Toluene Dioxygenase-Mediated *cis*-Dihydroxylation of Aromatics in Enantioselective Synthesis. Asymmetric Total Syntheses of Pancratistatin and 7-Deoxypancratistatin, Promising Antitumor Agents[1]

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Received February 23, 1996[⊗]

Abstract: Whole-cell biooxidation of bromobenzene with *Pseudomonas putida* 39D or the recombinant *Escherichia coli* JM109 (pDTG601) yields (1*S*,2*S*)-3-bromocyclohexa-3,5-diene-1,2-diol (**9a**), which is protected as the acetonide and converted to vinylaziridines **7**, **15a**, **63**, and **64**. Our route to (+)-pancratistatin features the coupling of a higher order cyanocuprate (derived by *ortho*-metalation from *N*,*N*-dimethyl-2-[(*tert*-butyldimethylsilyl)oxy]-3,4-(methylenedioxy)benzamide) with aziridine **7** to generate **28**, which contains the carbon framework of the title alkaloid. Functional group manipulations resulted in the preparation of epoxydiol **50**, which was transformed in a unique fashion and under mild conditions (H_2O/$PhCO_2Na$) to (+)-pancratistatin, thus completing a concise synthesis of (+)-pancratistatin in 14 steps from bromobenzene (2% overall yield). To improve this first generation attempt, a new route was devised utilizing carbomethoxyaziridine **64** and its coupling to the cuprate of 3,4-(methylenedioxy)-bromobenzene. The adduct was converted to (+)-7-deoxypancratistatin in a total of 11 steps from bromobenzene (3% overall yield), and the basis for further improvement toward a practical synthesis of pancratistatin-type alkaloids was formulated.

Introduction

The medicinal value of oil from the daffodil *Narciclasus poeticus L.* in the treatment of illnesses related to cancer was already known to physician Hippocrates of Cos[2] in ancient Grecian times, but it was not until 1877 that the first member of the Amaryllidaceae family of alkaloids, lycorine (**1**, Figure 1), was isolated from *Narcissus pseudonarcissus*.[3] Since that time, more than 100 structurally diverse alkaloids have been isolated from various Amaryllidaceae species. In 1958, lycorine was shown to possess antitumor acivity.[4] Lycoricidine (**2**) and narciclasine (**3**) were discovered in 1968 in the bulbs of *Lycoris radiate*.[5] Sixteen years later, another highly oxygenated phenanthridone alkaloid was extracted from *Pancratium littorale*.[6] The compound was named pancratistatin (**4**);[7] it subsequently attracted considerable attention because of its spectrum of antineoplastic activities.[6c] Although pancratistatin's mechanism of action remains to be elucidated, that of narciclasine has been studied, and it is believed that the compound disrupts protein biosynthesis in eukaryotes.[8] Both lycoricidine and

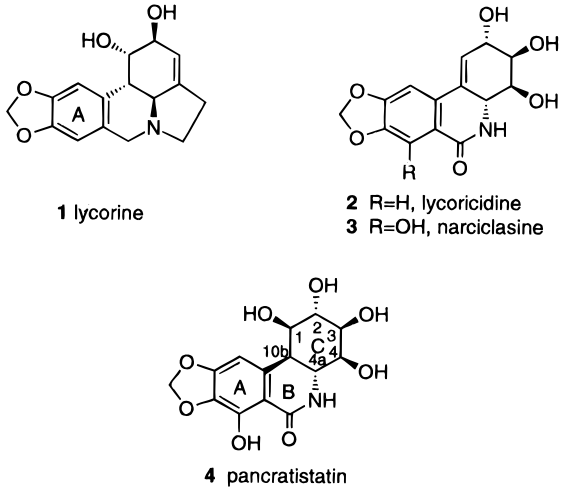

Figure 1.

[†] Undergraduate Research Participant, Summer 1993.

[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1996.

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(7) The word pancratistatin should more appropriately be spelled pancratistatinum in correct "chemical" Latin. It implies an "all-powerful breaker or stopper" of some activity, in this case cell division. The derivation is of some interest here. The name of the plant translates literally as "all-powerful from the shore of a lake" and is a Latin rendition of a Greek word *pankration*, which means "victory by any and all means". It refers to an ancient wrestling contest which was frequently fought to the death or unconditional surrender of one of the opponents. Barred from this match was only the use of biting or gouging—all else was allowed. The root of the word *pankration* in Greek implies power or strength (*kratos*) and in Latin hurdles or obstacles. We thank Dr. Thomas MacAdoo (Virginia Tech) for this interesting elucidation.

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S0002-7863(96)00596-3 CCC: $12.00

narciclasine show activities against Ehrlich carcinoma,[5] but the most promising activity resides with pancratistatin, which is active against murine P-5076 ovarian sarcoma, as well as murine P-388 lymphocytic leukemia.[6c] To date, no focused structure−activity study has been conducted with these alkaloids, perhaps as a consequence of the minute quantity of material available from isolation (6.5 g of pancratistatin and 10 g of lycoricidine were extracted from 45 kg of bulbs).[6] Tests on *seco*-derivatives of pancratistatin, which lack the piperonyl unit, indicated no activity.[9] The biogenesis of the alkaloids remains unconfirmed except for the biosynthesis of narciclasine, investigated in the early 1970s.[10]

The chemistry of Amaryllidaceae alkaloids is rich and detailed, and many syntheses of lycorine and related structures have been published.[11,12] Driven by the promise of biological activities, the synthetic community reacted to the discovery of lycoricidine and pancratistatin with focused rigor—to date, lycoricidine has been prepared by several groups.[13] Narciclasine has not yet been synthesized despite several attempts;[14] the first racemic preparation of pancratistatin was published by Danishefsky and Lee in 1989.[15] The latter synthesis builds up the C-ring skeleton of **4** by means of a Diels−Alder reaction between a butadiene attached to C10a of the aromatic moiety and β-nitrovinyl sulfone, affording a 1,4-cyclohexadiene, which is further elaborated to the fully oxygenated alkaloid in 2% overall yield from the diene. Two asymmetric syntheses of **4** were achieved in 1995—the first by our group as disclosed in a preliminary report,[1a] and the second by Trost and Pulley,[16] who employed Pd-catalyzed asymmetrization of a symmetric 1,4-bis(methoxycarboxy)-2-cyclohexene with a nitrogen nucleophile, followed by CuCN-catalyzed S_N2' substitution to introduce the aromatic moiety. Keck et al.[17] and we[1b] have recently published syntheses of 7-deoxypancratistatin.[17,1b] Starting from readily available D-gulono-1,4-lactone-2,3-acetonide, Keck builds up a linear C-ring precursor and closes the crucial C10b−C4a bond by radical addition to an oxime. The work published so far suggests that these molecules are far more difficult to construct than they appear at first glance. There have been several reports of model studies concerned with the efficient attachment of the aryl moiety to a suitable residue,[18] but despite these efforts, no efficient, practical preparation has materialized to date. The chemistry of Amaryllidaceae alkaloids having antitumor activity has recently been reviewed.[19]

In order to elucidate the mode of activity of pancratistatin and its congeners and to initiate a rational design of more active medicinal substances from these promising lead compounds, it is essential to be able to access a large number of diversely functionalized derivatives of the parent system. Any such synthetic design must accommodate structural variation and efficiently lead to the brief preparation of the target class of compounds. A first step toward this goal has been realized by combining biocatalytic methods for generating chirality with new methodology of carbon−carbon bond formation. In this article, the enantioselective syntheses of pancratistatin and 7-deoxypancratistatin are described.

Results and Discussion

The major difficulty with any approach to the fully oxygenated Amaryllidaceae alkaloids has been in the control of stereochemistry at C10b−C4a and in introducing (and/or retaining) the oxygenation in the C-ring. Our approach is based on the advantageous configuration of the *cis*-diol at C3−C4, envisioned to be the controlling element of the relative and absolute stereochemistry, introduced by toluene dioxygenase-mediated *cis*-dihydroxylation of aromatic rings.[20−22] The *trans*-diol at C1−C2 and the *trans* disposition of the aryl fragment to the C4a nitrogen suggested opening of epoxides and aziridines, respectively, as a means for control of the configuration of the six contiguous stereocenters in the C-ring. The initial disconnection assumed a convergent approach and a minimum of functional group manipulations, as depicted in Figure 2.

The assumption that diaxial opening of the epoxide in **5** would be accomplished with concomitant hydrolysis of the acetonide was based on our successful performance of both of these tasks by means of a catalytic amount of sodium benzoate in water during the synthesis of D-*chiro*-inositol.[23] Epoxide **5** was to be derived from phenanthridone **6**, where the β-face is blocked by the *endo*-situated methyl group of the acetonide. The crucial C−C bond formation was expected to arise from the *trans* opening of the aziridine in **7** with an organometallic species derived from the known amide **8**.[24] From the results obtained in a preliminary study of the opening of aziridines of type **7** with different organometallic species,[25] we were confident that *trans* 1,2-opening of the vinylaziridine **7** with aromatic carbon

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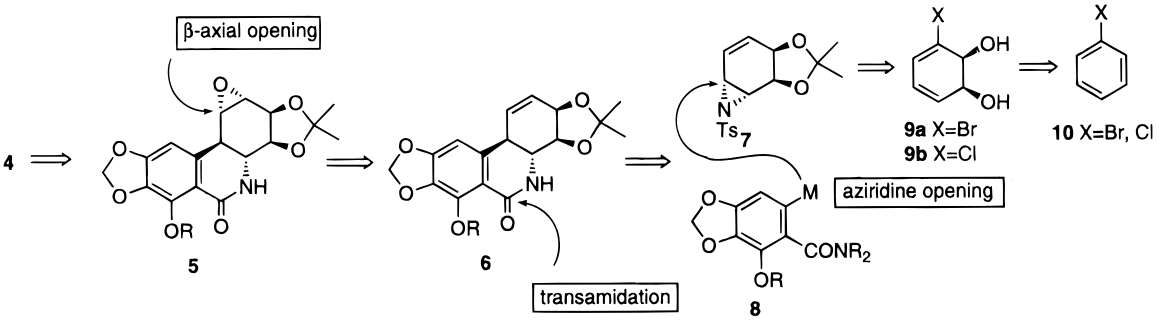


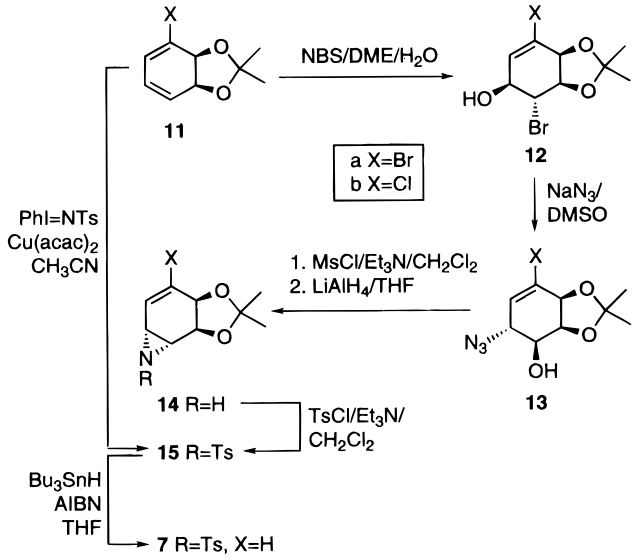
Figure 2. Disconnection approach to pancratistatin.

nucleophiles would be possible. The core of our approach would be the introduction of the 3,4-*cis*-diol unit of pancratistatin in the required absolute stereochemistry by the oxidation of halobenzene[20] to diene diol **9**, mediated by toluene dioxygenase (from *Pseudomonas putida* 39/D), offering fast access to aziridine **7**.

Asymmetric dihydroxylation of aromatic substrates, pioneered by Gibson et al. almost 30 years ago,[20,21] has witnessed increasing use in organic synthesis since 1988.[26,27] The latest synthetic applications have recently been reviewed[28] and include the use of recombinant *E. coli* JM109 (pDTG601), which contains the information for toluene dioxygenase on a plasmid[22] and allows production of diene diols in higher yields and renders transformations of noninducing substrates easier.

Preparation of Vinylaziridines. Enantiomerically pure diols **9a**,**b**[29] were prepared by oxidation of halobenzenes **10** with whole cells of *P. putida* 39/D or recombinant *E. coli* JM109 (pDTG601) according to the established procedure[30] and stored at −78 °C. After protection as their acetonides, dienes **11** were used immediately to avoid dimerization through Diels−Alder cycloaddition.[31] Initially, the aziridines investigated in this study were prepared as shown in Scheme 1. The intermediate *β*-epoxide (generated from bromohydrin **12** in situ) was opened with azide; subsequent mesylation of **13** followed by $LiAlH_4$ reduction afforded aziridine **14**. Tosylation of **14** gave tosyl-

Scheme 1



aziridines **15** for both the chlorine (X = Cl) and bromine (X = Br) series. A more efficient protocol to acquire **15** and dehalogenated derivative **7** was found by the use of Yamada's iodonium ylide.[32] Treatment of **11a** (X = Br) or **11b** (X = Cl) with (*N*-tosylimino)phenyliodinane according to Evans's procedure[33] afforded 59% and 20% overall yields of aziridines **15a** and **15b**, respectively. Dehalogenation of **15a** with Bu_3SnH/AIBN/THF furnished vinylaziridine **7** in 78% yield. Although this aziridination procedure is vastly superior to the stepwise preparation of **15**, the latter has the advantage that it leads to the free aziridines **14**, which can be functionalized with groups other than tosyl. With aziridine **7** in hand, a detailed investigation of the crucial C10a−C10b bond formation by opening of the aziridine with suitable carbon nucleophiles was now possible.

Ring Opening of Endocyclic Vinylaziridine 7. The chemistry of vinylaziridines has been confined for the most part to their use in rearrangement sequences leading to functionalized pyrrolines.[34−38] The lack of data concerning the nucleophilic opening of vinylaziridines with carbon nucleophiles surprised us, in view of the expected similarity of such systems to the well-studied vinyloxiranes.[34,39] There were no disclosures of

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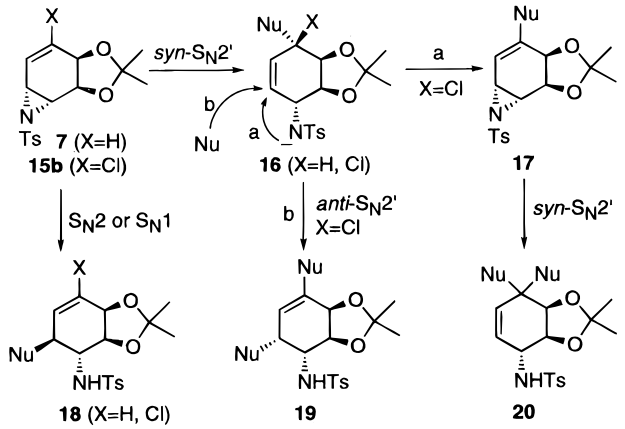
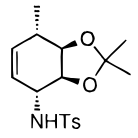
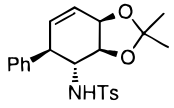
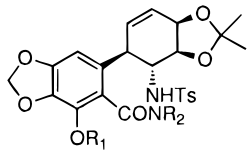


Figure 3. Mechanistic rationale for vinylaziridine opening.

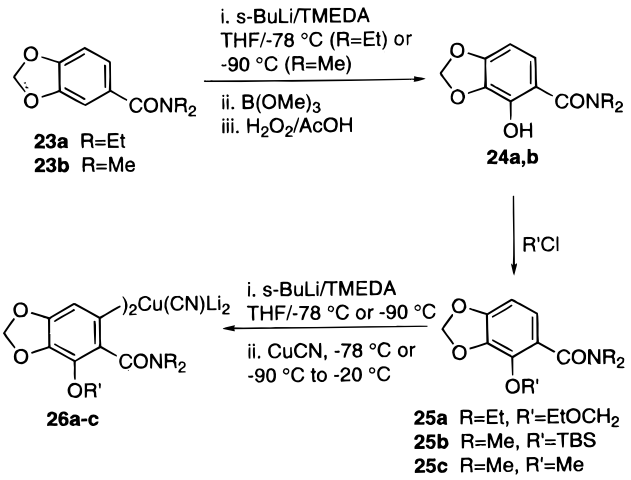
corresponding trends for vinylaziridines prior to our preliminary report on parallel reactivities of vinyloxiranes and vinylaziridines with organometallic reagents.[25] Recently, several papers have appeared describing the interaction of cuprates and other organometallics with acyclic vinylaziridines.[40] Our results indicated that the ring opening of endocyclic vinylaziridines **7** and **15** with Grignard and cuprate reagents can be described as either *anti*-1,2-addition or *syn*-1,4-addition. In the case of halovinylaziridines **15**, the latter process is followed by a second 1,4-addition, forming 2,4- or 4,4-disubstituted products (Figure 3). The reactions are strongly dependent on the nature of the nucleophile and the structure of the vinylaziridine. Some generalizations formulated during the study are delineated in Figure 3. Whereas the reaction of an aliphatic or aromatic cuprate or a Grignard reagent with aziridine **7** yields predominantly *syn*-1,4-addition,[25] there is an interesting difference in reactivity for higher order cuprates. Lithium dimethylcyanocuprate affords *syn*-1,4-addition (**21**, 37%), while lithium diphenylcyanocuprate shows *anti*-1,2-addition (**22**, 70% yield; Table 1, entries 1 and 2). Currently, we have no explanation for this divergent reactivity. The assignment of stereochemistry was achieved by decoupling experiments and analysis of ^{1}H-NMR coupling constants, as well as ^{1}H-NMR−NOE experiments.

The isolation of **22**, with established *trans*-stereochemistry, provided a good basis for the application of this method (opening of aziridine **7** with a higher order cyanocuprate) in the synthesis of the title alkaloids. The aromatic portion required for pancratistatin was synthesized according to the established protocol by means of *ortho*-lithiation[41] of a diethyl- or dimethylamide species, as shown in Scheme 2. The requisite amides were made from piperonic acid according to literature methods.[18c,24,42] Lithiation of amides **23**,[43] followed by quenching with trimethyl borate and oxidation with H_2O_2, afforded phenols **24**, which were protected as either ethoxymethoxy, TBS, or methoxy derivatives **25** using standard methods. A second metalation, followed by cuprate formation according to Lipshutz et al.,[44] provided the required higher order cyanocuprates **26**.

Table 1. Reactions of Vinylaziridine **7**

Entry	Nucleophile/Conditions	Product(s) (yield, %)
1	$(CH_3)_2CuLi$/THF -78 °C to -40 °C	 (37)
2	$Ph_2Cu(CN)Li_2/BF_3{\cdot}Et_2O$ THF/ -78 °C to RT	 (70)
3	**26a** / $BF_3{\cdot}Et_2O$ THF/-78 °C to RT	 (49)
4	**26b** / $BF_3{\cdot}Et_2O$ THF/-78 °C to RT	**28** R_1=TBS, R_2=Me (75)
5	**26c** / $BF_3{\cdot}Et_2O$ THF/-78 °C to RT	**29** R_1=R_2=Me (72)

Scheme 2



The addition to activated aziridine **7** gave 49%, 75%, and 72% yields respectively of adducts **27**, **28**, and **29** (Table 1, entries 3−5). To our knowledge, this is the first example of a preparation of higher order cyanocuprates via *ortho*-metalation directed by the amide group. The stage was now set for the completion of the total synthesis, as these adducts already possess the carbon framework of the title alkaloids.

(a) *trans*-Amidation Route. After the successful attainment of adduct **27**, we initially chose to follow Heathcock's *trans*-amidation procedure applied in his model study[45] as shown to close the B-ring (Scheme 3). Reduction of adduct **27** with

(39) (a) Smith, J. D. *Synthesis* **1984**, 629. (b) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503.

(40) (a) Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Fujii, N.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 652. (b) Wipf, P.; Fritch, P. C. *J. Org. Chem.* **1994**, *59*, 4875.

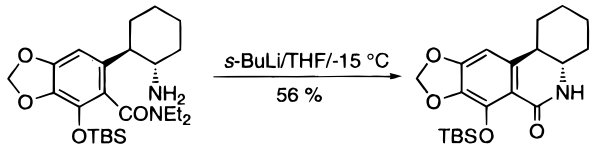
(41) (a) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(42) See also for the lithiation of diethylamides: Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34.

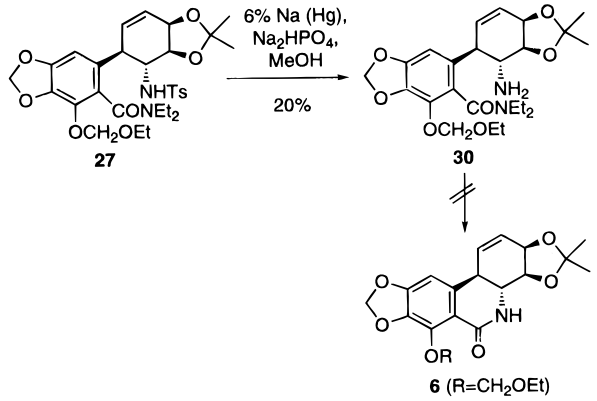
(43) Astley, S. T.; Stephenson, G. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1953.

(44) Lipshutz, B. H.; Kozlowski, J. Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305.

(45) Transamidation according to Heathcock:[18c]



Scheme 3

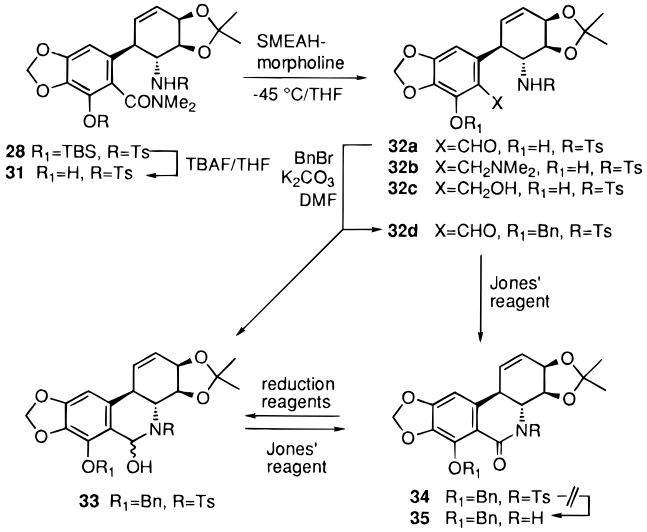


sodium amalgam[46] gave the free amine **30** in 20% yield, which was subjected to a variety of conditions to accomplish the desired ring closure to lactam **6** (R = CH_2OEt). All these efforts met with failure, most likely because of the greatly enhanced acidity of C10b hydrogen as compared to Heathcock's model compound,[45] leading to elimination and epimerization.

The benzamide proved exceptionally resistant to transformation into a group more amenable to cyclization onto the amine or tosylamide. Attempts to hydrolyze or reduce this amide met with complete failure.[51] The presence of large groups in both *ortho* positions was viewed as the main reason for failure to manipulate this group. Other *ortho*-metalation procedures, such as the method of Comins et al.[57] and the recently reported *ortho*-metalation of lithium benzoates,[58] were also attempted but did not afford the desired products of aziridine opening.

(b) Reductive Route. Literature reports indicate that *N*,*N*-dimethylbenzamides reduce more easily than the corresponding diethyl derivatives.[59] However, reduction of amide **28** under conditions applied to **27** also failed. We assumed that the smaller phenol-protecting group would allow easier approach of reagents to the amide. Thus, the reduction of methoxy derivative **29** (Table 1) smoothly afforded the corresponding tertiary amine as the sole product. The sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH, or Red-Al) reduction of the free phenol **31**, obtained by TBAF desilylation of **28**, initially gave the desired aldehyde **32a**, together with the overreduced amine **32b** and alcohol **32c** (Scheme 4). Modifying SMEAH

Scheme 4



with 1 equiv of morpholine[60] and performing the reduction at −45 °C afforded chiefly aldehyde **32a** with only a trace of **32b**. Phenol **32a** was protected as its benzyl ether, formed as a mixture of aldehyde **32d** and hemiaminal **33**. Oxidation of this mixture with Jones reagent provided **34**, which could not be detosylated to **35** with a variety of reagents including sodium amalgam,[46] sodium naphthalenide,[61] and SmI_2,[62] but formed the hemiaminal **33** instead. We believe that the lactam in **34** is somewhat strained, thus favorizing rehybridization of the carbonyl carbon to the sp^3 state. At this point, the removal of the tosyl group prior to the cyclization to the lactam seemed logical.

During all these attempts, we observed that adducts **27** (R_1 = CH_2OEt) and **28** (R_1 = TBS) engage in atropisomerism, as shown in Figure 4. The cuprate addition generates solely the β-atropisomer, which isomerizes to the α-isomer during workup and chromatography. The α-isomer shows hydrogen bonding between the sulfonamide NH and the carboxamide carbonyl, evidenced by the 3 ppm downfield shift of the NH in the ^{1}H-NMR spectrum. Three possibilities exist for the structure of the β-isomer ($\beta1-\beta3$), since atropisomerism is possible not only around the C10a−C10b bond but also for the *o*,*o*′-disubstituted aromatic amide.[63] These findings provide an explanation for the complete lack of reactivity of the C1−C2 olefin toward epoxidation: The carboxamide in the more stable α-form severely restricts approach of reagents to the α-face of the cyclohexene in **27** or **28**. In addition, the deactivation by the flanking allylic ether and aromatic moiety also may be partially responsible for this lack of reactivity.

(c) Successful Route. In an attempt to reduce the tosyl group before closure to the lactam, we returned to adduct **28** and acylated the tosylamide moiety with $(BOC)_2O$ following a report on the decreased reduction potential of acyltosylamides[64] and their easy reduction to carbamates.[49b] Treatment of **28** with *s*-BuLi at 0 °C and reaction with $(BOC)_2O$ gave a mixture of at least three atropisomers, **36**, as evidenced by ^{1}H-NMR. It was subsequently shown that **28**α (Figure 4) was much slower

(46) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477. Sodium/ammonia,[47] sodium/naphthalene,[48] and other conditions reported for the cleavage of tosylamides[49,50] were ineffective.

(47) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311.

(48) Vigneud, V. Du.; Behrens, O. K. *J. Biol. Chem*. **1937**, *117*, 27.

(49) (a) Roemmele, R, C.; Rapoport, H. *J. Org. Chem.* **1988**, *53*, 2367. (b) Singer, S. P.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1448. (c) Hamada, T.; Nishida, A.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 140.

(50) Martens, J.; Scheunemann, M. *Tetrahedron Lett.* **1991**, *32*, 1417.

(51) Among others, the following reagents were attempted: KO*t*Bu/H_2O/THF,[52] $LiAlH_4$,[53] DIBAL-H/BuLi,[54] SMEAH (sodium bis(methoxyethoxy)-aluminum hydride),[53,55] $LiEt_3BH$.[56]

(52) Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc*. **1976**, *98*, 1275.

(53) Brown, H.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089.

(54) Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1717.

(55) Brown, H.; Tsukamoto, A. *J. Am. Chem. Soc.* **1959**, *81*, 502.

(56) Sibi, M. P.; Shankaran, K.; Alo, B. I.; Hahn, W. R.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 2933.

(57) (a) Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979. (b) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1983**, *24*, 5465. (c) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078.

(58) Mortier, J.; Moyroud, J.; Bennetau, B.; Cain, P. A. *J. Org. Chem.* **1994**, *59*, 4042.

(59) Brown, H. C.; Kim, S. C. *Synthesis* **1977**, 635.

(60) Kanazawa, R.; Tokoroyama, T. *Synthesis* **1976**, 526.

(61) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792.

(62) Vedejs, E.; Lin, S. *J. Org. Chem.* **1994**, *59*, 1602.

(63) (a) We thank Dr. Jonathan Clayden, University of Manchester, for bringing this possibility to our attention. (b) For a recent article describing atropisomerism in substituted biaryls, see: Kamikawa, K.; Watanabe, T.; Uemura, M. *Synlett* **1995**, 1040.

(64) (a) Cottrell, P. T.; Mann, C. K. *J. Am. Chem. Soc.* **1971**, *93*, 3579. (b) Horner, L.; Singer, R. J. *Tetrahedron Lett.* **1969**, 1545.

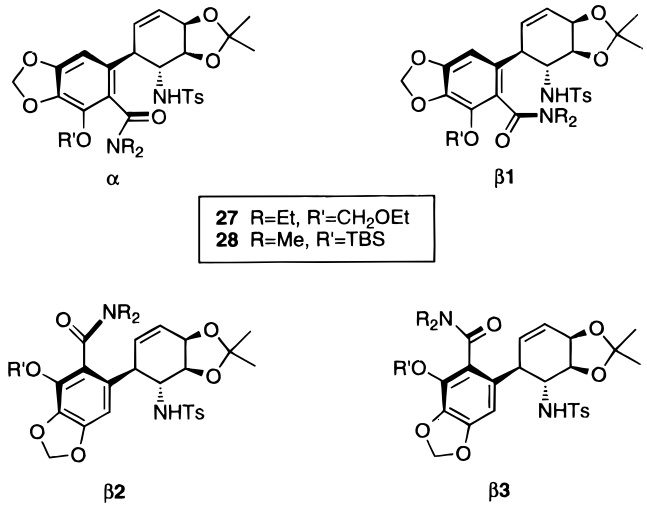
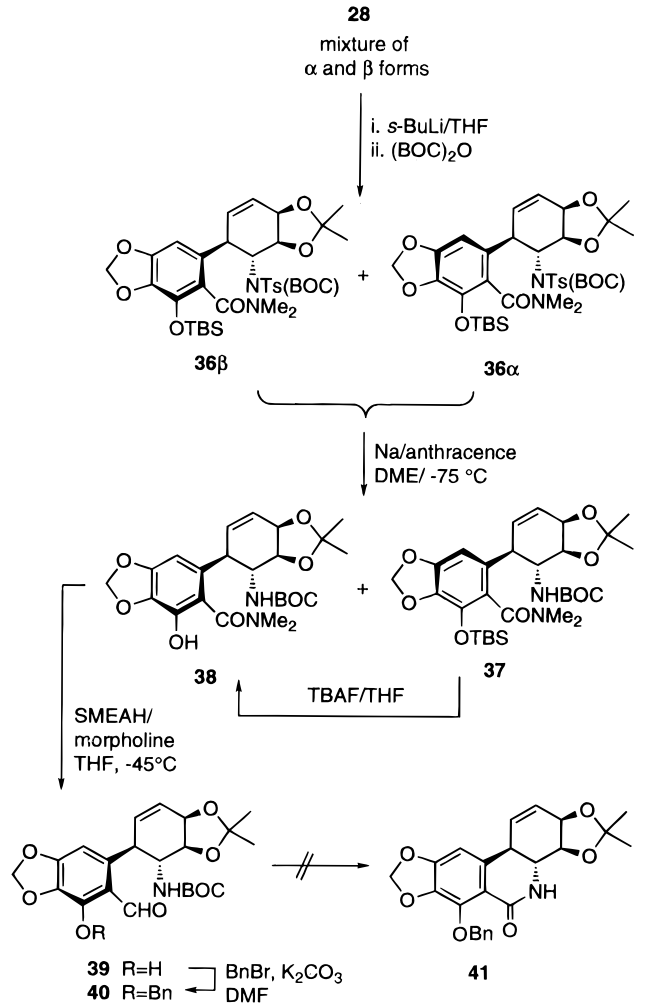


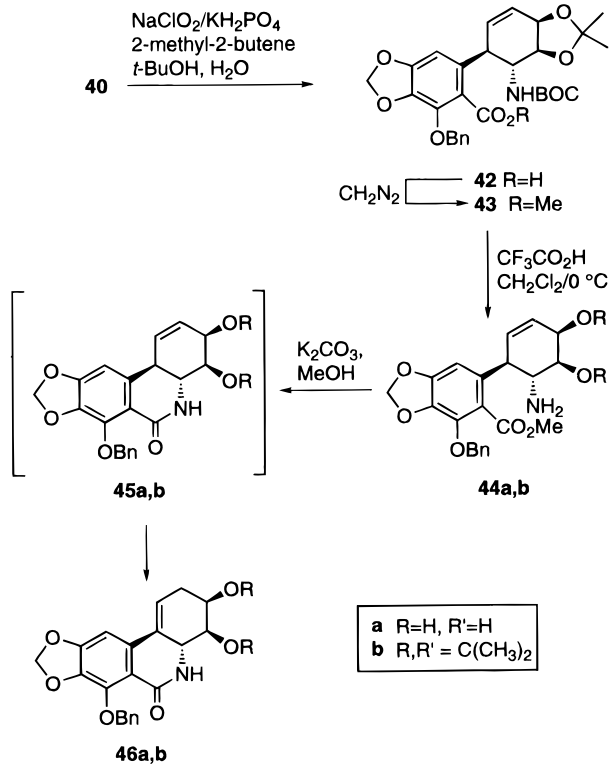
Figure 4. Atropoisomerism of amides **27** and **28**.

Scheme 5



to acylate to **36**, presumably because of steric congestion around the NH of the tosylamide situated on the α-face and hindered by the dimethylamide moiety. The mixture of atropisomers was detosylated using Na/anthracene/DME[65] to afford a mixture of **37** and **38** in a combined 82% yield. The ratio of these two products depended on the α/*β* ratio of atropisomers **36** used in the reaction, the α-form being concomitantly desilylated to afford **38**. The equilibration of **37***β* to **37**α was slow at −78 °C and allowed isolation of **37**, which was desilylated with TBAF to yield **38** in 93%, Scheme 5.

Scheme 6



Reduction of **38** to aldehyde **39** as outlined above (72% yield) and protection of the phenol with benzyl bromide (83% yield) afforded **40** (Scheme 5). Oxidative cyclization of this aldehyde was then attempted under a variety of conditions. Unlike the aldehyde **32d**, compound **40** did not cyclize to the tosyllactam **41** with Jones reagent; however, sodium chlorite oxidation[66,67] provided a quantitative yield of acid **42**, which was immediately methylated to afford **43** (Scheme 6). Neither the acid nor the ester cyclized under a variety of conditions—we judged this reluctance to be the function of an unfavorable conformation of the bulky BOC-protected amine and the comparative rigidness of the C-ring bearing the acetonide.

It appeared to be necessary that the C-ring olefin should be fully functionalized prior to the *trans*-amidation. The presence of the olefin proved troublesome because it increased the acidity of hydrogen at C10b and also appeared to restrict the conformational flexibility of the C-ring. Efforts to epoxidize the C1−C2 olefin under a host of conditions met with no success, save the observation of complex mixtures of products.[68]

We therefore attempted to remove the BOC group and retain the acetonide at the same time in order to achieve the ring closure (Scheme 6). In an attempt to selectively cleave the acetonide, treatment of **43** with CF_3CO_2H under carefully monitored conditions revealed a mixture of **44a**,**b**. Cyclization of the mixture of amino esters under precedented conditions[13c,d] smoothly gave a mixture of lactams **45a**,**b**, confirming the supposition relating to the unfavorable conformation of the

(65) Johnson, C. R.; Lavergne, O. *J. Org. Chem.* **1989**, *54*, 986.

(66) Bal. B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(67) (a) Hillis, L. R.; Ronald, R. C. *J. Org. Chem.* **1985**, *50*, 471. (b) Ley, S. V.; Madin, A.; Monck, N. J. T. *Tetrahedron Lett.* **1993**, *34*, 7479.

(68) Conditions attempted: *m*-CPBA, dimethyldioxirane,[69] H_2O_2/urea/$(CF_3CO)_2O$,[70] $MO(CO)_6$.[71]

(69) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.

(70) Copper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533.

(71) Duke, R. K.; Rickards, R. W. *J. Org. Chem.* **1984**, *49*, 1898.

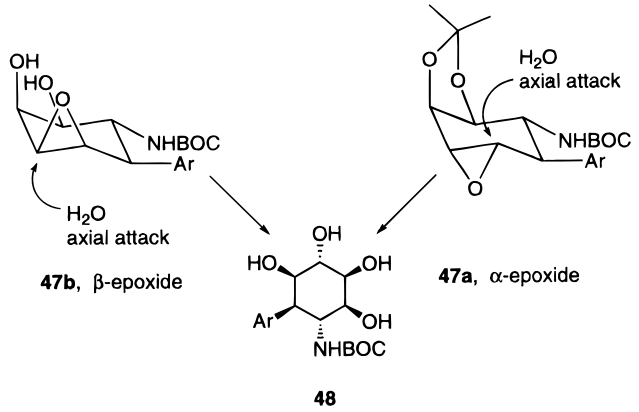


Figure 5. Diaxial opening of α- and *β*-oxiranes.

BOC-protected amine toward cyclization. Unfortunately, under these cyclization conditions, the olefin migrated to the conjugated position, giving the C2 deoxynarciclasine structures **46a**,**b**.

A fortuitous change in strategy presented itself upon analysis of the conformations of the α- and *β*-epoxides of type **47**—the assumption of *trans*-diaxial opening of either substrate allows the prediction of a doubly degenerate pathway to the correct C-ring configuration of pancratistatin in **48**, as shown in Figure 5. To test this assumption, ester **43** was first subjected to acidic conditions to remove the acetonide (HOAc/H_2O/THF 2:1:1, 60 °C, 73%), and the free diol **49** was epoxidized under Sharpless and Michaelson's conditions (*t*-BuOOH/VO(acac)$_2$, 57%),[72] as shown in Scheme 7. With the *β*-epoxide **50** in hand, we turned to the conditions of epoxide hydrolysis reported for D-*chiro*-inositol synthesis.[23] When **50** was heated in refluxing water in the presence of a catalytic amount of sodium benzoate, a remarkable series of events occurred. First, the BOC group was cleaved, instead of epoxide opening, presumably by thermal retro-ene-type cleavage,[73] giving the epoxylactam **51**, as evidenced by NMR analysis of reaction aliquots. To our knowledge, this is the first example of a thermal cleavage of the BOC group in H_2O. Second, after approximately 2 h, the hydrolysis of the epoxide started, cleanly forming the benzyl-protected pancratistatin **52**. At this point, ^{1}H-NMR showed four signals corresponding to the C-ring oxomethines. The doublet at 2.89 ppm (J = 11 Hz) was the most characteristic of these signals and confirmed the correct configuration of H10b and the *trans* relationship of H10b and H4a.

Third, the debenzylation of **52** to (+)-pancratistatin **4** was observed. After 6 days, this most unusual reaction thus furnished the title alkaloid in 51% yield from **50**. Alternatively, pure **52**, isolated after 48 h of hydrolysis, was quantitatively hydrogenated to pancratistatin **4** with H_2/Pd(OH)$_2$ in EtOAc. R_f values in several solvent systems, ^{1}H-NMR spectral data, and optical rotation ($[\alpha]^{26}_D = +41°$, *c* 1.0, DMSO; lit.[6c] $[\alpha]^{34}_D = +48°$, *c* 1.0, DMSO) of synthesized pancratistatin matched well with those of an authentic sample.[74] Thus, the first enantioselective synthesis of pancratistatin was achieved, after a somewhat arduous route, in ~2% overall yield for the 14-step sequence (from bromobenzene).

The observed unusual debenzylation reaction of **52** was studied with a model compound (methyl *o*-(benzyloxy)benzoate) without any evidence of cleavage of the benzyl or methyl

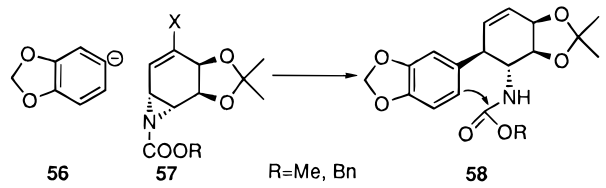


Figure 6.

groups. We therefore speculate that this reaction might be unique to the enolized *β*-ketoamide system present in pancratistatin, in which the formation of the more stable and hydrogen-bonded phenolamide is responsible for driving the reaction to completion. Under the reaction conditions, the formation of *O*-benzyl iminoester by an intramolecular transfer could be considered, although this may be contrary to the Beak postulates.[75]

(d) Second Generation Synthesis: 7-Deoxypancratistatin. The evaluation of our first generation synthesis required solutions to two major problems. The first was the need to eliminate the presence of the benzamide moiety from future synthetic designs, because of the drastic conditions or lengthy manipulations required for its removal. The second was the search for a new aziridine protecting group that would alleviate the problems encountered during the removal of the otherwise convenient[50,76] *N*-tosyl group. A second generation route was conceived on the basis of the assumption that the amide carbon of pancratistatin could also assume the function of the protecting group of the aziridine, as shown in Figure 6. Precedent for such transformation existed in the report by Banwell et al., who used an activated aromatic ring as a nucleophile for an intramolecular amide formation from a carbamate similar to **58**.[18f] In a preliminary investigation, cuprate **59**, derived from 5-bromo-1,3-benzodioxole by metal—halogen exchange (*n*-BuLi, THF, −78 °C, 1 h, then CuCN, 1 h), was condensed with aziridine **7** (BF_3·Et_2O, −78 to −30 °C, 32%) to generate tosylamide **60** (Scheme 8), which was converted to carbamate **62** by a two-step procedure consisting of treatment with *s*-BuLi/$(CH_3OCO)_2O$ (76%) to yield **61**, followed by reduction with sodium/anthracene (73%) as described above. This sequence was subsequently improved by a direct synthesis of **62** via *N*-carbomethoxyaziridine **63**, prepared from diene acetonide **11a** by adaptation of a procedure for carbethoxyaziridination of olefins ($CH_3OCONHOSO_2PhNO_2$, base).[77] The aziridination was not without problems. A large excess of the reagent is required, and the diene **11a** is prone to Diels—Alder dimerization during prolonged reaction times. A summary of yields and conditions is shown in Table 2. Improvements in this procedure will have to be attempted by investigation of different leaving groups on the reagent (trifluoromethanesulfonate, methanesulfonate), as well as various basic conditions for the fragmentation of the reagent. Subsequent debromination of **63** with Bu_3SnH/AIBN/THF afforded aziridine **64** in 40—54% yield, which was reacted with cuprate **59** to afford coupling product **62** (34% yield). The synthesis of **62** was thus achieved in just three steps from acetonide **11a** (five from bromobenzene). We suppose that the low yields in the opening of aziridines **7** and **64** with cuprate **59**, as compared to the formation of the corresponding *N*,*N*-dialkylcarboxamides **27**—**29**, are caused by

(72) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(73) (a) Rawal, V. H.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 19. (b) Wasserman, H. H.; Berger, G. D.; Cho, K. R. *Tetrahedron Lett.* **1982**, *23*, 465.

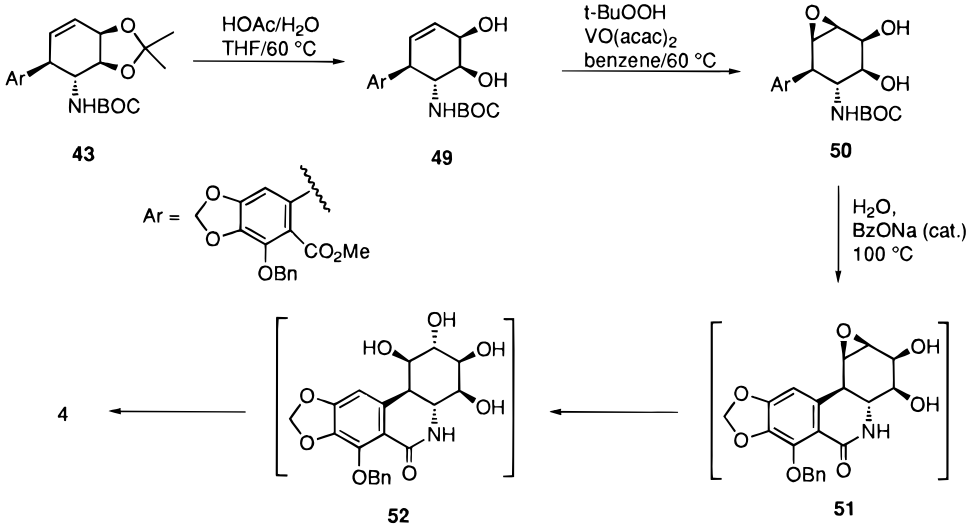
(74) A sample of **4** was kindly provided by Prof. G. R. Pettit of Arizona State University.

(75) Beak, P. *Acc. Chem. Res.* **1992**, *25*, 215.

(76) Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 613.

(77) Methyl carbamate was prepared according to the procedure for the corresponding ethyl carbamate: Lwowski, W.; Maricich, T. J.; Mattingly, T. W., Jr. *J. Am. Chem. Soc.* **1963**, *85*, 1200. For the aziridination, compare: (a) Lwowski, W.; Maricich, T. J. *J. Am. Chem. Soc.* **1965**, *87*, 3630. (b) Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Tetrahedron Lett.* **1993**, *34*, 4353.

Scheme 7



Scheme 8

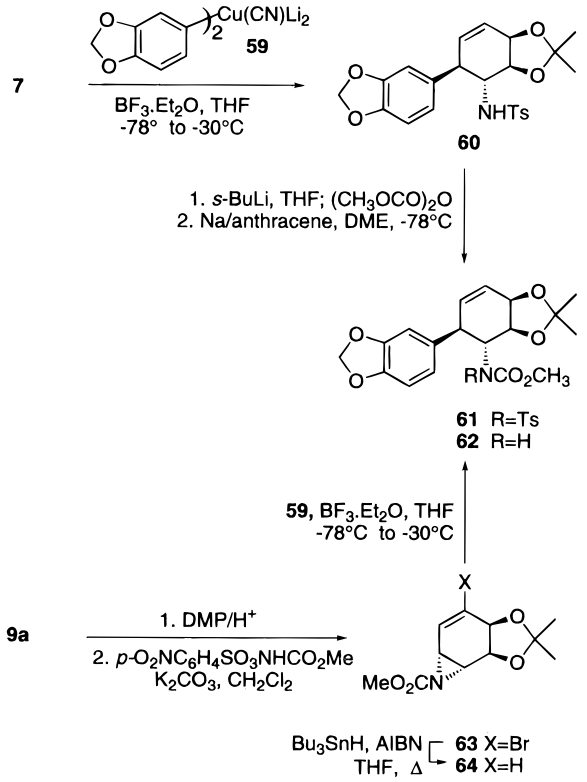


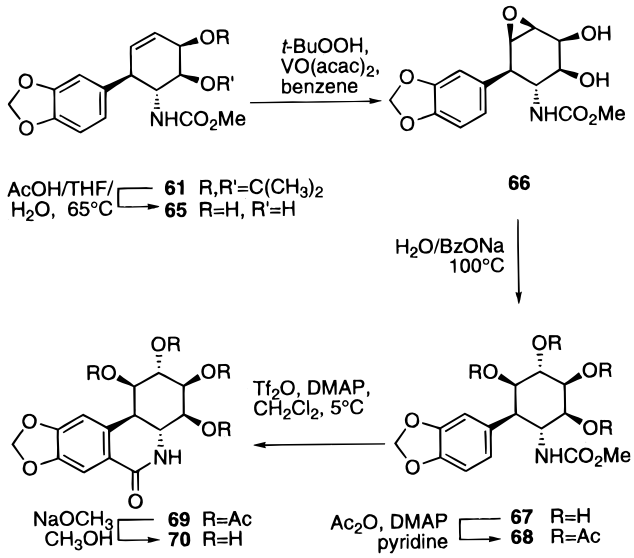
Table 2. Synthesis of Aziridine **63**

conditions	p-NO_2PhSO_2O-$NHCO_2CH_3$ (equiv)	yield[a] (%)	11a[b] (% remaining)
K_2CO_3/rt	0.66	14.3	70
K_2CO_3/rt	2	22	50
K_2CO_3/0 °C	2	23	50
K_2CO_3/18-crown-6	2	37	20
K_2CO_3/18-crown-6	3	44	0
Et_3BnNCl, $NaHCO_3/H_2O$	2	38	40
Et_3BnNCl, $NaHCO_3/H_2O$	3.7	51	10

[a] From diene **11a**. [b] Amount of remaining diene **11a** after disappearance of the reagent. Estimated by TLC.

the low stability of the lithiated species formed during the metal−halogen exchange reaction, which therefore cannot be warmed to −30 °C for reaction with CuCN, as described above. This presumably led to incomplete cuprate formation. Our

Scheme 9



observations correspond to similar difficulties experienced by Trost and Pulley in their synthesis of pancratistatin.[16] The coupled product **62** was converted to epoxydiol **66** (HOAc/THF/H_2O, 65 °C, 94% (forming **65**), then *t*-BuOOH, $VO(acac)_2$, benzene, 70 °C, 85%) and ultimately to the tetraol **67** by refluxing in water containing a catalytic amount of sodium benzoate (82%, Scheme 9), following our previously successful route. Peracetylation to **68** (84%) was followed by a triflate-catalyzed Bischler−Napieralski-type cyclization analogous to that of Banwell et al.,[18f] which provided **69** in 61% yield. This material compared well with the acetate reported by Keck et al.[17] and was deprotected (NaOMe/MeOH, 72%) to 7-deoxypancratistatin (**70**) [$[\alpha]^{25}_D = +78.5°$ (*c* 0.75, DMF); lit.[13c] $[\alpha]^{20}_D = +82.6°$ (*c* 1.1, DMF)] to complete the synthesis in 11 steps from bromobenzene and an overall yield of 3%. In the next generation attempt, redundant steps as well as the yields of individual steps and the development of more efficient aziridination reagents will have to be addressed.

Conclusion and Outlook

A new approach to pancratistatin via enantiomerically pure azabicyclo[4.1.0]heptenes derived from bromobenzene was completed. The first generation synthesis was, of necessity, quite exploratory in nature and was plagued with a number of

problems in functional group manipulation. The first and the major of these was the incorporation into the synthetic scheme of *ortho*-metalation. Unfortunately, the best directing group for this purpose proved also the most robust toward any further transformations. To date, there are no mild procedures available for hydrolysis of benzamides, and the main area for any improvements in the second generation synthesis, therefore, was a new way of generating the organometallic species for aziridine opening without relying on the benzamide group. The second major improvement required for the generality of the synthetic scheme was the preparation of aziridines with groups that are either more easily removed or play a further role in the assembling of the carbon skeleton (i.e., CO_2Me). The 14-step approach (from bromobenzene) to pancratistatin (overall yield 2%) and the improved 11-step route to deoxypancratistatin (overall yield 3%) described in this article represent a solid basis for solving the supply problem for pancratistatin and its congeners upon further optimization. The evolution of the multigeneration design of pancratistatin synthesis also allows for the access to the (−)-enantiomer of pancratistatin for evaluation of potential biological activity. Because the C-ring of pancratistatin contains symmetry elements identical to those found in the enantiomers of pinitol[78] and D-*chiro*-inositol,[23] it lends itself to the same design features with respect to the antipodal compound. The concept of "latent symmetry" [27a,77] as it pertains to the preparation of (−)-pancratistatin has recently been disclosed[79] and requires only that the order of attachment of the aryl moiety be regulated by employing either the vinylaziridine (in the approach to the (+)-enantiomer) or the vinyloxirane (in the approach to the (−)-enantiomer). These and other concerns are currently being addressed in the context of the next generation synthesis of this important alkaloid and some of its congeners, as well as its unnatural derivatives, and will be reported in due course.

Experimental Section

All reactions were carried out in an argon atmosphere with standard techniques for the exclusion of air and moisture. Glassware used for moisture-sensitive reactions was flame-dried under vacuum. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane, DMF, toluene, and TMEDA were distilled from calcium hydride. Flash column chromatography was performed on Merck silica gel (grade 60, 230−400 mesh). Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

General Procedure for the Formation of Aziridines 15a,b. Method A (via PhI═NTs). A mixture of 5 equiv of (1*S*,2*S*)-3-halo-1,2-(isopropylidenedioxy)cyclohexa-3,5-diene (**11a**,**b**), 1 equiv of *p*-(tosylimino)phenyliodinane (PhI═NTs), and 0.08 equiv of $Cu(acac)_2$ in 10 mL $mmol^{-1}$ of CH_3CN was stirred at room temperature. After consumption of PhI═NTs, the mixture was filtered through a pad of silica gel and concentrated in vacuo. The crude product was recrystallized from hexane/ethyl acetate.

(1*R*,4*S*,5*S*,6*R*)-3-Bromo-4,5-(isopropylidenedioxy)-7-(4′-methylphenylsulfonyl)-7-azabicyclo[4.1.0]hept-2-ene (15a). From **11a** (10.52 g, 45.5 mmol), **15a** (1.97 g, 54% from PhI═NTs) was obtained according to method A (reaction time 1 h): white solid; R_f 0.48 (hexane/EtOAc 3:1); mp 206−207 °C (hexane/EtOAc); $[\alpha]^{25}_D$ −33.7° (*c* 1.05, $CHCl_3$); IR (KBr) ν 3060, 2980, 2900, 1640, 1590 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.82 (dm, J = 8.2 Hz, 2H), 7.37 (dm, J = 8.2 Hz, 2H), 6.35 (dd, J = 5.0, 1.2 Hz, 1H), 4.64 (ddd, J = 6.5, 1.7, 0.6 Hz, 1H), 4.34 (dd, J = 6.5, 1.2 Hz, 1H), 3.44 (dd, J = 6.5, 1.7 Hz, 1H), 3.28 (dd, J = 6.5, 5.0 Hz, 1H), 2.46 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.1 (C), 134.1 (C), 129.92 (2CH), 129.89 (C), 127.9 (2CH), 123.9 (CH), 111.5 (C), 73.8 (CH), 71.4 (CH), 37.4 (CH), 36.4 (CH), 27.4 (CH_3), 26.1 (CH_3), 21.6 (CH_3); MS (CI+) *m/z* (relative intensity) 400 ($(M + H)^+$, 2), 384 (1.5), 372 (1.5), 344 (23), 314 (12), 262 (29), 244 (11), 228 (7), 187 (29), 155 (100), 108 (60), 91 (31); HRMS (CI+) calcd for $C_{16}H_{18}BrNO_4S$+H 400.0218, found 400.0231.

(1*R*,4*S*,5*S*,6*R*)-3-Chloro-4,5-(isopropylidenedioxy)-7-(4′-methylphenylsulfonyl)-7-azabicyclo[4.1.0]hept-2-ene (15b). The compound was obtained from **11b** in 20.5% yield (from PhI═NTs) according to method A (reaction time 18 h): R_f 0.43 (hexane/EtOAc 3:1); white solid; mp 202−203 °C (hexane/EtOAc); $[\alpha]^{25}_D$ −75.5° (*c* 1.54, $CHCl_3$); IR (KBr) ν 3060, 2980, 2910, 1645, 1590, 1410 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.82 (dm, J = 8.2 Hz, 2H), 7.37 (dm, J = 8.2 Hz, 2H), 6.09 (dd, J = 4.9, 1.2 Hz, 1H), 4.65 (ddd, J = 6.6, 1.8, 0.7 Hz, 1H), 4.30 (dd, J = 6.6, 1.0 Hz, 1H), 3.44 (dd, J = 6.5, 1.8 Hz, 1H), 3.34 (dt, J = 0.6, 6.5 Hz, 1H), 2.46 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 145.3 (C), 138.06 (C), 134.41 (C), 130.06 (2CH), 128.07 (2CH), 119.96 (CH), 111.72 (C), 73.04 (CH), 71.68 (CH), 37.17 (CH), 36.74 (CH), 27.51 (CH_3), 26.07 (CH_3), 21.74 (CH_3); MS (CI+) *m/z* (relative intensity) 356 ($(M + H)^+$, 3), 340 (6), 298 (27), 262 (23), 200 (36), 155 (100), 142 (36), 114 (60), 91 (43). Anal. Calcd for $C_{16}H_{18}ClNO_4$: C, 54.00; H, 5.12; N, 3.94. Found: C, 53.92; H, 5.12; N, 3.86.

Method B (via Bromohydrin 12a,b). To (1*S*,2*S*)-3-chlorocyclohexa-3,5-diene-1,2-diol (**9b**, 5.00 g, 34.11 mmol) in acetone (20 mL, HPLC grade) were added 2,2-dimethoxypropane (30 mL) and *p*-toluenesulfonic acid monohydrate (175 mg). After 20 min at room temperature, TLC analysis indicated that no more diol **9b** remained in the reaction mixture. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated. The crude acetonide **11b** was placed under high vacuum for 15 min, and then 1,2-dimethoxyethane (140 mL) and distilled H_2O (35 mL) were added. This solution was cooled to −10 °C in an ice/NaCl bath, and NBS (1.6 equiv based on **9b**, 54.6 mmol, 9.72 g) was added. The mixture was stirred at 0 °C for 10 h, at which point the reaction appeared complete by TLC. To the solution was added brine (100 mL), and the mixture was extracted with EtOAc. The EtOAc extracts were combined and dried with $MgSO_4$. Removal of volatiles gave 4.20 g of crude product, which was dissolved in hot hexanes and decanted to another flask. Upon cooling, a white precipitate formed [this was an undesired diastereomeric bromohydrin (270 mg, 0.952 mmol, 2.8% yield from diol **9b**) which was difficult to remove by chromatography, R_f 0.30 (hexane/EtOAc 4:1)]. The solution was again decanted, hexanes were removed to give an oily residue, and column chromatogaphy was performed using acetone/CH_2Cl_2 (1:50) to give the desired bromohydrin **12b** (2.97 g, 10.5 mmol, 30.7% from diol **9b**) as a clear oil: R_f 0.35 (hexane/EtOAc 4:1); mp 43−47 °C; $[\alpha]^{23}_D$ + 17.2° (*c* 1.16, $CHCl_3$); IR (neat) ν 3485, 3025, 3000, 2940, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.10 (d, J = 4.4 Hz, 1H), 4.61 (dm, J = 2.27 Hz, 2H), 4.35 (dddm, J = 9.1, 4.4, 4.2 Hz, 1H), 4.27 (m, 1H), 2.88 (d, J = 9.1 Hz, 1H), 1.51 (s, 3H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 133.1 (C), 126.9 (CH), 112.2 (C), 78.1 (CH), 75.3 (CH), 70.2 (CH), 48.6 (CH), 27.9 (CH_3), 26.4 (CH_3); MS (CI, 70 eV) *m/z* (relative intensity) 285 (MH^+, 0.25), 283 (MH^+, 0.4), 269 (40), 267 (38), 209 (65), 207 (50). Anal. Calcd for $C_9H_{12}BrClO_3$: C, 38.12; H, 4.27. Found: C, 38.00; H, 4.26.

The bromohydrin was treated with excess sodium azide in DMSO, affording the azido alcohol **13b** in 87% yield: $[\alpha]^{23}_D$ −110° (*c* 1.3, $CHCl_3$); IR (neat) ν 3485, 3025, 3000, 2940, 2110, 1650, 1380, 1220, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.80 (d, J = 2.1 Hz, 1H), 4.58 (m, 2H), 4.28 (dt, J = 8.7, 1.8 Hz, 1H), 3.82 (td, J = 7.5, 2.1 Hz, 1H), 2.55 (d, J = 7.5 Hz, 1H), 1.43 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 134.2 (C), 124.0 (CH), 111.2 (C), 76.7 (CH), 76.5 (CH), 72.1 (CH), 61.0 (CH), 27.4 (CH_3), 26.4 (CH_3); MS (CI+) *m/z* (relative intensity) 246 (35, MH^+), 230 (40), 218 (100), 182 (90), 160 (50). Anal. Calcd for $C_9H_{12}ClN_3O_3$: C, 44.00; H, 4.92; N, 17.10. Found: C, 40.08; H, 4.92; N, 17.10.

Analogous procedures provided, via the bromohydrin, bromoazido alcohol **13a**: $[\alpha]^{23}_D$ −93.7° (*c* 2.5, $CHCl_3$); IR ($CHCl_3$) ν 3420, 3025, 3000, 2940, 2110, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.03 (d, J = 2.1 Hz, 1H), 4.63 (dd, J = 5.2, 2.1 Hz, 1H), 4.53 (dd, J = 5.2, 2.5 Hz, 1H), 4.21 (dt, J = 8.6, 2.0 Hz, 1H), 3.82 (td, J = 8.7, 2.5 Hz, 1H), 2.60 (d, J = 7.5 Hz, 1H), 1.44 (s, 3H), 1.43 (s, 3H); ^{13}C NMR ($CDCl_3$)

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δ 128.0 (CH), 125.0 (C), 111.0 (C), 78.0 (CH), 76.6 (CH), 71.7 (CH), 61.5 (CH), 27.4 (CH_3), 26.4 (CH_3); MS (CI+) *m/z* (relative intensity) 292 (70, MH^+), 290 (70, MH^+), 249 (55), 247 (55), 191 (90), 189 (90); HRMS calcd for $C_9H_{12}BrN_3O_3$+H 290.0140, found 290.0141.

Azido alcohols **13** were converted to *N*-tosylaziridines **15** by a mesylation, reduction/elimination, and tosylation sequence without isolation of any further intermediates (30−40% yield).

(1*R*,4*R*,5*S*,6*R*)-4,5-(Isopropylidenedioxy)-7-(4′-methylphenylsulfonyl)-7-azabicyclo[4.1.0]hept-2-ene (7). A mixture of **15a** (10.1 g, 25.2 mmol), tributyltin hydride (11.6 g, 39.8 mmol), and AIBN (413 mg) in THF (200 mL) was stirred at reflux. After 2 h, the mixture was washed with excess saturated KF aqueous solution, and the organic layer was separated and dried over Na_2SO_4. Removal of solvent and column chromatography (silica gel, hexane/EtOAc 3:1) afforded **7** (6.32 g, 78%): R_f 0.37 (hexane/EtOAc 3:1); white solid; mp 106−107 °C (hexane/EtOAc); $[\alpha]^{25}_D$ −183° (*c* 2.3, $CHCl_3$); IR (KBr) ν 3040, 2970, 1601 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 5.95 (ddd, J = 10.2, 4.4, 1.7 Hz, 1H), 5.76 (dd, J = 10.2, 2.4 Hz, 1H), 4.54 (dd, J = 6.7, 1.5 Hz, 1H), 4.39 (dt, J = 6.7, 1.0 Hz, 1H), 3.37 (dd, J = 6.5, 1.8 Hz, 1H), 3.27 (dd, J = 6.5, 4.7 Hz, 1H), 2.46 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 144.8, 134.6, 132.4, 129.8 (2C), 127.9 (2C), 120.9, 110.7, 70.6, 69.3, 36.4, 35.5, 27.8, 26.1, 21.6; MS (CI+) *m/z* (relative intensity) 322 ($(M + H)^+$, 12), 292 (11), 264 (100), 236 (44), 155 (80); HRMS (CI+) calcd for $C_{16}H_{19}NO_4S$+H 322.1113, found 322.1106. Anal. Calcd for $C_{16}H_{19}NO_4S$: C, 59.80; H, 5.96; N, 4.36. Found: C, 59.90; H, 5.99; N, 4.36.

(1*R*,4*S*,5*R*,6*S*)-*N*-[4-Methyl-5,6-(isopropylidenedioxy)cyclohex-2-enyl]-(4′-methylphenyl)sulfonamide (21). To a suspension of CuCN (67 mg, 0.75 mmol) in THF (15 mL) was added a solution of methyllithium in hexanes (1.07 mL, 1.4 M, 1.50 mmol) slowly at −78 °C. After 5 min, the turbid suspension was allowed to warm to −30 °C, stirred for 10 min, and recooled to −78 °C. Compound **7** (200 mg, 0.62 mmol), dissolved in THF (5 mL), was added, precooled, by canula, followed by $BF_3{\cdot}Et_2O$ (116 mg, 0.82 mmol). The reaction is was stirred for 2 h at −78 °C, after which TLC indicated no more aziridine. The mixture was quenched with dilute aqueous ammonium chloride containing ammonia (pH 9, 10 mL), warmed to room temperature, and extracted with EtOAc (3 × 20 mL). Drying over sodium sulfate, concentration in vacuo, and chromatography (hexane/EtOAc 2:1, R_f 0.36) afforded **21** (78 mg, 0.23 mmol, 37%): white crystalline solid; R_f 0.36 (hexane/EtOAc 2:1); mp 122−123 °C (hexane/EtOAc); $[\alpha]^{25}_D$ +2.5° (*c* 1.3, CH_3OH); IR (KBr) ν 3298, 1417, 1379 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 5.67 (dt, J = 9.5, 2.8 Hz, 1H), 5.53 (dt, J = 9.5, 2.8 Hz, 1H), 4.82 (d, J = 5.7 Hz, 1H), 3.85 (t, J = 6.9 Hz, 1H), 3.77 (dd, J = 7.2, 5.8 Hz, 1H), 3.59 (m, 1H), 2.42 (s, 3H), 2.19 (m, 1H), 1.23 (s, 3H), 1.185 (d, J = 7.3 Hz, 3H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5 (C), 136.9 (C), 133.5 (CH), 129.5 (2CH), 128.0 (CH), 127.5 (2CH), 109.0 (C), 79.1 (CH), 78.2 (CH), 54.9 (CH), 34.7 (CH), 27.1 (CH_3), 25.0 (CH_3), 21.5 (CH_3), 19.1 (CH_3); MS (CI+) *m/z* (relative intensity) 338 (4, MH^+), 280 (23), 172 (32), 109 (100); HRMS (FAB) calcd for $C_{17}H_{23}NO_4S$+H 338.1426, found 338.1438. Anal. Calcd for $C_{17}H_{23}NO_4S$: C, 60.51; H, 6.87; N, 4.15. Found: C, 60.59; H, 6.93; N, 4.08.

(1*R*,2*R*,5*R*,6*S*)-*N*-[5,6-(Isopropylidenedioxy)-2-phenylcyclohex-3-enyl]-(4′-methylphenyl)sulfonamide (22). A suspension of dry CuCN (161 mg, 1.80 mmol) in THF (20 mL) was treated with phenyllithium solution (1.8 M, 2.0 mL) at −78 °C. The mixture was warmed to −10 °C with stirring to dissolve CuCN, and after cooling to −78 °C, a solution of **7** (182 mg, 0.57 mmol) in THF (2 mL) was added, followed by $BF_3{\cdot}Et_2O$ (0.22 mL). The mixture was stirred at −78 °C for 3 h and then quenched with aqueous NH_4Cl solution (5 mL, containing ammonia, pH 8). After being stirred at room temperature for 30 min, the mixture was extracted with EtOAc (3 × 15 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel, eluting with 10:1 $CHCl_3$/acetone, to give **22** (159 mg, 70%): R_f 0.36 (hexanes/EtOAc 2:1); white solid; mp 165−167 °C ($CHCl_3$/acetone); $[\alpha]^{25}_D$ −17.8° (*c* 1.07, $CHCl_3$); IR (KBr) ν 3300, 3030, 2890, 1590 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.42 (dm, J = 8.3 Hz, 2H), 7.24 (m, 3H), 7.09 (m, 4H), 6.00 (ddd, J = 9.9, 3.5, 2.7 Hz, 1H), 5.87 (dd, J = 9.9, 1.5 Hz, 1H), 4.67 (br t, J = 4.7 Hz, 1H), 4.52 (d, J = 8.2 Hz, 1H), 4.14 (dd, J = 9.0, 6.0 Hz, 1H), 3.65 (q, J = 9.0 Hz, 1H), 3.24 (dq, J = 8.6, 1.9 Hz, 1H), 2.38 (s, 3H), 1.44 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.4 (C), 140.1 (C), 138.6 (C), 134.6 (CH), 129.1 (2CH), 128.61 (2CH), 128.57 (2CH), 127.14 (CH), 126.96 (2CH), 124.2 (CH), 109.93 (C), 77.58 (CH), 72.16 (CH), 58.95 (CH), 47.70 (CH), 27.79 (CH_3), 25.83 (CH_3), 21.41 (CH_3); MS (CI+) *m/z* (relative intensity) 400 (MH^+, 15), 370 (23), 342 (99), 312 (19), 171 (100); HRMS calcd for $C_{22}H_{25}NO_4S$+H 400.1582, found 400.1568. Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51. Found: C, 66.05; H, 6.36; N, 3.49.

***N*,*N*-Dimethyl-4-[(*tert*-butyldimethylsilyl)oxy]-1,3-benzodioxole-5-carboxamide (25b).** *tert*-Butyldimethylsilyl chloride (1.73 g, 11.5 mmol) in CH_2Cl_2 (10 mL) was added to a solution of *N*,*N*-dimethyl-4-hydroxy-1,3-benzodioxole-5-carboxamide (**24b**,[24] 2.0 g, 9.56 mmol) and imidazole (2.0 g, 29 mmol) in CH_2Cl_2 (60 mL). The solution was stirred for 12 h at room temperature, during which time a white solid precipitated. The mixture was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography on silica (hexane/EtOAc 1:1) afforded **25b** (2.95 g, 95%) as a semicrystalline solid: R_f 0.60 (hexane/EtOAc 1:1); IR (KBr) ν 2920, 2870, 2840, 1610, 1460 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.75 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 5.92 (s, 2H), 3.03 (s, 3H), 2.87 (s, 3H), 0.94 (s, 9H), 0.16 (br s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9 (C), 149.3 (C), 137.0 (C), 135.5 (C), 124.9 (C), 121.4 (CH), 102.8 (CH), 101.0 (CH_2), 38.2 (CH_3), 34.9 (CH_3), 25.4 ($3CH_3$), 18.1 (C), −4.6 ($2CH_3$); MS (CI+) *m/z* (relative intensity) 423 ($(M + H)^+$, 52), 308 (40), 279 (12), 266 (100); HRMS calcd for $C_{16}H_{25}NO_4Si$+H 324.1631, found 324.1623.

***N*,*N*-Diethyl-4-(ethoxymethoxy)-6-{(1*R*,4*R*,5*S*,6*R*)-4,5-(isopropylidenedioxy)-6-[(4′-methylphenylsulfonyl)amino]-2-cyclohexen-1-yl}-1,3-benzodioxole-5-carboxamide (27).** *s*-BuLi in hexane (1.28 M, 10.2 mL) was added to a solution of TMEDA (2.0 mL, 13.25 mmol) in THF (50 mL) at −78 °C. The yellow mixture was stirred for 15 min, and then a solution of amide **25a** (3.55 g, 12.0 mmol) in THF (15 mL) was added, precooled, by cannula. The resulting deep red solution was stirred at −78 °C for 1 h and transferred by cannula to a round-bottom flask charged with CuCN (538 mg, 6.0 mmol). The tannish solution was warmed to −20 °C, furnishing a dark purple solution, which was recooled to −78 °C, and a solution of vinylaziridine **7** (774 mg, 2.4 mmol) in THF (10 mL) was added, followed by $BF_3{\cdot}Et_2O$ (0.74 mL, 6.0 mmol). The reaction mixture was then warmed slowly to room temperature and saturated aqueous NH_4Cl solution (10 mL, containing NH_4OH, pH 8) was added. The mixture was stirred at room temperature for 30 min, the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel eluting with hexane/EtOAc (3:2) (for one atropisomer), followed by hexane/EtOAc (2:3) (for the other atropisomer), to give 724 mg (49%) of **27** as a glassy solid. α-Atropisomer: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.58 (d, J = 6.2 Hz, 1H), 7.51 (d, J = 8.1 Hz, 2H) 7.08 (d, J = 8.1 Hz, 2H), 6.12 (s, 1H), 6.0 (m, 2H), 5.85 (d, J = 1.3 Hz, 1H), 5.72 (d, J = 9.8 Hz, 1H), 5.40 (d, J = 6.1 Hz, 1H), 5.17 (d, J = 6.1 Hz, 1H), 4.63 (m, 1H), 4.04 (dd, J = 9.4, 7.1 Hz, 1H), 3.7−3.9 (m, 3H), 2.95−3.35 (m, 5H), 2.36 (s, 3H), 1.60 (s, 3H), 1.38 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.1 Hz, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 168.2 (C), 149.8 (C), 141.1 (C), 139.5 (C), 135.9 (C), 135.1 (C), 134.1 (CH), 132.0 (C), 128.4 (2CH), 127.0 (2CH), 125.7 (CH), 123.7 (C), 109.6 (C), 102.5 (CH), 101.4 (CH_2), 95.7 (CH_2), 79.3 (CH), 72.5 (CH), 65.2 (CH_2), 58.3 (CH), 42.9 (CH_2), 42.7 (CH), 39.6 (CH_2), 27.8 (CH_3), 25.9 (CH_3), 21.3 (CH_3), 14.8 (CH_3), 14.1 (CH_3), 12.7 (CH_3); MS (EI) *m/z* (relative intensity) 617 (M^+, 20), 601 (7), 570 (30), 559 (20), 513 (7), 363 (100), 249 (28); HRMS calcd for $C_{31}H_{41}N_2O_9S$ 617.2533, found 617.2559.

***N*,*N*-Dimethyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-{(1*R*,4*R*,5*S*,6*R*)-4,5-(isopropylidenedioxy)-6-[(4′-methylphenylsulfonyl)amino]-2-cyclohexen-1-yl}-1,3-benzodioxole-5-carboxamide (28).** *s*-BuLi in hexane (1.28 M, 40 mL) was added to a solution of TMEDA (7.68 mL) in THF (160 mL) at −78 °C. The yellow mixture was stirred for 10 min before cooling to −90 °C, and then a solution of amide **25b** (14.71 g, 45.47 mmol) in THF (60 mL) was added, precooled, by cannula. The resulting deep red solution was stirred at −90 °C for 1.5

h, and then CuCN (2.08 g, 22.75 mmol) was added. The mixture was warmed to −20 °C over 1 h, furnishing a dark purple solution, which was recooled to −78 °C, and a solution of vinylaziridine **7** (4.81 g 14.96 mmol) in THF (40 mL) was added, followed by $BF_3{\cdot}Et_2O$ (2.8 mL). The reaction mixture was then warmed slowly to room temperature, and saturated aqueous NH_4Cl solution (100 mL, containing aqueous ammonia, pH 8) was added. The mixture was stirred at room temperature for 30 min, the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel, eluting with hexanes/EtOAc (3:2) (for one atropisomer), followed by hexane/EtOAc (2:3) (for the other atropisomer), to give 6.88 g (75%) of **28** as a glassy solid. α-Atropisomer: R_f 0.21 (hexane/EtOAc 1:1); $[\alpha]^{26}_D = +33.7°$ (*c* 2.0, $CHCl_3$); IR (KBr) ν 3422, 3120, 2930, 2859, 1622, 1479 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.62 (m, 3H), 7.09 (d, $J = 8.1$ Hz, 2H), 6.26 (s, 1H), 5.9−6.05 (m, 3H), 5.79 (d, $J = 9.8$ Hz, 1H), 4.58 (m, 1H), 3.99 (dd, $J = 9.5$, 6.2 Hz, 1H), 3.34 (td, $J = 10.1$, 6.4 Hz, 1H), 3.10 (d, $J = 10.1$ Hz, 1H), 3.08 (s, 3H), 2.87 (s, 3H), 2.36 (s, 3H), 1.45 (s, 3H), 1.29 (s, 3H), 0.97 (s, 9H), 0.27 (s, 3H), 0.23 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 169.08 (C), 149.68 (C), 141.14 (C), 139.89 (C), 135.93 (C), 134.71 (C), 134.58 (CH), 132.21 (C), 128.25 (2CH), 127.00 (2CH), 125.16 (CH), 123.66 (C), 109.28 (C), 101.66 (CH), 101.11 (C), 79.11 (CH), 72.53 (CH), 58.59 (CH), 42.91 (CH), 37.77 (CH), 34.90 (CH), 27.68 (CH_3), 25.80 (CH_3), 25.44 ($3CH_3$), 21.94 (CH_3), 17.94 (C), −4.57 ($2CH_3$); MS (EI) *m/z* (relative intensity) 644 (M^+, 17), 629 (27), 587 (58), 391 (100), 334 (31) 261 (28); HRMS (EI) calcd for $C_{32}H_{44}N_2O_8SSi$ 644.2588, found 644.2591. Anal. Calcd for $C_{32}H_{44}N_2O_8SSi$: C, 59.60; H, 6.88. Found: C, 59.95; H, 6.87.

***N,N*-Dimethyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-{(1*R*,4*R*,5*S*,6*R*)-6-[*N*-(*tert*-butyloxycarbonyl)-*N*-[(4′-methylphenylsulfonyl)amino]]-4,5-(isopropylidenedioxy)-2-cyclohexen-1-yl}-1,3-benzodioxole-5-carboxamide (36).** *s*-BuLi in hexane (1.28 M, 7.02 mL) was added to a solution of tosylamide **28** (5.04 g, 8.17 mmol) in THF (25 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min, and di-*tert*-butyl dicarbonate (7.13 g, 32.67 mmol) was added. After refluxing for 4 days, the reaction mixture was quenched with brine (10 mL), the organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Chromatography of the residue (silica gel, hexane/EtOAc 3:2) afforded 4.14 g (68%) of a mixture of atropisomers **36**. A pure sample for analysis could not be obtained due to the presence of several atropisomers. The mixture was used in the next reaction without further separation.

***N,N*-Dimethyl-6-{(1*R*,4*R*,5*S*,6*R*)-4-(*tert*-butyldimethylsilyl)-6-[(*tert*-butyloxycarbonyl)amino]-4,5-(isopropylidenedioxy)-2-cyclohexen-1-yl}-1,3-benzodioxole-5-carboxamide (37) and *N,N*-Dimethyl-6-{(1*R*,4*R*,5*S*,6*R*)-6-[(*tert*-butyloxycarbonyl)amino]-4,5-(isopropylidenedioxy)-2-cyclohexen-1-yl}-4-hydroxy-1,3-benzodioxole-5-carboxamide (38).** A solution of sodium anthracenide (ca. 0.6 N) was added dropwise under Ar at −78 °C to a stirred solution of **36** (5.68 g, 7.62 mmol) in DME (30 mL) until a blue color persisted for 15 min. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL), and the solvent was removed in vacuo. The residue was taken up in EtOAc and filtered. Concentration and chromatography of the residue (silica gel, hexane/EtOAc 2:3) gave **37** (2.81 g, 62%) and **38** (0.75, 20%) as glassy solids.

Compound 37: R_f 0.43 (hexanes/EtOAc 1:1); $[\alpha]^{26}_D$ +46.2° (*c* 1.27, $CHCl_3$); IR (KBr) ν 3280, 1710, 1620, 1475 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.48 (s, 1H), 6.13 (br d, $J = 9.0$ Hz, 1H), 5.98 (dt, $J = 9.7$, 3.2 Hz, 1H), 5.93 (m, 2H), 5.84 (m, 2H), 4.62 (m, 1H), 3.95 (dd, $J = 10.1$, 5.9 Hz, 1H), 3.73 (q, $J = 10.0$ Hz, 1H), 3.07 (br s, 4H), 2.85 (s, 3H), 1.61 (s, 3H), 1.39 (s, 3H), 1.24 (s, 9H), 0.96 (s, 9H), 0.23 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 168.61 (C), 156.31 (C), 149.50 (C), 135.74 (C), 135.24 (CH), 134.44 (C), 132.78 (C), 125.03 (CH), 124.28 (C), 109.46 (C), 101.91 (CH), 101.04 (CH_2), 78.68 (CH), 77.80 (C), 72.89 (CH), 55.34 (CH), 43.41 (CH), 37.77 (CH_3), 34.81 (CH_3), 28.16 ($3CH_3$), 28.05 (CH_3), 26.19 (CH_3), 25.50 ($3CH_3$), 18.07 (C), −4.30 (CH_3), −4.55 (CH_3); MS (CI+) *m/z* (relative intensity) 591 (MH^+); HRMS (CI+) calcd for $C_{30}H_{46}N_2O_8Si+H$ 591.3102, found 591.3143.

Compound 38: R_f 0.41 (EtOAc); $[\alpha]^{26}_D$ −17.1° (*c* 1.31, $CHCl_3$); mp 133 °C (EtOAc) dec; IR (KBr) ν 3270 (broad), 2970, 2930, 1710, 1630 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.73 (br s, 1H), 6.39 (m, 2H), 5.98 (d, $J = 9.6$ Hz, 1H), 5.82 (m, 2H), 4.59 (t, $J = 4.2$ Hz, 1H), 3.60−4.40 (m, 3H), 2.98−3.40 (m, 7H), 1.53 (s, 3H), 1.38 (s, 3H), 1.20 (s, 9H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 169.72 (C), 155.38 (C), 149.26 (C), 136.56 (C), 136.24 (CH), 134.94 (C), 133.37 (C), 122.87 (CH), 121.13 (C), 109.35 (C), 102.08 (CH), 101.27 (CH_2), 78.94 (C), 77.49 (CH), 72.35 (CH), 55.86 (CH), 44.32 (CH), 35.55 (CH_3), 35.35 (CH_3), 28.03 (CH_3), 27.91 ($3CH_3$), 26.06 (CH_3); MS (EI) *m/z* (relative intensity) 476 (M^+, 6), 376 (16), 318 (30), 277 (59), 256 (20); HRMS (EI) calcd for $C_{24}H_{32}N_2O_8$ 476.2158, found 476.2153.

Deprotection of 37. A solution of tetrabutylammonium fluoride in THF (1 M, 9.8 mL) was added to a solution of **37** (2.81 g, 4.76 mmol) in THF (35 mL) at 0 °C. The resulting brown solution was stirred at 0 °C for 1.5 h, the solvent was removed in vacuo, and the residue was chromatographed (silica gel, EtOAc) to furnish **38** (2.11 g, 93%).

6-{(1*R*,4*R*,5*S*,6*R*)-6-[(*tert*-Butyloxycarbonyl)amino]-4,5-(isopropylidenedioxy)-2-cyclohexen-1-yl}-4-hydroxy-1,3-benzodioxole-5-carbaldehyde (39). Sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) in toluene (1.02 M) was modified with morpholine (1.0 equiv) at room temperature (30 min). Modified SMEAH solution (20 mL, 20 mmol) was added to a stirred solution of **38** (2.82 g, 5.9 mmol) in THF (80 mL) at −45 °C. After 9 h, additional SMEAH solution (9 mL) was added, and the mixture was stirred for another 22 h. The reaction was then quenched with saturated NH_4Cl solution (10 mL) and brine (10 mL). The organic phase was separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). Drying of the combined organic layers, concentration, and chromatography (silica gel, EtOAc) of the residue gave aldehyde **39** as a white solid (853 mg, 72% based on recovered **38**) and recovered starting material (1.52 g): R_f 0.36 (hexane/EtOAc 3:2); mp 168 °C (hexane/EtOAc) dec; $[\alpha]^{25}_D$ +5.9° (*c* 1.04, $CHCl_3$); IR (KBr) ν 3360, 1650 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 10.18 (s, 1H), 6.45 (s, 1H), 6.07 (br s, 3H), 5.93 (d, $J = 10.0$ Hz, 1H), 4.68 (m, 2H), 4.50 (br s, 1H), 4.36 (br s, 1H), 3.31 (br s, 1H), 1.51 (s, 3H), 1.41 (s, 3H), 1.32 (s, 9H); ^{13}C NMR δ 193.45 (CH), 155.20 (C), 154.83 (C), 147.20 (C), 143.01 (C), 134.64 (CH), 133.02 (C), 124.62 (CH), 116.16 (C), 109.78 (C), 102.66 (CH_2), 102.15 (CH), 79.85 (C), 75.85 (CH), 75.51 (CH), 72.23 (CH), 57.84 (CH), 28.22 (CH_3), 28.10 (CH_3), 25.81 ($3CH_3$); MS (FAB) *m/z* (relative intensity) 434 ($(M + H)^+$, 46), 378 (16), 320 (50), 258 (46), 240 (100). Anal. Calcd for $C_{22}H_{27}NO_8$: C, 60.96; H, 6.28. Found: C, 60.91; H, 6.27.

6-[(1*R*,4*R*,5*S*,6*R*)-6-{(*tert*-Butyloxycarbonyl)amino]-4,5-(isopropylidenedioxy)-2-cyclohexen-1-yl}-4-(phenylmethoxy)-1,3-benzodioxole-5-carbaldehyde (40). Benzyl bromide (0.351 mL) was added to a suspension of phenol **39** (853 mg, 1.97 mmol) and K_2CO_3 (544 mg, 3.94 mmol) in DMF (8 mL). The reaction mixture was stirred at room temperature for 4 h and then quenched with saturated aqueous $CuSO_4$ solution (5 mL) and brine (5 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic layers were dried over Na_2SO_4. Removal of the solvent and chromatography (silica gel, hexane/EtOAc 3:1) of the residue afforded **40** (869 mg, 83%) as a glassy solid: R_f 0.48 (hexane/EtOAc 3:2); $[\alpha]^{25}_D$ −86.4° (*c* 1.14, $CHCl_3$); IR (KBr) ν 3370 (broad), 1710, 1670, 1605, 1475 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.37 (m, 5H), 6.63 (s, 1H), 6.02 (d, $J = 12.6$ Hz, 2H), 6.00 (m, 1H), 5.82 (d, $J = 9.9$ Hz, 1H), 5.34 (s, 2H), 4.83 (d, $J = 10.8$ Hz, 1H), 4.65 (m, 2H), 4.06 (dd, $J = 10.3$, 5.1 Hz, 1H), 3.71 (q, $J = 10.4$ Hz, 1H), 1.54 (s, 3H), 1.40 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 192.83 (CHO), 155.54 (C), 153.82 (C), 145.59 (C), 140.88 (C), 136.30 (C), 135.69 (CH), 135.13 (C), 128.62 (2CH), 128.50 (2CH), 127.94 (CH), 124.10 (CH), 121.52 (C), 109.60 (C), 104.52 (CH), 101.85 (CH_2), 78.57 (C), 77.87 (CH), 74.58 (CH_2), 72.80 (CH), 56.48 (CH), 40.87 (CH), 28.15 ($4CH_3$), 26.19 (CH_3); MS (CI+) *m/z* (relative intensity) 524 (MH^+, 76), 506 (82), 466 (61), 406 (100), 348 (25), 330 (34); HRMS (CI+) calcd for $C_{29}H_{34}NO_8+H$ 524.2284, found 524.2263. Anal. Calcd for $C_{29}H_{33}NO_8$: C, 66.53; H, 6.35; N, 2.67. Found: C, 66.57; H, 6.51; N, 2.54.

Methyl 6-{(1*R*,4*R*,5*S*,6*R*)-6-[(*tert*-Butyloxycarbonyl)amino]-4,5-(isopropylidenedioxy)-2-cyclohexen-1-yl}-4-(phenylmethoxy)-1,3-benzodioxole-5-carboxylate (43). Aldehyde **40** (507 mg, 0.97 mmol)

was dissolved in *t*-BuOH (24 mL) and 2-methyl-2-butene (6.6 mL, 85% purity). A solution of sodium chlorite (1.18 g, 10.43 mmol) and potassium dihydrogen phosphate (1.07 g, 7.86 mmol) in H_2O (10 mL) was added dropwise over a 10 min period. The yellow solution was stirred overnight at room temperature. Volatiles were removed under high vacuum, brine (3 mL) was added to the residue, and the aqueous layer was extracted with EtOAc (4 × 20 mL). The organic extract was dried over Na_2SO_4, and the crude acid **42** was treated with excess diazomethane. Removal of the solvent and chromatography (silica gel, hexane/EtOAc 3:2) gave the methyl ester **43** (526 mg, 98%) as a glassy solid: R_f 0.40 (hexane/EtOAc 3:2); $[\alpha]^{25}_D$ +17.1° (*c* 1.07, $CHCl_3$); IR (KBr) ν 3370, 1705, 1620; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.26−7.39 (m, 5H), 6.54 (s, 1H), 5.84−5.99 (m, 4H), 5.21 (s, 2H), 4.94 (br s, 1H), 4.63 (t, J = 4.4 Hz, 1H), 4.01 (br s, 1H), 3.79 (s, 3H), 3.73 (q, J = 10.1 Hz, 1H), 3.36 (br s, 1H), 1.61 (s, 3H), 1.40 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 168.14 (C), 155.51 (C), 150.56 (C), 139.46 (C), 136.99 (C), 135.80 (C), 135.19 (CH), 134.01 (C), 128.29 (CH), 127.94 (2CH), 127.63 (2CH), 124.22 (CH), 121.42 (C), 109.56 (C), 103.29 (CH), 101.48 (CH_2), 78.67 (C), 77.37 (CH), 74.27 (CH_2), 72.54 (CH), 55.52 (CH), 52.09 (CH_3), 43.84 (CH), 29.58 (4CH_3), 26.06 (CH_3); MS (FAB) *m/z* (relative intensity) 554 (MH^+, 8), 440 (19), 346 (13). Anal. Calcd for $C_{30}H_{35}NO_9$: C, 65.09; H, 6.37; N, 2.53. Found: C, 65.29; H, 6.61; N, 2.34.

Methyl 6-{(1*R*,4*R*,5*S*,6*R*)-6-[(*tert*-Butyloxycarbonyl)amino]-4,5-dihydroxy-2-cyclohexen-1-yl}-4-(phenylmethoxy)-1,3-benzodioxole-5-carboxylate (49). Methyl ester **43** (488 mg, 0.88 mmol) was dissolved in a mixture of acetic acid, THF, and H_2O (2:1:1, 8 mL), and the solution was heated at 60 °C for 3 h. The solvent was removed in vacuo, and the residue was subjected to chromatography (hexane/EtOAc 1:4) to afford the 4,5-diol **49** (324 mg, 73%) as a white solid: R_f 0.19 (hexane/EtOAc 2:3); mp 129−131 °C (hexane/EtOAc); $[\alpha]^{25}_D$ +73.7° (*c* 0.91, $CHCl_3$); IR (KBr) ν 3270, 3360, 3290, 1715, 1695, 1620 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.27−7.40 (m, 5H), 6.61 (s, 1H), 6.15 (br s, 1H), 5.97 (m, 3H), 5.59 (d, J = 9.1 Hz, 1H), 5.29 (d, J = 11.3 Hz, 1H), 5.18 (d, J = 11.3 Hz, 1H), 4.83 (br s, 1H), 4.23 (t, J = 3.3 Hz, 1H), 3.87 (m, 1H), 3.73 (s, 3H), 3.61 (m, 1H), 3.31 (br s, 1H), 3.29 (d, J = 10.2 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 168.83 (C), 158.68 (C), 151.08 (C), 139.38 (C), 136.92 (C), 136.10 (C), 134.91 (C), 132.75 (CH), 128.40 (2CH), 128.13 (CH), 127.80 (2CH), 126.98 (CH), 120.88 (C), 103.60 (CH), 101.72 (CH_2), 80.03 (C), 74.86 (CH), 74.39 (CH_2), 66.68 (CH), 54.66 (CH), 52.50 (CH_3), 45.02 (CH), 28.29 (3CH_3); MS (FAB) *m/z* (relative intensity) 514 (MH^+, 6), 414 (40), 382 (6), 256 (7); HRMS calcd for $C_{27}H_{31}NO_9$+H 514.2077, found 514.2165. Anal. Calcd for $C_{27}H_{31}NO_9$: C, 63.15; H, 6.08; N, 2.73. Found: C, 62.48; H, 6.19; N, 2.57.

Methyl 6-{(1*R*,2*R*,3*S*,4*S*,5*S*,6*R*)-6-[(*tert*-Butyloxycarbonyl)amino]-5,6-epoxy-3,4-dihydroxycyclohex-1-yl}-4-(phenylmethoxy)-1,3-benzodioxole-5-carboxylate (50). *tert*-Butyl hydroperoxide in decane (5 M, 0.45 mL) was added to a solution of **49** (280 mg, 0.55 mmol) and vanadyl acetylacetonate (7 mg, 0.026 mmol) in benzene (10 mL). After being stirred for 2 h at 60 °C, the reaction mixture was concentrated under reduced pressure and subjected to chromatography (hexane/EtOAc 1:5) to afford epoxide **50** (129 mg, 53% yield based on recovered starting material) as a glassy solid and recovered starting material (42 mg): R_f 0.18 (hexane/EtOAc 1:4); $[\alpha]^{25}_D$ +28.6° (*c* 1.48, $CHCl_3$); IR (KBr) ν 3380, 1705, 1615 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.27−7.40 (m, 5H), 7.04 (s, 1H), 5.99 (d, J = 2.3 Hz, 2H), 5.68 (br d, J = 7.3 Hz, 1H), 5.24 (AB, J = 11.3 Hz, $\Delta\delta$ = 0.07 ppm, 2H), 4.28 (t, J = 5.0 Hz, 1H), 3.83 (m, 4H), 3.35−3.46 (m, 3H), 3.07 (d, J = 10.9 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 168.72 (C), 158.06 (C), 151.18 (C), 139.47 (C), 136.86 (C), 136.42 (C), 132.46 (C), 128.37 (2CH), 128.12 (CH), 127.82 (2CH), 121.31 (C), 103.52 (CH), 101.73 (CH_2), 79.85 (C), 74.46 (CH), 74.39 (CH_2), 66.28 (CH), 58.09 (CH), 52.70 (CH), 52.46 (CH_3), 50.49 (CH), 43.29 (CH), 29.23 (3CH_3); MS (FAB) *m/z* (relative intensity) 530 ((M + H)$^+$, 17), 474 (6), 430 (53); HRMS calcd for $C_{27}H_{31}NO_{10}$+H 530.2026, found 530.2050.

Pancratistatin (4). A suspension of epoxide **50** (109 mg, 0.21 mmol) and sodium benzoate (1 mg) in water (8 mL) was stirred at 100 °C for 6 days. The mixture was then concentrated and subjected to chromatography (chloroform/methanol 4:1) to afford pancratistatin (35 mg, 51%): R_f 0.40 (chloroform/methanol 4:1); mp 260 °C (chloroform/methanol) dec; $[\alpha]^{26}_D$ +40.9° (*c* 1.0, DMSO), lit.[6c] $[\alpha]^{34}_D$ + 48° (*c* 1.0, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 7.51 (s, 1H), 6.48 (s, 1H), 6.05 (d, J = 1.0 Hz, 1H), 6.02 (d, J = 1.0 Hz, 1H), 5.35 (d, J = 4 Hz, 1H), 5.09 (d, J = 6 Hz, 1H), 5.03 (d, J = 6 Hz, 1H), 4.84 (d, J = 7.5 Hz, 1H), 4.27 (m, 1H), 3.95 (q, J = 3.6 Hz, 1H), 3.84 (m, 1H), 3.74 (m, 2H), 2.96 (d, J = 11.5 Hz, 1H).

***N*-[(1*R*,2*R*,5*R*,6*S*)-2-(1,3-Benzodioxol-5-yl)-5,6-(isopropylidenedioxy)cyclohex-3-en-1-yl]-4-methylbenzenesulfonamide (60).** *n*-BuLi (1.9 M in hexane, 10 mL) was added to a solution of 5-bromo-1,3-benzodioxole (16.6 mmol) in THF (65 mL) at −78 °C. The reaction mixture was stirred for 40 min at −78 °C, and CuCN (744 mg, 8.3 mmol) was added. After the mixture was stirred at −78 °C for 1 h, a solution of aziridine **7** (1.27 g, 3.95 mmol) in THF (10 mL) was added, followed by $BF_3{\cdot}Et_2O$ (0.4 mL). The reaction mixture was allowed to warm slowly to room temperature with stirring, and saturated aqueous NH_4Cl solution (10 mL) was added. The organic layer was separated, and the aqueous phase was extracted with EtOAc (4 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed (silica gel, CH_2Cl_2/acetone 12:1) to give tosylamide **60** (552 mg, 32%) as a white solid: mp 75−76 °C (CH_2Cl_2/acetone); $[\alpha]^{22}_D$ +44.6° (*c* 1.16, $CHCl_3$); IR (KBr) ν 3260, 1480 cm^{-1}; ^{1}H NMR (200 MHz, $CHCl_3$) δ 7.43 (d, J = 8.2 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 6.49 (m, 3H), 5.95 (m, 3H), 5.76 (dd, J = 9.9, 1.6 Hz, 1H), 5.34 (d, J = 8.5 Hz, 1H), 4.61 (t, J = 4.5 Hz, 1H), 4.13 (dd, J = 9.1, 6.0 Hz, 1H), 3.51 (q, J = 9.2 Hz, 1H), 3.13 (br d, J = 9.8 Hz, 1H), 2.38 (s, 3H), 1.50 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (50 MHz, C_6D_6) δ 147.87 (C), 146.86 (C), 141.57 (C), 140.58 (C), 135.10 (CH), 135.02 (C), 129.02 (2CH), 126.93 (2CH), 124.30 (CH), 122.28 (CH), 109.88 (C), 109.20 (CH), 108.38 (CH), 100.74 (CH_2), 78.18 (CH), 72.72 (CH), 59.62 (CH), 47.51 (CH), 28.31 (CH_3), 26.28 (CH_3), 21.11 (CH_3); HRMS (EI) calcd for $C_{23}H_{25}NO_6S$ 443.1403, found 443.1416. Anal. Calcd for $C_{23}H_{25}NO_6S$: C, 62.28; H, 5.68; N, 3.18. Found: C, 62.11; H, 5.91; N, 3.05.

***N*-[(1*R*,2*R*,5*R*,6*S*)-2-(1,3-Benzodioxol-5-yl)-5,6-(isopropylidenedioxy)cyclohex-3-en-1-yl]-*N*-(methoxycarbonyl)-4-methylbenzenesulfonamide (61).** *s*-BuLi (1.68 mL, 1.85 mmol) was added to a solution of tosylamide **60** (745 mg, 1.68 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred for 5 min, and then dimethyl pyrocarbonate (0.8 mL, 7.5 mmol) was added. After being stirred at room temperature for 10 h, the reaction was quenched with aqueous NH_4Cl (10 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The organic layers were combined and washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed (silica gel, hexane/EtOAc 2:1) to give urethane **61** (642 mg, 76%): white solid; R_f 0.32 (hexane/EtOAc); mp 98−99 °C (hexane/EtOAc); $[\alpha]^{24}_D$ +59.7° (*c* 1.24, $CHCl_3$); IR (KBr) ν 2990, 1725, 1480 cm^{-1}; ^{1}H NMR (200 MHz, $CHCl_3$) δ 7.26 (d, J = 8.2 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 6.77 (d J = 7.7 Hz, 1H), 6.63 (m, 2H), 5.96 (m, 4H), 4.83 (m, 2H), 4.62 (t, J = 10.2 Hz, 1H), 4.14 (d, J = 10.9 Hz, 1H), 3.62 (s, 3H), 2.36 (s, 3H), 1.69 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 152.38 (C), 148.01 (C), 147.00 (C), 143.61 (C), 137.20 (C), 136.69 (CH), 134.49 (C), 128.63 (2CH), 128.54 (2CH), 123.11 (CH), 121.87 (CH), 110.39 (C), 109.04 (CH), 108.56 (CH), 100.98 (CH_2), 73.24 (CH), 73.12 (CH), 63.32 (CH), 53.23 (CH), 43.47 (CH_3), 27.64 (CH_3), 25.89 (CH_3), 21.51 (CH_3); HRMS (EI) calcd for $C_{25}H_{27}NO_8S$ 501.1457, found 501.1459.

Methyl *N*-[(1*R*,2*R*,5*R*,6*S*)-2-(1,3-Benzodioxol-5-yl)-5,6-(isopropylidenedioxy)cyclohex-3-en-1-yl]carbamate (62). Method A. Na/anthracene was added to a stirred solution of tosylamide **61** (554 mg, 1.08 mmol) in DME (11 mL) at −78 °C until a blue color persisted. The reaction was quenched with brine (5 mL), and the reaction mixture was extracted with EtOAc (4 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated, and the residue was chromatographed (silica gel, hexane/EtOAc 3:2) to give **62** (261 mg, 69%): white solid; R_f 0.30 (hexane/EtOAc 3:2); mp 190−191 °C (hexane/EtOAc); $[\alpha]^{25}_D$ +83.8° (*c* 1.23, $CHCl_3$); IR (KBr) ν 3321, 1725, 1536, 1480; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, J = 7.9 Hz, 1H), 6.66 (d, J = 1.7 Hz, 1H), 6.62 (dd, J = 7.8, 1.7 Hz, 1H), 5.98 (m, 1H), 5.93 (m, 2H), 5.90 (m, 1H), 4.67 (t, J = 4.9 Hz, 1H), 4.59 (br s, 1H), 4.39 (br s, 1H), 3.54 (s, 3H), 3.40 (m, 1H), 1.53 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.46 (C), 147.68 (C), 146.45 (C), 136.00 (CH), 134.73 (C), 123.46 (CH), 121.40 (CH), 109.56 (C), 108.35

(CH), 108.08 (CH), 100.86 (CH_2), 76.18 (CH), 72.33 (CH), 57.08 (CH), 51.80 (CH), 45.81 (CH_3), 28.13 (CH_3), 25.87 (CH_3); HRMS (CI) calcd for $C_{18}H_{21}NO_6+H^+$ 348.1447, found 348.1508. Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H 6.09; N, 4.03. Found: C, 62.01; H, 6.01; N, 3.91.

Method B: from Aziridine 64. *n*-BuLi (2.5 M in hexane, 0.425 mL) was added to a solution of 5-bromo-1,3-benzodioxole (213 mg, 1.06 mmol) in THF (10 mL at −78 °C. The reaction mixture was stirred for 50 min at −78 °C, and CuCN (48 mg, 0.53 mmol) was added. After the mixture was stirred at −78 °C for 90 min, a solution of aziridine **64** (50 mg, 0.22 mmol) in THF (10 mL) was added, precooled by a cannula, followed by $BF_3{\cdot}Et_2O$ (0.067 mL, 0.53 mmol). The reaction mixture was allowed to warm up to −60 °C over 2 h, or until TLC analysis indicated complete consumption of aziridine **64**. Saturated NH_4Cl solution (10 mL) was added, the mixture warmed up to room temperature, the organic layer separated, and the aqueous phase extracted with EtOAc (4 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed (silica gel, CH_2Cl_2/acetone 12:1) to give carbamate **62** (23 mg, 30%) as a white solid.

Methyl (1*R*,4*S*,5*S*,6*R*)-3-Bromo-4,5-(isopropylidenedioxy)-7-azabicyclo[4.1.0]hept-2-ene-7-carboxylate (63). To (1*S*,2*S*)-3-bromocyclohexa-3,5-diene-1,2-diol (**9a**, 1.15 g, 6.02 mmol) in dichloromethane (40 mL) were added 2,2-dimethoxypropane (1.15 g, 11.0 mmol) and *p*-TsOH (25 mg). After being stirred for 60 min at room temperature, the turbid solution was washed with 1 N NaOH (2 × 25 mL) and brine (25 mL). The solution was dried over Na_2SO_4 and concentrated in vacuo to afford the pure acetonide **11a** (1.30 g). A solution of $NaHCO_3$ (1.28 g, 15.2 mmol) in water (17 mL) was added to a solution of acetonide **11a** (1.30 g), methyl (*p*-nitrophenylsulfonyl)-oxycarbamate (3.09 g, 11.2 mmol), and benzyltriethylammonium chloride (0.28 g, 1.22 mmol) in dichloromethane (25 mL) and stirred vigorously for 16 h at room temperature. After phase separation, the aqueous phase was extracted twice with dichloromethane, and the combined organic phases were washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (silica gel, hexane/EtOAc 80:20) to afford pure aziridine **63** (0.648 g, 38% from the acetonide) as a white solid: mp 97−99 °C (ethyl ether); $[\alpha]^{25}_D$ +30.0° (*c* 1.66, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.48 (dd, J = 5.0, 1.4 Hz, 1H), 4.90 (ddd, J = 6.1, 1.9, 0.8 Hz, 1H), 4.38 (dd, J = 6.3, 1.4 Hz, 1H), 3.75 (s, 3H), 3.20 (dd, J = 5.8, 1.6 Hz, 1H), 2.98 (t, J = 4.9 Hz, 1H), 1.45 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 128.3, 125.7, 111.2, 73.8, 72.2, 53.9, 35.3, 34.9, 27.5, 26.1; HRMS calcd for $C_{11}H_{15}NBrO_4$ 304.0184, found 304.0185. Anal. Calcd for $C_{11}H_{14}BrNO_4$: C, 43.44; H, 4.63; N, 4.60. Found: C, 43.64; H, 4.73; N, 4.55.

Methyl (1*R*,4*R*,5*S*,6*R*)-4,5-(Isopropylidenedioxy)-7-azabicyclo-[4.1.0]hept-2-ene-7-carboxylate (64). To a degassed solution of bromide **63** (500 mg, 1.64 mmol) in THF (50 mL) at reflux were added tributyltin hydride (574 mg, 1.97 mmol) and AIBN (50 mg, 0.304 mmol), and the solution was heated under reflux until TLC (hexane/EtOAc 3:1) indicated no remaining starting material (∼60 min). The mixture was concentrated in vacuo, followed by chromatography (hexane/EtOAc 3:1), to afford **64** (302 mg, 82%; average yield range: 40−50%) as an oil: R_f 0.30 (hexane/EtOAc 3:1); $[\alpha]^{22}_D$ −94° (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2 film) 1734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (ddd, J = 10.0, 4.4, 1.7 Hz, 1H), 5.71 (dm, J = 10.0 Hz, 1H), 4.80 (dm, J = 6.6 Hz, 1H), 4.43 (dt, J = 6.6, 2.0 Hz, 1H), 3.74 (s, 3H), 3.14 (dd, J = 5.9, 2.0 Hz, 1H), 2.96 (t, J = 5.1 Hz, 1H), 1.39 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 130.9, 122.6, 110.4, 70.9, 70.1, 53.8, 34.6, 33.2, 27.8, 26.1.

Methyl *N*-[(1*R*,2*R*,5*R*,6*S*)-2-(1,3-Benzodioxol-5-yl)-5,6-dihydroxy-cyclohex-3-en-1-yl]carbamate (65). Acetonide **62** (465 mg, 1.34 mmol) in AcOH/THF/H_2O (2:1:1; 5 mL) was heated at 65 °C for 3 h. The solvent was evaporated in vacuo, and the residue was recrystallized from EtOAc/methanol to give diol **65** (390 mg, 94%) as a white solid: R_f 0.35 ($CHCl_3$/CH_3OH 8:1); mp 200−201 °C (EtOAc/MeOH); $[\alpha]^{25}_D$ +107.7° (*c* 1.22, MeOH); IR (KBr) ν 3400, 3320, 3300, 2868, 1690, 1535 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 6.72 (m, 3H), 5.89 (m, 3H), 5.65 (dd, J = 9.9, 2.0 Hz, 1H), 4.61 (s, 1H), 4.21 (t, J = 4.3 Hz, 1H), 3.74 (m, 1H), 3.60 (m, 1H), 3.50 (m, 3H), 3.30 (m, 3H); ^{13}C NMR (50 MHz, CD_3OD) δ 159.85 (C), 149.12 (C), 147.91 (C), 137.29 (C), 134.90 (CH), 127.89 (CH), 122.80 (CH), 109.64 (CH), 108.85 (CH), 102.18 (CH_2), 73.63 (CH), 67.98 (CH), 56.11 (CH), 52.34 (CH), 50.26 (CH_3); HRMS (FAB) calcd for $C_{15}H_{17}NO_6+H^+$ 308.1134, found 308.1188. Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.62; H, 5.58; N, 4.56. Found: C, 58.93; H, 5.59; N, 4.50.

Methyl *N*-[(1*R*,2*R*,3*R*,4*R*,5*S*,6*S*)-2-(1,3-Benzodioxol-5-yl)-5,6-dihydroxy-3,4-epoxycyclohex-1-yl]carbamate (66). $VO(acac)_2$ (25 mg, 0.07 mmol) was added to a solution of olefin **65** (351 mg, 1.14 mmol) and *t*-BuOOH (5 M, 1.14 mL) in benzene (20 mL), and the mixture was heated at 70 °C for 3 h. The solvent was evaporated, and the residue was chromatographed (silica gel, $CHCl_3$/MeOH 8:1) to give epoxide **66** (315 mg, 85%): white solid; R_f 0.26 ($CHCl_3$/CH_3OH 8:1); mp 194−195 °C ($CHCl_3$/MeOH); $[\alpha]^{25}_D$ +68.0° (*c* 0.9, MeOH); IR (KBr) ν 3305, 2980, 2880, 1680, 1535, 1480 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 6.96 (d, J = 1.5 Hz, 1H), 6.84 (dd, J = 7.9, 1.5 Hz, 1H), 6.72 (d, J = 7.9 Hz, 1H), 5.90 (s, 2H), 4.25 (t, J = 5.1 Hz, 1H), 3.78 (t, J = 10.7 Hz, 1H), 3.46 (s, 3H), 3.38 (m, 3H), 3.08 (d, J = 10.9 Hz, 1H); ^{13}C NMR (50 MHz, CD_3OD) δ 159.71 (C), 149.09 (C), 148.19 (C), 135.16 (C), 123.32 (CH), 109.99 (CH), 108.86 (CH), 102.22 (CH_2), 73.17 (CH), 67.68 (CH), 59.36 (CH), 54.29 (CH), 52.33 (CH), 51.93 (CH_3), 48.39 (CH); HRMS (FAB) calcd for $C_{15}H_{17}NO_7+H^+$ 324.1083, found 324.1044. Anal. Calcd for $C_{15}H_{17}NO_7$: C, 55.73; H 5.30; N, 4.33. Found: C, 55.76; H, 5.49; N, 4.18.

Methyl *N*-[(1*R*,2*R*,3*R*,4*S*,5*S*,6*S*)-2-(1,3-Benzodioxol-5-yl)-3,4,5,6-tetrahydroxycyclohexyl]carbamate (67). Sodium benzoate (6 mg) was added to epoxide **66** (214 mg, 0.62 mmol) and water (5 mL), and the mixture was heated at 100 °C under argon for 7 days. Water was removed in vacuo, and the residue was chromatographed (silica gel, $CHCl_3$/MeOH 6:1) to give aryl aminocyclitol **67** (173 mg, 82%): white solid; R_f 0.22 ($CHCl_3$/CH_3OH 6:1); mp 86 °C ($CHCl_3$/CH_3OH) dec; $[\alpha]^{24}_D$ −1.73° (*c* 1.21, MeOH); IR (KBr) ν 3400, 2900, 1695; ^{1}H NMR (200 MHz, CD_3OD) δ 6.87 (d, J = 1.6 Hz, 1H), 6.77 (dd, J = 8.0, 1.6 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 5.87 (m, 2H), 4.32 (m, 1H), 4.03 (m, 2H), 3.74 (m, 2H), 3.49 (s, 3H), 3.30 (s, 1H), 3.14 (dd, J = 12.2, 2.0 Hz, 1H); ^{13}C NMR (50 MHz, CD_3OD) δ 159.91 (C), 148.61 (C), 147.53 (C), 134.93 (C), 123.69 (CH), 110.86 (CH), 108.56 (CH), 101.96 (CH_2), 76.02 (CH), 73.47 (CH), 73.35 (CH), 71.84 (CH), 52.29 (CH), 51.30 (CH_3), 48.3 (CH); HRMS (CI) calcd for $C_{15}H_{20}NO_8$+H 342.1188, found 342.1144.

Methyl *N*-[(1*R*,2*R*,3*R*,4*S*,5*S*,6*S*)-2-(1,3-Benzodioxol-5-yl)-3,4,5,6-tetraacetoxycyclohexyl]carbamate (68). Aryl aminocyclitol **67** (40 mg) was dissolved in pyridine (1 mL) and acetic anhydride (1 mL), and the mixture was stirred at room temperature for 16 h. The solvent was evaporated in vacuo, and the residue was chromatographed (silica gel, hexane/EtOAc 1:1) to furnish tetraacetate **68** (50 mg, 84%): white solid; R_f 0.43 (hexane/EtOAc 2:3); mp 109−110 °C (hexane/EtOAc); $[\alpha]^{25}_D$ +14.1° (*c* 0.86, $CHCl_3$); IR (KBr) ν 3360, 2950, 1740, 1520 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.72 (m, 3H), 5.93 (s, 2H), 5.35 (s, 1H), 5.23 (m, 1H), 5.09 (m, 2H), 4.70 (m, 1H), 4.40 (br d, J = 9.0 Hz, 1H), 3.54 (s, 3H), 3.22 (d, J = 11.4 Hz, 1H), 2.18 (s, 6H), 2.02 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.53 (C), 169.33 (C), 168.82 (C), 168.25 (C), 156.56 (C), 147.74 (C), 146.96 (C), 129.58 (C), 122.19 (CH), 109.06 (CH), 108.16 (CH), 101.02 (CH_2), 72.06 (CH), 71.11 (CH), 68.71 (CH), 68.09 (CH), 52.19 (CH), 48.07 (CH_3), 47.20 (CH), 20.79 ($2CH_3$), 20.62 ($2CH_3$); HRMS (CI) calcd for $C_{23}H_{27}NO_{12}$+H 510.1611, found 510.1543. Anal. Calcd for $C_{23}H_{27}NO_{12}$: C, 54.22; H 5.34; N, 2.75. Found: C, 54.49; H, 5.41; N, 2.57.

(1*R*,2*S*,3*S*,4*S*,4a*R*,11b*R*)-1,2,3,4-Tetraacetoxy-1,3,4,4a,5,10b-hexahydro-1,3-dioxolo[4,5-*j*]phenanthridin-6-(2*H*)-one (69). Freshly distilled Tf_2O (121 mg, 0.432 mmol) was added at 0 °C to a solution of tetraacetate **68** (44 mg, 0.864 mmol) and DMAP (32 mg, 0.259 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at 5 °C for 16 h, the solvent was removed in vacuo, and then THF (2 mL) and aqueous HCl (0.2 mL, 2 N) were added, and the mixture was stirred at room temperature for 5 h. Neutralization with aqueous $NaHCO_3$, extraction with EtOAc (3 × 15 mL), drying of the organic phase over $MgSO_4$, and concentration afforded a residue, which was chromatographed (silica gel, hexane/EtOAc 1:1) to furnish the cyclized product **69** (25 mg, 61%): white solid; R_f 0.50 (hexane/EtOAc 1:2); mp 232−238 °C (hexane/EtOAc); $[\alpha]^{25}_D$ +75.2° (*c* 1.2, $CHCl_3$); IR (KBr) ν 3330, 2920, 1750, 1665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 6.59 (s, 1H), 6.56 (s, 1H), 6.03 (m, 2H), 5.58 (m, 1H), 5.47 (t, J = 2.9 Hz,

1H), 5.23 (t, J = 2.7 Hz, 1H), 5.20 (dd, J = 3.5, 10.8 Hz, 1H), 4.30 (dd, J = 12.8, 11.0 Hz, 1H), 3.46 (dd, J = 13.0, 2.7 Hz, 1H), 2.16 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.03 (C), 169.77 (C), 169.04 (C), 168.27 (C), 165.07 (C), 151.77 (C), 147.25 (C), 131.52 (C), 123.32 (C), 108.44 (CH), 103.68 (CH), 101.86 (CH_3), 71.53 (CH), 67.67 (CH), 66.92 (CH), 66.32 (CH), 48.21 (CH), 39.46 (CH), 20.79 (CH_3), 20.76 (CH_3), 20.62 (CH_3), 20.59 (CH_3); HRMS (CI) calcd for $C_{22}H_{23}NO_{11}$+H 478.1349, found 478.1351.

Deoxypancratistatin (70). Sodium methoxide (0.5 M in methanol, 1.1 mL) was added to a solution of tetraacetate **69** (26 mg, 0.054 mmol) in THF (1 mL). The reaction mixture was stirred at room temperature for 10 h, and saturated NH_4Cl aqueous solution (2 mL) was added. The aqueous layer was extracted exhaustively with EtOAc, and the organic layer was dried over Na_2SO_4. Concentration and column chromatography (silica gel, $CHCl_3$/CH_3OH 4:1) gave deoxypancratistatin **70** (12 mg, 72%): R_f 0.30 ($CHCl_3$/CH_3OH 4:1); mp 306−309 °C; $[\alpha]^{25}_D$ +78.5° (*c* 0.75, DMF); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 (s,1H), 6.90 (s, 1H), 6.84 (s, 1H), 6.06 (s, 2H), 5.36 (d, J = 4.0 Hz, 1H), 5.07 (d, J = 5.8 Hz, 1H), 5.05 (d, J = 6.1 Hz, 1H), 4.77 (d, J = 7.5 Hz, 1H), 4.31 (m, 1H), 3.97 (q, J = 3.5 Hz, 1H), 3.84 (m, 1H), 3.72 (m, 2H), 2.97 (d, J = 12.0 Hz, 1H).

Acknowledgment. The authors thank the National Science Foundation (CHE-9315684 and CHE-9521489), Genencor International, Inc., TDC Research, Inc., and The University of Florida for generous financial support. The authors also thank Prof. G. E. Keck (University of Utah) for the kind provision of TLC, $[\alpha]_D$, and ^{1}H-NMR data of the tetraacetate of 7-deoxypancratistatin, as well as Prof. G. R. Pettit (Arizona State University) for a sample of (+)-pancratistatin. Stefan Schilling, Dr. Paul Higgs, and Dr. Josie Reed are thanked for additional experimental work and for editing the manuscript, respectively.

Supporting Information Available: Experimental procedures and key physical data for compounds **29**, **30**, **31**, **32a**, **32d**, **33**, and **34** (3 pages). See any current masthead page for ordering and Internet access instructions.

JA960596J