Synthetic Studies on Actinobolin and Bactobolin: Synthesis of *N*-Desalanyl-*N*-[2-(trimethylsilyl)ethanesulfonyl] Derivatives from a Common Intermediate and Attempted Removal of the SES Protecting Group

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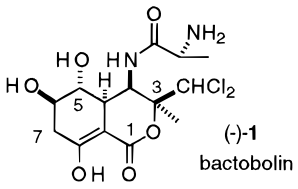
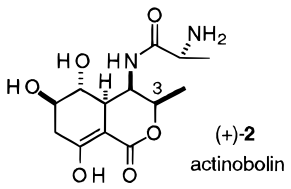
Two closely related syntheses of 5,6-*O*-(2-propylidene)-*N*-desalanyl-*N*-2-(trimethylsilyl)ethanesulfonyl]bactobolin (**9b**) from (+)-**12**, an intermediate previously prepared from D-glucose, are reported. In each case, the key step involves a precedented stereoselective addition of $LiCHCl_2$ in the presence of $CeCl_3$ to a suitably protected α-amino ketone. Intermediates from both synthetic routes to **9b** can be prepared by degradation of actinobolin (**2**) thereby establishing a potential method for the transformation of actinobolin into bactobolin. An efficient route to 5,6-*O*-(2-propylidene)-*N*-desalanyl-*N*-[[2-(trimethylsilyl)ethanesulfonyl]actinobolin (**7b**) from (+)-**12** involving an unexpected cyclization of **29** was discovered. The 2-(trimethylsilyl)ethanesulfonyl (SES) protecting group in **7b** was removed by reaction with Bu_4NF in wet THF. The nature of the Bu_4NF reagent was found to be important to the outcome of the reaction. Several improvements over our previously reported synthesis of actinobolin from D-glucose are noted. Although precedented, the removal of the SES protecting group from **9b** could not be achieved thereby preventing completion of a total synthesis of bactobolin.

The isolation of bactobolin (**1**) from liquid cultures of *Pseudomonas yoshidomiensis* was first reported in 1979.[1] Elucidation of the bactobolin structure was facilitated by its close relationship to actinobolin (**2**),[2] a metabolite of *Streptomyces griseoviridus* var *atropaciens* isolated 20 years earlier. X-ray crystallography confirmed that the absolute configurations of (−)-**1**[1b] and (+)-**2**[2d] were identical at all equivalent stereogenic centers; the only structural difference being at the C-3 position where the $CHCl_2$ group present in **1** has replaced (with inversion of configuration) the H in **2**. Both bactobolin and actinobolin are broad-spectrum antibiotics and have antitumor activity but bactobolin is significantly more potent.[3]

The synthesis of **1** and **2** has attracted considerable attention[4] and several syntheses of the actinobolin skeleton have been published.[5,6] The structural similarities between **1** and **2** suggested that simple modification of a successful synthetic route to actinobolin would produce bactobolin.[4] Despite several efforts to pursue such a strategy,[7] the only reported synthesis of bactobolin is that due to Weinreb *et al.* (Scheme 1).[8] A unique feature of Weinreb's syntheses of bactobolin and actinobolin is the introduction of the lactone carbonyl group at a late stage



(-)-**1**
bactobolin



(+)-**2**
actinobolin

via an intramolecular acylation reaction (e.g. **8** → **9**). Although Weinreb's intermediates were racemic, optically pure final products (−)-**1** and (+)-**2** were obtained by separation of the diastereomeric amides formed by acylation of the amines resulting from deprotection of (±)-**7** and (±)-**9**, respectively, with L-alanine. We prepared (+)-**12** ($[\alpha]_D$ +19; *c* 0.23, MeOH) by a stereoselective [3+3] annulation[9] of the D-glucose-derived aldehyde **10** with 3-(phenylthio)-2-[(trimethylsilyl)methyl]propene (**11**) and followed an intramolecular acylation strategy for the conversion of (+)-**12** into actinobolin (Scheme 1).[5g] We now report an improved actinobolin synthesis and the extension of the synthetic scheme to include the bactobolin series by the efficient transformations of (+)-**12** into

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(4) For a review, see: Fraser-Reid, B.; López, J. P. In *Recent Advances in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: Heidelberg, 1990; pp 285−319.

(5) (a) Yoshioka, M.; Nakai, H.; Ohno, M. *J. Am. Chem. Soc.* **1984**, *106*, 1133; *Heterocycles* **1984**, *21*, 121. (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; **1987**, *52*, 622. (d) Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1985**, *107*, 7790; **1990**, *112*, 3475. (e) Kozikowski, A. P.; Konoike, T.; Nieduzak, T. R. *J. Chem. Soc., Chem. Commun.* **1986**, 1350. (f) Kozikowski, A. P.; Nieduzak, T. R.; Konoike, T.; Springer, J. P. *J. Am. Chem. Soc.* **1987**, *109*, 5167. (g) Ward, D. E.; Kaller, B. F. *Tetrahedron Lett.* **1993**, *34*, 407; *J. Org. Chem.* **1994**, *59*, 4230.

(6) For other synthetic studies on actinobolins see: (a) Rao, M. V.; Nagarajan, M. *Indian J. Chem.* **1988**, *27B*, 718. (b) Kates, S. A. Ph.D. Thesis, Brandeis University, Waltham, MA, 1988; *Diss. Abstr. Int. B* **1989**, *49*, 2651. (c) Marjerle, R. S. K. Ph.D. Thesis, University of Minnesota, Minneapolis, MN; *Diss. Abstr. Int. B* **1990**, *50*, 2932.

(7) (a) Underwood, R.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 731. (b) Also see refs 5a and 5c.

(8) (a) Garigipati, R. S.; Weinreb, S. M. *J. Org. Chem.* **1988**, *53*, 4143. (b) Also see ref 5d.

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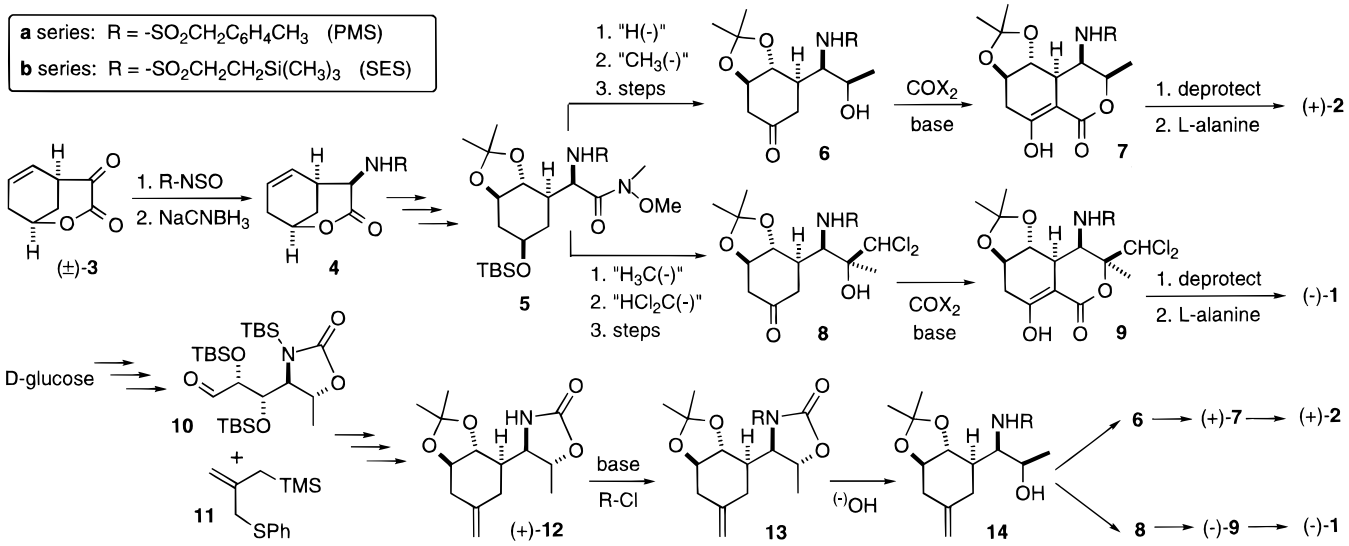
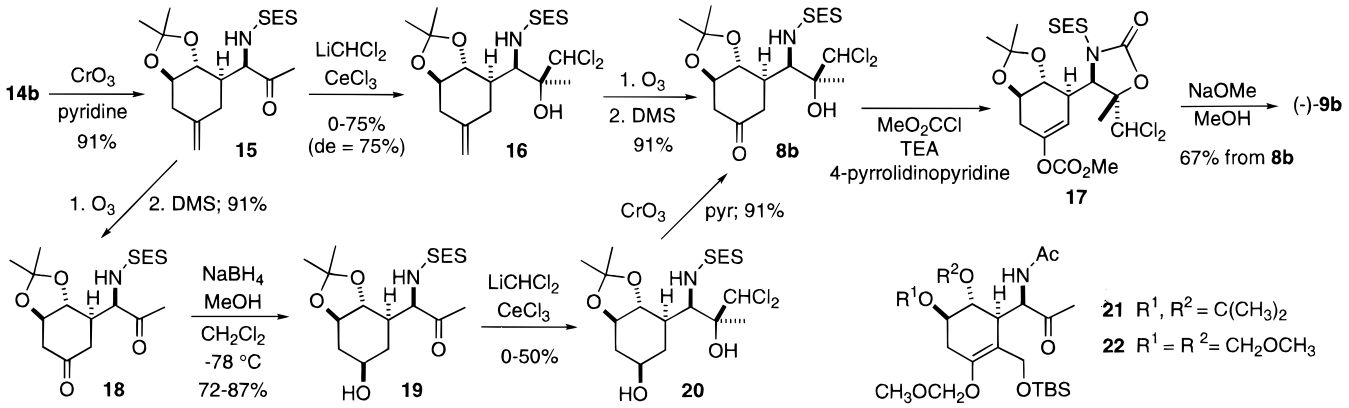
Scheme 1



Scheme 2



the 5,6-*O*-(2-propylidene)-*N*-desalanyl-*N*-[2-(trimethylsilyl)ethanesulfonyl] derivatives of bactobolin [(−)-**9b**; $[\alpha]_D$ −26; *c* 0.60, $CHCl_3$] and actinobolin [(+)-**7b**; $[\alpha]_D$ +21.5; *c* 1.10, CH_2Cl_2].[10]

For the synthesis of bactobolin, Weinreb *et al.* initially pursued a strategy which exploited **5a**, a late stage intermediate from their elegant actinobolin synthesis (Scheme 1).[8] In that synthesis,[5d] the choice of the (4-methylphenyl)methanesulfonyl (PMS) protecting group was based on earlier work by Ohno *et al.*[5a] that established an efficient conversion of (+)-**7a** into **2**. They successfully converted **5a** into (±)-**9a**; however, in contrast to **7a**, the PMS group could not be removed from **9a** without destruction of the substrate. To solve this problem, the [2-(trimethylsilyl)ethane]sulfonyl (SES) group was introduced as a new amine protecting group.[11] Application of the SES group to the bactobolin synthesis required substantial retooling since the amine protecting group was introduced early in the synthesis. The preparation of (±)-**9b** from (±)-**4b** proceeded in analogy to that of **9a**, and after removal of the SES group with fluoride, (±)-**9b** was successfully converted into (−)-**1** (∼15% overall yield).[8]

Considering the above, we selected the SES protecting group for **12** and reasoned that both **1** and **2** should be available from **14b** (Scheme 1). Treatment of **12** with BuLi followed by SES-Cl[11] gave **13b** which was converted into **14b** by reaction with NaOMe in MeOH (88% overall). Ozonolysis of **14b** gave **6b** which was transformed into (+)-**7b** using Weinreb's procedure[5d] (Im_2CO, NaH; 80%).[12] Because we were unable[12] to remove the SES protecting group from (+)-**7b** using the reported[8,11] conditions (*vide infra*) and to conserve synthetic material, we resorted to the use of the precedented[5a,5d] PMS group to complete the synthesis of actinobolin from **12**.[5g]

In contemplating a synthesis of bactobolin from **14b**, the most direct route would involve incorporation of the dichloromethyl substituent before oxidation of the exocyclic methylene group to the required ketone group. Collins' oxidation[13] of **14b** produced the desired methyl ketone **15** in 91% yield (Scheme 2). Our initial attempts to effect addition of $LiCHCl_2$ with[8] or without[7a] added $CeCl_3$ to the ketone group in **15** were unsuccessful. Others had observed that this reaction is particularly sensitive to subtle changes in the substrate structure.[7a,8] For example, Weinreb observed[8] that the addition of $LiCHCl_2/CeCl_3$ to (±)-**19** was dramatically more stereoselective (>20:1 vs 3:1) than a similar addition to the TBS ether-protected derivative of (±)-**19**; attempted reactions without $CeCl_3$ failed to produce the desired product. Fraser-Reid reported that addition of $LiCHCl_2$ (without $CeCl_3$) to **21** gave a complex mixture of products whereas

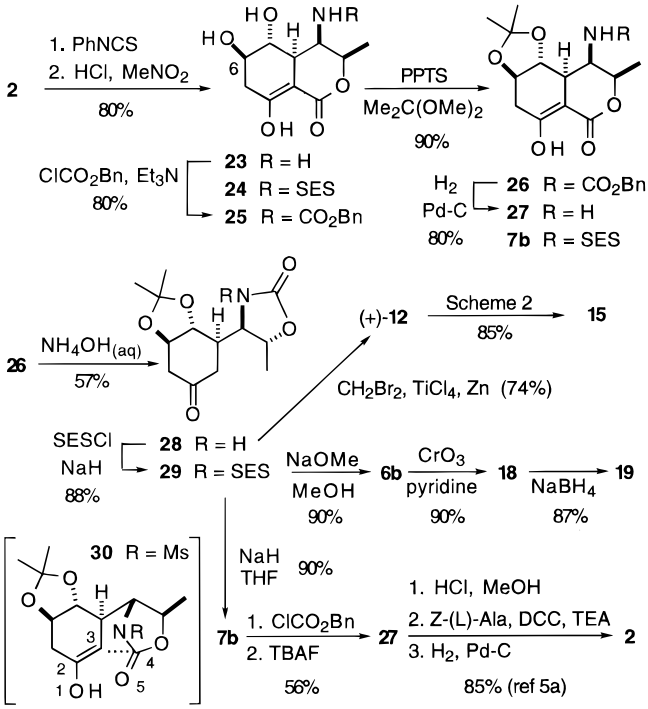
(10) A preliminary account has been reported: Ward, D. E.; Gai, Y.; Kaller, B. F. *Tetrahedron Lett.* **1994**, *35*, 3485.
(11) Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099.
(12) Kaller, B. F. Ph.D. Thesis, University of Saskatchewan, 1993.
(13) Ratcliffe, R. W. *Org. Synth.* **1976**, *55* , 74.

a similar reaction with **22** gave a single adduct in good yield.[7a] Because the amount of synthetic **15** was limited, we decided to proceed to bactobolin by the known[8] route via **19** (Scheme 2).

The preparation of **19** from **15** was facilitated by using a route that obviated the need for a protecting group strategy (Scheme 2). Ozonolysis of **15** gave the dione **18** in excellent yield. Reduction of **18** with $NaBH_4$ according to our previously developed protocol (50% MeOH in CH_2Cl_2, −78 °C, 0.5 h)[14] resulted in the chemoselective and stereoselective[15] reduction of the cyclohexanone carbonyl in the presence of the methyl ketone to give the desired (−)-**19** ($[\alpha]_D$ −44; *c* 0.56, $CHCl_3$) in 72% yield (92% based on consumed **18**) along with recovered **18** (22%).[16] The direct conversion of **15** into **19** was attempted by employing $NaBH_4$ (rather than dimethyl sulfide) for reductive workup of the ozonolysis reaction; however, reduction of the putative methoxy hydroperoxide intermediate with $NaBH_4$ under the above conditions to give **18** was not sufficiently rapid at −78 °C to be efficacious. For example, reaction for 0.5 h gave **19** in <50% yield; after 1 h, the diol resulting from reduction of both carbonyl groups in **18** could be detected along with **18** and **19** (1:2, respectively). The spectroscopic properties of (−)-**19** (MS, IR, ^{1}H, and ^{13}C NMR) agreed closely with those previously reported[8] for (±)-**19**. The preparation of (−)-**19** from (+)-**12** represented a formal enantiospecific[17] synthesis of bactobolin from D-glucose since the conversion of (±)-**19** into (−)-**1** had been reported.[8]

Our attempts to reproduce the reported[8] addition of $LiCHCl_2$ to **19** on small scale (10−20 mg of **19**) were, as with **15**, also unsuccessful. To obtain material for further study of these reactions, we considered the preparation of **19** (and **15**) from actinobolin (**2**) rather than from D-glucose.[18] In the context of the structure elucidation of actinobolin, Nelson and Munk had reported[19] the reaction of 5,6-*O*-(2-propylidene)-*N*-acetylactinobolin (**7**; R = COCH(Me)NHAc) with aqueous ammonia to produce *N*-(acetylalanyl)actinobolone (**6**; R = COCH(Me)NHAc) in 52% yield. The presence of the acetonide protecting group was shown to be important in preventing elimination of the C-6 hydroxy group (actinobolin numbering) and subsequent formation of actinobicyclone and actinobolamine derivatives under the reaction conditions.[19] We reasoned that a similar reaction with **7b** would produce **6b** which could be easily converted into **19**. The preparation of **23** by Edman degradation of **2** has been reported (Scheme 3).[20a] In our hands, direct acylation of **23** with SES-Cl failed to give the desired **24**. We prepared **26** from **23** by a slight modification of the known procedure.[20] Although **7b** could be obtained by acylation of amine **27** obtained by hydrogenolysis of **26**, we found that reaction

Scheme 3



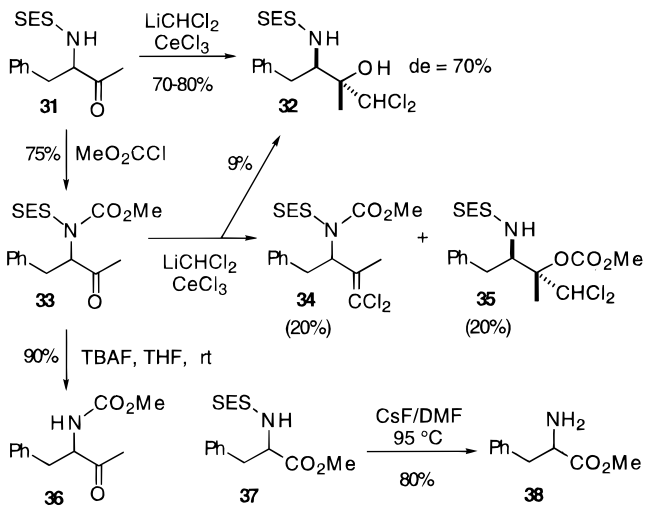
of **26** with aqueous ammonia to give **28** (57%) presented a superior route to **19**. Treatment of **28** with SES-Cl in the presence of NaH followed by hydrolysis of the resulting **29** gave **6b** whose spectral data were identical to those from the **6b** obtained previously from D-glucose via **14b** (Scheme 1). Oxidation of **6b** produced **18**, thus allowing the preparation of **19** from **2** (Scheme 3) and establishing a formal route to bactobolin from actinobolin (cf. Scheme 2).

The preparation of **15** from **2** would require methylenation of the cyclohexanone carbonyl group in one of the intermediates. Reactions of **29** with Ph_3PCH_2 gave the desired **13b** in low yields (15−20%); the major product was **7b** (20−30%). Cyclization of **29** was easily avoided by methylenation under Lombardo's conditions[21] to give **13b** in 72% yield. Alternatively, reaction of **28** under these conditions or with Ph_3PCH_2 gave (+)-**12** ($[\alpha]_D$ +20; *c* 0.50, MeOH) which was identical to that previously synthesized from D-glucose.[5g] As shown in Scheme 3, both **15** and **19** were available via nine-step sequences from actinobolin (**2**) in ∼19% overall yield for each case.

The cyclization of **29** was unexpected in light of the earlier speculation by Weinreb *et al.*[8] that an analogous reaction in their bactobolin synthesis was stereoelectronically disfavored (*vide infra*). The formation of **7b** clearly indicated that a direct cyclization of **29** under basic conditions was feasible. Indeed, this process could be optimized and treatment of **29** with NaH in THF gave **7b** in excellent yield. Molecular mechanics calculations[22] on **30** as a model for the enol of **29** located a stable conformation (local minimum) 3.4 kcal/mol above the global minimum which places the enolic carbon within 3.5 Å of the carbonyl carbon. The relationship between

(14) Ward, D. E.; Rhee, C. K. *Can. J. Chem.* **1989**, *67*, 1206.
(15) Stereoisomers of **20** were not detected in the reaction mixture.
(16) Increasing the reaction time to 1 h did not improve the yield of **20**; however, diol (∼10%) was detected in the reaction mixture. A larger scale reaction run at higher concentration on material derived from degradation of actinobolin gave **19** in 87% yield (see Experimental Section).
(17) We use this term to describe a diastereoselective synthesis of a specific enantiomer as opposed to a diastereoselective synthesis of a racemate or an enantioselective synthesis. For example, see: Ward, R. S. *Chem. Br.* **1991**, *27*, 803.
(18) We thank the Parke-Davis Pharmaceutical Research Divison of Warner-Lambert Co. for a generous gift of actinobolin sulfate.
(19) Nelson, D. B.; Munk, M. E. *J. Org. Chem.* **1970**, *35*, 3832.
(20) Rahman, M. A.; Kelly, D. R.; Ravi, P.; Underwood, R.; Fraser-Reid, B. *Tetrahedron* **1986**, *42*, 2409. (b) We found **23** to be insoluble in the reported[20a] solvent (EtOAc) even in the presence of Et_3N; thus a 1.3:1 mixture of EtOH and EtOAc was used as the medium for acylation with BnOCOCl.
(21) Lombardo, L. *Org. Synth.* **1987**, *65*, 81.
(22) Molecular mechanics using the MM2 forcefield included in the CAChe Worksystem (version 3.7 from CAChe Scientific Inc.). Structures were minimized with the Newton-Raphson block diagonal method to 0.001 kcal/mol convergence. Relevant minima were located by minimizing at least 10 initial conformations generated from driving the dihedral angles for each rotatable bond.

Scheme 4



the enol and carbonyl groups in this conformation "loosely" resembles[23b] the twist-boat TS for addition of acetaldehyde enolate to formaldehyde;[23a] a closer relationship is revealed by examining minimized structures with the enolic carbon to carbonyl carbon distance constrained to shorter distances.[23c]

As a prelude to investigating the addition of $LiCHCl_2$ to **15** and **19**, we used **31** as a model compound to calibrate and optimize the reaction conditions (Scheme 4).[24] Reaction of **31** with 3 equiv of $LiCHCl_2/CeCl_3$ failed to give **32** although a similar reaction with 3,4,5-trimethoxyacetophenone gave the expected adduct in >90% yield. The use of 8 equiv of $LiCHCl_2/CeCl_3$ gave a 70−80% yield of **32** as a 5.5:1 mixture of stereoisomers; a result that could be reproduced on small scale (0.08 mmol of **31**). The stereoselectivity of the reaction presumably results from a chelation-controlled addition and is consistent with previous observations.[7a,8] The yield of **32** was not improved by using up to 20 equiv of $LiCHCl_2/CeCl_3$. Subjecting **19** (0.05−0.08 mmol) to these conditions (20−35 equiv of $LiCHCl_2/CeCl_3$) gave **20** as a single isomer (20−30%) along with recovered **19** (40−60%) thereby reproducing the results reported by Weinreb *et al.*[8] (although with lower yield). Similar reactions of **15** (0.05−0.08 mmol) with $LiCHCl_2/CeCl_3$ (20−35 equiv) gave **16** (20−45% yield) as inseparable mixtures of stereoisomers (∼85:15) along with recovered **15** (30−45%). The major isomer of **16** was correlated with **20** (*vide infra*) which confirmed the expected chelation-controlled stereoselectivity. Considering that the low conversions in the reactions of $LiCHCl_2/CeCl_3$ with **15** and **19** might be due to the acidity of the sulfonamide NH group, we examined the reaction with **33**; however, a mixture of products was obtained in poor yield (Scheme 4).

The oxidation[8] of **20** proceeded without incident to give (−)-**8b** ($[\alpha]_D$ −16; *c* 0.68, $CHCl_3$) whose spectral data agreed closely with that previously reported[8] for (±)-**8b**. Ozonolysis of the 85:15 mixture of **16** stereoisomers gave a separable mixture of the corresponding ketone stereoisomers (91%); the major isomer was identical to (−)-**8b** in all respects. In our hands, treatment of **8b** with MeO_2CCl gave the enol carbonate **17** in excellent yield.[25] The presence of an enolic CH group in **17** was strongly implicated by the δ_H 5.37 (1H, dd, J = 1, 1 Hz) and δ_C 112.1 (d) signals in the NMR spectra and the other spectral data fully supported the assigned structure. Completion of the bactobolin skeleton was effected by cyclization of **17** with NaOMe to give (−)-**9b** ($[\alpha]_D$ −26; *c* 0.60, $CHCl_3$); spectroscopic data (IR, MS, ^1H and ^{13}C NMR) agreed closely with that reported for (±)-**9b**.[8] The syntheses of (−)-**9b** from (+)-**12** (seven steps via **15**, 30%; nine steps via **19**, 21%) constitute formal syntheses of bactobolin from D-glucose.

Contrary to expectations but similar to our previous experience with **7b**,[12] attempts to remove the SES group from **9b** under the reported conditions (TBAF, THF, 52 °C)[8,26] or with CsF (DMF, 95 °C)[11] failed to produce the desired product. With a ready supply of **7b** available from **2** (Scheme 3), we decided to investigate this reaction further. We were hopeful that identifying suitable reaction conditions for removal of the SES group from **7b** would be facilitated because the desired product (**27**) was independently available from **26** (see Scheme 3). Initially, we established that **27** was stable to TBAF[27,28] in THF solution at 50 °C for several hours; however, heating under reflux led to slow decomposition of **27** into unidentified products (<10% of **27** remains after 6 h). Unfortunately, no reaction was observed after treatment of **7b** with TBAF[28a,b] in THF at 50 °C for 6 h (64% recovery of **7b**); the presence of **27** was not detected in the reaction mixture even after prolonged heating under reflux, conditions which lead to the slow decomposition of **7b** (and **27**). Similarly, we were unable to remove the SES group from **37** with TBAF[28b] in THF; however, reaction of **37** with CsF in DMF at 95 °C cleanly produced **38**, as previously reported (Scheme 4).[11] Treatment of **7b** with CsF/DMF led to decomposition without accumulation of **27**.

A recent report by Campbell and Hart[29] indicated that the SES group could be removed from *N*-acyl SES sulfonamides under mild conditions. We found that reaction of **33** with TBAF[28b] in THF at rt for 15 min gave **36** in excellent yield; however, despite considerable experimentation,[30] we were unable to prepare an *N*-acyl derivative of **7b**. Considering that **27** may form at a rate slower than its decomposition, we attempted to trap **27** by reaction of **7b** with TBAF in the presence of BnOCOCl under various conditions; in no case was **26** (or **27**) detected in the reaction mixtures.

(23) (a) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481. For the twist-boat TS: torsion 1−2−3−4 = ϕ_1 = −57°, torsion 2−3−4−5 = ϕ_2 = 25°, angle 2−3−4 = α_N = 90°, angle 3−4−5 = α_E = 104°, distance 3−4 = 2.35 Å. (b) ϕ_1 = −66°, ϕ_1 = 23°, α_N = 143°, α_E = 128°. (c) for example, with the 3−4 distance fixed at 2.7 Å: ϕ_1 = −63°, ϕ_1 = 24°, α_N = 127°, α_E = 112° (this conformation was 10.1 kcal/mol above the global minimum).

(24) We used a slight modification of Weinreb's protocol[8] to accommodate a smaller scale. We obtained better reproducibility using MeLi (as opposed to BuLi) as the base to generate $LiCHCl_2$ and used $CeCl_3$ in a 1.05:1 molar ratio with respect to MeLi (as opposed to 1:1).

(25) Under the same conditions, the formation of the ketone corresponding to **17** (cf. **29**) was indicated although spectral data for this product were not reported.[8]

(26) We thank Professor Weinreb and Dr. Garigipati for helpful discussions concerning this reaction.

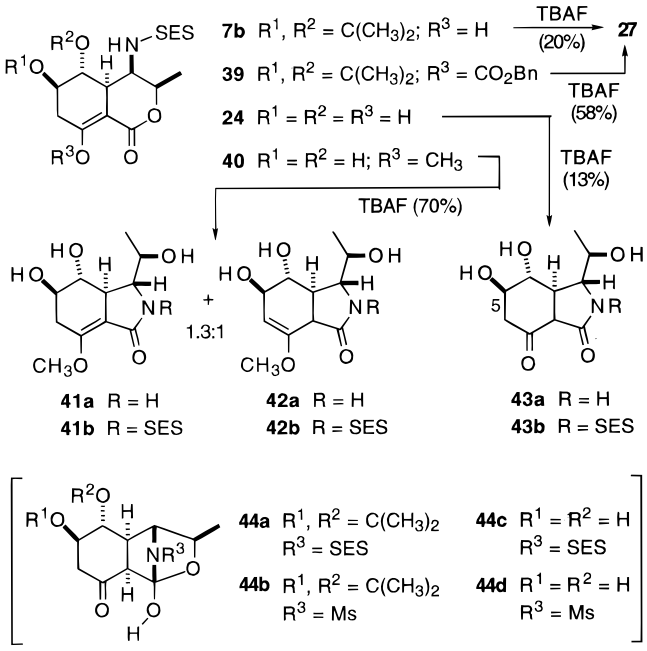
(27) Similar results were obtained using anhydrous or "wet" TBAF.

(28) An excess of reagent (∼3 equiv) was dispensed from a stock solution (1 M in THF). (a) Commercial TBAF (1 M in THF) was from Aldrich Chemical Company (Milwaukee, WI) and was labeled as containing ∼5 wt % water. This reagent was ∼2 years old and had been used successfully to remove TBDMS ethers. (b) Anhydrous TBAF solutions (1 M in THF) prepared from dry TBAF obtained by heating the hydrate *in vacuo*: Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216. (c) Wet TBAF solutions (1 M in THF) prepared by adding 5% of water (v/v) to an anhydrous solution.

(29) Campbell, J. A.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 2900.

(30) Neustadt, B. R. *Tetrahedron Lett.* **1994**, *35*, 379.

Scheme 5



The diol **24** was readily available by hydrolysis of the acetonide group in **7b**. Reaction of **24** with TBAF[28b] in refluxing THF gave **43a** which slowly was converted into a product of undetermined structure[31] (Scheme 5). Reaction of **23** under the same conditions produced neither **43a** nor its decomposition product. This result indicated that the lactam in **43a** was formed before the loss of the SES group and suggested the intermediacy of **43b**. Encouraged by a successful (although unproductive) removal of the SES group, we attempted to decrease the propensity for intramolecular acylation (cf. **44**)[32] by preparation of the enol ether **40** (from **7b** and CH_2N_2 followed by acid). Reaction of **40** with TBAF[28b] in refluxing THF cleanly produced a 1.3:1 mixture of **41a** and **42a** without evidence of an intermediate. These results suggest that the facile loss of the SES group from **24** and **40** results from the formation of *N*-SES lactams (i.e. **43b** and **41b**, respectively) which are activated toward deprotection (cf. **33**).[29] Presumably, the analogous reaction of **7b** is impeded in favor of other decomposition pathways by the increased strain in the tetrahedral intermediate for transacylation (cf. **44a** and **44c**) due to the *trans* fused acetonide.[33]

To determine if the formation of an *N*-SES lactam (cf. **44a**) was feasible for **7b**, we reexamined the reaction with TBAF in an effort to detect the acetonide derivative of **43a**. As before, reaction of **7b** with anhydrous TBAF[28b] in refluxing THF led only to decomposition without evidence for formation of a lactam analogous to **43a**. Surprisingly, reaction with "wet" TBAF[28c] in refluxing THF gave **27** in low yield (Scheme 3).[34] The optimal result was obtained after reaction for 1 h to give **27** in 20% yield along with recovered **7b** (50%). A superior procedure involved reaction of the enol benzyl carbonate derivative **39** under similar conditions (reflux, 30 min) to give the desired **27** in 58% yield. Unfortunately and despite considerable experimentation, we were unable to successfully remove the SES group from **9b** or its enol benzyl carbonate derivative **45** (not shown, cf. **39**) under these or similar conditions.

In conclusion, we have completed two closely related syntheses of 5,6-*O*-(2-propylidene)-*N*-desalanyl-*N*-[2-(trimethylsilyl)ethanesulfonyl]bactobolin (**9b**) from (+)-**12**, an intermediate previously prepared from D-glucose. Intermediates from both synthetic routes to **9b** can be prepared by degradation of actinobolin (**2**) thereby establishing a potential method for converting actinobolin into bactobolin. Although the conversion of **9b** into bactobolin has been previously reported,[8] in our hands the removal of the SES group from **9b** could not be achieved. By contrast, effective conditions were identified to remove the SES group from 5,6-*O*-(2-propylidene)-*N*-desalanyl-*N*-[2-(trimethylsilyl)ethanesulfonyl]actinobolin (**7b**) to give **27**, from which actinobolin (**2**) is readily prepared (85% yield) according to the published procedure.[5a] The recently reported[9b] enhancements in the [3+3] annulation of **10** with **11** to produce **12** along with the efficient synthesis of **7b** by direct cyclization of **29** and the successful amine deprotection represent a considerable improvement over our previously reported total synthesis of actinobolin.

Experimental Section[35]

(3a*R*,8*R*,9*R*,9a*R*,9b*R*)-*N*-[3a,4,8,9,9a,9b-Hexahydro-5-hydroxy-2,2,8-trimethyl-6-oxo-6*H*-1,3-dioxolo[4,5-*f*][2]-benzopyran-9-yl]-2-(trimethylsilyl)ethanesulfonamide (7b). From 6b: A solution of 1,1′-carbonyldiimidazole (4.2 mg, 0.026 mmol) and **6b** (7.0 mg, 0.017 mmol) in THF (0.5 mL) was stirred at rt for 16 h. Excess NaH (60% dispersion in oil, ~10 mg, 0.25 mmol) was added, and the mixture was stirred at rt for 1 h. The reaction was quenched by addition of saturated $NH_4Cl_{(aq)}$ (~1 mL), and the mixture was diluted with water and extraced with EtOAc (×3). The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by PTLC (5% MeOH in CH_2Cl_2) to give recovered **6b** (3 mg, 43%) and **7b** (3 mg, 46%). **From 29:** A solution of **29** (80 mg, 0.18 mmol) in THF (7 mL) was added to NaH (washed with hexane; 20 mg, 0.8 mmol), and the mixture was stirred at rt for 5 h. The reaction mixture was diluted with EtOAc [**caution**: H_2 evolution], washed with brine, dried over Na_2SO_4, concentrated, and fractionated by PTLC (5% MeOH in CH_2Cl_2) to give **7b** (72 mg, 90%): $[\alpha]_D$ +21.5 (*c* 1.10, CH_2Cl_2); IR ν_{max} 3274, 2952, 2923, 2853, 1780, 1721, 1644, 1593, 1229, 858 cm^{-1}; ^1H NMR δ 13.56 (1H, s), 4.60 (1H, dq, J = 1.5, 6.5 Hz), 4.17 (1H, d, J = 10 Hz), 4.00 (1H, ddd, J = 1.5, 3.5, 10

(31) This compound could not be obtained in pure form. Spectral data suggested a structure related to actinobolamine[2,19] (i.e. elimination of the C-5 hydroxy group and intramolecular conjugate addition of the amine nitrogen).

(32) The feasibility of intramolecular acylation via an intermediate like **44** is supported by the formation of **43a** from **24**, the cyclization of **29** to **7b**, and by Ohno's actinobolin synthesis.[5a]

(33) This can be evaluated qualitatively, for example, by comparing the difference in the calculated[22] total strain energy for **44b** and **7** (R = Ms, keto form) (48.9−27.1 = 21.8 kcal/mol) with that for the corresponding diols **44d** and **24** (R = Ms, keto form) (40.5−19.1 = 21.4 kcal/mol).

(34) We have no convincing explanation for the discrepancy in the results obtained using commercial[28a] vs prepared[28c] "wet" TBAF solutions.

(35) General procedures are included in the supporting information and are similar to those recently described.[5g] Optical rotations were determined at ambient temperature on a Perkin-Elmer 141 polarimeter using a 1 mL, 10 dm cell; concentrations (*c*) are in g/100 mL. Unless otherwise noted: chemical ionization mass spectra (CIMS) were recorded at 50 eV with NH_3 as the reagent gas; IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell; NMR spectra were measured in $CDCl_3$ solution at 300 MHz for ^1H and 75 MHz for ^{13}C with signals from the solvent used as internal standards ($CHCl_3$: 7.26 δ; $CDCl_3$ 77.0 δ). The ^1H NMR chemical shifts and coupling constants were determined assuming first-order behavior and multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent). The multiplicity of ^{13}C NMR signals refers to the number of attached H's (i.e., s = C, d = CH, t = CH_2, q = CH_3) and was determined by J modulation.

Hz), 3.79 (1H, ddd, J = 5.5, 9, 11 Hz), 3.52 (1H, dd, J = 9, 10 Hz), 3.13−2.96 (2H, m), 2.95 (1H, dd, J = 5.5, 17 Hz), 2.92 (1H, m), 2.66 (1H, ddd, J = 3, 11, 17 Hz), 1.48 (3H, d, J = 6.5 Hz), 1.46 (3H, s), 1.45 (3H, s), 1.12 (2H, m), 0.06 (9H, s); ^{13}C NMR δ 176.5 (s), 170.6 (s), 112.0 (s), 89.9 (s), 78.3 (d), 76.1 (d), 74.0 (d), 51.1 (t), 50.4 (d, C-4), 41.3 (d), 34.6 (t), 27.3 (q), 26.8 (q), 18.1 (q), 10.5 (t), -1.6 (q); CIMS *m/z* (relative intensity) 451 ([M + 18]$^+$, 26), 434 ([M + 1]$^+$, 100), 418 (12), 284 (13), 90 (79), 73 (38).

(1′*R*,2′*S*,3a*R*,4*R*,7a*R*)-*N*-[3,3-Dichloro-1-(hexahydro-2,2-dimethyl-6-oxo-1,3-benzodioxol-4-yl)-2-hydroxy-2-methylpropyl]-2-(trimethylsilyl)ethanesulfonamide (8b). From 20: Solid CrO_3 (83 mg, 0.83 mmol) was added to a solution of pyridine (0.23 mL, 0.22 g, 2.8 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C.[13] The mixture was stirred at rt for 10 min, and and then a solution of **20** (27 mg, 0.055 mmol) in CH_2Cl_2 (0.5 mL) was added. After 35 min, the mixture was filtered through a pad of celite, and the filter cake was washed with EtOAc. The combined filtrate and washings were concentrated, and the resulting residue was fractionated by FCC (40% EtOAc in hexane) to provide **8b** (25 mg, 93%):[36] $[\alpha]_D$ −16 (*c* 0.68, $CHCl_3$); IR ν_{max} 3468, 3299, 2986, 1715, 1326, 1141, 1110, 858, 842 cm^{-1}; ^{1}H NMR δ 6.01 (1H, s), 4.62 (1H, d, J = 10 Hz), 4.26 (1H, d, J = 10 Hz), 3.72 (2H, m), 3.11 (2H, m), 2.93 (1H, m), 2.70 (1H, dd, J = 2, 11 Hz), 2.65 (1H, s br), 2.58 (1H, dd, J = 13, 14.5 Hz), 2.31 (2H, m), 1.53 (3H, s), 1.50 (3H, s), 1.46 (3H, s), 1.12 (2H, m), 0.08 (9H, s); ^{13}C NMR δ 206.8 (s), 111.9 (s), 78.9 (s), 78.7 (d), 78.1 (d), 76.6 (d), 55.4 (d), 51.0 (t), 45.0 (t), 40.4 (t), 37.2 (d), 27.1 (q), 27.0 (q), 19.3 (q), 10.9 (t), −1.8 (q); CIMS *m/z* (relative intensity) 494 (1), 492 (4), 490 ([M + 1]$^+$, 6), 403 (98), 294 (100), 90 (97), 73 (56). **From 16:** A stream of ozone in oxygen was bubbled through a solution of **16** (23 mg, 0.047 mmol; a 6:1 mixture of 2′*S*:2′*R* isomers) in 20% MeOH in CH_2Cl_2 (1 mL) at −78 °C until a blue color was persistent. A stream of Ar was bubbled through the solution to remove the excess ozone, and then pyridine (2 drops) and dimethyl sulfide (0.1 mL) were added, and the solution was allowed to stand in a refrigerator (3 °C) overnight. The solution was concentrated to provide an oil which was fractionated by MPC (2.5% MeOH in CH_2Cl_2) to provide **8b** as a 5:1 mixture of 2′*S*: 2′*R* isomers (^{1}H NMR) (21 mg, 91%). The isomers were separated by MPC (30% EtOAc in hexane) to give **8b** (16 mg, 70%) and the corresponding 2′*R* isomer (2.2 mg, 10%) **(1′*R*,2′*R*,3a*R*,4*R*,7a*R*)-*N*-[3,3-Dichloro-1-(hexahydro-2,2-dimethyl-6-oxo-1,3-benzodioxol-4-yl)-2-hydroxy-2-methylpropyl]-2-(trimethylsilyl)ethanesulfonamide**: IR ν_{max} 3455, 3342, 2986, 1713, 1650, 1230, 1142, 837 cm^{-1}; ^{1}H NMR δ 5.76 (1H, s), 4.62 (1H, d, J = 10 Hz), 4.22 (1H, dd, J = 10 Hz), 3.75 (1H, ddd, J = 4.5, 9, 12.5 Hz), 3.66 (1H, dd, J = 9, 9.5 Hz), 3.08 (1H, m), 2.95 (1H, ddd, J = 2, 4.5, 14.5 Hz), 2.71 (1H, m), 2.68 (1H, s), 2.56 (1H, dd, J = 13, 14.5 Hz), 2.35 (1H, dd, J = 12.5, 14.5 Hz), 2.28 (1H, m), 1.60 (3H, s), 1.50 (3H, s), 1.45 (3H, s), 1.21 (2H, ddd, J = 4, 7, 14 Hz), 0.08 (3H, s); CIMS (isobutane) *m/z* (relative intensity) 494 (9), 492 (32), 490 ([M + 1]$^+$, 40), 342 (66), 340 (94), 101 (100).

(3a*R*,8*S*,9*R*,9a*R*,9b*R*)-*N*-[8-(Dichloromethyl)-3a,4,8,9,9a,9b-hexahydro-5-hydroxy-2,2,8-trimethyl-6-oxo-6*H*-1,3-dioxolo[4,5-*f*][2]benzopyran-9-yl]-2-(trimethylsilyl)ethanesulfonamide (9b). NaOMe (1 M in MeOH, 0.033 mL, 0.033 mmol) was added to a solution of **17** (5 mg, 0.0087 mmol) in dry MeOH (1.5 mL), and the mixture was stirred at rt and monitored by TLC (3% MeOH in CH_2Cl_2). After 6.5 h, additional NaOMe (0.020 mL, 0.020 mmol) was added and, after stirring for 1.5 h, the mixture was diluted with EtOAc, washed with saturated NH_4Cl, dried over Na_2SO_4, concentrated, and fractionated by MPC (3% MeOH in CH_2Cl_2) to give **9b** (3 mg, 67%):[36] $[\alpha]_D$ −26, (*c* 0.60, $CHCl_3$); IR ν_{max} 3238, 1743 (sh), 1652, 1585, 1382, 1233, 1103 cm^{-1}; ^{1}H NMR δ 11.90 (1H, s), 6.04 (1H, s), 4.46 (1H, dd, J = 3.5, 10.5 Hz), 4.27 (1H, d, J = 10.5 Hz), 3.82 (1H, ddd, J = 6, 9, 11 Hz), 3.63 (1H, dd, J = 9, 9 Hz), 3.14 (3H, m), 3.00 (1H, dd, J = 6, 18 Hz), 2.71 (1H, ddd, J = 2.5, 11, 18 Hz), 1.72 (3H, s), 1.50 (6H, s), 1.13 (2H, m), 0.08 (9H, s); ^{13}C NMR δ 179.6 (s), 169.2 (s), 112.2 (s), 88.2 (s), 86.1 (s), 75.4 (d), 74.4 (d), 73.8 (d), 51.7 (t), 51.6 (d), 37.8 (d), 35.0 (t), 26.9 (q), 26.7 (q), 19.2 (q), 10.7 (t), −2.0 (q); CIMS *m/z* (relative intensity) 537 (3), 535 (1), 533 ([M + 18]$^+$, 15), 520 (7), 518 (28), 516 ([M + 1]$^+$, 34), 90 (100), 73 (18).

(3a*R*,4*R*,4′*R*,5*R*,7a*R*)-4-[Hexahydro-2,2-dimethyl-6-methylene-1,3-benzodioxol-4-yl]-5-methyl-3-[2-(trimethylsilyl)ethanesulfonyl]-2-oxazolidinone (13b). From 12: BuLi (2.5 M in hexane) was added to a solution of **12** (12 mg, 0.045 mmol) and 1,10-phenanthroline (trace) in THF (1 mL) at 0 °C until a red color persisted. After 5 min, SES-Cl[11] (0.025 mL, 27 mg, 0.14 mmol) was added, and the mixture was stirred at 0 °C for 30 min. The mixture was diluted with CH_2Cl_2; washed sequentially with NaOH (2 M), brine and water; dried over Na_2SO_4; concentrated; and fractionated by FCC (30% ethyl acetate in hexane) to give **13b** as an oil (17 mg, 88%). **From 29:** The methylenation reagent was prepared from activated Zn (5.75 g, 88 mmol), CH_2Br_2 (5.01 g, 28.8 mmol), and $TiCl_4$ (3.91 g, 20.6 mmol) in THF (50 mL) according to Lombardo's procedure[21] and stored in a freezer (∼−20 °C). An aliquot of the above reagent (7.2 mL, ∼2.7 mmol) was added to a solution of **29** (118 mg, 0.27 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and then was poured onto saturated $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (30% EtOAc in hexane) to give **13b** (84 mg, 72%): IR ν_{max} 2994, 2862, 1778, 1137, 842 cm^{-1}; ^{1}H NMR δ 4.93 (2H, m), 4.73 (1H, dq, J = 1.5, 6.5 Hz), 4.03 (1H, dd, J = 1.5, 4 Hz), 3.67 (1H, ddd, J = 4, 14, 14 Hz), 3.34 (3H, m), 2.74 (1H, dd, J = 1, 4, 13 Hz), 2.47 (1H, ddd, J = 1, 4, 13 Hz), 2.28−2.15 (2H, m), 1.88 (1H, br dd, J = 13, 13 Hz), 1.47 (3H, d, J = 6.5 Hz), 1.42 (3H, s), 1.39 (3H, s), 1.20 (1H, ddd, J = 4, 14, 14 Hz), 1.09 (1H, ddd, J = 4, 14, 14 Hz), 0.06 (9H, s); ^{13}C NMR δ 152.4 (s), 140.7 (s), 115.2 (t), 110.6 (s), 79.5 (d), 79.0 (d), 73.5 (d), 63.9 (d), 50.4 (t), 41.0 (d), 37.3 (t), 33.9 (t), 27.0 (q), 26.4 (q), 20.9 (q), 9.0 (t), −2.0 (q); CIMS *m/z* (relative intensity) 449 ([M + 18]$^+$, 23), 432 ([M + 1]$^+$, 100), 416 (16), 282 (20), 268 (22), 210 (11), 172 (26).

(1′*R*,2′*R*,3a*R*,4*R*,7a*R*)-*N*-[1-(Hexahydro-2,2-dimethyl-6-methylene-1,3-benzodioxol-4-yl)-2-hydroxypropyl]-2-(trimethylsilyl)ethanesulfonamide (14b). Excess NaH (∼5 mg) was added to a stirred solution of **13b** (30 mg, 0.069 mmol) in MeOH (3 mL). After stirring for 3 h, the mixture was diluted with CH_2Cl_2, washed with saturated NH_4Cl and with brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (40% EtOAc in hexane) to provide **14b** (28 mg, 99%): IR ν_{max} 3512, 3279, 2983, 1648, 1450, 1118, 859 cm^{-1}; ^{1}H NMR δ 4.90 (2H, m), 4.74 (1H, d, J = 9 Hz), 4.15 (1H, dq, J = 2, 6.5 Hz), 3.45 (1H, dd, J = 9, 10 Hz), 3.34 (1H, ddd, J = 4, 8.5, 12 Hz), 3.26 (1H, ddd, J = 2, 6.5, 9 Hz), 2.99 (2H, m), 2.72 (1H, ddd, J = 1.5, 4.5, 12 Hz), 2.59 (1H, ddd, J = 3, 13 Hz), 2.22 (1H, dd, J = 12, 13 Hz), 1.99 (1H, dd, J = 13, 13 Hz), 1.83 (1H, m), 1.48 (3H, s), 1.44 (3H, s), 1.30 (3H, dd, J = 6.5 Hz), 1.10 (2H, m), 0.07 (9H, s); ^{13}C NMR δ 141.9 (s), 114.4 (t), 110.2 (s), 81.0 (d), 79.6 (d), 67.3 (d), 61.8 (d), 50.6 (t), 43.5 (d), 37.4 (t), 36.5 (t), 27.0 (q), 26.9 (q), 20.6 (q), 10.8 (t), −1.9 (q); CIMS *m/z* (relative intensity) 406 ([M + 1]$^+$, 100), 332 (14), 330 (20), 199 (68), 196 (53), 90 (88).

(1′*R*,3a*R*,4*R*,7a*R*)-*N*-[1-(Hexahydro-2,2-dimethyl-6-methylene-1,3-benzodioxol-4-yl)-2-oxopropyl]-2-(trimethylsilyl)ethanesulfonamide (15). CrO_3 oxidation of **14b** (76 mg, 0.19 mmol) according to the general procedure described for the preparation of **8b** gave **15** (74 mg, 98%) after fractionation by FPC (40% EtOAc in hexane): IR ν_{max} 3278, 2954, 1720, 1649, 1420, 1147, 835 cm^{-1}; ^{1}H NMR δ 5.21 (1H, d, J = 9.5 Hz), 4.87 (2H, m), 4.32 (1H, dd, J = 3, 9.5 Hz), 3.41 (2H, m), 2.89 (2H, m), 2.71 (1H, dd, J = 4, 12.5 Hz), 2.32 (3H, s), 2.20 (1H, m), 1.99 (3H, m), 1.46 (3H, s), 1.45 (3H, s), 1.04 (2H, m), 0.07 (9H, s); ^{13}C NMR (C_6D_6) δ 205.6 (s), 142.3 (s), 114.4 (t), 110.4 (s), 79.7 (d), 79.3 (d), 62.6 (d), 49.8 (t), 41.2 (d), 37.7 (t), 33.0 (t), 27.3 (q), 27.2 (q), 27.1 (q), 10.5 (t), −2.1 (q); CIMS *m/z* (relative intensity) 421 ([M + 18]$^+$, 27), 404 ([M + 1]$^+$, 100), 199 (49), 90 (64).

(1′*R*,2′*R,3a*R*,4*R*,7a*R*)-*N*-[3,3-Dichloro-1-(hexahydro-2,2-dimethyl-6-methylene-1,3-benzodioxol-4-yl)-2-hydroxy-2-methylpropyl]-2-(trimethylsilyl)ethanesulfonamide (16).** MeLi (1.0 M in diethyl ether, 1.5 mL, 1.5 mmol) was added to a solution of CH_2Cl_2 (0.25 mL; freshly distilled from CaH_2) in THF (0.30 mL) at −100 to −110 °C (bath). After the mixture

was stirred for 30 min, diethyl ether (3.2 mL; freshly distilled from sodium) was added dropwise to the resulting white supension. Anhydrous $CeCl_3$ (383 mg, 1.55 mmol; prepared[37] by heating *in vacuo* according to Imamoto's procedure) was added portionwise via a side arm. The heterogeneous reaction mixture was stirred at −100 to −110 °C for 1 h, and then a solution of **15** (19 mg, 0.047 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise. The reaction mixture was stirred at −100 to −110 °C for 2 h and quenched by dropwise addition of MeOH (1 mL). The mixture was diluted with EtOAc, washed with saturated NH_4Cl, dried over $MgSO_4$, concentrated, and fractionated by MPC (25% EtOAc in hexane) to give recovered **15** (8 mg, 42%) and **16** as a 6:1 mixture of the 2′*S*:2′*R* isomers (10.2 mg, 44%): IR ν_{max} 3456, 3308, 2986, 2954, 1450, 1420, 1142, 837 cm^{-1}; ^1H NMR δ for major isomer 6.10 (1H, s), 4.90 (2H, m), 4.65 (1H, d, J = 10 Hz), 4.12 (1H, br d, J = 10 Hz), 3.40 (2H, m), 3.08 (2H, m), 2.73 (1H, dd, J = 4, 12.5 Hz), 2.59 (1H, m), 2.22 (1H, dd, J = 11.5, 12.5 Hz), 1.99 (2H, m), 1.52 (3H, s), 1.44 (3H, s), 1.41 (3H, s), 1.10 (2H, m), 0.07 (9H, s), δ for minor isomer 5.81 (1H, s); ^{13}C NMR δ for major isomer 142.4 (s), 114.5 (t), 110.3 (s), 80.2 (d), 79.0 (d), 78.8 (s), 78.4 (d), 56.2 (d), 50.9 (t), 41.0 (d), 37.7 (t), 34.0 (t), 27.2 (q), 26.9 (q), 19.5 (q), 10.9 (t), −1.8 (q); CIMS *m/z* (relative intensity) 492 (8), 490 (29), 488 ($[M + 1]^+$, 38), 196 (19), 181 (23), 90 (100).

(3a*R*,4*R*,4′*R*,5′*S*,7a*R*)-4-[5,5-(Dichloromethyl)-5-methyl-3-(2-(trimethylsilyl)ethanesulfonyl)-2-oxo-oxazolidin-4-yl]-3a,4,7,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxol-6-yl Methyl Carbonate (17). A solution of **8b** (28 mg, 0.057 mmol), methyl chloroformate (0.9 mL), and 4-pyrrolidinopyridine (2 mg, 0.013 mmol) in Et_3N (6 mL) was stirred at rt for 15 h. The reaction mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (20% ethyl actate in hexane) to give **17** as an oil (29 mg, 88%) which contained a small amount (∼15% by ^1H NMR) of the corresponding methyl carbamate alcohol (i.e. the precursor for oxazolidinone formation):[25] IR ν_{max} 2986, 1793, 1761, 1697, 1441, 1359, 1258, 1098, 843 cm^{-1}; ^1H NMR δ 5.80 (1H, s), 5.37 (1H, dd, J = 1, 1 Hz), 4.90 (1H, d), 3.82 (3H, s), 3.79 (2H, m), 3.57 (2H, m), 2.94 (1H, m), 2.68 (1H, m), 2.55 (1H, m), 1.76 (3H, s), 1.46 (6H, s), 1.13 (2H, m), 0.08 (9H, s); ^{13}C NMR δ 153.3 (s), 151.5 (s), 149.8 (s), 112.1 (d), 111.5 (s), 86.5 (s), 76.4 (d), 75.5 (d), 74.8 (d), 58.7 (d), 55.5 (q), 51.8 (t), 40.4 (d), 32.5 (t), 27.2 (q), 26.7 (q), 15.7 (q), 9.3 (t), −2.1 (q); CIMS *m/z* (relative intensity) 595 (4), 593 (14), 591 ($[M + 18]^+$, 18), 160 (65), 138 (100), 132 (52), 90 (58).

(1′*R*,3a*R*,4*R*,7a*R*)-*N*-[1-(Hexahydro-2,2-dimethyl-6-oxo-1,3-benzodioxol-4-yl)-2-oxopropyl]-2-(trimethylsilyl)-ethanesulfonamide (18). From 6b: CrO_3 oxidation of **6b** (96 mg, 0.23 mmol) according to the general procedure described for the preparation of **8b** gave **18** (85 mg, 89%) after fractionation by FCC (40% EtOAc in hexane). **From 15:** Ozonolysis of **15** (5.0 mg, 0.012 mmol), according to the procedure described for the preparation of **8b**, gave **18** as an oil (4.4 mg, 91%) after fractionation by FCC (50% EtOAc in hexane): IR ν_{max} 3273, 2953, 1720, 1120, 858 cm^{-1}; ^1H NMR δ 5.28 (1H, d, J = 9 Hz), 4.40 (1H, dd, J = 2.5, 9 Hz), 3.85 (1H, dd, J = 9, 10 Hz), 3.70 (1H, ddd, J = 4.5, 9, 13.5 Hz), 2.91 (3H, m), 2.59 (1H, dd, J = 13.5, 13.5 Hz), 2.39 (1H, dddd, J = 2.5, 5.5, 10, 10 Hz), 2.33 (3H, s), 2.19 (2H, m), 1.52 (3H, s), 1.50 (3H, s), 1.03 (2H, m), 0.04 (9H, s); ^{13}C NMR (C_6D_6) δ 204.4 (s), 202.7 (s), 111.6 (s), 78.0 (d), 76.6 (d), 61.7 (d), 49.3 (t), 44.5 (t), 38.5 (t), 37.2 (d), 26.9 (q), 26.8 (q), 26.6 (q), 10.3 (t), −2.4 (q); CIMS *m/z* (relative intensity) 423 ($[M + 18]^+$, 100), 406 ($[M + 1]^+$, 35), 199 (82), 90 (63).

(1′*R*,3a*R*,4*R*,6*R*,7a*R*)-*N*-[1-(Hexahydro-6-hydroxy-2,2-dimethyl-1,3-benzodioxol-4-yl)-2-oxopropyl]-2-(trimethylsilyl)ethanesulfonamide (19). Excess $NaBH_4$ (50 mg, 1.3 mmol) was added to a solution of **18** (165 mg, 0.41 mmol) in 1:1 MeOH:CH_2Cl_2 (10 mL) at −78 °C. After stirring for 30 min, the reaction was quenched by addition of acetaldehyde (0.2 mL) and stirred for an additional 30 min at −78 °C. The reaction mixture was allowed to warm to rt and then was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, concentrated, and fractionated by FCC (75% EtOAc in hexane) to give **19** (145 mg, 87%). A similar reaction on much smaller scale (**18**: 4.0 mg, 0.0099 mmol) and lower concentration (1 mL of solvent) gave recovered **18** (0.9 mg, 22%) and **19** (2.9 mg, 72%):[36] $[\alpha]_D$ −44 (*c* 0.56, $CHCl_3$); IR ν_{max} 3488, 3287, 2952, 1718, 1370, 1325, 840 cm^{-1}; ^1H NMR δ 5.20 (1H, d, J = 9.5 Hz), 4.30 (1H, dd, J = 3.5, 9.5 Hz), 3.86 (1H, m), 3.42 (2H, m), 2.89 (2H, m), 2.46 (1H, m), 2.31 (3H, s), 2.07 (1H, m), 1.80−1.50 (3H, m), 1.43 (6H, ap s), 1.04 (2H, m), 0.04 (9H, s); ^{13}C NMR δ 205.9 (s), 111.2 (s), 79.2 (d), 68.3 (d), 62.3 (d), 49.7 (t), 37.8 (d), 37.1 (t), 33.7 (t), 27.9 (q), 27.0 (q), 26.9 (q), 10.2 (t), −2.0 (q); CIMS *m/z* (relative intensity) 425 ($[M + 18]^+$, 4), 408 ($[M + 1]^+$, 9), 255 (13), 229 (34), 199 (100), 90 (40).

(1′*R*,2′*S*,3a*R*,4*R*,7a*R*)-*N*-[3,3-Dichloro-1-(hexahydro-6-hydroxy-2,2-dimethyl-1,3-benzodioxol-4-yl)-2-hydroxy-2-methylpropyl]-2-(trimethylsilyl)ethanesulfonamide (20). Reaction of **19** (27 mg, 0.066 mmol) with $LiCHCl_2/CeCl_3$ (20 equiv) according to the general procedure described for the preparation of **16** gave recovered **19** (11 mg, 40%) and **20** (10 mg, 31%) after PTLC (40% EtOAc in hexane):[36] IR ν_{max} 3448, 3324, 2986, 2953, 1371, 1252, 1139, 840 cm^{-1}; ^1H NMR δ 6.08 (1H, s), 4.78 (1H, d, J = 10 Hz), 4.11 (1H, dd, J = 2, 10 Hz), 3.91 (1H, m), 3.43 (1H, ddd, J = 3.5, 9, 12 Hz), 3.33 (1H, dd, J = 9, 9.5 Hz), 3.07 (2H, m), 2.51−2.42 (1H, m), 2.33−2.25 (1H, m), 2.08−1.95 (1H, m), 1.60−1.26 (2H, s), 1.52 (3H, s), 1.43 (3H, s), 1.41 (3H, s), 1.11 (2H, s), 0.07 (9H, s); ^{13}C NMR δ 110.9 (s), 80.0 (d), 78.9 (s), 78.3 (s), 77.1 (d), 68.7 (d), 55.9 (d), 51.0 (t), 37.8 (d), 37.5 (t), 34.9 (t), 27.1 (q), 26.9 (q), 19.4 (q), 10.8 (t), −1.8 (q); CIMS *m/z* (relative intensity) 494 (1), 492 (4), 490 ($[M + 1]^+$, 7), 200 (60), 199 (30), 142 (40), 90 (100), 86 (73).

(3a*R*,8*R*,9*R*,9a*R*,9b*R*)-9-Amino-3a,4,8,9,9a,9b-hexahydro-5-hydroxy-2,2,8-trimethyl-6*H*-1,3-dioxolo[4,5-*f*][2]-benzopyran-6-one (27). From 7b: TBAF (1 M in THF containing 5% H_2O (v/v); 0.053 mL, 0.053 mmol)[28c] was added to a solution of **7b** (7.6 mg, 0.017 mmol) in dry THF (0.5 mL), and the mixture was heated under reflux for 1 h (preheated bath). The cooled (rt) reaction mixture was concentrated and fractionated by FCC (40% EtOAc in hexane; 5% MeOH in CH_2Cl_2) to give **7b** (3.8 mg, 50%) and **27** (1 mg, 20%). **From 39:** TBAF (1 M in THF containing 5% H_2O (v/v); 0.039 mL, 0.039 mmol)[28c] was added to a solution of **39** (6.4 mg, 0.011 mmol) in dry THF (0.5 mL), and the mixture was heated under reflux for 30 min (preheated bath). Workup as above gave **27** (1.8 mg, 58%). **From 26:**[20] A suspension of **26** (18 mg, 0.045 mmol) and 10% Pd−C (∼5 mg) in EtOH (1.5 mL) was stirred at rt under H_2 (1 atm) for 30 min. The mixture was filtered with the aid of EtOAc, and the combined filtrate and washings were concentrated and fractionated by MPC (5% MeOH in CH_2Cl_2) to give **27** (9.5 mg, 79%): IR ν_{max} 3325, 2984, 1655, 1593, 1226, 1094 cm^{-1}; ^1H NMR δ 4.51 (1H, dq, J = 1.5, 6.5 Hz), 3.77 (1H, ddd, J = 6, 9.5, 11 Hz), 3.62 (1H, dd, J = 9.5, 9.5 Hz), 3.21 (1H, dd, J = 1.5, 3.5 Hz), 2.92 (1H, ddd, J = 1, 6, 17.5 Hz), 2.81 (1H, ddd, J = 1, 3, 3.5, 9.5 Hz), 2.62 (1H, ddd, J = 3, 11, 17.5 Hz), 1.48 (3H, s), 1.45 (3H, s), 1.41 (3H, d, J = 6.5 Hz); ^{13}C NMR δ 175.1 (s), 171.1 (s), 111.6 (s), 90.6 (s), 78.9 (d), 76.1 (d), 74.4 (d), 47.3 (d), 42.0 (d), 34.8 (t), 27.2 (q), 27.0 (q), 17.5 (q); CIMS *m/z* (relative intensity) 270 ($[M + 1]^+$, 100), 212 (12), 57 (69).

(3a*R*,4*R*,4′*R*,5*R*,7a*R*)-4-[Hexahydro-2,2-dimethyl-6-oxo-1,3-benzodioxol-4-yl]-5-methyl-3-[2-(trimethylsilyl)ethanesulfonyl]-2-oxazolidinone (29). From 28: NaH (80% dispersion in oil, 21 mg, 0.70 mmol) was added to a stirred solution of **28** (63 mg, 0.23 mmol) in THF (4 mL) at 0 °C. After 5 min, SES-Cl[11] (180 mg, 0.90 mmol) was added, and the mixture was stirred at 0 °C for 1 h and at rt for an additonal 2 h. The reaction mixture was diluted with EtOAc, washed with saturated NH_4Cl, dried over Na_2SO_4, concentrated, and fractionated by FCC (40% EtOAc in hexane) to give recovered **28** (19 mg, 30%) and **29** as an oil (68 mg, 69%). **From 13b:** Ozonolysis of **13b** (23 mg, 0.053 mmol), according to the procedure described for the preparation of **8b**, gave **29** as an oil (21 mg, 91%) after fractionation by FCC (50% EtOAc in hexane): IR ν_{max} 2985, 2849, 1778, 1720, 1354, 1139 cm^{-1}; ^1H

(36) The spectral data agreed closely with those previously reported[5d] for (±)-isomer.

(37) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

NMR δ 4.73 (1H, dq, J = 1.5, 6.5 Hz), 4.08 (1H, dd, J = 1.5, 3 Hz), 3.78−3.62 (3H, m), 3.38 (1H, ddd, J = 5, 14, 14 Hz), 2.95 (1H, dd, J = 1.5, 4.5 Hz), 2.63−2.35 (3H, m), 2.16 (1H, dd, J = 12, 16 Hz), 1.50 (3H, d, J = 6.5 Hz), 1.49 (3H, s), 1.45 (3H, s), 1.19 (1H, ddd, J = 4, 15, 15 Hz), 1.08 (1H, ddd, J = 4, 15, 15 Hz), 0.07 (9H, s); ^{13}C NMR δ 203.7 (s), 152.5 (s), 112.5 (s), 78.7 (d), 77.0 (d), 74.3 (d), 63.4 (d), 50.6 (t), 44.8 (t), 40.1 (t), 38.0 (d), 27.1 (q), 26.7 (q), 21.0 (q), 9.3 (t), −1.9 (q); CIMS *m*/*z* (relative intensity) 451 ([M + 18]$^+$, 100), 434 ([M + 1]$^+$, 31), 418 (13), 284 (28), 172 (41).

(3a*R*,8*R*,9*R*,9a*R*,9b*R*)-3a,4,8,9,9a,9b-Hexahydro-2,2,8-trimethyl-9-[[2-(trimethysilyl)ethanesulfonyl]amino]-6-oxo-6*H*-1,3-dioxolo[4,5-f][2]benzopyran-5-yl Phenylmethyl Carbonate (39). NaH (prewashed with hexane, 3 mg, 0.12 mmol) was added to solution of **7b** (22 mg, 0.051 mmol) and benzyl chloroformate (48 mg, 0.28 mmol) in THF (1.5 mL) at rt under argon. The reaction mixture was stirred for 1.5 h and then was diluted with EtOAc, washed with aqueous $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by FCC (30% EtOAc in hexane) to provide **39** (27 mg, 96%): IR ν_{max} 3278, 2986, 1762, 1721, 1618, 1188, 842 cm^{-1}; ^{1}H NMR δ 7.39 (5H, m), 5.28 (1H, d, J = 12 Hz), 5.23 (1H, d, J = 12 Hz), 4.86 (1H, d, J = 10 Hz), 4.62 (1H, dq, J = 2, 6.5 Hz), 4.08 (1H, ddd, J = 3, 3, 10 Hz), 3.84 (1H, ddd, J = 5.5, 10, 10 Hz), 3.68 (1H, dd, J = 10, 10 Hz), 3.03 (3H, m), 2.87 (1H, ddd, J = 2, 5.5, 18 Hz), 2.63 (1H, ddd, J = 4.5, 10, 18 Hz), 1.47 (3H, s), 1.46 (3H, s), 1.45 (3H, d, J = 6.5 Hz), 1.12 (2H, m), 0.04 (9H, s); ^{13}C NMR δ 160.4 (s), 159.7 (s), 151.4 (s), 134.2 (s), 128.8 (d), 128.6 (d), 128.5 (d), 112.6 (s), 110.2 (s), 78.6 (d), 75.6 (d), 73.1 (d), 71.1 (d), 51.4 (t), 51.1 (d), 42.8 (d), 35.0 (t), 27.1 (q), 26.8 (q), 18.3 (q), 10.5 (t), −1.9 (q); CIMS *m*/*z* (relative intensity) 585 ([M + 18]$^+$, 21), 568 ([M + 1]$^+$, 9), 524 (16), 434 (62), 358 (17), 418 (25), 91 (100), 90 (46).

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Supporting Information Available: Experimental procedures and spectral data for **6b**, **12**, **24**, **28**, **31**−**36**, **40**−**43**, and **45**; ^{13}C NMR spectra for **8b**, **9b**, **19**, and **20**; ^{1}H NMR spectra for all compounds (45 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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