 (q, J = 7.3 Hz, 1H), 2.67 (apt, J = 7.3 Hz, 1H), 3.06 (brapt, J = 10.9 Hz, 1H), 3.24 (brd, J = 10 Hz, 1H), 3.34 (brd, J = 11.5, Hz, 1H), 3.72 and 3.91 (1:5.5, s, 1H), 3.82 and 4.13 (1:5.5, dd, J = 11.3, 7.4 Hz, 1H), 4.54 and 4.93 (1:5.5, brs, 1H), 5.02 and 5.28 (5.5:1, dd, J = 10.9, 5.2 Hz, 1H), 5.50 (brs, 1H), 7.28−7.51 (m, 6H), 7.68−7.81 (m, 4H), 0.8−2.4 (remaining H, m); MS (FAB, NBA) 757 (M + H); HRMS (FAB, NBA) calcd for $C_{45}H_{61}O_8Si$ 757.4136, found 757.4095.

Pentaol 94α. A THF (2 mL) solution of **92**α (11 mg, 0.018 mmol) and TBAF (55 μL, 0.055 mmol) was heated at reflux for 1 h, cooled, concentrated, and redissolved in aqueous MeOH (2 mL, 15% H_2O). K_2CO_3 (25.6 mg, 0.185 mmol) was added and the reaction mixture was heated at reflux for 1 h. The mixture was diluted with EA (20 mL), washed with brine (2 × 10 mL), and concentrated and sgc (1% MeOH/EA) afforded 8 mg (90%) of pentaol **94**α. ^{1}H NMR (CD_3OD) δ 5.39 (1H, brs), 4.74 (1H, brs), 4.18 (1H, dd, J = 11.0, 8.0 Hz), 3.77 (1H, dd, J = 11.0, 4.7 Hz), 3.50 (1H, m), 2.37 (1H, q, J = 7.1 Hz), 2.23 (1H, dd, J = 12.0, 8.0 Hz), 1.27 (3H, s), 1.12 (3H, s), 1.07 (3H, d, J = 7.2 Hz), 0.89 (3H, s); MS (EI) 460 (M − H_2O), 314 (base), (CI) 461 (M + H − H_2O, base); HRMS (EI) calcd for $C_{27}H_{40}O_7$ 460.2825, found 460.2835.

Pentaol 94*β*. Following the same procedure for making **94**α, polyol **94*β*** was obtained in 82% yield. ^{1}H NMR (C_5D_5N) δ 6.56 (1H, s), 6.38 (1H, d, J = 9.4 Hz), 6.28 (1H, brt), 5.96 (1H, brs), 5.58 (1H, s), 5.44 (1H, brs), 4.59 (2H, m), 3.72 (2H, m), 3.44 (1H, q, J = 7.5 Hz), 2.80 (1H, dd, J = 11.5, 8.0 Hz), 1.88 (3H, s), 1.64 (3H, d, J = 7.5 Hz), 1.60 (3H, s), 0.79 (3H, s); MS (EI) 460 (M − H_2O), 314 (base), (CI) 461 (M + H − H_2O, base); HRMS (EI) calcd for $C_{27}H_{40}O_7$ 460.2825, found 460.2835.

α-Bromoketone 95. Utilizing standard protocols,[1g] ketone **91**α (84 mg, 0.097 mmol) and PTAB (38 mg, 0.10 mmol) afforded after sgc 73 mg (80%) of α-bromoketone **95** and 12 mg (14%) of starting material **91**α. ^{1}H NMR δ 7.84 (2H, m), 7.73 (2H, m), 7.42 (6H, m), 5.56 (1H, brs), 5.03 (1H, dd, J = 11.0, 5.1 Hz), 4.93 (1H, brs), 4.71 (1H, dd, J = 13.0, 6.2 Hz), 4.31 (1H, dd, J = 10.0, 8.0 Hz), 3.99 (1H, s), 3.10 (1H, d, J = 10 Hz), 2.97 (1H, d, J = 10 Hz), 2.55 (1H, dd, J = 13, 6.3 Hz), 2.46−2.42 (2H, m), 1.99 (3H, s), 1.23 (3H, s), 1.13 (3H, s), 1.11 (3H, d, J = 7.1 Hz), 1.10 (3H, s), 1.00 (9H, s), 0.74 (9H, s), −0.15 (3H, s), −0.16 (3H, s), 2.2−0.8 (remaining H's, m); ^{13}C NMR δ 200.5, 170.2, 150.6, 135.9, 135.5, 133.6, 132.6, 130.2, 129.8, 128.0, 127.6, 122.7, 116.4, 93.1, 89.2, 81.9, 74.2, 73.9, 69.1, 53.7, 53.3, 52.2, 50.9, 46.9, 44.2, 43.6, 39.2, 37.5, 33.1, 28.1, 27.8, 27.4, 26.6, 25.9, 25.6, 21.3, 19.2, 18.2, 13.6, 11.9, 8.7, −5.6, −5.8; MS (FAB, NBA) 949 (M + H); HRMS (FAB, NBA) calcd for $C_{51}H_{74}BrO_8Si_2$ 949.4106, found 949.4125; $[\alpha]^{23}_D$ + 45° in CH_2Cl_2 (*c* 1.0).

α-Azidoketone 5. TMGA (17 mg, 0.11 mmol) was dissolved in CH_3NO_2 (0.8 mL), added to a solution of bromoketone **95** (26 mg, 0.027 mmol) in CH_3NO_2 (2 mL), and stirred for 6 h. The CH_3NO_2 was removed in vacuo and the product was filtered through silica (15% EA in Hex) to afford **5** (25 mg, 100%) as a white film. ^{1}H NMR δ −0.16 (s, 3H), −0.15 (s, 3H), 0.74 (s, 9H), 1.00 (s, 9H), 1.10 (s, 3H), 1.11 (d, J = 7.1 Hz, 3H), 1.13 (s, 3H), 1.23 (s, 3H), 1.99 (s, 3H), 2.45 (q, J = 7.1 Hz, 1H), 2.97 (d, J = 10 Hz, 1H), 3.10 (d, J = 10 Hz, 1H), 3.96 (dd, J = 13, 6.3 Hz, 1H), 3.99 (s, 1H), 4.31 (dd, J = 10, 8.0 Hz, 1H), 4.93 (brs, 1H), 5.03 (dd, J = 11, 5.1 Hz, 1H), 5.56 (brs, 1H), 7.36−7.46 (m, 6H), 7.72−7.75 (m, 2H), 7.83−7.86 (m, 2H), 0.8−2.4 (remaining H, m); ^{13}C NMR: δ −5.8, −5.6, 8.7, 12.3, 13.6, 18.2, 19.2, 21.3, 25.6, 25.9 (3C), 26.6 (3C), 27.5, 27.9, 28.2, 33.1, 37.2, 37.5, 43.5, 44.2, 44.9, 47.1, 52.3, 53.3, 63.7, 69.1, 73.9, 74.2, 81.9, 89.2, 93.1, 116.4, 122.7, 127.6 (2C), 128.0 (2C), 129.8, 130.2, 132.6, 133.6, 135.5 (2C), 135.9 (2C), 150.6, 170.2, 204.5; MS (FAB, NBA) 912 (M + H); HRMS (FAB, NBA) calcd for $C_{51}H_{74}N_3O_8Si_2$ 912.5015, found 912.4987; $[\alpha]^{22}_D$ +64.3° (CH_2Cl_2, *c* 1).

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Supporting Information Available: NMR spectra of compounds studied (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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