Stereoselective Total Syntheses of the Antitumor Antibiotics (+)-Actinobolin and (-)-Bactobolin from a Common Bridged Lactone Intermediate[1]

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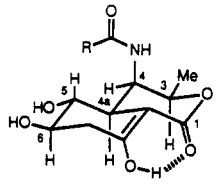
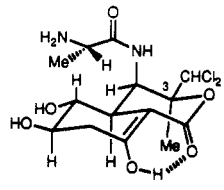
Abstract: Efficient, highly stereoselective approaches have been developed to (+)-actinobolin (**1**) and (-)-bactobolin (**3**) from bridged α-keto lactone **11**, which can be readily prepared via intramolecular $SnCl_4$ catalyzed ene reaction of cyclohexenol glyoxylate (**5**). A novel method has been developed for direct, stereoselective reductive sulfonamidation of **11** to simultaneously introduce a protected C-4 amino group of the natural products and generate the C-4/4a relative stereochemistry. It was found that a PMS ((*p*-methylbenzyl)sulfonyl) nitrogen protecting group was useful in the actinobolin synthesis, but for bactobolin the SES ((β-(trimethylsilyl)ethyl)sulfonyl) group was necessary. The C-3 substitution and stereochemistry of the antibiotics was established by manipulation of the carbonyl group of the bridged lactone intermediates, and in particular, a novel organocerium reagent was applied to this part of the bactobolin synthesis (cf. **35** → **37**). In both syntheses an unprecedented intramolecular enolate C-acylation was used to prepare the bicyclic enol lactone systems.

Thirty years ago Haskell and Bartz reported isolation of actinobolin from the microorganism *Streptomyces griseoviridus*.[2] The compound was of biological interest since it possessed broad-spectrum antibiotic activity[3] along with reasonable antileukemic activity.[4] The structure of actinobolin was elegantly elucidated as **1** by Struck et al.[5] and by Munk and co-workers[6] using chemical and spectroscopic methods. This original formulation was subsequently confirmed by X-ray crystallography.[7] More recently the structurally related metabolite bactobolin (**3**) was discovered in the culture broths of a *Pseudomonas* species.[8] Bactobolin, like actinobolin, has antitumor activity exerted via inhibition of protein synthesis.[9] However, **3** has markedly stronger antitumor properties. The antibiotics are identical in structure except for the substitution pattern at C-3.



1 R = 

2 R = Me



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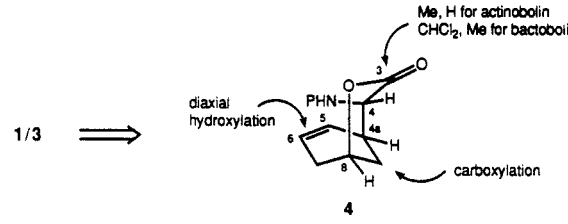
Scheme I



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The unique structures and potent activity of actinobolin and bactobolin have engendered a flurry of synthetic activity.[1,10] Ohno and co-workers reported the first total synthesis of actinobolin starting from L-threonine using an intramolecular Diels-Alder reaction as the key step in constructing the bicyclic framework of **1**.[10a] Kozikowski et al. also completed an actinobolin synthesis from L-threonine, but instead used an intermolecular Diels-Alder strategy.[10d] In an alternative approach, Rahman and Fraser-Reid prepared *N*-acetylactinobolamine (**2**) in optically active form via a [4 + 2]-cycloaddition of a carbohydrate-derived dienophile with an oxygenated diene.[10b] Finally, Danishefsky and co-workers effected a synthesis of racemic *N*-acetylactinobolamine (**2**) featuring a key siloxy Cope rearrangement.[10c]

We envisioned a synthetic approach to *both* actinobolin and bactobolin from a common bicyclic olefinic δ-lactone such as **4** (Scheme I). Compound **4** possesses the C-4 nitrogen of the antibiotics as well as the requisite C-4/4a stereochemistry. It was anticipated that the alkene function of **4** could be modified into the C-5/6 diequatorial vicinal diol and the lactone bridge was meant to play a critical role in this transformation. Since it is generally easier to effect 1,2-diaxial than diequatorial hydroxylation of cyclohexenes, the axial disposition of C-3/4 in **4** enforced by the lactone bridge was expected to facilitate the direct establishment of the desired relative stereochemistry at C-4/4a/5/6 of both antibiotics. We hoped to use the lactone carbonyl group of **4** to introduce the sets of C-3 substituents necessary for **1** and **3** relying upon the C-4 chiral center to control relative stereochemistry. Finally, we planned to introduce the carboxyl group at C-9 via a C-8 ketone enolate acylation.

(1) For preliminary accounts of this work, see: Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1985**, *107*, 7790. Garigipati, R. S.; Weinreb, S. M. *J. Org. Chem.* **1988**, *53*, 4143. Weinreb, S. M.; Garigipati, R. S. *Pure Appl. Chem.* **1989**, *61*, 435.

(2) Haskell, T. H.; Bartz, Q. R. *Antibiot. Ann.* **1958-59**, 505.

(3) Pittillo, R. W.; Fisher, M. W.; McAlpine, R. J.; Thompson, P. E.; Ehrlich, J. *Antibiot. Ann.* **1958-59**, 497. Hunt, D. E.; Navia, J. M.; Lopez, H. *J. Dent. Res.* **1971**, 371.

(4) Merker, P. C.; Woolley, G. W. *Antibiot. Ann.* **1958-59**, 515. Teller, M. N.; Merker, P. C.; Palm, J. E.; Woolley, G. W. *Ibid.* **1958-59**, 518. Sugiura, K.; Reilly, H. C. *Ibid.* **1958-59**, 522. Smithers, D.; Bennett, L. L.; Struck, R. F. *Mol. Pharmacol.* **1969**, *5*, 433.

(5) Struck, R. F.; Thorpe, M. C.; Coburn, W. C.; Shealy, Y. F. *Tetrahedron Lett.* **1967**, 4589.

(6) Antotz, F. J.; Nelson, D. B.; Herald, D. L., Jr.; Munk, M. E. *J. Am. Chem. Soc.* **1970**, *92*, 4933 and references cited therein.

(7) Wetherington, J. B.; Moncrief, J. W. *Acta Crystallogr.* **1975**, *B31*, 501.

(8) Isolation and structure: Kondo, S.; Horiuchi, Y.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1979**, *32*, 1069. Ueda, I.; Munakata, T.; Sakai, J. *Acta Crystallogr.* **1980**, *B36*, 3128. Munakata, T.; Ikeda, Y.; Matsuki, H.; Isagai, K. *Agric. Biol. Chem.* **1983**, *47*, 929. For some closely related compounds, see: Okumoto, T.; Kontani, M.; Hoshino, H.; Nakanishi, M. *J. Pharm. Dyn.* **1980**, *3*, 177.

(9) Munakata, T. *Yakugaku Zasshi* **1981**, *101*, 138. Munakata, T.; Okumoto, T. *Chem. Pharm. Bull.* **1981**, *29*, 891. Hori, M.; Suzukake, K.; Ishikawa, C.; Asakura, H.; Umezawa, H. *J. Antibiot.* **1981**; *34*, 465.

(10) (a) Yoshioka, M.; Nakai, H.; Ohno, M. *J. Am. Chem. Soc.* **1984**, *106*, 1133. Yoshioka, M.; Nakai, H.; Ohno, M. *Heterocycles* **1984**, *21*, 151. (b) Rahman, M. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1985**, *107*, 5576. (c) Askin, D.; Angst, C.; Danishefsky, S. *J. Org. Chem.* **1985**, *50*, 5005. Askin, D.; Angst, C.; Danishefsky, S. *Ibid.* **1987**, *52*, 622. (d) Kozikowski, A. P.; Konoike, T.; Nieduzak, T. R. *J. Chem. Soc., Chem. Commun.* **1986**, 1350. Kozikowski, A. P.; Nieduzak, T. R.; Konoike, T.; Springer, J. P. *J. Am. Chem. Soc.* **1987**, *109*, 5167.

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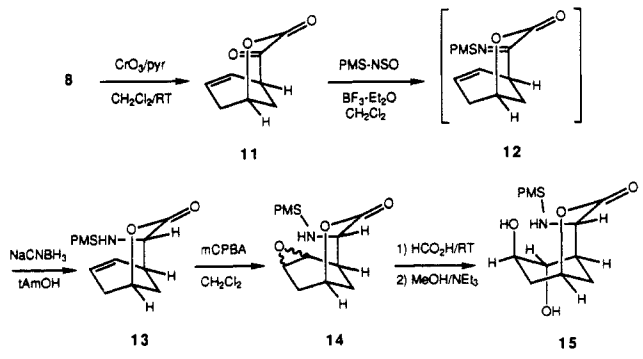
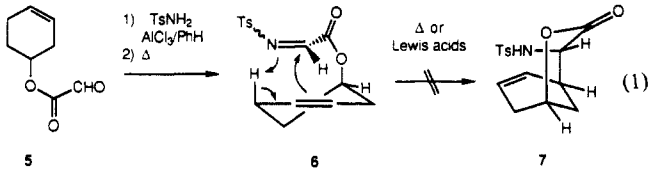
Scheme II



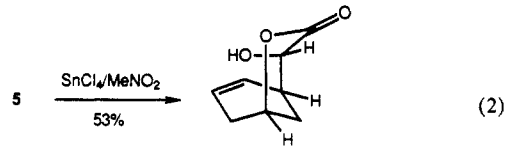
The most direct approach we could envision for preparation of lactone **4** involved an intramolecular imino ene reaction[11] of *N*-sulfonyl imine **6** derived from glyoxylate **5**[12] (eq 1). A con-



(1)

certed pericyclic reaction of **6**[11] through the exo conformation shown (endo not feasible) would provide **7**. In fact, conversion of **6** to **7** either thermally or under Lewis acid catalysis could not be effected.[13] It is not clear whether the problem here is due to the relative instability of *N*-sulfonyl imines and/or the fact that this type of imino ene reaction generally prefers to occur via an endo transition state.[11]

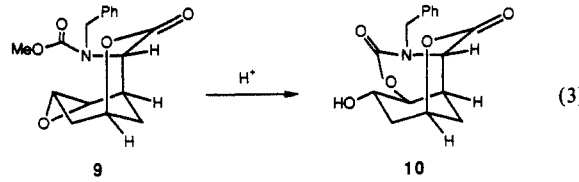
Fortunately, we were able to effect an alternative ene reaction directly on glyoxylate **5** by using stannic chloride in nitromethane at room temperature to afford α-hydroxy lactone **8** as a single stereoisomer in moderate yield (eq 2).[14] Interestingly, other Lewis



(2)

acids (e.g., $EtAlCl_2$, $TiCl_4$, $AlCl_3$, $FeCl_3$, $ZnCl_2$, etc.) in various solvents gave only trace amounts or none of **8**.

Two major concerns in the synthesis were addressed next, that is, repacement of the hydroxyl group of **8** by nitrogen and determination of the most suitable amine protecting group. On the basis of some preliminary studies,[13] it was found that *N*-acyl protection was unsuitable for two reasons: (1) lactone **4**, where P = COMe, was subject to ready epimerization at C-4 and (2) the *N*-acyl group came into play unfavorably in functionalization of the C-5/6 double bond. For example, epoxy carbamate **9**, prepared via a nitrone-based route,[12] cyclized to **10**, which has the incorrect diol stereochemistry (eq 3).[13] This transformation



(3)

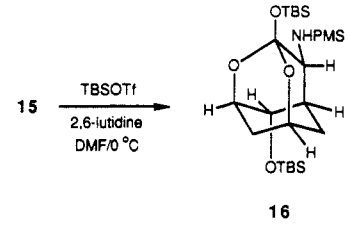
presumably occurs via intramolecular opening of a boat epoxy cyclohexane.[15] We therefore decided to use a sulfonyl protecting group, specifically (*p*-methylbenzyl)sulfonyl (PMS),[16] which Ohno and co-workers had successfully applied in their actinobolin synthesis.[10a]

In order to introduce the nitrogen functionality, hydroxy lactone **8** was first oxidized with Collins reagent to α-keto lactone **11** (80%) (Scheme II). It might be noted that other oxidants (PCC, PDC, Swern, Me_2S/NCS, $BaMnO_4$, etc.) gave much lower yields. It was possible to effect reductive aminations of **11** with ammonium bromide or benzyl amine in combination with sodium cyanoborohydride to produce the corresponding amino lactones with the desired C-3 stereochemistry (cf. **4**). Unfortunately, these amines were so hindered they could not be N-sulfonylated.

An alternative route was thus developed which allowed the direct "reductive sulfonamidation" of keto lactone **11**. Treatment of **11** with *N*-sulfinyl-(*p*-methylphenyl)methanesulfonamide, prepared from PMS sulfonamide and thionyl chloride,[17] gave *N*-sulfonyl imine **12**,[18] which without isolation was reduced with sodium cyanoborohydride in *tert*-amyl alcohol[19] from the least hindered face to afford sulfonamide **13** stereoselectively (80%).[20]

Treatment of olefinic lactone **13** with *m*-chloroperbenzoic acid gave a 1.5/1 mixture of two isomeric epoxides **14** (95%). This result was somewhat surprising, since one would expect the top face of alkene **13** to be blocked by the large NHPMS group. Perhaps the sulfonamide group participates in a directing (Henbest) effect.[21] The fact that a mixture of epoxides was obtained was of no concern since solvolytic diaxial opening of both isomers provided the *same* diaxial diol **15** (100%).

We considered the possibility of protecting the diol functionality of **15** as the bis(*tert*-butyldimethylsilyl) ether prior to further transformations. In fact, silylation of lactone diol **15** did not give the desired product, but instead provided the interesting adamantane-like bis-*O*-silyl ortho lactone **16** (eq 4). Although **16**



(4)

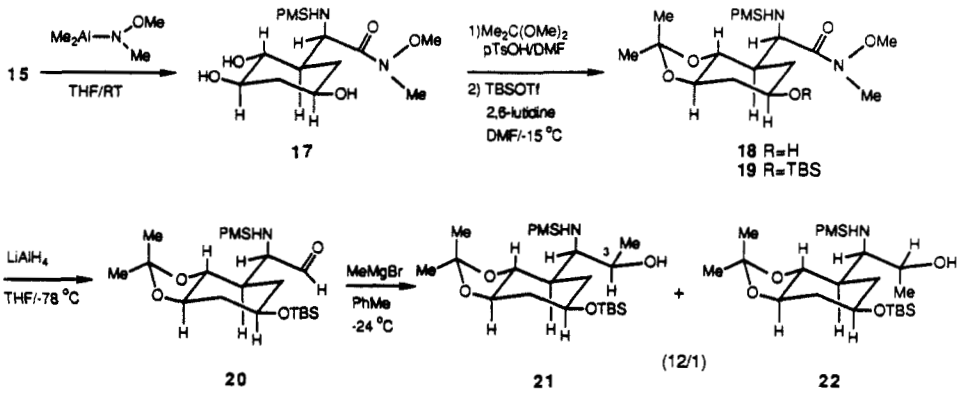
was not useful in the total synthesis, analysis of its ^1H NMR spectrum provided good interim support for the structure and stereochemistry of **15**.

Protection of the alcohol groups of **15** actually proved unnecessary. Opening of the lactone ring of **15** could be effected with an excess of the aluminum amide reagent[22] derived from *N*,*O*-dimethylhydroxylamine to produce amido triol **17** (Scheme III). The 1,2-diol functionality of **17** was protected as acetonide **18** (60% from **15**) and the remaining hydroxyl group was converted to the TBS ether **19** (97%). Subsequent reduction of the *N*-methyl-*O*-methoxy amide group of **19** with lithium aluminum hydride yielded aldehyde **20**[23] (92%).

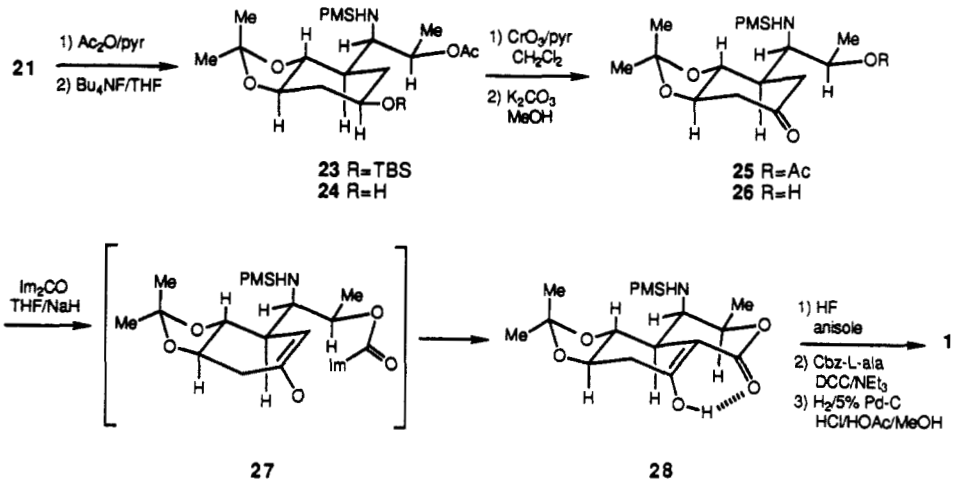
The C-3 functionality and stereochemistry were next established by addition of methylmagnesium bromide to aldehyde **20**. The

(11) Tschaen, D. M.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058.
(12) Tschaen, D. M.; Whittle, R. R.; Weinreb, S. M. *J. Org. Chem.* **1986**, *51*, 2604.
(13) Tschaen, D. M. Ph.D. Thesis, The Pennsylvania State University, University Park, PA, 1984.
(14) cf Lindner, D. L.; Doherty, J. B.; Shoham, G.; Woodward, R. B. *Tetrahedron Lett.* **1982**, *23*, 5111.
(15) cf Gross, P. H.; Brendel, K.; Zimmerman, H. K. *Liebigs Ann. Chem.* **1964**, *680*, 159.
(16) Fukuda, T.; Kitada, C.; Fujino, M. *J. Chem. Soc., Chem. Commun.* **1978**, 220.
(17) Hori, T.; Singer, S. P.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1456.
(18) Albrecht, R.; Kresze, G.; Mlakar, B. *Chem. Ber.* **1964**, *97*, 483. Albrecht, R.; Kresze, G. *Chem. Ber.* **1965**, *98*, 1431.
(19) If ethanol was used as solvent only the product of addition of alcohol to the imine was produced.
(20) This reductive sulfonamidation process has recently been generalized: Alexander, M. D.; Anderson, R. E.; Sisko, J.; Weinreb, S. M. *J. Org. Chem.*, submitted.
(21) cf Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org. Chem.* **1987**, *52*, 5127.
(22) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.
(23) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

Scheme III



Scheme IV

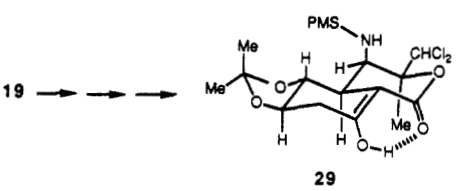


stereochemical outcome was found to be dependent upon the reaction temperature and solvent. The optimum ratio of the desired stereoisomer **21** to epimer **22** (12/1) was obtained in toluene at −24 °C. The formation of **21** is consistent with a Cram chelation controlled addition to aldehyde **20**, perhaps involving a deprotonated sulfonamide.[24,25]

In order to prepare an intermediate for the planned introduction of the remaining carboxyl group, alcohol **21** was processed as outlined in Scheme IV to give keto alcohol **26** in high overall yield. Since the α-positions of ketone **26** are nearly sterically equivalent, it seemed unlikely that an enolate could be formed regioselectively for the carboxylation step. We therefore decided to effect this key carboxylation intramolecularly, a transformation which has surprisingly little precedent. Treatment of keto alcohol **26** with 1,1′-carbonyldiimidazole, followed by sodium hydride afforded the desired enol lactone **28** in 80% yield. These conditions probably lead to an equilibrating mixture of enolates, but only regioisomer **27** can undergo intramolecular C-acylation. Some prior concerns had arisen about the possibility of the other enolate suffering irreversible β-elimination of the acetonide oxygen. However, the rigid, tightly fused trans-6,5-ring system cannot easily achieve the proper stereoelectronic orientation for this process to occur.

The synthesis of actinobolin from enol lactone **28** was achieved as described by the Ohno group.[10a] Liquid HF served to remove both the PMS[16] and acetonide protecting groups to afford racemic actinobolamine, which was acylated with Cbz-L-alanine. Separation of the resulting diastereomers and hydrogenolytic Cbz group removal afforded (+)-actinobolin hydrochloride identical with natural material.[26]

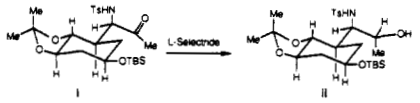
Our original approach to bactobolin (**3**) was to modify PMS-protected intermediate amide **19** to establish the requisite C-3 substitution and stereochemistry. In fact, with the use of a strategy identical with the one discussed below, amide **19** could be converted to PMS-protected bactobolamine derivative **29** (eq 5) (see supplementary material for experimental details). However, despite prolonged effort, **29** could not be deprotected without destruction. The compound simply lost the acetonide moiety under conditions used to deprotect **28** (HF/anisole or Me_2S/HF/*m*-cresol[27]). Moreover, neither a variety of reductive (e.g. H_2/Pd-C/HF) nor oxidative conditions (e.g. LiHMDS/O_2 or MoOPH) afforded any of the desired amine.



(5)

In view of these disappointing results it became necessary to find an alternative nitrogen protecting group, and we chose the (β-(trimethylsilyl)ethyl)sulfonyl (SES) group which we recently introduced.[28] α-Keto lactone **11** was transformed to **30** (80%)

(24) This analysis is also consistent with the observed stereoselective addition of hydride to methyl ketone i to afford alcohol ii.



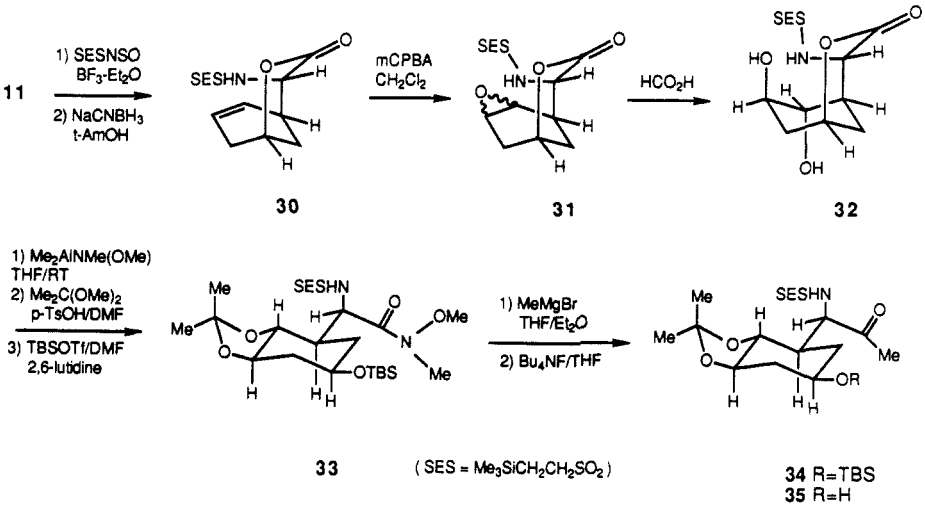
(25) For a recent review of nucleophilic additions to α-amino and related ketones, see: Tramontini, M. *Synthesis* **1982**, 605. See also: Hanson, G. J.; Lindberg, T. *J. Org. Chem.* **1985**, *50*, 5399.

(26) Natural (+)-actinobolin sulfate was kindly provided by Drs. J. H. Dodd and J. French (Warner-Lambert Co.). This compound was converted to the chloride using Dowex AG-1-X8 (chloride form) resin.

(27) Tam, J. P.; Heath, W. F.; Merrifield, R. B. *J. Am. Chem. Soc.* **1983**, *105*, 6442.

(28) Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099.

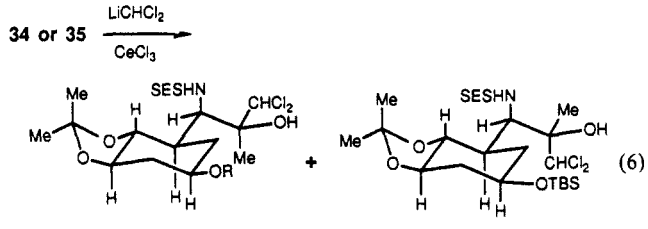
Scheme V



by using our reductive sulfonamidation procedure starting with *N*-sulfinyl-β-(trimethylsilyl)ethanesulfonamide (Scheme V). Compound **30** was converted via epoxides **31** (84%) to diol **32**, and subsequently to *N*-methyl-*N*-methoxy amide **33** (61% from **31**).

Treatment of amide **33** with methylmagnesium bromide cleanly provided the desired methyl ketone **34** (88%).[23] A number of attempts were made to add lithio dichloromethane[29] to this ketone to produce (dichloromethyl)carbinol **36**. However, only dark intractable material was produced in these reactions.

It was finally found that if lithiodichloromethane is converted to the cerium reagent[30] addition to ketone **34** occurs to give a separable 3/1 mixture of epimeric adducts **36** and **38**.[31] In what



turned out to be a fortunate occurrence, attempts at deprotecting **36** with fluoride sources gave complex mixtures of products lacking the dichloromethyl group.[32] Thus, the organo cerium reagent was instead added to alcohol **35**, derived from keto silyl ether **34**, and to our surprise *only* diol **37** (90%) was produced, along with some unreated ketone.[31] There seems to be no obvious explanation for this fortuitous improvement in selectively. As in the addition to aldehyde **20**, a Cram chelation controlled process is consistent with the observed results.

Oxidation of the secondary alcohol group of **37** was uneventful and cyclohexanone **39** was obtained in 90% yield (Scheme VI). As one might have expected, the tertiary hydroxyl functionality in **39** was resistant to acylation with a wide variety of phosgene-derived reagents. Eventually a set of conditions was found which produced the cyclic carbamate **40** in good yield. This compound probably arises via initial N-acylation followed by an intramolecular O-acylation. At first glance carbamate **40** appears to be a potentially useful cyclization substrate. However, upon inspection of models it is clear that a direct intramolecular enolate acylation is disfavored stereoelectronically. On the other hand, it seemed reasonable to expect that the cyclic carbamate might open with a nucleophile with extrusion of the *N*-sulfonyl group to afford a carbonate derivative which could be trapped intramolecularly by an enolate. In fact, treatment of **40** with sodium methoxide in methanol afforded enol lactone **42** in 70% yield, probably via an intermediate **41**.

The crucial nitrogen deprotection of SES derivative **42** could then be effected successfully with fluoride and, after acetonide hydrolysis, amine hydrochloride **43** was isolated. Application of the methodology used for actinobolin to **43** provided (−)-bactobolin identical with an authentic sample.[33]

We have therefore developed total syntheses of both (+)-actinobolin (**1**) and (−)-bactobolin (**3**) from the α-keto lactone **11**. Both syntheses are highly stereoselective and efficient. Actinobolin requires 16 steps from **11** and bactobolin, the more complex congener, can be prepared in about the same number of steps.

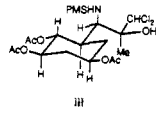
Experimental Section

***endo*-4-Hydroxy-2-oxabicyclo[3.3.1]non-6-en-3-one (8).** A solution of 1.20 g (7.8 mmol) of glyoxylate **5** in 20 mL of dry nitromethane was added to 2.00 g (7.8 mmol) of stannic chloride in 15 mL of nitromethane over 3 h. The resulting red solution was stirred at room temperature for 2 h and was diluted with ethyl acetate. The mixture was washed with saturated NaF and NaCl solutions, dried over Na_2SO_4, and evaporated in vacuo. The crude product was purified by flash chromatography eluting with ethyl acetate/hexane (1/1.5) to afford 0.64 g (53%) of the α-hydroxy lactone **8**. An analytical sample of **8** recrystallized from CH_2Cl_2/hexane had mp 124–126 °C: IR (film) 3420, 3040, 2925, 1730, 1420, 1380, 1330, 1310, 1240, 1220, 1190, 1160, 1115, 920, 910, 840, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 6.03 (m, 1 H), 5.75 (m, 1 H), 4.92 (m, 1 H), 4.25 (d, J = 5.1 Hz, 1 H), 3.30 (br s, 1 H), 2.83 (m, 1 H), 2.45 (m, 2 H), 2.28 (m, 1 H), 2.10 (dd, J = 4.7, 13.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.95, 127.40, 124.43, 75.96, 72.03, 33.42, 32.84, 27.78; mass spectrum, m/z (relative intensity) 155 (1.9), 154 (19.6), 95 (10.8), 86 (12.1), 84 (18.8). Anal. Calcd for $C_8H_{10}O_3$: C,

(29) Kobrich, G.; Flory, K.; Drischel, W. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 513.

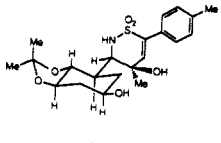
(30) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.

(31) The PMS-protected analogue of **37** was converted to triacetate iii, which was found by X-ray crystallography to have the desired C-3 stereochemistry (see supplementary material). We thank Dr. M. Parvez for this structure determination.



iii

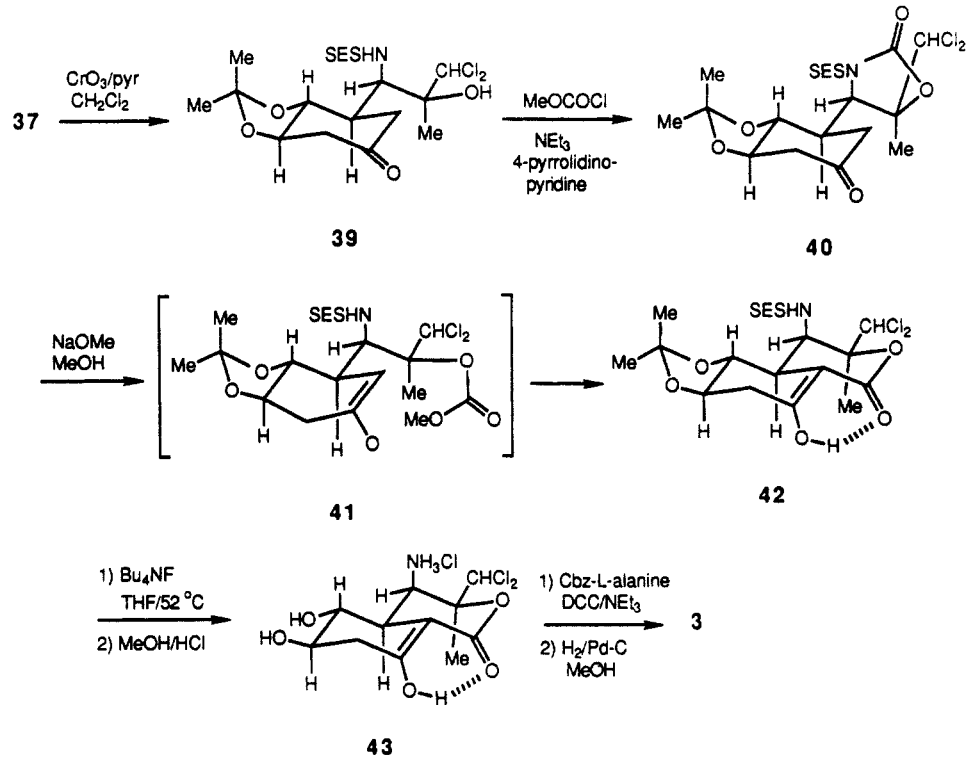
(32) One of the products of these desilylation attempts has been tentatively characterized as iv.



iv

(33) We are grateful to Dr. T. Munakata, Yoshitomi Pharmaceutical Industries, Ltd. (Japan), for a generous sample of natural (−)-bactobolin (**3**).

Scheme VI



62.33; H, 6.54. Found: C, 61.98; H, 6.19.

2-Oxabicyclo[3.3.1]non-6-ene-3,4-dione (11). To a solution of 21.0 g (0.26 mmol) of pyridine in 400 mL of dichloromethane was added 16.0 g (0.16 mmol) of chromium trioxide in four equal portions at 0 °C. The mixture was stirred at room temperature for 30 min, and 4.1 g (0.026 mmol) of α-hydroxy lactone **8** in 100 mL of CH_2Cl_2 was added. After stirring for 20 min, the solution was filtered through a pad of Florisil, and the filter cake was washed with 600 mL of dichloromethane. The solvent was removed in vacuo, and the residue was purified by flash chromatography eluting with 2% acetone in dichloromethane to afford 3.2 g (80%) of α-keto lactone **11** as a white solid. An analytical sample of **11** purified by bulb-to-bulb distillation [bp 100 °C (0.05 Torr)] had mp 90–92 °C: IR (film) 3475, 3040, 2950, 1750, 1370, 1290, 1250, 1170, 1150, 1120, 970, 920, 870, 810, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 6.05 (dt, J = 3.3, 9.7 Hz, 1 H), 5.70 (ddt, J = 2.0, 3.3, 7.1 Hz, 1 H), 5.02 (m, 1 H), 3.46 (m, 1 H), 2.5–2.8 (m, 3 H), 2.35 (ddd, J = 0.9, 3.4, 14.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 182.95, 156.89, 130.0, 121.20, 74.04, 43.14, 31.42, 26.77; mass spectrum, m/z (relative intensity) 154 (0.6), 153 (1.3), 153 (14.1), 86 (10.2), 84 (16.2), 80 (100), 79 (87.7), 77 (16.4). Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 62.89; H, 5.30.

Preparation of Lactone Sulfonamide 13. A suspension of 3.1 g (0.016 mmol) of (*p*-methylphenyl)methanesulfonamide, 0.015 g of *N,N*-dichloro-*p*-toluenesulfonamide, and 4.0 g (0.034 mmol) of thionyl chloride in 3.2 mL of dry benzene was refluxed for 28 h.[17] Removal of solvent in vacuo yielded 3.8 g of *N*-sulfinyl(*p*-methylphenyl)methanesulfonamide as an orange-red solid which was used without further purification.

A solution of 0.80 g (5.3 mmol) of α-keto lactone **11**, 1.36 g (5.9 mmol) of *N*-sulfinyl(*p*-methylphenyl)methanesulfonamide, and 1.6 mL (5.3 mmol) of boron trifluoride etherate in 10 mL of dichloroethane was stirred at 42 °C for 27 h. After the mixture was cooled to 0 °C, a solution of 0.60 g (8.8 mmol) of sodium cyanoborohydride in 5 mL of amyl alcohol was added (exothermic, caution!), and the mixture was stirred for 1 h. The reaction mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$ and NaCl solutions, dried over Na_2SO_4, and was evaporated in vacuo. The crude product was purified by flash chromatography eluting with 3% ether in dichloromethane to afford 1.35 g (80%) of sulfonamide **13** as a white solid. An analytical sample of **13** recrystallized from CH_2Cl_2/hexane had mp 152–154 °C: IR (film) 3275, 3050, 2925, 1730, 1520, 1380, 1320, 1310, 1160, 1120, 1110, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.36 (d, J = 7.9 Hz, 2 H), 7.18 (d, J = 7.8 Hz, 2 H), 5.95 (m, 1 H), 5.77 (m, 1 H), 5.03 (d, J = 6.4 Hz, NH), 4.92 (m, 1 H), 4.40 (AB q, J = 13.9 Hz, 2 H), 4.10 (dd, J = 4.5, 6.5 Hz, 1 H), 2.82 (m, 1 H), 2.44 (m, 2 H), 2.35 (s, 3 H), 2.25 (m, 1 H), 2.05 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.88, 138.63, 130.77, 129.39, 126.21, 126.17, 125.67, 75.60, 59.17, 58.56, 32.57, 27.72, 21.14; mass spectrum, m/z (relative intensity) 337 (0.4), 321 (2.1), 120 (15.9), 105 (100). Anal. Calcd for $C_{16}H_{19}NO_4S$: C, 59.79; H, 5.96. Found: C, 59.52; H, 5.95.

Preparation of Epoxides 14. To a solution of 4.45 g (0.014 mol) of lactone alkene **13** in 40 mL of dry dichloromethane was added 7.17 g (0.041 mol) of 85% *m*-chloroperoxybenzoic acid. After the mixture was stirred for 24 h, 150 mL of ethyl acetate was added. The mixture was washed with saturated $NaHSO_3$, $NaHCO_3$, and NaCl solutions and dried over Na_2SO_4. Removal of the solvent in vacuo yielded the crude epoxides which could be separated by flash chromatography. Elution of the column with ethyl acetate/hexane (1/1) yielded 1.77 g (38%) of one epoxide as a white solid. An analytical sample recrystallized from CH_2Cl_2/hexane had mp 183–185 °C: IR (film) 3375, 3050, 2925, 1730, 1510, 1380, 1330, 1160, 1130, 1100, 940, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.35 (d, J = 8.0 Hz, 2 H), 7.20 (d, J = 7.9 Hz, 2 H), 5.40 (d, J = 3.8 Hz, NH), 4.59 (br s, 1 H), 3.39 (m, 1 H), 3.05 (m, 1 H), 2.88 (m, 1 H), 2.36 (s, 3 H), 2.32 (m, 1 H), 2.14 (dd, J = 4.0, 16.5 Hz, 1 H), 2.00 (dd, J = 4.2, 14.3 Hz, 1 H), 1.82 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.89, 138.92, 130.69, 130.53, 129.47, 125.39, 74.32, 59.08, 56.69, 51.43, 47.65, 32.30, 31.70, 24.47, 21.17; mass spectrum, m/z (relative intensity) 337 (0.5), 120 (12.5), 105 (100). Anal. Calcd for $C_{16}H_{19}NO_5S$: C, 56.96; H, 5.68. Found: C, 56.70; H, 5.55.

Elution of the column with ethyl acetate/hexane (2/1) yielded 2.66 g (57%) of the second epoxide as a white solid. An analytical sample recrystallized from CH_2Cl_2/hexane had mp 209–210 °C: IR (film) 3275, 3025, 2925, 1730, 1510, 1390, 1330, 1320, 1260, 1160, 1120, 1040, 820, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.41 (d, J = 8.0 Hz, 2 H), 7.19 (d, J = 7.8 Hz, 2 H), 5.41 (d, J = 8.2 Hz, NH), 4.68 (br s, 1 H), 4.47 (AB q, J = 13.8 Hz, 2 H), 4.03 (dd, J = 5.2, 8.2 Hz, 1 H), 3.45 (dd, J = 3.8, 6.0 Hz, 1 H), 3.28 (br s, 1 H), 2.95 (m, 1 H), 2.63 (d, J = 16.4 Hz, 1 H), 2.36 (s, 3 H), 2.05 (m, 1 H), 1.96 (ddd, J = 2.7, 4.1, 16 Hz, 1 H), 1.74 (dd, J = 4.4, 14.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.19, 138.51, 130.91, 129.41, 125.97, 73.10, 59.41, 55.69, 52.27, 50.95, 33.52, 30.20, 26.60, 21.21, 21.17; mass spectrum, m/z (relative intensity) 337 (0.6), 279 (5.1), 167 (17.9), 156 (17.9), 149 (51.9), 139 (20.6), 120 (18.8), 111 (14.9), 105 (100). Anal. Calcd for $C_{16}H_{19}NO_5S$: C, 56.96; H, 5.68. Found: C, 56.53; H, 5.58.

Solvolysis of Epoxides 14 to Diol 15. A solution of 0.40 g (1.2 mmol) of the crude mixture of epoxides **14** in 10 mL of anhydrous formic acid was stirred for 3 h and was evaporated in vacuo. The residue was dissolved in 5 mL of methanol, and two drops of triethylamine was added. The mixture was stirred for 1 h, and the solvent was evaporated in vacuo to yield 0.42 g (100%) of the diol **15** which was used directly in the next step: IR (film) 3500, 3300, 2975, 2925, 1740, 1510, 1390, 1330, 1260, 1190, 1160, 1090, 930, 810 cm^{-1}; ^1H NMR (CD_3CN/CD_3OD, 200

MHz) δ 7.36 (d, J = 8.1 Hz, 2 H), 7.22 (d, J = 7.9 Hz, 2 H), 4.63 (br, 1 H), 4.49 (s, 2 H), 4.40 (d, J = 6.5 Hz, 1 H), 4.05 (m, 1 H), 3.88 (m, 2 H), 2.37 (s, 3 H), 2.27 (m, 1 H), 2.02 (m, 3 H); mass spectrum, m/z (relative intensity) 355 (0.2), 106 (10.7), 105 (100).

Dimethylaluminum *N,O*-Dimethylhydroxylamide. A solution of potassium hydroxide (15 g) in water (15 mL) was frozen in liquid nitrogen and *N,O*-dimethylhydroxylamine hydrochloride (20 g, 94% purity) was added. The reaction flask was evacuated, and the mixture was warmed to room temperature. *N,O*-Dimethylhydroxylamine was distilled (bp 42 °C/760 mmHg) into a flask containing potassium hydroxide pellets. The compound (9.2 g, 78%) was dried over 3-Å molecular sieves before use.

A 2 M solution of trimethylaluminum in hexane (1.8 mL, 3.6 mmol) was added to *N,O*-dimethylhydroxylamine in dry THF (5 mL) at 0 °C. The mixture was stirred for 30 min at room temperature, yielding a 0.46 M solution of dimethylaluminum *N,O*-dimethylhydroxylamide.

Conversion of Diol 15 to Amide 19. A solution of 0.46 M dimethylaluminum *N,O*-dimethylhydroxylamide in THF (17.8 mL, 8.2 mmol) was added to 0.42 g (1.2 mmol) of diol **15** and the mixture was stirred for 24 h. Saturated NH_4Cl solution was added dropwise to the reaction mixture until the excess aluminum amide was destroyed, and the resulting gelatinous precipitate was washed with 500 mL of acetone. Removal of the solvent yielded the intermediate triol [IR (film): 3600–3100 (br), 2925, 1650, 1510, 1410, 1390, 1330, 1150, 1010, 820 cm^{-1}] which was used without further purification.

A solution of the above crude amido triol **17**, 16.5 mL of 2,2-dimethoxypropane, and 0.2 g of *p*-toluenesulfonic acid monohydrate in 17.8 mL of DMF was stirred at room temperature for 20 h. The reaction mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$ and NaCl solutions, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography eluting with ethyl acetate/hexane (3/1) to afford 0.32 g (60%) of alcohol **18**: IR (film) 3450, 3250, 2975, 2925, 1650, 1510, 1380, 1320, 1230, 1150, 1130, 850 cm^{-1}.

To a solution of 1.57 g (3.4 mmol) of alcohol **18** in 10 mL of DMF were added 0.7 mL (5.8 mmol) of 2,6-lutidine and 1.2 mL (5.1 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate at −15 °C. The mixture was stirred at −15 °C for 2 h, diluted with ice-cold ethyl acetate (30 mL), and was washed with ice-cold 5% HCl and NaCl solutions. The organic extract was dried over Na_2SO_4 and was concentrated in vacuo. Purification of the residue by flash chromatography eluting with 6% ether in CH_2Cl_2 yielded 1.90 g (97%) of silyl ether **19**. An analytical sample of **19** recrystallized from CH_2Cl_2/hexane had mp 179–181 °C: IR (film): 3250, 2975, 2950, 2925, 2875, 2850, 1660, 1510, 1460, 1380, 1350, 1250, 1230, 1130, 1090, 1050, 840, 770, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.32 (d, J = 7.9 Hz, 2 H), 7.17 (d, J = 7.9 Hz, 2 H), 5.40 (d, J = 3.8 Hz, NH), 4.55 (dd, J = 4.4, 9.6 Hz, 1 H), 4.20 (AB q, J = 13.7 Hz, 2 H), 3.75 (m, 1 H), 3.67 (s, 3 H), 3.39 (t, J = 10.1 Hz, 1 H), 3.31 (m, 1 H), 3.21 (s, 3 H), 2.35 (s, 3 H), 2.25 (m, 1 H), 1.95 (m, 2 H), 1.50 (m, 1 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 1.25 (m, 1 H), 0.87 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.80, 138.49, 130.74, 129.34, 125.72, 110.73, 79.50, 77.09, 68.86, 61.45, 59.58, 53.92, 39.04, 37.63, 35.15, 26.87, 25.70, 17.97, −4.75; CIMS (m + 1/z) 573, 572, 571. Anal. Calcd for $C_{26}H_{26}N_2O_7SSi$: C, 56.80; H, 8.12. Found: C, 56.39; H, 8.11.

Preparation of Bis(silyl ether) 16. To a solution of 0.037 g (0.1 mmol) of diol **15** in 0.1 mL of dry DMF was added 40 μL (0.35 mmol) of 2,6-lutidine and 70 μL (0.31 mmol) of *tert*-butyldimethylsilyl trifluoromethanesuflonate at 0 °C. The mixture was stirred at room temperature for 24 h, diluted with ethyl acetate, washed with 5% HCl and NaCl solutions, and dried over Na_2SO_4. Removal of the solvent in vacuo and purification of the residue by preparative TLC eluting with ethyl acetate/hexane (1/1) yielded 0.030 g (50%) of silyl ether **16**. An analytical sample of **16** recrystallized from pentane had mp 58–60 °C: IR (film) 3300, 2950, 2925, 2850, 1510, 1460, 1320, 1280, 1250, 1220, 1160, 1110, 1090, 1050, 990, 910, 840, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.32 (d, J = 8.1 Hz, 2 H), 7.18 (d, J = 8.0 Hz, 2 H), 4.63 (d, J = 6.2 Hz, 1 H), 4.25 (AB q, J = 13.6 Hz, 2 H), 4.25 (m, 1 H), 3.99 (m, 1 H), 3.60 (dd, J = 3.6, 6.3 Hz, 1 H), 2.45 (m, 1 H), 2.40 (s, 3 H), 2.17–1.90 (m, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.22 (s, 3 H), 0.18 (s, 3 H), 0.10 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 138.48, 130.50, 129.47, 125.91, 106.23, 73.67, 70.83, 64.25, 59.70, 59.14, 39.94, 28.91, 26.72, 25.82, 25.63, 25.52, −2.95, −3.07, −4.87, −4.94; CIMS (m + 1/z) 588, 587, 586, 585, 584, 583. Anal. Calcd for $C_{28}H_{49}NO_6SSi_2$: C, 57.59; H, 8.46. Found: C, 57.73; H, 8.33.

Reduction of Amide 19 to Aldehyde 20. A 1 M solution of $LiAlH_4$ in THF (1 mL, 0.98 mmol) was added to 0.140 g (0.24 mmol) of amide **19** in 2 mL of dry THF at −78 °C, and the mixture was stirred for 90 min. The reaction mixture was poured into a beaker containing silica gel (15 g) and chloroform, and the mixture was stirred for 5 min. The mixture was filtered, and the filtrate was concentrated in vacuo. Purification of the residue by preparative TLC eluting with ethyl acetate/hexane (1/2) afforded 0.112 g (92%) of aldehyde **20**: IR (film) 3275, 2950, 2925, 2850, 1730, 1510, 1370, 1330, 1260, 1230, 1160, 1090, 830, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 9.59 (s, 1 H), 7.30 (d, J = 8.1 Hz, 2 H), 7.20 (d, J = 8.0 Hz, 2 H), 5.25 (d, J = 9.1 Hz, 1 H), 4.26 (AB q, J = 13.8 Hz, 2 H), 3.90 (dd, J = 4.1, 9.0 Hz, 1 H), 3.76 (m, 1 H), 3.33 (m, 1 H), 2.36 (s, 3 H), 2.30 (m, 1 H), 1.45–2.50 (m, 4 H), 1.40 (s, 6 H), 0.86 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 198.84, 138.89, 130.67, 129.54, 129.46, 125.58, 111.41, 79.71, 77.28, 68.67, 63.11, 59.86, 38.17, 35.49, 26.90, 26.78, 25.67, 17.95, −4.83; CIMS (m + 1/z) 514, 513, 512, 511, 510.

Preparation of Alcohols 21 and 22. A 3 M solution of methylmagnesium bromide in ether (0.4 mL, 1.1 mmol) was added to 0.094 g (0.18 mmol) of aldehyde **20** in 2 mL of dry toluene at −24 °C, and the mixture was stirred for 3 h. The reaction mixture was diluted with saturated NH_4Cl solution and was concentrated in vacuo. Purification of the residue by preparative TLC (3% acetone in CH_2Cl_2) afforded 0.095 g (99%) of alcohols **21** and **22** (^1H NMR indicated a diastereomer mixture in the ratio of 12/1 which was used in the next step): IR (film) 3500, 3300, 2975, 2950, 2925, 1510, 1460, 1370, 1330, 1260, 1230, 1150, 1130, 1090, 1020, 840, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.33 (d, J = 8.1 Hz, 2 H), 7.19 (d, J = 8.0 Hz, 2 H), 4.74 (d, J = 9.3 Hz, NH), 4.29 (s, 2 H), 4.08 (m, 1 H), 3.76 (m, 1 H), 3.2–3.4 (m, 2 H), 2.47 (m, 1 H), 2.37 (s, 3 H), 2.28 (m, 1 H), 2.02 (m, 1 H), 1.45–1.60 (m, 2 H), 1.41 (s, 6 H), 1.25 (d, J = 6.3 Hz, 3 H), 0.88 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 138.60, 130.57, 129.51, 129.43, 110.70, 80.60, 68.81, 67.00, 61.46, 60.31, 40.11, 37.68, 37.62, 26.87, 26.78, 25.71, 21.19, 20.76, 17.99, −4.75; CIMS (m + 1/z) 529, 528, 527.

Synthesis of Acetate 23. A mixture of 0.305 g (0.58 mmol) of alcohols **21** and **22**, 3 mL of acetic anhydride, and 2 mL of pyridine was stirred at room temperature for 20 h. The solvent was removed in vacuo, and the residue was purified by preparative TLC eluting with ethyl acetate/hexane (1/2) to yield 0.313 g (95%) of acetate **23**: IR (film) 3275, 2975, 2950, 2925, 2825, 1740, 1510, 1430, 1370, 1330, 1230, 1150, 1090, 1060, 830, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.33 (d, J = 8.0 Hz, 2 H), 7.20 (d, J = 7.9 Hz, 2 H) 5.08 (dq, J = 2.4, 6.2 Hz, 1 H), 4.85 (d, J = 9.8 Hz, NH), 4.30 (AB q, J = 14 Hz, 2 H), 3.69 (m, 1 H), 3.47 (td, J = 2.2, 7.5 Hz, 1 H), 3.19 (m, 1 H), 3.15 (t, J = 8.7 Hz, 1 H), 2.37 (s, 3 H), 2.27 (m, 1 H), 2.03 (s, 3 H), 1.40–1.71 (m, 4 H), 1.41 (s, 3 H), 1.38 (s, 3 H), 1.31 (d, J = 7.5 Hz, 3 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.93, 138.59, 130.62, 130.50, 129.52, 129.42, 126.20, 110.78, 80.50, 69.39, 68.84, 60.41, 58.95, 39.69, 37.69, 36.43, 27.08, 26.80, 25.67, 21.36, 21.21, 18.50, 17.95, −4.70, −4.80; CIMS (m + 1/z) 571, 570, 569.

Preparation of Acetoxy Alcohol 24. To a solution of 0.310 g (0.54 mmol) of silyl ether **23** in 8 mL of dry THF was added 3.3 mL (3.27 mmol) of a 1 M solution of tetrabutylammonium fluoride in THF, and the mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with saturated NH_4Cl solution and was extracted with ethyl acetate. The organic extract was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography eluting with ethyl acetate/hexane (3/1) to afford 0.240 g (97%) of acetoxy alcohol **24**: IR (film) 3500, 3300, 3000, 2950, 2875, 1740, 1510, 1440, 1370, 1330, 1240, 1150, 1130, 1050, 950, 920, 840, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.32 (d, J = 8.0 Hz, 2 H), 7.19 (d, J = 7.9 Hz, 2 H), 5.10 (dq, J = 2.8, 6.3 Hz, 1 H), 4.80 (d, J = 9.8 Hz, NH), 4.30 (s, 2 H), 3.75 (m, 1 H), 3.50 (m, 1 H), 3.28 (m, 1 H), 3.17 (t, J = 9.6 Hz, 1 H), 2.40 (m, 1 H), 2.36 (s, 3 H), 2.04 (s, 3 H), 1.40–1.87 (m, 4 H), 1.40 (s, 3 H), 1.39 (s, 3 H), 1.33 (d, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.15, 138.69, 130.61, 129.45, 126.11, 110.89, 80.52, 77.43, 69.56, 68.32, 60.36, 58.99, 53.66, 39.43, 37.18, 35.97, 27.04, 26.77, 21.38, 21.17, 20.73, 18.42; CIMS (m + 1/z) 457, 456, 455.

Synthesis of Keto Acetate 25. To a solution of 0.34 mL (4.17 mmol) of pyridine in 4 mL of dichloromethane was added 0.250 g (2.50 mmol) of chromium trioxide in two equal portions at 0 °C. The mixture was stirred at room temperature for 20 min, and 0.190 g (0.417 mmol) of alcohol **24** in 7.5 mL of dichloromethane was added. After the mixture was stirred for 35 min, the solution was filtered through a pad of Florisil, and the filter cake was washed with 250 mL of ethyl acetate. The filtrate was evaporated in vacuo, and the residue was purified by flash chromatography eluting with ethyl acetate/hexane (1/2) to yield 0.181 g (96%) of keto acetate **25**: IR (film) 3275, 2975, 2925, 1740, 1720, 1510, 1440, 1370, 1330, 1240, 1160, 1120, 950, 920, 850, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.31 (d, J = 8.0 Hz, 2 H), 7.18 (d, J = 7.9 Hz, 2 H), 5.09 (dq, J = 3.1, 6.3 Hz, 1 H), 4.81 (d, J = 9.8 Hz, 1 H), 4.32 (AB q, 2 H), 3.48–3.62 (m, 2 H), 2.85 (ddd, J = 1.7, 4.1, 14.3 Hz, 1 H), 2.48 (m, 1 H), 2.35 (s, 3 H), 2.32 (m, 1 H), 2.15 (t, J = 14.0 Hz, 1 H), 2.05 (s, 3 H), 1.80 (m, 1 H), 1.45 (s, 3 H), 1.44 (s, 3 H), 1.31 (d, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 204.79, 170.12, 138.99, 130.54, 129.56, 125.91, 111.98, 79.34, 69.66, 60.34, 58.36, 44.75, 41.08,

38.78, 27.05, 26.83, 21.34, 21.13, 18.33; CIMS ($m + 1/z$) 456, 455, 454, 453.

Preparation of Keto Alcohol 26. To a solution of 0.145 g (0.32 mmol) of acetate **25** in 6 mL of methanol and 0.5 mL of water was added 0.225 g (1.6 mmol) of potassium carbonate. The reaction mixture was stirred at room temperature for 2 h, diluted with ethyl acetate, washed with water, and dried over Na_2SO_4. Evaporation of the solvent in vacuo and purification of the residue by flash chromatography eluting with ethyl acetate/hexane (1/1) yielded 0.127 g (97%) of keto alcohol **26**: IR (film) 3500, 3275, 2975, 2925, 1710, 1510, 1390, 1370, 1320, 1230, 1150, 1120, 1020, 850, 820, 780, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.30 (d, J = 7.9 Hz, 2 H), 7.17 (d, J = 7.9 Hz, 2 H), 5.25 (d, J = 9.1 Hz, 1 H), 4.32 (AB q, J = 14.0 Hz, 2 H), 3.91 (m, 1 H), 3.46–3.66 (m, 3 H), 2.82 (m, 2 H), 2.56 (m, 2 H), 2.34 (s, 3 H), 2.03 (m, 1 H), 1.45 (s, 6 H), 1.20 (d, J = 8.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 205.6, 138.84, 130.57, 129.53, 125.93, 111.87, 79.45, 67.69, 60.19, 44.66, 41.57, 39.28, 26.94, 26.86, 21.15, 8.13.

Cyclization to Enol Lactone 28. A solution of 0.30 g (0.073 (mmol) of keto alcohol **26** and 0.015 g (0.091 mmol) of 1,1′-carbonyldiimidazole in anhydrous THF was stirred at room temperature for 10 h, and excess sodium hydride was added. The reaction mixture was stirred for 1 h, and the sodium hydride was carefully destroyed with saturated NH_4Cl solution. The resulting suspension was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by preparative TLC eluting with ethyl acetate/hexane (1/1) afforded 0.025 g (80%) of enol lactone **28**. An analytical sample of **28** recrystallized from CH_2Cl_2/hexane had mp 196–198 °C: IR (film) 3700–3300 (br), 3225, 2975, 2925, 2875, 1620, 1510, 1450, 1320, 1230, 1140, 1090, 1040, 950, 800, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz), δ 13.62 (s, 1 H), 7.31 (d, J = 8.2 Hz, 2 H), 7.20 (d, J = 8.1 Hz, 2 H), 4.60 (dq, J = 1.5, 6.4 Hz, 1 H), 4.37 (AB q, J = 13.3 Hz, 2 H), 4.39 (d, J = 9.8 Hz, NH), 4.41 (ddd, J = 1.3, 6.3, 9.8 Hz, 1 H), 3.83 (m, 1 H), 3.57 (t, J = 9.3 Hz, 1 H), 2.9–3.05 (m, 2 H), 2.65 (ddd, J = 2.8, 10.5, 17.7 Hz, 1 H), 2.37 (s, 3 H), 1.50 (s, 3 H), 1.49 (s, 3 H), 1.45 (d, J = 6.4 Hz, 3 H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 176.40, 170.46, 138.86, 130.50, 129.58, 125.35, 112.14, 89.75, 78.25, 76.09, 73.95, 60.27, 50.42, 40.90, 34.86, 26.97, 26.84, 21.20, 17.91. Anal. Calcd for $C_{21}H_{27}NO_7S$: C, 59.70; H, 6.68. Found: C, 59.50; H, 6.40.

(+)-Actinobolin Hydrochloride (1). Anhydrous HF (30 g) was condensed into a Teflon round-bottomed flask containing 0.013 g (0.03 mmol) of sulfonamide **28** and 1 mL of anisole. The reaction mixture was stirred for 2 h, and HF was removed via an aspirator. Removal of anisole at 0.05 Torr yielded 0.008 g (99%) of amine hydrofluoride which was used in the next step without purification.

A solution of 0.008 g (0.03 mmol) of the above amine hydrofluoride, 0.009 g (0.041 mmol) of Cbz-L-alanine, 0.015 g (0.076 mmol) of dicyclohexylcarbodiimide, and 5 μL of triethylamine in 0.8 mL of dry DMF was stirred for 10 h. Concentration of the mixture in vacuo, and purification of the residue by preparative TLC (three elutions with 5% MeOH in $CHCl_3$) yielded the diastereomeric N-acylation products (0.006 and 0.007 g, 90% combined yield).

To a solution of 0.006 g of the diastereomer with the lower R_f in 1.2 mL of HOAc/MeOH (1/10) was added 25 mg of 5% Pd/C and 0.05 mL of 0.2 N HCl. The mixture was stirred under one atmosphere of hydrogen for 1 h and was filtered through a pad of Celite. The filter cake was washed with 100 mL of methanol. Evaporation of the solvent yielded 0.004 g of (+)-actinobolin hydrochloride which was identical to natural (+)-actinobolin hydrochloride (TLC, reverse phase TLC, ^1H NMR, IR). $[\alpha]^{20}_D$ = +44 [(+)-actinobolin hydrochloride $[\alpha]^{20}_D$ = +48].

***endo*-(±)-*N*-(3-Oxo-2-oxabicyclo[3.3.1]non-6-en-4-yl)-2-(trimethylsilyl)ethanesulfonamide (30).** A solution of 1.1 g (6.1 mmol) of β-(trimethylsilyl)ethanesulfonamide, 0.005 g of *N,N*-dichloro-*p*-toluenesulfonamide, and 1 mL (14.0 mmol) of thionyl chloride in 1.7 mL of benzene was refluxed for 28 h. Evaporation of the solvent yielded *N*-sulfinyl-β-(trimethylsilyl)ethanesulfonamide which was used without purification.

A solution of 0.80 g (5.3 mmol) of α-keto lactone **11**, 1.34 g (5.9 mmol) of *N*-sulfinyl-β-(trimethylsilyl)ethanesulfonamide, and 1.6 mL (5.3 mmol) of boron trifluoride etherate in 10 mL of 1,2-dichloroethane was stirred at 42 °C for 27 h. After the mixture was cooled to 0 °C, a solution of 0.60 g (8.8 mmol) of sodium cyanoborohydride in 5 mL of amyl alcohol was added (exothermic, caution!), and the mixture was stirred for 1 h. The reaction mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$ and NaCl solutions, dried over Na_2SO_4, and was evaporated in vacuo. The crude product was purified by flash chromatography eluting with 5% ether in dichloromethane to afford 2.24 g (80%) of sulfonamide **30** as a white solid. An anlytical sample of **30** recrystallized from ethyl acetate/hexane had mp 94–96 °C: IR (film) 3245, 3050, 2960, 2900, 1740, 1450, 1430, 1370, 1350, 1320, 1250, 1220, 1175, 1165, 1130, 1105, 1045, 1010, 900, 870, 850, 810, 755, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 6.03 (m, 1 H), 5.85 (m, 1 H), 5.07 (d, J = 6.9 Hz, NH), 4.95 (m, 1 H), 4.15 (dd, J = 4.9, 7.0 Hz, 1 H), 3.15 (m, 2 H), 2.88 (m, 1 H), 2.2–2.5 (m, 3 H), 2.10 (dd, J = 4.5, 13.8 Hz, 1 H), 1.13 (dt, J = 4.8, 13.5 Hz, 1 H), 1.02 (dt, J = 4.8, 13.5 Hz, 1 H), 0.02 (s, 9 H); ^{13}C NMR ($CDCl_3$, 360 MHz) δ 171.01, 126.26, 126.16, 75.48, 58.17, 49.45, 33.29, 32.80, 28.22, 10.28, −2.13; mass spectrum, m/z (relative intensity) 318 (0.1), 317 (0.2), 225 (1.7), 152 (39.4), 130 (12.1), 108 (7.3), 80 (30), 79 (50), 75 (20). Anal. Calcd for $C_{13}H_{23}O_4NSSi$: C, 49.18; H, 7.30. Found: C, 49.25; H, 7.44.

Preparation of Epoxides 31. To a solution of 5.64 g (0.018 mol) of alkene **30** in 40 mL of dry dichloromethane was added 9.32 g (0.054 mol) of 85% *m*-chloroperoxybenzoic acid. After the mixture was stirred for 24 h, 150 mL of ethyl acetate was added. The mixture was washed with saturated $NaHSO_3$, $NaHCO_3$, and NaCl solutions and dried over Na_2SO_4. Removal of the solvent in vacuo yielded the crude epoxides **31** which could be separated by flash chromatography. Elution of the column with ethyl acetate/hexane (2/3) yielded 1.35 g (23%) of one epoxide as a white solid. An analytical sample recrystallized from ethyl acetate/hexane had mp 133–135 °C: IR (film) 3280, 2950, 2920, 1740, 1450, 1430, 1360, 1350, 1250, 1175, 1150, 1125, 1105, 955, 860, 850, 780, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 5.34 (d, J = 5.4 Hz, NH), 4.64 (m, 1 H), 4.36 (t, J = 5.3 Hz, 1 H), 3.50 (m, 1 H), 3.00–3.13 (m, 3 H), 2.38 (m, 1 H), 1.90–2.20 (m, 3 H), 1.00–1.13 (m, 3 H), 0.07 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.10, 74.43, 56.54, 51.51, 49.18, 47.66, 32.66, 31.83, 24.64, 10.40, −2.01; CIMS ($m + 1/z$) 335, 334, 333. Anal. Calcd for $C_{13}H_{23}O_5NSSi$: C, 46.82; H, 6.95. Found: C, 46.95; H, 7.05.

Elution of the column with ethyl acetate/hexane (3/2) yielded 3.98 g (61%) of the second epoxide as a white solid. An analytical sample recrystallized from ethyl acetate/hexane had mp 145–147 °C: IR (film) 3280, 2960, 1740, 1380, 1340, 1320, 1255, 1150, 1125, 1050, 990, 960, 900, 870, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 5.41 (d, J = 8.5 Hz, NH), 4.67 (s, 1 H), 4.00 (dd, J = 5.2, 8.5 Hz, 1 H), 3.56 (t, J = 4.9 Hz, 1 H), 3.33 (s, 1 H), 3.00–3.20 (m, 3 H), 2.61 (d, J = 16.4 Hz, 1 H), 2.09 (dd, J = 3.3, 14.1 Hz, 1 H), 1.97 (ddd, J = 2.8, 3.9, 16.4 Hz, 1 H), 1.77 (dd, J = 4.5, 14.1 Hz, 1 H), 1.23 (dt, J = 4.2, 13.8 Hz, 1 H), 1.04 (dt, J = 4.2, 13.8 Hz, 1 H), 0.03 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.18, 73.03, 55.42, 52.36, 50.92, 49.73, 39.76, 30.18, 26.58, 10.30, −2.1; CIMS ($m + 1/z$) 335, 334, 320, 319, 318. Anal. Calcd for $C_{13}H_{23}O_5NSSi$: C, 46.82; H, 6.95. Found: C, 46.64; H, 7.03.

Synthesis of Amide 33 from Epoxides 31. A solution of 0.700 g (2.0 mmol) of the crude mixture of epoxides **31** in 10 mL of anhydrous formic acid was stirred for 3 h, and the solvent was evaporated in vacuo. The residue was treated with a solution of 0.46 M dimethylaluminum *N,O*-dimethylhydroxylamide in THF (31 mL, 14.7 mmol), and the mixture was stirred for 28 h. Saturated NH_4Cl solution was added dropwise to the reaction mixture until the excess aluminum amide was destroyed, and the resulting gelatinous precipitate was washed with 500 mL of acetone. Removal of the solvent yielded the intermediate triol [IR (film): 3600–3100 (br), 3000, 1680, 1450, 1420, 1370, 1280, 1200, 1170, 1080, 890, 870, 790, 770 cm^{-1}] which was used without further purification.

A solution of the above crude triol, 28 mL of 2,2-dimethoxypropane, and 0.35 g of *p*-toluenesulfonic acid monohydrate in 31 mL of DMF was stirred at room temperature for 20 h. The reaction mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$ and NaCl solutions, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography eluting with ethyl acetate/hexane (2/1) to afford 0.610 g (64%) of acetonide alcohol: IR (film) 3550–3100 (br), 3000, 2980, 1680, 1420, 1400, 1350, 1255, 875, 860, 760 cm^{-1}.

To a solution of 1.79 g (3.9 mmol) of the above alcohol in 7 mL of DMF was added 0.8 mL (6.7 mmol) of 2,6-lutidine and 1.4 mL (5.9 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate at −15 °C. The mixture was stirred at −15 °C for 2 h, diluted with ice-cold ethyl acetate (30 mL), and was washed with ice-cold 5% HCl and NaCl solutions. The organic extract was dried over Na_2SO_4 and was concentrated in vacuo. Purification of the residue by flash chromatography eluting with 6% ether in CH_2Cl_2 yielded 2.12 g (95%) of silyl ether **33**. An analytical sample of **33** recrystallized from ethyl acetate/hexane had mp 128–130 °C: IR (film): 3250, 2990, 2960, 2940, 2900, 2860, 1670, 1465, 1415, 1385, 1335, 1255, 1235, 1180, 1145, 1100, 1060, 1030, 1010, 1000, 940, 895, 945, 920, 780, 755, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 5.30 (d, J = 10.2 Hz, NH), 4.54 (dd, J = 4.6, 10.2 Hz, 1 H), 3.75 (s, 3 H), 3.70 (t, J = 9.4 Hz, 1 H), 3.28 (m, 1 H), 3.18 (m, 3 H), 2.85 (m, 2 H), 2.24 (m, 1 H), 1.90 (m, 2 H), 1.49 (dd, J = 11.2, 18.0 Hz, 1 H), 1.38 (s, 3 H), 1.36 (s, 3 H), 1.27 (m, 1 H), 1.02 (dd, J = 8.3, 9.4 Hz, 2 H), 0.83 (s, 9 H), 0.02 (s, 6 H), 0.01 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.43, 110.48, 79.34, 68.71, 61.46, 53.61, 49.52, 39.04, 37.55, 35.14, 32.42, 26.84, 26.75, 25.59, 17.83, 10.07, −2.16, −4.87; CIMS ($m + 1/z$) 568, 567, 565. Anal. Calcd for $C_{24}H_{50}N_2O_7SSi_2$: C, 50.85; H, 8.89. Found: C, 50.74; H, 8.82.

Preparation of Methyl Ketone 34. To a solution of 0.164 g (0.29 mmol) of amide **33** in 3 mL of anhydrous THF was added 0.34 mL (1.02 mmol) of 3 M methylmagnesium bromide in ether, and the mixture was stirred at room temperature for 90 min. The reaction mixture was poured into a beaker containing 24 g of silica gel and chloroform and was stirred for 5 min. The mixture was filtered, and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography eluting with ethyl acetate/hexane (1/6) afforded 0.133 g (88%) of methyl ketone **34**: IR (film) 3280, 3000, 2960, 2940, 2900, 2870, 1725, 1390, 1375, 1310, 1260, 1240, 1160, 1150, 1100, 1070, 1030, 850, 785, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 5.22 (d, J = 9.6 Hz, NH), 4.26 (dd, J = 3.3, 9.6 Hz, 1 H), 3.38 (m, 1 H), 3.3–3.45 (m, 2 H), 2.87 (dt, J = 4.0, 6.9 Hz, 2 H), 2.28 (s, 3 H), 2.02 (m, 1 H), 1.5–1.6 (m, 2 H), 1.41 (s, 6 H), 1.25–1.40 (m, 2 H), 1.02 (dt, J = 4.2, 6.8 Hz, 2 H), 0.83 (s, 9 H), 0.018 (s, 15 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.82, 110.86, 78.97, 76.91, 68.62, 62.23, 49.46, 37.82, 37.50, 33.99, 27.75, 26.82, 26.71, 25.55, 17.80, 9.99, −2.13, −4.86, −4.96; CIMS (m + 1/z) 524, 523, 522, 521.

***N*-[1-(Hexahydro-6-hydroxy-2,2-dimethyl-1,3-benzodioxol-4-yl)-2-oxopropyl]-2-(trimethylsilyl)ethanesulfonamide (34).** To a solution of 0.075 g (0.14 mmol) of silyl ether **34** in 2 mL of dry THF was added 0.43 mL (0.43 mmol) of 1 M tetrabutylammonium fluoride in THF, and the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with ethyl acetate and washed with saturated NH_4Cl solution. The organic extract was dried over Na_2SO_4 and was concentrated in vacuo. The residue was purified by flash chromatography eluting with ethyl acetate/hexane (2/1) to afford 0.056 g (95%) of keto alcohol **35**. An analytical sample of **35** recrystallized from ethyl acetate/hexane had mp 158–160 °C: IR (film) 3550, 3300, 3000, 2960, 1725, 1385, 1375, 1335, 1255, 1230, 1180, 1150, 1120, 1050, 1015, 865, 845, 790, 765, 745, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.28 (d, J = 9.5 Hz, NH), 4.30 (dd, J = 3.3, 9.5 Hz, 1 H), 3.85 (m, 1 H), 3.45 (m, 2 H), 2.90 (dt, J = 3.7, 7.0 Hz, 2 H), 2.48 (m, 1 H), 2.32 (s, 3 H), 2.05 (m, 1 H), 1.50–1.80 (m, 3 H), 1.45 (s, 3 H), 1.04 (dt, J = 3.8, 7.0 Hz, 2 H), 0.04 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.38, 110.94, 79.02, 77.00, 68.01, 62.25, 49.59, 37.68, 36.91, 33.57, 27.73, 26.93, 26.77, 9.97, −2.05. Anal. Calcd for $C_{17}H_{33}NO_6SSi$: C, 50.22; H, 7.93. Found: C, 49.73; H, 8.27.

***N*-[3,3-Dichloro-1-(hexahydro-6-hydroxy-2,2-dimethyl-1,3-benzodioxol-4-yl)-2-hydroxy-2-methylpropyl]-2-(trimethylsilyl)ethanesulfonamide (37).** To a solution of 1 mL of dichloromethane freshly distilled from CaH_2 in 1.3 mL of dry THF was added 3.1 mL (4.0 mmol) of 1.3 M n-butyllithium solution in hexane at −100 °C, and the mixture was stirred for 10 min. The reaction mixture was diluted with 12 mL of anhydrous ether, and cerium trichloride (1.0 g, 4 mmol) was added. The heterogenous mixture was stirred at −100 °C for 1 h, and 0.108 g (0.26 mmol) of methyl ketone **35** in 2 mL of dry dichloromethane was added. The reaction mixture was stirred for 2 h at −100 °C and was diluted with 5 mL of methanol. The resulting solution was stirred for 2 min at −78 °C, diluted with ethyl acetate, washed with saturated NH_4Cl solution, and dried over Na_2SO_4. Concentration of the solution in vacuo and purification of the residue by preparative TLC eluting with 5% MeOH in $CHCl_3$ yielded 0.043 g of starting methyl ketone **35** and 0.070 g (90% based on recovered ketone) of dichloromethyl carbinol **37**: IR (film) 3470, 3350, 2980, 2950, 2870, 1455, 1420, 1380, 1370, 1320, 1280, 1255, 1230, 1180, 1160, 1150, 1100, 1065, 1045, 1010, 900, 865, 840, 780, 755, 710 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 6.10 (s, 1 H), 4.01 (d, J = 1.7 Hz, NH), 3.70 (m, 1 H), 3.29 (m, 1 H), 3.20 (t, J = 9.5 Hz, 1 H), 3.06 (m, 2 H), 1.80–2.25 (m, 5 H), 1.30 (s, 3 H), 1.29 (s, 3 H), 1.27 (s, 3 H), 0.95 (m, 2 H), 0.03 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 110.0, 79.47, 77.92, 76.71, 67.47, 55.37, 50.30, 36.87, 36.48, 33.51, 26.14, 17.82, 10.11, −2.77; CIMS (m + 1/z) 495, 494, 493, 492, 491.

***N*-[3,3-Dichloro-1-(hexahydro-2,2-dimethyl-6-oxo-1,3-benzodioxol-4-yl)-2-methylpropyl]-2-(trimethylsilyl)ethanesulfonamide (39).** To a solution of 0.35 mL (4.1 mmol) of pyridine, in 4 mL of dry dichloromethane was added 0.250 g (2.4 mmol) of chromium trioxide at 0 °C. The mixture was stirred at room temperature for 20 min, and 0.20 g (0.40 mmol) of diol **37** in 6 mL of dichloromethane was added. After the mixture was stirred for 35 min, the solution was filtered through a pad of Florisil, and the filter cake was washed with 150 mL of ethyl acetate. The solvent was removed in vacuo, and the residue was purified by preparative TLC eluting with ethyl acetate/hexane (1/1) to afford 0.179 g (90%) of keto (dichloromethyl)carbinol **39**: IR (film) 3450, 3300, 3000, 2970, 2940, 2910, 1715, 1430, 1390, 1330, 1260, 1240, 1175, 1150, 1120, 1035, 975, 950, 870, 850, 790, 770, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 6.02 (s, 1 H), 4.85 (d, J = 9.9 Hz, 1 H), 3.60–3.80 (m, 2 H), 3.18 (s, 1 H), 3.12 (dt, J = 3.2, 9.1 Hz, 2 H), 2.91 (ddd, J = 1.8, 4.5, 14.4 Hz, 1 H), 2.69 (dd, J = 1.5, 11.4 Hz, 1 H), 2.58 (dd, J = 12.9, 14.3 Hz, 1 H), 2.25–2.40 (m, 1 H), 1.52 (s, 3 H), 1.48 (s, 3 H), 1.45 (s, 3 H), 1.10 (dt, J = 4.9, 9.0 Hz, 2 H), 0.07 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.08, 111.84, 78.83, 78.56, 77.99, 76.52, 55.34, 50.89, 44.92, 40.35, 37.04, 26.99, 26.89, 19.16, 10.72, −1.87; CIMS (m + 1/z) 494, 493, 492, 491, 490, 489.

Preparation of Keto Oxazolone 40. To a solution of 0.100 g (0.20 mmol) of keto (dichloromethyl)carbinol **39** and a catalytic amount of 4-pyrrolidinopyridine in 30 mL of triethylamine was added 4.5 mL of methyl chloroformate, and the mixture was stirred at room temperature for 28 h. The reaction mixture was diluted with ethyl acetate, washed with saturated NaCl, dried over Na_2SO_4, and concentrated. Purification of the residue by preparative TLC eluting with ethyl acetate/hexane (1/1) yielded 0.096 g (90%) of oxazolone **40**: IR (film) 3000, 2980, 1805, 1760, 1700, 1490, 1450, 1420, 1380, 1360, 1275, 1260, 1185, 1165, 1150, 1110, 1085, 1030, 975, 955, 905, 855, 800, 760, 710 cm^{-1}.

***N*-[8-(Dichloromethyl)-3a,4,8,9,9a,9b-hexahydro-5-hydroxy-2,2,8-trimethyl-6*H*-1,3-dioxolo[4,5-*f*][2]benzopyran-9-yl]-2-(trimethylsilyl)-ethanesulfonamide (42).** To a solution of 0.020 g (0.039 mmol) of oxazolone **40** in 5 mL of methanol was added 0.1 mL (0.1 mmol) of 1 M sodium methoxide in methanol, and the mixture was stirred for 5 h at room temperature. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate, washed with saturated NH_4Cl solution, and dried over Na_2SO_4. Concentration of the solution in vacuo and purification of the residue by preparative TLC eluting with ethyl acetate/hexane (1/1) afforded 0.014 g (70%) of enol lactone **42**: IR (film) 3450, 3250, 2990, 2960, 2930, 1640, 1590, 1420, 1385, 1330, 1270, 1225, 1240, 1145, 1105, 1080, 1045, 850, 800, 770, 745, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 13.57 (s, 1 H), 6.04 (s, 1 H), 4.46 (dd, J = 3.2, 10.2 Hz, 1 H), 4.26 (d, J = 10.2 Hz, NH), 3.81 (m, 1 H), 3.64 (t, J = 9.2 Hz, 1 H), 3.16 (m, 3 H), 3.01 (dd, J = 5.9, 17.7 Hz, 1 H), 2.73 (m, 1 H), 1.73 (s, 3 H), 1.51 (s, 6 H), 1.16 (m, 2 H), 0.08 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 179.40, 168.91, 112.17, 85.99, 77.20, 75.34, 74.23, 73.73, 51.65, 51.57, 37.71, 34.89, 26.86, 26.70, 19.18, 10.74, −2.03; CIMS (m + 1/z) 522, 521, 520, 519, 518, 517, 516, 515, 514.

(−)-Bactobolin (3). To a solution of 0.006 g (0.012 mmol) of enol lactone **42** in 1 mL of anhydrous THF was added 30 μL (0.03 mmol) of 1 M tetrabutylammonium fluoride in THF, and the mixture was stirred at 52 °C for 6 h. The reaction mixture was concentrated, and the residue was purified by preparative TLC eluting with 30% methanol in ethyl acetate to yield a white solid. To a solution of this amine in 1 mL of methanol were added two drops of 5% methanolic HCl, and the mixture was stirred for 1 h. The solvent was evaporated in vacuo to yield 0.002 g (50%) of the amine hydrochloride **43** which was used in the next step without purification.

A solution of 0.002 g (0.006 mmol) of amine hydrochloride **43**, 0.002 g (0.009 mmol) of Cbz-L-alanine, 0.004 g (0.01 mmol) of dicyclohexylcarbodiimide, and 2 μL of triethylamine in 0.5 mL of dry DMF was stirred for 12 h. Concentration of the mixture in vacuo and purification of the residue by preparative TLC (two elutions with 5% MeOH in $CHCl_3$) yielded the diastereomeric acylation products (0.001 g and 0.001 g, 60% combined yield).

To a solution of 0.001 g of the diastereomer with the lower R_f in 1 mL of methanol was added 20 mg of 5% Pd/C, and the mixture was stirred under 1 atm of hydrogen for 2 h. The reaction mixture was filtered through a pad of Celite, and the filter cake was washed with 75 mL of methanol. Evaporation of solvent yielded 0.6 mg of (−)-bactobolin (**3**) which was identical to the natural bactobolin (TLC, reverse phase TLC, ^1H NMR; $[\alpha]^{25}_D$ = −10 [natural (−)-bactobolin $[\alpha]^{25}_D$ = −7]).

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Supplementary Material Available: Experimental details for preparation of PMS-bactobolamine derivative **29** and tables of X-ray data for triacetate iii (17 pages). Ordering information is given on any current masthead page.