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Total Synthesis and Biological Evaluation of *Amaryllidaceae* Alkaloids: Narciclasine, *ent*-7-Deoxypancratistatin, Regioisomer of 7-Deoxypancratistatin, 10b-*epi*-Deoxypancratistatin, and Truncated Derivatives[1]

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Biocatalytic approaches have yielded efficient total syntheses of the major *Amaryllidaceae* alkaloids, all based on the key enzymatic dioxygenation of suitable aromatic precursors. This paper discusses the logic of general synthetic design for lycoricidine, narciclasine, pancratistatin, and 7-deoxypancratistatin. Experimental details are provided for the recently accomplished syntheses of narciclasine, *ent*-7-deoxypancratistatin, and 10b-*epi*-deoxypancratistatin via a new and selective opening of a cyclic sulfate over aziridines followed by aza-Payne rearrangement. The structural core of 7-deoxypancratistatin has also been degraded to a series of intermediates in which the amino inositol unit is cleaved and deoxygenated in a homologous fashion. These truncated derivatives and the compounds from the synthesis of the unnatural derivatives have been tested against six important human cancer cell lines in an effort to further develop the understanding of the mode of action for the most active congener in this group, pancratistatin. The results of the biological activity testing as well as experimental, spectral, and analytical data are provided in this manuscript for all relevant compounds.

Introduction

Plants in the *Amaryllidaceae* family have been used for thousands of years as herbal remedies; the ancient Greeks knew their medicinal value.[2] The alkaloids from their extracts have been the object of active chemical investigation for nearly 200 years.[3] Lycorine (**1**), the first alkaloid of this group to be isolated,[4] was studied for its antitumor properties long before more oxygenated congeners were identified.[5] Over the past two decades, lycoricidine (**2**), narciclasine (**3**), pancratistatin (**5**), and 7-deoxypancratistatin (**4**) have been isolated,[6] screened for antitumor activity,[7] and synthesized[8−10] by a number of research groups. The history of the *Amaryllidaceae* alkaloids, their structure elucidation, and their biological profiles, as well as their syntheses, have been summarized on several occasions.[3] These alkaloids are available only in minute quantities from natural sources,[6j] and their future as therapeutic agents depends on their availability. Because isolation in larger quantity is not

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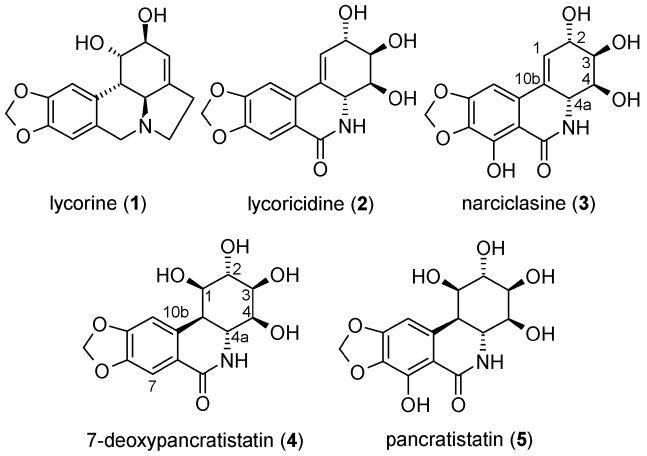

FIGURE 1. Representative members of the *Amaryllidaceae* family of alkaloids.

practical, there is a strong case for development of syntheses or semisyntheses of these alkaloids, their derivatives, and potential prodrugs.[11]

Some of these alkaloids also display antiglycosidic (and hence antiviral) activity because of the similarity of their oxygenation pattern to that of natural sugars.[12] This additional biological spectrum of activities provides for even stronger justification of synthetic effort toward these alkaloids. The synthesis of *Amaryllidaceae* alkaloids is pursued by 10 or more research groups, and at least three of these groups have made substantial multigenerational improvement of synthetic protocols toward these compounds.

This paper describes the details of our most recent syntheses of narciclasine (8 operations), *ent*-7-deoxypancratistatin (12 operations), and *epi*-7-deoxypancratistatin (12 operations) by three different approaches. All are connected by a common motif: each synthesis begins with the biooxidation of an aromatic compound. Some truncated derivatives of 7-deoxypancratistatin have been prepared for biological evaluation, and the results are reported herein.

Synthetic Strategy. We have proposed that 15 steps be the limit for a practical synthesis for any desired compound.[13] Arguments for acceptance of this limit are offered by basic algebraic considerations of "assumed" yields of 90% in each step—an optimistic projection at best. The success of inventing a short synthesis of the oxygenated phenanthridone nucleus is likely to be hampered by the need of protective and deprotective operations required to preserve the integrity of the oxygenated ring, which can be visualized as a C-substituted aminoinositol.

The best strategy for an efficient synthesis of any of these alkaloids is to attach the aryl fragment to an electrophilic synthon that already contains most of the oxygenated centers. Because enantiomeric alkaloids may or may not be active, such a strategy should also accommodate the preparation of both enantiomers. Symmetry arguments similar to those already applied to the synthesis of inositols[14−16] indicate that the enantiomeric series of pancratistatin is related by the "switch of the

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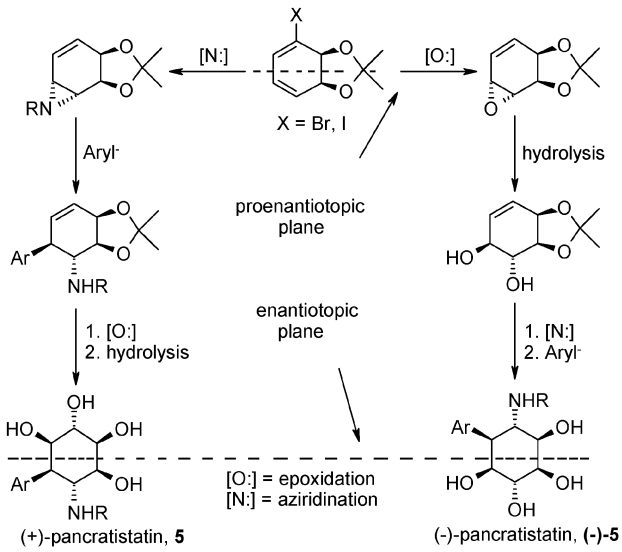
SCHEME 1



trans-disposed functionalities" as indicated in Scheme 1. If one considers that the trans diol and the β-arylamine are interchangeable across the enantiotopic plane[15a] shown, then a common strategy can be devised for both enantiomers by two identical routes from a single enantiomer of the material which contains the cis-diol unit "protected" from symmetrization by the presence of a removable group.

Such a strategy is implemented by performing two sequences of identical functionalizations in a different order, as shown in Scheme 1. Successful applications of this kind of strategy to sugar and inositol syntheses have been reported.[13,15] The creation of either an electrophilic aziridine or an electrophilic oxirane at the more electron-rich olefin allows the rest of the synthesis to be completed by a series of identical chemical steps, executed in different order, as demonstrated for the first time in our enantiodivergent synthesis of (+)- and (−)-pinitol.[15a] Several reviews offer an expanded version of this argument.[13,17]

Other solutions for the enantiodivergent synthesis of arene cis-diols have been reported. Boyd's strategy[18] is based on the directing effects in the enzymatic oxidation and the greater rate of reduction of the directing group (iodine) by chemical means (R_3SnH). Because toluene dioxygenase-mediated oxidation of *para*-substituted dihalobenzenes produces mixtures of poor enantiomeric enrichment, Johnson's[19] lipase resolution of intermediates derived from such mixtures must be used to enrich the optical purity of the desired ent-diols. We have used both strategies in the synthesis of *ent*-7-deoxypancratistatin.

Discussion

Narciclasine. Two possible disconnections were considered, both leading to amino enone **14**, via a nitroso Diels−Alder reaction, Scheme 2. On the basis of our experience in the synthesis of lycoricidine and various conduramines, we anticipated that the conduramine unit of narciclasine (**3**) would be formed by a regio- and stereospecific nitroso Diels−Alder addition to the diol derived from 1,3-dibromobenzene (**7**).

o-Vanillin (**11**) serves to furnish the aromatic fragment of narciclasine in the form of borate **10**,[20] and 1,3-dibromobenzene (**6**) provides the asymmetric portion of the molecule by means of toluene dioxygenase oxidation to the corresponding *cis*-cyclohexadiene diol **7**. The two bromine atoms are located in different proenantiotopic spaces by virtue of the particular symmetry present in the *cis*-cyclohexadiene diols, which we have exploited extensively in several preparations.[15a,17a,21,22]

1,3-Dibromobenzene was subjected to whole-cell fermentation with *E. coli* JM109 (pDTG601A), an organism developed by Gibson[23] for the overexpression of toluene dioxygenase (TDO). Biooxidation yielded the new metabolite **7** (4 g/L, >99% ee), a compound that possesses unique latent symmetry and two chemically different vinylic bromine atoms. Diol **7** was transformed in a one-pot operation to bicyclic oxazine **9** in 70% yield (Scheme 3). The acetonide is prepared in neat 2,2-dimethoxypropane (DMP), which is also a suitable solvent for the Diels−Alder cycloaddition. Thus, after verification of complete conversion of diol **7** into acetonide **8**, the periodate and the hydroxamic acid were added. In this way, we were able to shorten the preparation and avoid isolating acetonide **8** which tends to dimerize in its pure state.[24]

Oxazines such as **9** were formed according to ample precedents for the reactions of *cis*-cyclohexadienediols with nitroso dienophiles.[25,26] Our synthesis of cyclitols[25,27] and the alkaloid lycoricidine were based on these reactions.[9h,e,25b,] Reduction of **9** under Keck's conditions[28] yielded the conduramine oxidation state as previously reported,[25a] but gave predominantly the fully dehalogenated conduramine derivative (−)-**15**. This result, although unfavorable for the narciclasine synthesis, pro-

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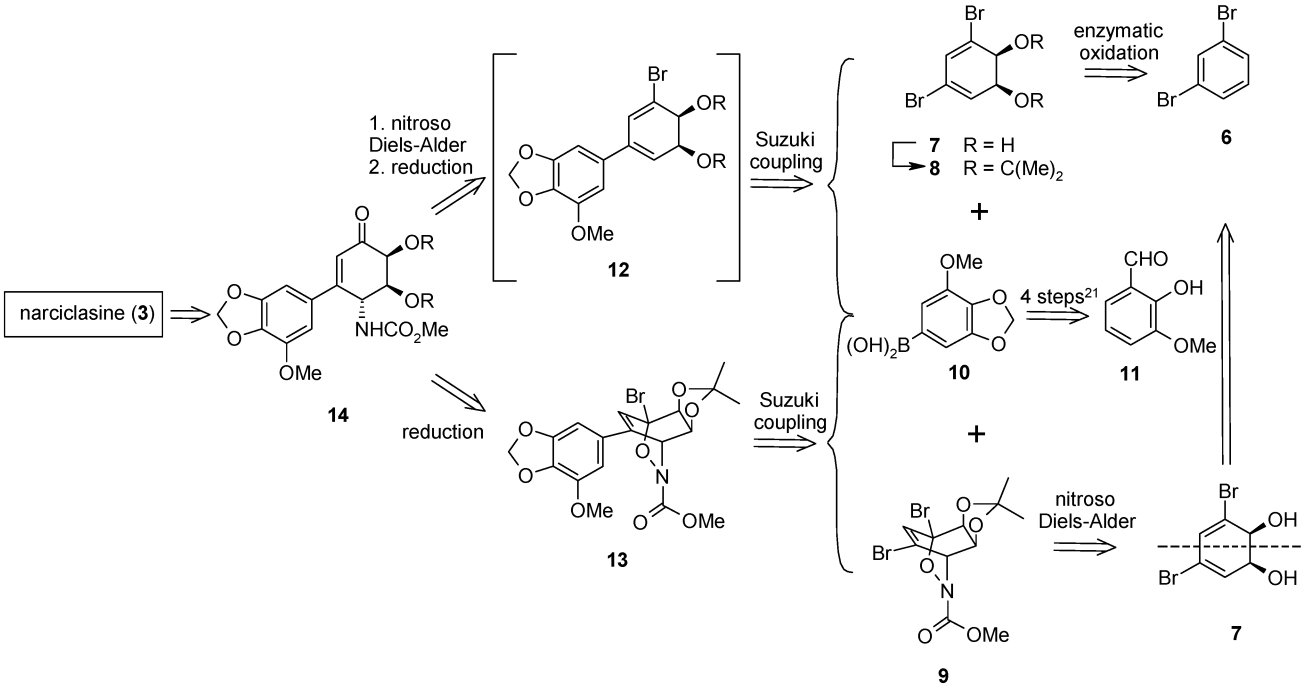
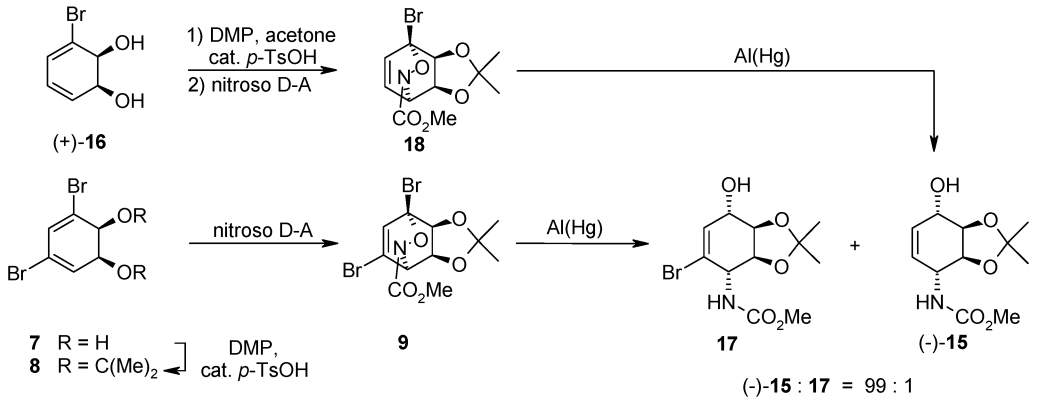
SCHEME 2



SCHEME 3

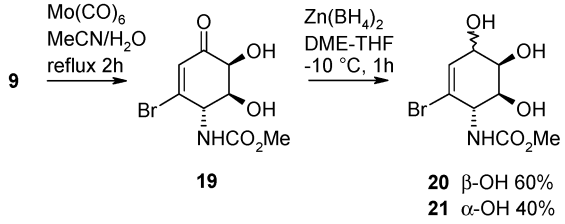


vided conclusive proof of the absolute stereochemistry of diol **7**. Conduramine derivative (−)-**15** was independently prepared from bromodiol (+)-**16**, whose absolute stereochemistry is well established (Scheme 3).[9e,25a] This structure proof also confirmed the assumption that the polarized halodiene would undergo regiospecific nitroso Diels−Alder reaction.[25,27,28]

We studied the reduction of the oxazine in some detail. Our initial plan was to follow the previous reports by Keck et al.[28] by opening the oxazine bridge by reduction with aluminum amalgam in order to obtain a brominated amino conduritol derivative such as **17**. However, we found the same type of overreduction problems that we had observed in the synthesis of lycoricidine.[9e] The vinylic bromine on C10a (narciclasine numbering) was reduced under these conditions, and we isolated the fully debrominated conduramine derivative (−)-**15** and the desired **17** in a 99:1 ratio (HPLC).

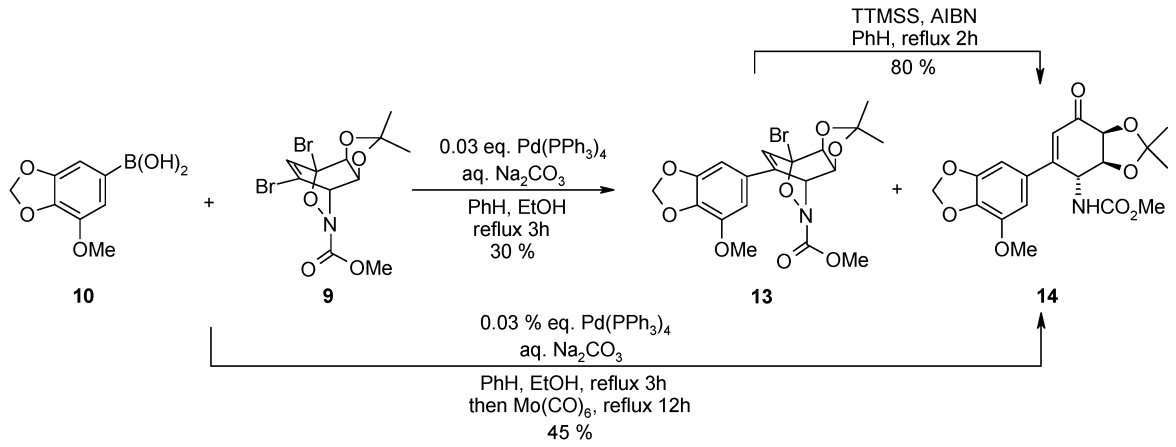
Both tributyltin hydride and tris-trimethylsilylsilane (TTMSS), normally suited for reduction of oxazine **9** to unsaturated ketone **19** cannot be applied here as dehalogenation is unavoidable under such conditions. However, $Mo(CO)_6$[29] cleanly reduced dibrominated oxazine **9** to the corresponding bromo enone **19** with concomitant cleavage of the acetonide protecting group (Scheme 4). Because the mechanism of the cleavage with $Mo(CO)_6$ does not involve radical formation but is rather a metal insertion process,[29a] it can be performed successfully in the presence of vinylic halides.

SCHEME 4



(29) (a) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; Desarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351. (b) Ritter, A. R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4602. (c) Geneste, F.; Racelma, N.; Moradpour, A. *Synth. Commun.* **1997**, *27*, 957. (d) Olivo, H. F.; Hemenway, M. S.; Hartwig, A. C.; Chan, R. *Synlett* **1998**, 247.

SCHEME 5



We explored directed hydride reduction by means of $Zn(BH_4)_2$[30,31] or $NaB(AcO)_3H$.[32] Because of the strong chelating properties of the zinc cation, the reagent has been used to attain anti selectivity in the reduction of acyclic α-hydroxy ketones[33] and has been also exploited for the reduction of *β*-hydroxy ketones with high selectivity.[32] However, in our hands only a disappointing 20% diasteromeric excess has been observed in these reductions (Scheme 4).

To circumvent the problem of overreduction[34] of the bromine atom at C10a, we decided to couple the aromatic portion of the alkaloid (borate **10**) directly to oxazine **9** and postpone the bridge opening to a later stage in the synthesis. The coupling was performed under the standard Suzuki−Miyaura conditions[34] and proceeded only in fair yield (30%). Oxazine **13** was isolated along with 10−15% of ketone **14** (Scheme 5) and 20−25% of substituted biphenyls formed by homocoupling. Enone **14** was formed also through a palladium insertion mechanism similar to the regular cleavage of the nitrogen−oxygen bond in oxazine **9** by $Mo(CO)_6$ as discussed above. To the best of our knowledge, this is the first example of Suzuki coupling of a halo-oxazine and a phenyl borate.

Because **13** was resistant to aluminum amalgam reduction under Keck's conditions, and stronger reducing agents (sodium amalgam or H_2/Pd) led to fully saturated products we transformed **13** into unsaturated ketone **14** instead with *tris*-trimethylsilyl silane (TTMSS). Further improvement was obtained by adding acetonitrile and $Mo(CO)_6$ directly to the Suzuki reaction mixture after the coupling of **9** and **10** was completed. Heating this mixture for 12 h afforded ketone **14** in 45% yield. In this fashion we were able to optimize a preparation of the advanced intermediate **14** in *only three operations from 1,3-dibromobenzene* (Scheme 5).

To set the stereochemistry at C2 (narciclasine numbering), we applied a Luche reduction followed by Mitsunobu inversion as reported by Chida in his preparation of lycoricidine. This procedure gave the desired α-benzoate **23** cleanly in 60% yield from ketone **14** (Scheme 6).

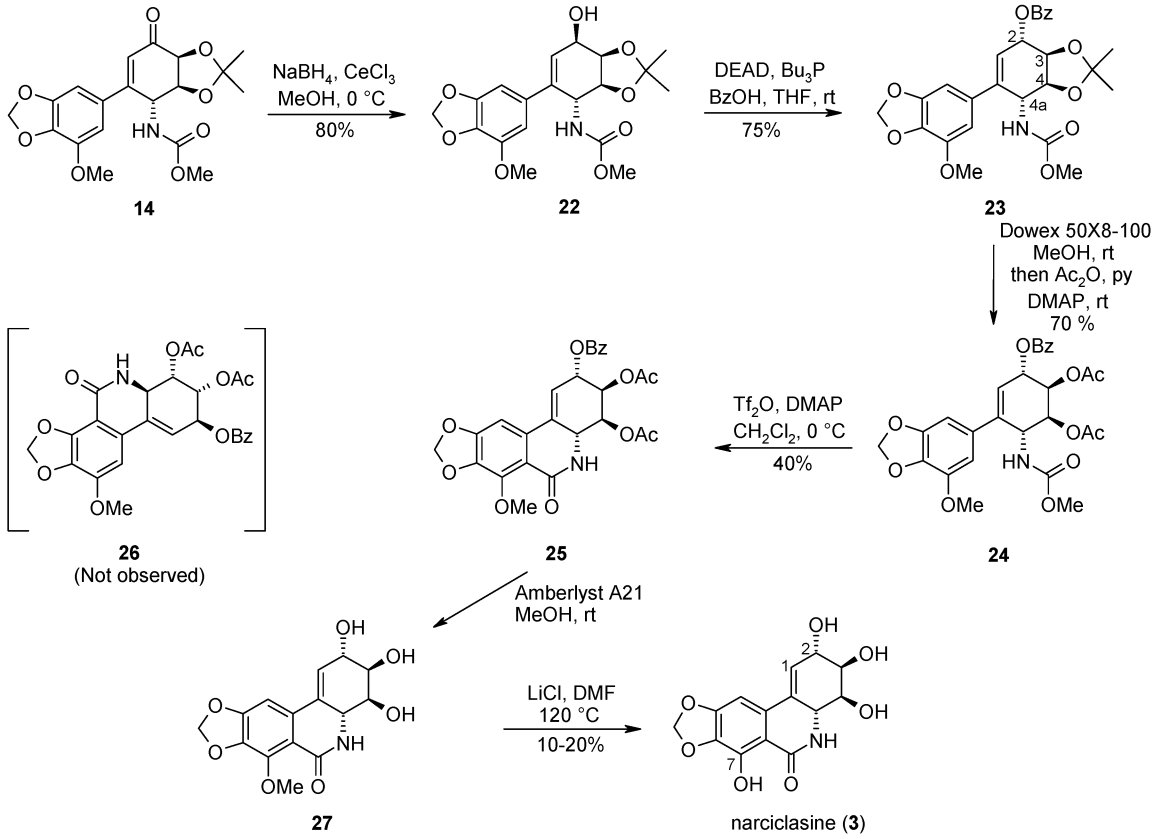
A modification of the Bischler−Napieralski reaction reported by Banwell[35] and applied with success in simplified models of phenanthridone alkaloids[36] was chosen for the last steps of the synthesis. This interesting variation uses a 5:3 mixture of trifluoromethanesulfonic anhydride and DMAP instead of $POCl_3$ to attain cyclization. The reaction has been applied successfully to sensitive molecules not only by Banwell[36] but also by us in the preparation of both enantiomers of 7-deoxypancratistatin, as described below and as previously reported.[10b,e] The acetonide protecting group in **23** was removed by an acidic resin in methanol. This method is convenient because the diols are generally very soluble in methanol and simple filtration of the resin yields a solution of essentially pure product which was treated with acetic anhydride and pyridine. The resulting diacetate **24** was obtained in 90% yield over the two steps (performed as a single operation).

Compound **24** was subjected to Banwell's conditions and afforded phenanthridone **25** in 40% yield. The particular ratio of Tf_2O and DMAP (5:3) was empirically determined by Banwell.[35] With an equimolar mixture, no cyclization is observed. The application of this reaction to other substrates (including acetonides **22** and **23**, and ketone **14**) afforded only phenolic material. Although the closure could result in two isomers (phenanthridones **25** and **26**), we never observed the formation of the latter product. A different result was obtained by Magnus in his synthesis of pancratistatin where a 3:1 ratio of isomers was detected in a related closure.[10h]

The esters in **25** were removed with a basic Amberlyst resin in methanol. The reaction worked efficiently to form a polar fluorescent solid whose ^1H NMR spectrum and optical rotation ($[\alpha]^{26}_D = +204$ (*c* 0.3, DMSO)) matched those of the compound prepared by methylation of natural narciclasine using Piozzi's procedure[6c] (diazomethane in ethanol, 5 days, 50%) ($[\alpha]^{26}_D = +219$ (*c* 1.0, DMSO)).

(30) Narasimhan, S.; Balakumar, R. *Aldrichimica Acta* **1998**, *31*, 19.
(31) Paquette, L. A. *Encyclopedia of Reagents for Organic Synthesis*; J. Wiley: New York, 1995; Vol. 8.
(32) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
(33) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653.
(34) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.
(35) Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockless, D. C. R.; Holman, J. W.; Read, R. W.; Wu, A. W. *J. Chem. Soc., Chem. Commun.* **1995**, 2551.
(36) Banwell, M. G.; Cowden, C. J.; Gable, R. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3515.

SCHEME 6



Cleavage of the methyl ether on the C7−OH of **27** proved to be problematic. After several trials under the conditions reported by Trost and Pulley (LiI, DMF, 80 °C, several hours) for the deprotection of 7-*O*-methylpancratistatin,[10c] we observed only degradation products. An improved and updated procedure[37] performed on 1.0 ± 0.1 mg of 7-*O*-methylnarciclasine (**27**) afforded a polar compound with strong yellow-green fluorescence. Purification of this material afforded 0.3 ± 0.1 mg of a compound that showed an identical ^{1}H NMR spectrum and a matching optical rotation with the literature data for narciclasine ($[\alpha]^{23}_D$ = +130 (*c* 0.03, DMSO), lit.[9j] +141.8). The TOCSY spectrum was fully consistent with structure **3**.

The total synthesis of narciclasine was completed from 1,3-dibromobenzene in 12 steps (14 from *o*-vanillin) and only eight individual operations. This was the second synthesis of narciclasine to be published,[1] and it is 11 steps shorter than the first preparation.[9j] Keck has reported the completion of the third total synthesis of this alkaloid in 12 steps.[9k]

***ent*-7-Deoxypancratistatin.** In a preliminary communication,[10m] we reported a 12-step synthesis of this compound prepared for biological evaluation. The only other *Amaryllidaceae* alkaloid prepared in the ent-series is *ent*-lycoricidine, reported by Keck.[9k] For our approach to the *ent*-alkaloid, we chose the corresponding *ent*-conduramine A, which would be manipulated to the required vinylaziridine by the recently published protocol of Olivo,[38] reporting an improved route to aziridine synthons of this type. The Mitsunobu protocol is greatly superior to the previously used aziridination by the Evans−Jacobsen−Yamada method,[39] which we used during all of our previous syntheses of pancratistatin and 7-deoxypancratistatin.

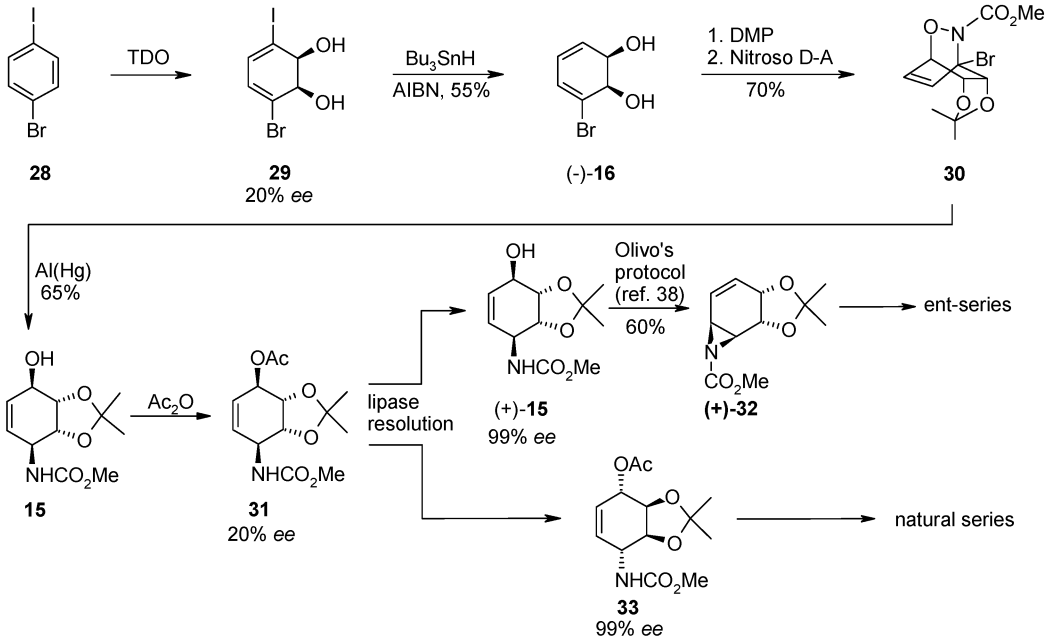
Recent studies by Boyd[18] have shown that the iodine atom present in dihalogenated *cis*-diols such as **29** (obtained by biooxidation with toluene dioxygenase expressed in the blocked mutant *P. putida* UV4) can be selectively removed by catalytic hydrogenolysis (H_2, Pd/C), a procedure which leads to a mixture of (2*S*,3*S*) and (2*R*,3*R*) enantiomers of bromodiol **16**. Boyd used a second fermentation step with a nonblocked strain of Pseudomonas (*P. putida* NCIB 8819) to metabolize the "normal" (2*S*,3*S*) isomer to increase its optical purity. Boyd's method provides a route to (2*R*,3*R*) enantiomers of monosubstituted *cis*-dihydrodiols; however, the valuable (2*S*,3*S*) isomer is destroyed in this procedure. As we were interested in both enantiomers of amino alcohol **15**, we developed an alternative route that would provide both enantiomers in high enantiomeric excess. In addition since the hydrogenolysis of **29** did not provide good results in our hands, the iodine atom was instead removed with Bu_3SnH /AIBN[21] to yield (−)-**16** (55%, 20% ee).

(37) After a personal communication with Dr. Pulley, we obtained the correct procedure that used LiCl in DMF at 120 °C for 2 h, not LiI as reported in ref 10c.

(38) Olivo, H. F.; Hemenway, M. S.; Hartwig, A. C.; Chan, R. *Synlett* **1998**, 247.

(39) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744. (b) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. (c) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361.

SCHEME 7



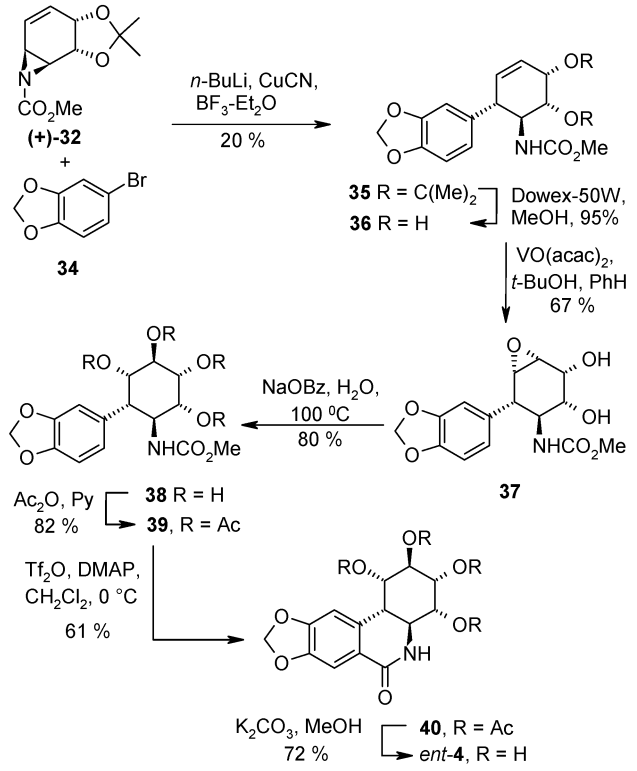
Enantiomerically impure diol (−)-**16** was converted to amino alcohol **15** via oxazine **30** as described in Scheme 7. Alcohol **15** was acetylated with acetic anhydride and pyridine to give **31**. To obtain the optically pure enantiomers, a method similar to that employed by Johnson was used.[19] Under carefully controlled conditions, crude porcine pancreatic lipase (PPL, Sigma type II crude) catalyzed the hydrolysis of optically impure **31** to afford (+)-amino alcohol (+)-**15** and acetate **33** with high enantiomeric purity (99% ee) for a 35−45% conversion of **31**.[19,40] The optical purity of (+)-**15** was determined by comparing the optical rotation value ($[\alpha]^{26}_D = +29.1$ (*c* 1.0, $CHCl_3$) to the corresponding value of the enantiomer (−)-**15** prepared from the "natural" bromocyclohexadiene *cis*-diol: $[\alpha]^{25}_D = -30.1$. (*c* 1.1, $CHCl_3$),[25a] (see Scheme 7).

After the conversion of (+)-**15** to the corresponding *ent*-aziridine (+)-**32**, the synthesis of *ent*-7-deoxypancratistatin was completed exactly as previously published for the natural isomer (Scheme 8),[10b] and the compound was submitted for biological evaluation (see the section on biological activity for a discussion of results).

Regioisomer of 7-Deoxypancratistatin. This alkaloid has served a number of investigators as a somewhat easier model on which to base approaches to the more complex pancratistatin, as the presence of the phenolic hydroxyl in pancratistatin makes for a more difficult synthesis.

After the first and second generation syntheses of the title compound, we turned to a completely new strategy inspired by two reports in the literature. The first was that of Gauthier and Bender, who reported successful intramolecular opening of an epoxide in **41** with a transmetalated arene as shown below.[41] Their ultimate

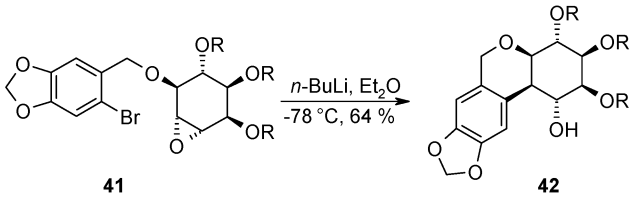
SCHEME 8



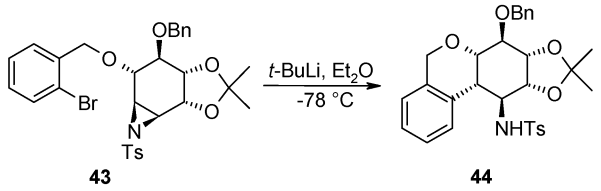
plan called for benzylic oxidation and recyclization of the "Danishefsky lactone" intermediate following the installation of an amine at C4a. However, the oxidation was not reported in the original disclosure, nor has a subsequent report appeared. The second report involved the intramolecular opening of aziridines, first reported by the Rapoport group[42] with studies continued by Bergmeier.[43]

In a model study directed at the synthesis of *ent*-7-deoxypancratistatin by a strategy similar to Bender's, we were also able to cyclize aryl bromide **43** onto the

(40) Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769.
(41) Gauthier, D. R., Jr.; Bender, S. L. *Tetrahedron Lett.* **1996**, *37*, 13.

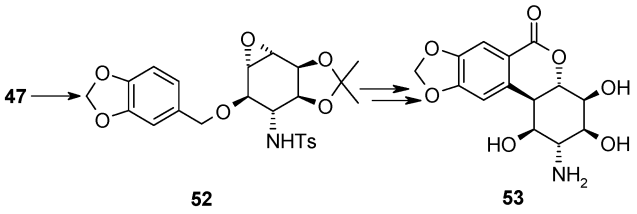


aziridine with *t*-BuLi/Et_2O to produce conduramine **44**, which possesses the ent-configuration required for the alkaloid.[44] However, extension of this model study to the piperonyl derivative of **43** was not successful.



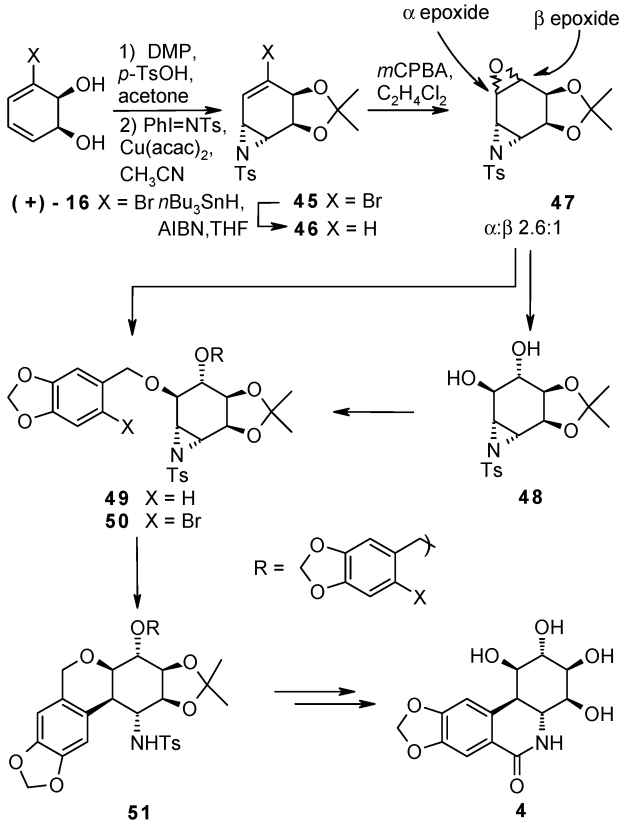
With these precedents, we formulated the strategy outlined in Scheme 9. Protection of the diol in **16** as the acetonide followed by aziridination under Evans's and Jacobsen's protocol[39] generated the tosyl aziridine **45** in 63% yield. Dehalogenation of vinyl bromide **45** under radical conditions followed by epoxidation at elevated temperature produced an inseparable mixture of epoxides **47** (α:β = 2.6:1).[45] Because of the redundant outcome [for definitions of redundant operations see ref 13] of the nucleophilic opening of epoxide **47**, we assumed that either trans diol **48** or trans piperonyl ethers **49** or **50** would be obtained from the isomeric mixture of epoxides **47** upon selective trans-diaxial opening of the oxirane with oxygen nucleophiles. Either transmetalation (**50**) or acid-catalyzed treatment (**49**) would then be used to open the aziridine.

As reported in a recent publication,[46a] the outcome of this approach led to the synthesis of an isomer of 7-deoxypancratistatin, **53**, via the initial opening of the aziridine with the oxygen nucleophile and the subsequent acid-catalyzed cyclization of epoxy ether **52**.



***epi*-7-Deoxypancratistatin.** The inability to open the oxirane selectively in **47** ultimately led to our investigation of the selectivity of nucleophilic opening of cyclic sulfates or sulfites[47] over aziridines contained in the same molecule. Such investigations have not been reported in the literature, to our knowledge. To this end, the cyclic sulfate **55** was prepared as shown in Scheme 10. The tosyl aziridine **46** was synthesized as previously reported.[10e,j] Dihydroxylation of **46** provided cis diol **54** in 85% yield. This material was converted to the cyclic sulfate **55** in 93% yield with sulfuryl chloride in CH_2Cl_2.

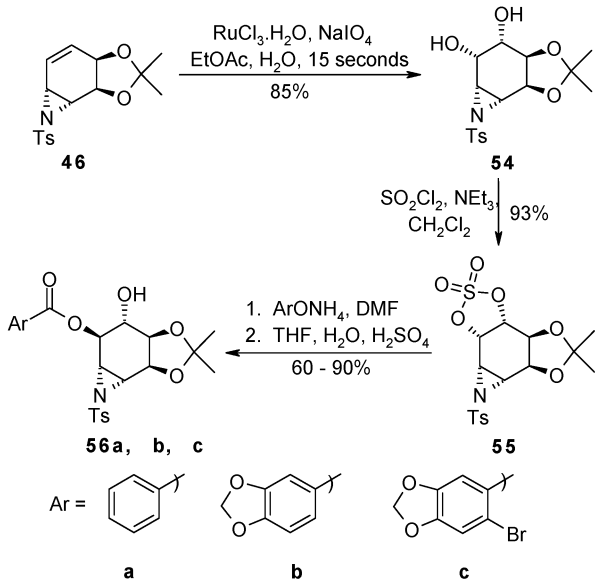
SCHEME 9



We were pleased to find that ammonium salts of several benzoic acid derivatives cleanly differentiated between the aziridine and the cyclic sulfate and led chemoselectively to the trans-disposed ester-alcohols **56a**−**c** in 60−90% yield.[48] In contrast, when epoxides **47**, sulfate **55** and the corresponding sulfite (prepared by reaction of diol **54** with thionyl chloride in CH_2Cl_2) were allowed to react with sodium or potassium salts of piperonol, decomposition or opening of the aziridine rather than the epoxide was observed. Only ammonium salts of carboxylic acids were found to differentiate clearly between these functional groups. Several benzoate derivatives were prepared by this method, namely piperonyl and *o*-bromopiperonyl esters, to study the possibility of intramolecular opening of the aziridine ring by either a

(42) Bergmeier, S. C.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 5019.
(43) Bergmeier, S. C.; Seth, P. P. *J. Org. Chem.* **1999**, *64*, 3237. (b) Bergmeier, S. C.; Fundy, S. L.; Seth, P. P. *Tetrahedron* **1999**, *55*, 8025. (c) Bergmeier, S. C.; Seth, P. P. *Tetrahedron Lett.* **1995**, *36*, 3793.
(44) McLamore, S. D. Ph.D. Dissertation, University of Florida, 1997.
(45) (a) Viehe, H. G.; Vaerman, J. L. *Tetrahedron* **1989**, *45*, 3183. (b) Viehe, H. G.; Vaerman, J. L.; Schmidtchen, F. P.; Kresze, G.; Burger, W.; Braun, H. *Tetrahedron: Asymmetry* **1990**, *1*, 403.
(46) (a) Schilling, S.; Rinner, U.; Chan, C.; Ghiviriga, I.; Hudlicky, T. *Can J. Chem.* **2001**, *79*, 1659. (b) We have reported the synthesis of 7-deoxypancratistatin by the intramolecular aziridine opening at many occasions at conferences. The proceedings of the Heterocyclic Congress in Vienna, August 1999, were published before the erroneous assignment was observed: Hudlicky, T. *J. Heterocycl. Chem.* **2000**, *37*, 535. The incorrectly assigned structure as well as reasons for not detecting this error has been reported as a full paper (ref 46a). The major lesson learned from these endeavor was the recognition that structure assignment of highly similar compounds is very difficult by NMR techniques alone.
(47) (a) Lohray, B. B. *Synthesis* **1992**, 1035. (b) Byun, H. S.; He, L. L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051.
(48) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 655.

SCHEME 10



Lewis acid-mediated process or by an organometallic species derived from **56c**. Unfortunately all attempts to close the ring failed.

Therefore, we decided to return to our original idea of intramolecular aziridine opening in an ether such as **49**. When ester **57** was treated with sodium methoxide in THF, migration of the TBS group took place and alcohols **59** and **60** were obtained, as shown in Scheme 11. We found that increasing the reaction time of the ester cleavage also increased the percentage of alcohol **60** in the reaction mixture. Eventually, we succeeded in preparing the free alcohol **59** without observing silyl migration when ester **57** was treated with excess sodium methoxide for a reaction time of less than 1 min.

Any attempts to alkylate the hydroxyl function in **59** to produce ether **65** failed, but instead gave the epoxide **64** via an aza-Payne rearrangement as shown in Scheme 11. Even deprotonation of the alcohol using *tert*-butyllithium at −30 °C followed by quenching of the alkoxide with excess piperonyl bromide only yielded compound **64**. Interestingly, alkylation of alcohol **60** by means of the same procedure also afforded epoxy amide **64**, which indicates that the reaction sequence involves silyl migration followed by an aza-Payne rearrangement yielding intermediate **63**, which is subsequently alkylated by piperonyl bromide.

Epoxy amide **64** smoothly cyclized to **66** with Me_2AlCl in CH_2Cl_2 in good yield (68%). Prior to $RuCl_3/NaIO_4$ oxidation of the benzylic position, the free hydroxyl group of alcohol **66** was protected as a methoxy methyl ether (**67**). Cleavage of the tosyl group in phenanthridone **69** under reductive conditions using Na/naphthalene in DME at −50 °C afforded amide **69** in 75% yield. Final deprotection of the acetonide, TBS- and MOM-ether with HCl/MeOH in one step[49] provided the cis-C10b epimer of 7-deoxypancratistatin, **70** ($[\alpha]^{25}_D = +5.8$ (*c* 0.49, CH_3OH), mp >280 °C, R_f 0.1 $CHCl_3$/MeOH 4:1).[50] The completion of the synthesis of the cis epimer of 7-deoxypancratistatin validated the strategy proposed originally by Haseltine.[51]

Truncated Derivatives of 7-Deoxypancratistatin. Little information is available concerning the mode of action of pancratistatin although a number of derivatives have been made and tested.[52] It seems likely, though, that the aminocyclitol portion is involved in the antiviral function whereas the anthramide portion plays a role in DNA interactions. We decided to provide truncated derivatives of 7-deoxypancratistatin in order to see at which point the activity of the parent compound would fall off. The synthesis of these compounds is straightforward and is outlined in Scheme 12.

Coupling of a higher order cyanocuprate, derived from 4-bromo-(1,2-methylenedioxy)benzene, with vinyl aziridine **46** or (−)-**32** under Lewis acid catalysis[10d,10f] gave the functionalized cyclohexenes **71**/**72** in yields of 21% and 18% respectively. Oxidation of the olefinic bond was achieved with ruthenium tetroxide, produced in situ, which provided diols **73**/**74** in good yields. A sequence involving deprotection of the acetonide under acidic conditions, oxidative degradation of all vicinal hydroxyl groups in the resulting tetrol, and reduction afforded diols **75**/**76** in 60% and 45% overall yields. Several reported methods for removal of the tosyl group were attempted on diol **75**, all of which were unsucessful. To facilitate removal of the tosyl group, diol **75** was acylated under conditions using excess base as well as excess di-*tert*-butyl dicarbonate which produced alcohol **77**; nevertheless, detosylation attempts still failed. Finally, deprotection of carbamate **76** was achieved by base hydrolysis (10% aq KOH) furnishing the free amine, which was subsequently isolated as the hydrochloride salt **78** as shown in Scheme 12.

Biological Activity Profile

Synthesis of the truncated derivatives, and especially of 7-deoxypancratistatin (**4**) and *ent*-7-deoxypancratistatin (*ent*-**4**), as well as the positional regioisomer of 7-deoxypancratistatin, **53**, and the 10b-epimer or *cis*-7-deoxypancratistain **70** provided the basis for an important extension of prior SAR[11,53−55] cancer cell growth inhibition studies of (+)-pancratistatin (**5**).[6i,j] Against a minipanel of six human cancer cell lines and the marine P388 lymphocytic leukemia cell line, the following results were obtained. Evaluation of 7-deoxypancratistatin (**4**) led to good cancer cell growth inhibition (GI_{50}, μg/mL):

(49) Mandel, M.; Hudlicky, T. *J. Org. Chem.* **1993**, *58*, 2331. (b) Hudlicky, T.; Mandel, M.; Rouden, J.; Lee, R. S.; Bachmann, B.; Dubbing, T.; Yost, K. J.; Merola, J. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1553.

(50) Rinner, U.; Siengalewicz, P.; Hudlicky, T. *Org. Lett.* **2002**, *4*, 115.

(51) Doyle, T. J.; Hendrix, M.; Haseltine, J. *Tetrahedron Lett.* **1994**, *35*, 8295.

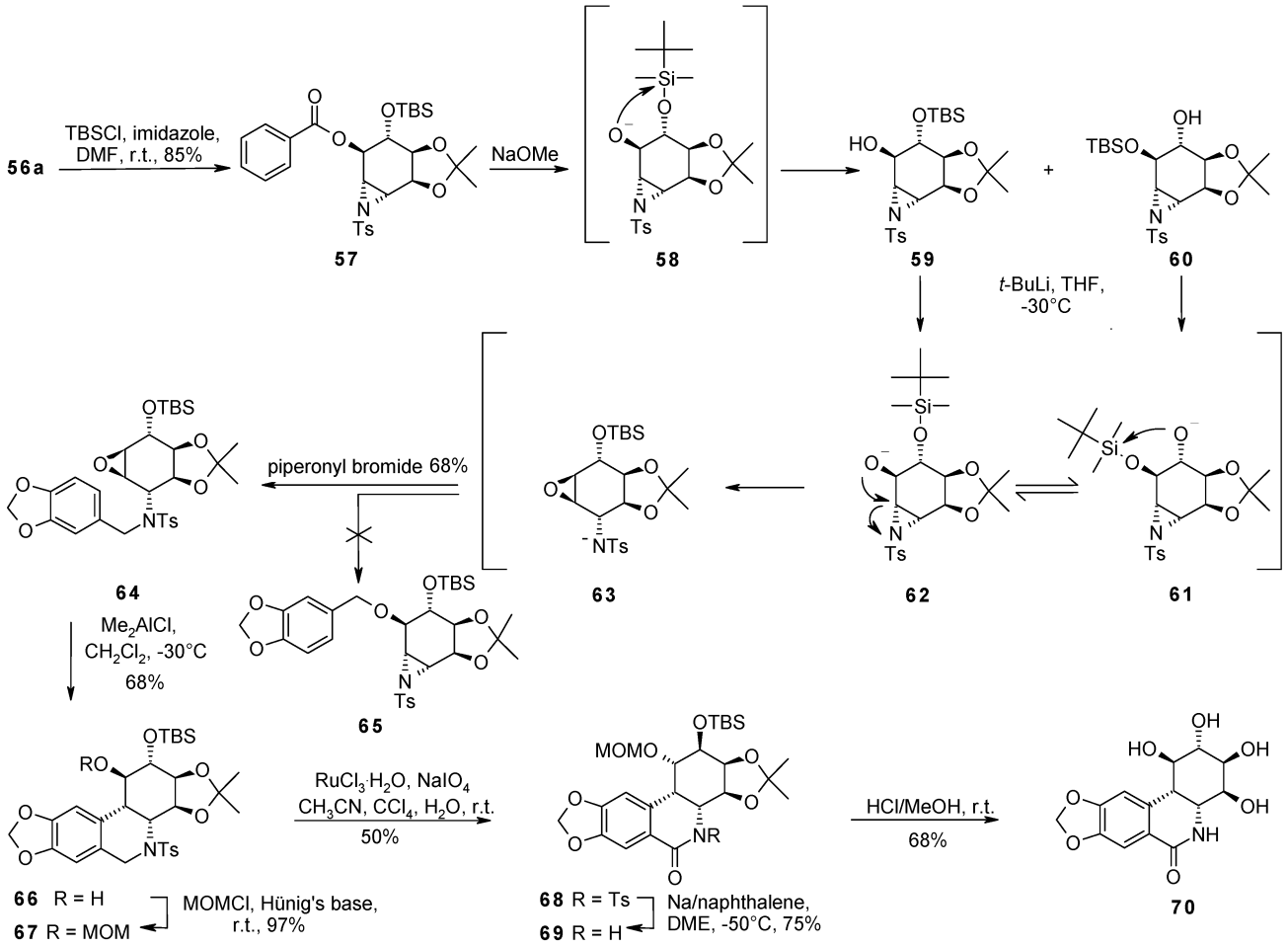
(52) (a) McNulty, J.; Mao, J.; Gibe, R.; Mo, R. W.; Wolf, S.; Pettit, G. R.; Herald, D. L.; Boyd, M, R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 169. (b) Pettit, G. R.; McNulty, J.; Herald, D. L.; Doubek, D. L.; Chapuis, J. C.; Schmidt, J. M.; Tackett, L. P.; Boyd, M. R. *J. Nat. Prod.* **1997**, *60*, 180.

(53) (a) Pettit, G. R.; Cragg, G. M.; Singh, S. B.; Duke, J. A.; Doubek, D. L. *J. Nat. Prod.* **1990**, *53*, 176. (b) Pettit, G. R.; Pettit, G. R., III; Backhaus, R. A. *J. Nat. Prod.* **1993**, *56*, 1682. (c) Pettit, G. R.; Melody, N.; O'Sullivan, M.; Thompson, M. A.; Herald, D. L.; Coates, B. *J. Chem. Soc., Chem. Commun.* **1994**, 2725.

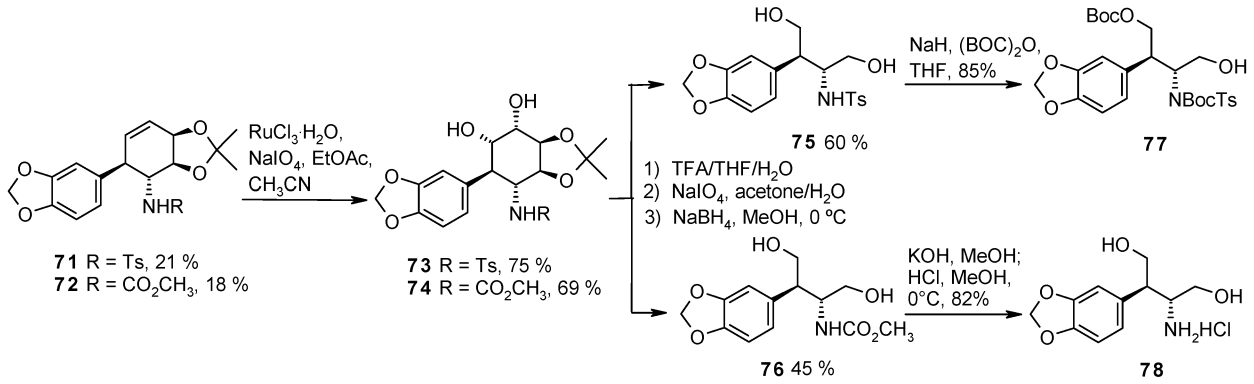
(54) Pettit, G. R.; Melody, N.; Herald, D. L. *J. Org. Chem.* **2001**, *66*, 2583.

(55) Kojima, K.; Mutsuga, M.; Inoue, M.; Ogihara, Y. *Phytochemistry* **1998**, *48*, 1199.

SCHEME 11

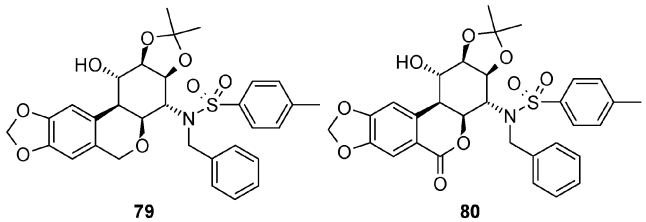


SCHEME 12



CNS SF-295 (0.29), colon KM 20L2 (0.22), lung NCI−H460 (0.29), melanoma SK-MEL-5 (0.23), ovary OVCAR-3 (0.24), renal A498 (0.47), and leukemia P388 (0.44), but the enantiomer with the opposite absolute configuration, *ent*-7-deoxypancratistatin (*ent*-**4**), was about 10-fold less active exhibiting GI_{50} values of 2.0−3.4 μg/mL. Among the truncated substances, only alcohol **77** (shown in Scheme 12) gave any indication of cancer cell line inhibition with GI_{50} 5.3 μg/mL against pancreas-a BX-PG-3 and 8.5 μg/mL with lung NCI−H460. The evaluation of the cis epimer **70** against the six major human cell lines found this compound to be inactive. This finding is interesting from the viewpoint of providing useful information about the precise stereochemical requirements for activity. Note for example that the opposite configuration (in 7-deoxypancratistatin) provides for moderate activity as does the sp^2 hybridization found in lycoricidine and narciclasine. Several derivatives related to the positional isomer **53**[46] have been tested against the same cell lines. Of these compounds, two were found to be moderately active **79** and **80**, which showed GI_{50} values of less than 10 (μg/mL) against the breast cancer cell line MCF-7. Of the compounds related to the cis-fused phenanthridine nucleus of *cis*-7-deoxypancratistatin **70** only **66** showed similar levels of activity against the cell line MCF-7. These results again emphasize the impor-

tance of a nearly intact pancratistatin (**5**) molecule including the phenolic hydroxyl for retaining maximum (e.g., P388 leukemia, GI_{50}, 0.03 μg/mL) cancer cell inhibitory properties.[11,53,54]



79 **80**

Conclusion

It appears that major improvements in the synthesis of important antitumor alkaloids of the *Amaryllidaceae* group have been attained. Our results provide for a synthesis of narciclasine that is only 12 steps and 8 operations. Certainly this brevity begins to support a case for total synthesis as a solution to a supply for natural sources. On the other hand, the several generations of syntheses of 7-deoxypancratistatin, its enantiomer and its 10b-epimer have witnessed only slight improvements over the first generation disclosure of a 14-step preparation of the most important member of this class, pancratistatin. Our 1995 disclosure of the first asymmetric synthesis of this alkaloid still stands as the shortest on record, due in no small part to the incorporation of enzymatic dioxygenation of aromatics into the synthetic strategy. Such oxygenation not only introduces the required asymmetry but plays a key role in all subsequent stereochemical events that are necessary for the attainment of the target. This strategy is at the core of all of our approaches to these compounds and is one of the major reasons for their brevity.

If major improvements in brevity and yields are to materialize, the synthetic strategy that is utilized must lead to the target in 6−8 steps. The experimental difficulties with such a goal are resident in the functionality at C1 and C10b in the fully functionalized alkaloid. By contrast, narciclasine, which bears unsaturation at these two centers, is attainable more easily.

Perhaps the solution to the brevity issue could be achieved by the discovery of a new method for the regio- and steroselective hydration of narciclasine, a strategy attended to by many recent investigatons[55] with no simple solution in sight.

In the area of structure−activity relationships, we have provided additional results and evidences that a full structural core, with the natural stereochemical relationship is required for high level of activity. Our efforts will now be focused solely on further improvements in the brevity of synthetic approaches to these fascinating compounds. We look forward to reporting new results in due course.

Experimental Section

3,5-Dibromo-(1*S*,2*S*)-3,5-cyclohexadiene-1,2-diol (7).[56] *Escherichia coli* JM109 (pDTG601A) was grown overnight at 35 °C with continuous shaking (150 rpm) in an enriched medium (9.6 g of K_2HPO_4, 8.4 g of KH_2PO_4, 3.0 g of $(NH_4)_2SO_4$, 9.0 g of yeast extract, 60 mg of ampicillin, dissolved in 600 mL of tap water). The preculture was then transferred to a 12-L fermentor containing 8 L of medium adjusted to pH 7.0 (60.0 g of KH_2PO_4, 16.0 g of citric acid, 40.0 g of $MgSO_4$, 9.6 mL of concentrated H_2SO_4, 9.6 mL of a 270.0 g/L solution of ferric ammonium citrate, 16.0 mL of a trace metal solution, 0.7 mL of antifoam, 2.69 g of thiamine hydrochloride, and 800 mg of ampicillin), and the cells were grown for approximately 26 h to an OD = 70 (λ = 660 nm). 1,3-Dibromobenzene (50.0 g, 0.32 mol) was added in portions to the culture, and the diol production was checked every 20 min by measuring a characteristic adsorbance peak in the UV region (λ = 282 nm). After all metabolic activity ceased (or no more diol formation was observed by UV), the fermentation was stopped, and the pH was adjusted to 7.5 with NH_4OH. The cells were separated from the broth by centrifugation at 7000 rpm for 20 min, and the resulting clear solution was saturated with sodium chloride and extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The crude diol was purified by recrystallization (methylene chloride/pentane) to yield **7** as a yellowish solid. Because of its instability to storage this material has to be used quickly following its isolation. Yield: 3−4 g/L; R_f 0.4 (hexanes/ethyl acetate, 1:1); mp 80−81 °C; $[\alpha]^{25}_D$ +21.3 (*c* 1.1, acetone); IR (KBr) ν 3255, 1588 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.43 (dd, *J* = 1.5, 0.9 Hz, 1 H), 6.25 (dd, *J* = 4.2, 1.5 Hz, 1 H), 4.41 (dd, *J* = 6.3, 4.2 Hz, 1 H), 4.29 (dd, *J* = 6.3, 0.9 Hz, 1 H), 2.80 (bs, 2 H); ^{13}C NMR (acetone-d_6 75.4 MHz) δ 131.7, 130.3, 129.9, 114.9, 72.1, 71.0; MS (−)ESI CH_3COO^- *m*/*z* 271($^{81}Br + {}^{81}Br$ (M − H)$^-$) 269($^{81}Br + {}^{79}Br$ (M − H)$^-$), 267-($^{79}Br + {}^{79}Br$ (M − H)$^-$). Anal. Calcd for $C_6H_6Br_2O_2 \cdot H_2O$ (phenol) C, 28.61; H 1.60. Found: C, 28.22; H 1.89.

1,8-Dibromo-11-carbomethoxy-4,4-dimethyl-(1*R*,2*S*,6*S*,7*S*)-3,5,10,11-trioxaazatricyclo[5.2.2.0^{2,6}]-8-undecene (9). To a solution of diol **7** (1.5 g, 5.6 mmol) in 2,2-dimethoxypropane (72 mL) was added a catalytic amount of *p*-toluenesulfonic acid. After complete consumption of starting material (TLC analysis), the solution was cooled to 0 °C before water (6 mL) was added. On a preparative scale, the intermediate acetonide was not isolated (analytical samples of **4,6-dibromo-2,2-dimethyl-(3a*S*,7a*S*)-benzo[*d*](1,3)-dioxole** (**8**) were purified by flash column chromatography). Data for the intermediate are as follows: R_f 0.5 (hexanes/ethyl acetate 4:1); $[\alpha]^{26}_D$ +23.3 (*c* 1.0, C_2H_5OH); ^1H NMR (DMSO-d_6, 500 MHz) δ 6.56 (m, 1 H), 6.40 (dd, *J* = 4.4, 1.2 Hz, 1 H), 4.80 (d, *J* = 8.8 Hz, 1 H), 4.76 (dd, *J* = 8.7, 4.4 Hz, 1 H), 1.33 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR (DMSO, 125 MHz) δ 129.3, 127.2, 125.8, 117.4, 106.3, 74.3, 73.5, 27.0, 25.2.

$NaIO_4$ (1.2 g, 5.6 mmol) was added to the reaction vessel before methyl carbamate (0.59 g, 5.6 mmol, in 10 mL of methanol) was added dropwise. After addition, the solution was allowed to warm to room temperature and stirred for 16 h. Upon completion of the reaction (TLC analysis), an excess of saturated aqueous sodium bisulfite was added carefully until a light straw color was obtained. The mixture was extracted with Et_2O (3 × 100 mL), the organic phase was washed with brine (2 × 15 mL) and dried over $MgSO_4$, and the solvent was removed in vacuo. The reaction product was isolated by flash column chromatography (hexanes/ethyl acetate 7:3) affording 1.3 g (60%) of **9** as a colorless solid. R_f 0.3 (hexanes/ethyl acetate 7:3); mp 150−152 °C; $[\alpha]^{25}_D$ +36.4 (*c* 1.1, $CHCl_3$); IR (KBr) ν 1724, 1601 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 6.37 (dd, *J* = 2.3, 0.9 Hz, 1 H), 5.13 (dd, *J* = 4.4, 2.3 Hz, 1 H), 4.24 (dd, *J* = 6.9, 1.0 Hz, 1 H), 4.07 (dd, *J* = 6.9, 4.3 Hz, 1 H), 3.26 (s,

(56) All nonhydrolytic reactions were carried out under an argon atmosphere. Glassware used for moisture sensitive reactions was flame-dried with an internal inert gas sweep. THF was distilled from sodium benzophenone. Analytical TLC was performed on silica gel 60-F_{254} plates. Flash chromatography was performed using Kieselgel 60 (230−400 mesh). IR spectra were recorded as neat samples on a Perkin-Elmer 1600 Series FT spectrometer. ^1H and ^{13}C NMR spectra were obtained on a Varian 300 or 500 MHz instrument. Proton and carbon chemical shifts are reported in ppm, relative to chloroform (7.24 and 77.23 ppm), respectively. Mass spectra were recorded on a Finnigan-Matt *95* instrument.

3 H), 1.20 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 158.2, 132.9, 121.2, 111.5, 87.9, 81.2, 74.6, 61.7, 53.4, 25.5, 24.9; MS (FAB) *m*/*z* 401 (^{81}Br + ^{81}Br, $[M + H]^+$), 400 (^{81}Br + ^{79}Br, $[M + H]^+$), 399 (^{79}Br + ^{79}Br, $[M + H]^+$); HRMS calcd for $C_{11}H_{14}NBr_2O_5$: 399.9219; Found: 399.9195. Anal. Calcd for $C_{11}H_{13}NBr_2O_5$: C 33.11, H 3.28, N 3.51. Found: C, 33.23; H 3.29; N, 3.43.

4-Methoxybenzo[*d*][1,3]dioxole-6-boronic Acid (10). To a solution of 6-bromo-4-methoxybenzo[*d*][1,3]dioxole (3.0 g, 13.0 mmol) in anhydrous THF (55 mL) cooled to −78 °C was added dropwise 0.7 M *tert*-butyllithium in hexane (10.0 mL). During the addition the solution turned dark purple. After 15 min, triethyl borate (3.1 mL, 18.2 mmol) was added dropwise. The dark purple color vanished 5 min after addition of the reagent was complete. After 2 h at −78 °C, the reaction was quenched with saturated aq NH_4Cl. Ethyl acetate (50 mL) and water (30 mL) were added, the layers were separated, and the aqueous phase was extracted with EtOAc (4 × 30 mL). The combined organic layer was washed with brine (2 × 15 mL), dried over $MgSO_4$, and concentrated to afford 2.5 g (97%) of **10** as a white-gray solid which decomposed on silica gel chromatography but was pure enough to be used for the next step. Mp > 200 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 6.96 (s, 1 H), 6.81 (s, 1 H), 5.82 (s, 2 H), 3.79 (s, 3 H); ^{13}C NMR (CD_3OD, 75 MHz) δ 115.4, 108.2, 103.1 (3 C), 102.3, 57.3.

1-Bromo-11-carbomethyoxy-4,4-dimethyl-8-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-(1*R*,2*S*,6*S*,7*S*)-3,5,10,11-trioxaazatricyclo[5.2.2.0^{2,6}]-8-undecene (13). To a solution of $Pd(PPh_3)_4$ (14.5 mg, 0.05 mmol) in benzene (3 mL) were added bromide **9** (100 mg, 0.26 mmol) and aq 2 M Na_2CO_3 (1 mL). Borate **10** (64 mg, 0.30 mmol) in ethanol (2 mL) was added, and the mixture was stirred at reflux until total consumption of the starting material (12 h). The product was extracted with Et_2O (3 × 25 mL), and the organic phase was washed with 5% hydrochloric acid (10 mL) and brine (3 × 10 mL) and then dried over $MgSO_4$ before the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexanes/ethyl acetate) affording **13** (52 mg, 44%). R_f 0.7 (hexanes/ethyl, acetate 7:3); mp 158−160 °C; $[\alpha]^{25}_D$ +37.1 (*c* 1.0, $CHCl_3$); IR (KBr) ν 4214, 3019, 2400, 1214 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 6.82 (d, J = 1.3 Hz, 1 H), 6.73 (d, J = 1.4 Hz, 1 H), 6.48 (dd, J = 2.1, 1.1 Hz, 1 H), 5.45 (dd, J = 4.1, 2.0 Hz, 1 H), 5.23 (m, 1), 4.52 (dd, J = 7.0, 1.0 Hz, 1 H), 4.31 (dd, J = 7.1, 4.3 Hz, 1 H), 3.43 (s, 3 H), 3.24 (s, 3 H), 1.12 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.3, 149.4, 143.8, 143.7, 136.4, 129.7, 124.0, 111.7, 106.1, 101.8, 100.3, 87.8, 81.2, 74.2, 56.6, 55.9, 54.1, 25.8, 25.3; FAB MS *m*/*z* 472 (^{81}Br $[M + H]^+$), 470 (^{79}Br $[M + H]^+$), 332, 290, 154; HRMS: Calcd for $C_{19}H_{21}N^{81}BrO_8$: 472.0434. Found: 472.0423; Calcd for $C_{19}H_{21}N^{79}BrO_8$: 470.0451. Found: 470.0360. Anal. Calcd for $C_{19}H_{20}NBrO_8$: C, 48.53; H, 4.29; N, 2.98. Found: C, 48.52; H, 4.33; N, 2.90.

7-Aminocarbomethyoxy-2,2-dimethyl-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-(3a*S*,7*R*,7a*S*)-4,7-dihydrobenzo[*d*][1,3]dioxol-4-one (14). To a degassed solution of oxazine **13** (370 mg, 0.78 mmol) in benzene (16 mL) was added tris(trimethylsilyl)silane (39 mg, 1.57 mmol). The reaction mixture was heated to reflux, and a catalytic amount of AIBN was added. Heating and stirring was continued for 90 min (total consumption of starting material) before the reaction mixture was allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue purified by flash column chromatography using a gradient of hexanes and ethyl acetate affording **14** (200 mg, 65%); R_f 0.50 (ethyl acetate); mp 81−84 °C; $[\alpha]^{26}_D$ −26.8 (*c* 1.1 $CHCl_3$); IR (neat on NaCl plates) ν 2806, 2706, 1980, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.83 (s, 1 H), 6.74 (d, J = 2.2 Hz, 1 H), 6.38 (s, 1 H), 5.99 (s, 2 H), 5.47 (d, J = 8.2 Hz, 1 H), 5.24 (d, J = 8.2 Hz, 1 H), 4.63 (dd, J = 5.0, 2.2 Hz, 1 H), 4.42 (d, J = 5.1 Hz, 1 H), 3.87 (s, 3 H), 3.65 (s, 3 H), 1.37 (s, 3 H), 1.28 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 195.7, 156.2, 153.2, 149.6, 143.8, 138.0, 129.9, 123.6, 110.4, 107.5, 102.2, 100.9, 77.1, 73.4, 56.6, 52.7, 47.9, 27.4, 25.9; MS (CI): 392 ($[M + H]^+$, 100), 391 (M^+, 92), 291 (18), 187 (7); HRMS Calcd for $C_{19}H_{22}NO_8$: 392.1345. Found: 392.1320. Anal. Calcd for $C_{19}H_{21}NO_8$: C, 58.31; H, 5.41; N 3.58. Found: C, 58.61; H, 5.56; N, 3.29.

Tandem Suzuki Coupling−Oxazine Reduction. To a solution of $Pd(PPh_3)_4$ (290 mg, 0.25 mmol) of benzene (45 mL) were added bromide **9** (2.0 g, 5.0 mmol), aq 2 M Na_2CO_3 (5 mL), and borate **10** (1.2 g, 6.0 mmol) in ethanol (2 mL). The reaction mixture was stirred at reflux for 8 h (total consumption of starting material) then $Mo(CO)_6$ (1.0 g, 3.8 mmol) was added. After 12 h, the resulting heterogeneous reaction mixture was allowed to cool to room temperature, and the mixture was filtered through a pad of silica gel. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, the solvent removed under reduced pressure, and the residue purified by flash column chromatography affording 600 mg (31%) of product **14**.

7-Aminocarbomethyoxy-2,2-dimethyl-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-(3a*R*,4*R*,7*R*,7a*S*)-4,7-dihydrobenzo[*d*][1,3]dioxol-4-ol (22). To a stirred solution of ketone **14** (1.30 g, 3.32 mmol) in methanol (22 mL) was added cerium chloride (1.23 g, 4.98 mmol). After 5 min, the mixture was cooled to 0 °C, and $NaBH_4$ (138 mg, 3.65 mmol) was added. The reaction mixture was stirred at 0 °C until total consumption of starting material (30 min). The reaction was quenched by adding a few drops of 50% acetic acid to neutral pH. Water (50 mL) and methylene chloride (50 mL) were added, and the heterogeneous mixture was extracted with methylene chloride (4 × 20 mL). The organic layer was washed with water (3 × 15 mL) and brine (2 × 15 mL). The combined organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography using gradient mixtures of ethyl acetate and hexanes affording **22** (400 mg, 50%) as colorless solid. (Note: On a smaller scale, 200 mg (0.511 mmol) of starting material **14**, 174 mg of **23** (80%) was isolated); R_f 0.2 (ethyl acetate); mp: 91−94 °C; $[\alpha]^{25}_D$ −14.4 (*c* 0.8, $CHCl_3$); IR (KBr) ν 2820, 2660, 1955, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.54 (s, 1 H), 6.53 (s, 1 H), 6.05 (s, 1 H), 5.92 (s, 2 H), 4.65 (m, 4 H), 4.40 (d, J = 9 Hz, 1 H), 3.85 (s, 3 H), 3.64 (s, 3 H), 2.88 (d, J = 10 Hz, 1 H), 1.30 (s, 3 H), 1.27 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.5, 149.1, 143.5, 137.0, 135.2, 133.6, 130.6, 109.2, 105.6, 101.5, 99.8, 66.5, 56.8, 52.3, 51.0, 26.1, 24.5; MS (CI) 392 ($[M - H]^+$), 334, 259, 173; HRMS Calcd for $C_{19}H_{24}NO_8$: 394.1502. Found: 394.1478. Anal. Calcd for $C_{19}H_{23}NO_8$: C, 58.01; H 5.89. Found: C, 58.07; H, 6.29.

7-Aminocarbomethyoxy-2,2-dimethyl-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-(3a*R*,4*S*,7*R*,7a*S*)-4,7-Dihydrobenzo[*d*][1,3]dioxol-4-yl Benzoate (23). To a solution of alcohol **22** (200 mg, 0.51 mmol) in anhydrous THF (10 mL) were added tributylphosphine (0.26 mL, 1.02 mmol), benzoic acid (125 mg, 1.02 mmol), and DEAD (0.16 mL, 1.02 mmol) at 25 °C, and the solution was stirred until total consumption of starting material (2 h). The mixture was concentrated, and the residue was purified by flash column chromatography using hexanes/ethyl acetate (6:4) affording ester **23** as an oil (133 mg, 52%). R_f 0.5 (hexanes/ethyl acetate, 6:4); $[\alpha]^{25}_D$ −12.22 (*c* 1.0, $CHCl_3$); IR (solution in $CHCl_3$) ν 3420, 1745, 1720, 1492 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 8.08 (d, J = 6.6 Hz, 2 H), 7.75 (d, J = 5.5 Hz, 1 H), 6.89 (s, 1 H), 6.80 (d, J = 1.1 Hz, 1 H), 6.28 (d, J = 6.6 Hz, 1 H), 5.85 (dd, J = 6.6, 1.4 Hz, 1 H), 5.40 (s, 2 H), 5.28 (s, 2 H), 4.58 (d, J = 6.9 Hz, 1 H), 4.37 (d, J = 6.9 Hz, 1 H), 3.92 (q, J = 7.1 Hz, 1 H), 3.80 (q, J = 7.1 Hz, 1 H), 3.50 (s, 3 H), 3.40 (s, 3 H), 1.29 (s, 3 H), 1.13 (s, 3 H); ^{13}C NMR (C_6D_6, 75 MHz) δ 165.0, 156.2, 149.9, 145.4, 144.3, 133.6, 133.4, 131.6, 129.9, 121.3, 108.7, 107.1, 101.43, 100.4, 78.0, 74.9, 69.0, 63.5, 62.4, 56.3, 52.1, 50.5, 26.5, 24.4, 14.2, 13.6; MS (CI): 497 (M^+), 480, 376, 318, 281, 215, 105; HRMS Calcd for $C_{26}H_{27}NO_9$ ($[M]^+$): 497.1686, Found: 497.1716; HRMS Calcd for $C_{26}H_{28}NO_9$ ($[M + H]^+$): 498.1764, Found: 498.1752.

6-Aminocarbomethoxy-1,2-dihydroxy-5-(7-methoxybenzo-[*d*][1,3]dioxol-5-yl)-4-cyclohexene-1-yl Benzoate (24). To a solution of benzoate **23** (120 mg, 0.241 mmol) in methanol (7 mL) was added a catalytic amount of Dowex 50 × 8−100 ion-exchange resin. After the mixture was stirred for 12 h at room temperature (until no more starting material could be detected by TLC), the resin was removed by filtration. The solvent was evaporated under reduced pressure to afford the intermediate diol. The crude product was dissolved in pyridine (1 mL, 12.5 mmol) and cooled to 0 °C. Acetic anhydride (0.5 mL, 5.3 mmol) and a catalytic amount of DMAP were added. The reaction mixture was stirred at room temperature until total consumption of the starting material (3 h). Ether (5 mL) and water (2 mL) were added, and the organic phase washed with 2 mL aliquots of 10% aq copper(II) sulfate and then 2 mL of brine. The organic layer was dried over $MgSO_4$, the solvent removed under reduced pressure, and the residue purified by flash column chromatography (hexanes/ethyl acetate) affording benzoate **24** as colorless solid (44.8 mg, 34%); R_f 0.3 (hexanes/ethyl acetate 2:1); mp 112−115 °C; $[\alpha]^{26}_D$ −11.5 (*c* 1.0, $CHCl_3$); IR (KBr) ν 3368 (br), 1750, 1720, 1602, 1521, 1447 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.04 (dd, J = 8.5, 1.7 Hz, 2 H), 7.57 (tt, J = 7.4, 1.4 Hz, 1 H), 7.44 (t, J = 7.7 Hz, 2 H), 6.58 (s, 1 H), 6.57 (s, 1 H), 6.10 (d, J = 3.0 Hz, 1 H), 5.94 (s, 2 H), 5.82 (dd, J = 6.9, 3.0 Hz, 2 H), 5.54 (dd, J = 4.4, 2.5 Hz, 1 H), 5.49 (dd, J = 7.1, 2.5 Hz, 1 H), 4.90 (m, 1 H), 4.80 (d, J = 8.8 Hz, 1 H), 3.86 (s, 3 H), 3.64 (s, 3 H), 2.12 (s, 3 H), 2.03 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2, 169.9, 165.9, 149.2, 143.5, 133.4, 131.2, 129.8, 129.5, 128.5, 123.2, 106.2, 101.7, 100.6, 70.9, 69.6, 69.0, 56.6, 52.6, 51.0, 20.9, 20.8 (3 quaternary carbons below noise level); MS (FAB) 541 (M^+, 2), 391 (60), 149 (100); HRMS Calcd for $C_{27}H_{27}NO_{11}$: 541.1584. Found: 541.1627.

Data for the intermediate diol: **6-Aminocarbomethoxy-1,2-dihydroxy-5-(7-methoxybenzo-[*d*][1,3]dioxol-5-yl)-4-cyclohexene-1-yl Benzoate.** ^1H NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, J = 8.0 Hz, 2 H), 7.75 (t, J = 7.7 Hz, 1 H), 7.41 (t, J = 7.7 Hz, 2 H), 6.58 (d, J = 4.1 Hz, 2 H), 6.04 (d, J = 2.8 Hz, 1 H), 5.93 (s, 2 H), 5.75 (dd, J = 6.3, 3.6 Hz, 1 H), 4.85 (bs, 2 H), 4.20 (s, 1 H), 4.13 (s, 1 H), 3.84 (s, 3 H), 3.60 (s, 3 H), 2.02 (s, 1 H).

3,4-Diacetoxy-7-methoxy-(2*S*,3*R*,4*S*,4a*R*)-2,3,4,6-tetrahydro[1,3]dioxolo[4,5-*j*]phenanthridin-6-one-2-yl Benzoate (25). To a solution of diacetate **24** (42 mg 0.08 mmol) and DMAP (28.4 mg, 0.23 mmol) in CH_2Cl_2 (2 mL) cooled to −10 °C was added trifluoromethanesulfonic anhydride (70 mL, 0.39 mmol). The reaction mixture was stirred for 5 h at −10 °C to −5 °C and for 12 h at 0 °C. After total consumption of starting material (TLC analysis), the solvents were removed under reduced pressure, and THF (2 mL) was added. The reaction mixture was cooled to 0 °C and two drops of 2 M aq HCl was added. The mixture was stirred for 2 h, and solid sodium bicarbonate was added. The solvent was removed under reduced pressure and the residue purified by flash column chromatography (hexanes/ethyl acetate, 6:4), affording ester **25** as a yellow oil (13.8 mg, 41%); R_f 0.1 (hexanes/ethyl acetate, 2:1); $[\alpha]^{26}_D$ +22.4 (*c* 1.1, $CHCl_3$); IR ν 3490 (br), 2940, 2858, 1660, 1613 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.04 (dd, J = 1.5, 7.0 Hz, 2 H), 7.56 (tt, J = 1.2, 7.3 Hz, 1 H), 7.43 (t, J = 7.8 Hz, 2 H), 6.79 (s, 1 H), 6.25 (m, 1 H), 6.11 (s, 1H), 6.08 (bs, 1H), 6.05 (d, J = 1.2 Hz, 1 H), 6.00 (d, J = 1.2 Hz, 1 H), 5.57 (m, 2 H), 5.35 (dd, J = 2.2, 8.9 Hz, 1 H), 4.57 (d, J = 9.1 Hz, 1 H), 4.03 (s, 3 H), 2.13 (s, 3 H), 2.09 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.6, 129.9, 128.6, 117.6, 102.0, 99.6, 71.6, 68.89, 68.2, 61.0, 50.0, 20.9, 20.8; HRMS calcd. for $C_{26}H_{24}NO_{10}$: 510.1400. Found: 510.1419.

2,3,4-Trihydroxy-7-methoxy-(2*S*,3*R*,4*S*,4a*R*)-2,3,4,6-tetrahydro[1,3]dioxolo[4,5-*j*]phenanthridin-6-one (7-Methylnarciclasine) (27). To a solution of phenanthridone **25** (10 mg, 0.024 mmol) in methanol (2 mL) was added a caralytic amount of Amberlyst A-21 weakly basic ion-exchange resin. The mixture was stirred for 2 h at room temperature until total consumption of starting material (TLC analysis), The resin was removed by filtration and the solvent removed under reduced pressure affording 6 mg (80%) of the known derivative of narciclasine **27**;[6c] R_f 0.40 (4:1 CH_2Cl_2−MeOH); $[\alpha]^{26}_D$ +204 (*c* 0.3, DMSO); IR (KBr) ν 3423 (br.), 2952, 2366, 1631, 1465 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 6.91 (s, 1 H), 6.17 (m, 1 H), 6.08 (d, J = 1.1 Hz, 1 H), 6.02 (d, J = 1.1 Hz, 1 H), 4.24 (m, 2 H), 3.98 (s, 3 H), 3.90 (m, 2 H); ^{13}C NMR (CD_3OD, 75 MHz) δ 154.1, 145.5, 140.2, 135.2, 133.7, 123.7, 115.0, 103.6, 100.5, 74.2, 71.0, 70.8, 61.1, 53.6; MS (LC/ESI MS): 653.5 ([M + H + M]$^+$), 322 ([M + H]$^+$).

2,3,4-Trihydroxy-7-methoxy-(2*S*,3*R*,4*S*,4a*R*)-2,3,4,6-tetrahydro[1,3]dioxolo[4,5-*j*]phenanthridin-6-one (7-Methylnarciclasine) (27). This derivative of (+)-narciclasine was prepared as described in the literature.[6c] A pure sample of natural narciclasine (**3**) (15 mg) was dissolved in excess freshly prepared diazomethane in ethanol/acetonitrile. The reaction mixture was stirred for several hours until the yellow color disappeared. The extent of the reaction was determined by TLC, and the product was purified by flash column chromatography using a mixture of methylene chloride and methanol. All data obtained for this compound matched the synthetic product, including ^1H NMR and optical rotation. $[\alpha]^{26}_D$ +219 (*c* 1.0, DMSO).

2,3,4,7-Tetrahydroxy-(2*S*,3*R*,4*S*,4a*R*)-2,3,4,6-tetrahydro-[1,3]dioxolo[4,5-*j*]phenanthridin-6-one (Narciclasine) (3). To a solution of crude triol **27** (15 mg, 0.047 mmol) in anhydrous DMF (2 mL) was added anhydrous LiCl (10 mg, 0.24 mmol) under a stream of argon. The mixture was heated to 120 °C until total consumption of starting material (4 h). After the solvent was removed under reduced pressure, the residue was adsorbed on silica gel and purified by flash column chromatography (methylene chloride/methanol 4:1) affording 3 mg of narciclasine (20%). For a detailed study of the NMR spectra of narciclasine see ref 6g. R_f 0.6 (CH_2Cl_2/MeOH, 4:1); ^1H NMR (DMSO-d_6, 500 MHz) δ 13.25 (s, 1 H), 7.88 (s, 1 H), 6.85 (s, 1 H), 6.15 (dd, J = 4.5, 2.8 Hz, 1 H), 6.08 (m, 2 H), 5.19 (d, J = 6.3 Hz, 1 H), 5.16 (d, J = 5.6 Hz, 1 H), 5.01 (d, J = 3.8 Hz, 1 H), 4.18 (ddd, J = 8.6, 2.4, 1.4 Hz, 1 H), 4.01 (m, 1 H), 3.79 (ddd, J = 8.0, 5.5, 2.2 Hz, 1 H), 3.69 (m, 1 H). Signals at 13.25, 7.88, 5.19, 5.16, and 5.01 can exchange with deuterium on addition of deuterium oxide. A TOCSY experiment confirmed the assigned structure. Optical rotation of this compound matched that obtained by Rigby as well as the value for the natural product.

3-(Methoxycarbonyl)-1-bromo-5,6-*O*-isopropylidene-2-oxa-3-azobicyclo[2.2.2]oct-7-ene-5,6-diol (30). To a solution of the acetonide of (−)-(**16**) (9.6 g, 0.042 mol) in MeOH/H_2O (16:4, 150 mL) at 0 °C were added $NaIO_4$ (8.9 g, 42 mmol) and *N*-hydroxymethyl carbamate (3.8 g, 42 mmol). The reaction mixture was allowed to warm to room temperature, and the solution was stirred until total consumption of the starting material (18 h). Water (100 mL) and concentrated aqueous $NaHSO_3$ (100 mL) were then added, and the resulting mixture was extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layer was washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure The residue was purified by flash column chromatography (hexane/ethyl acetate, 4:1) to yield **30** as colorless solid (7.7 g, 70%). R_f 0.23 (hexanes/ethyl acetate, 4:1); $[\alpha]^{28}_D$ −8.3 (*c* 1.19 $CHCl_3$);^1H NMR (300 MHz, $CDCl_3$) δ 6.51 (dd, J = 9.0, 1.5 Hz, 1H), 6.41 (m, 1H), 5.05 (m, 1H), 4.60 (d, J = 2.0 Hz, 2H), 3.77 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 134.0, 131.7, 111.5, 81.2, 74.1, 54.0, 53.0, 25.6, 25.4.

6-(*N*-Methoxycarbonyl)amino)-1,2-*O*-isopropylidenecyclohex-4-en-1,2,3-triol (15). To a solution of **30** (7.0 g, 22 mmol) in a mixture of THF (500 mL) and H_2O (50 mL) was added 4.15 g of Al (Hg) at 0 °C. The reaction mixture was stirred at for 3 h 0 °C and then at room temperature until total consumption of the starting material (12 h). The reaction mixture was diluted with THF (250 mL) and stirred for 10 min, filtered through Celite, and concentrated in vacuo. The

residue was purified by flash column chromatography (hexanes/ethyl acetate, 1:2) to yield alcohol **15** (3.7 g, 65%); R_f: 0.57 (hexanes/ethyl acetate, 1:2); $[\alpha]^{28}_D$ +7.6 (*c* 1.20, $CHCl_3$); ^{1}H NMR (300 MHz,$CDCl_3$) δ 5.86 (dd, J = 10.0, 2.7 Hz, 1 H), 5.74 (dd J = 10.0, 1.6 Hz, 1 H), 5.50 (d, J = 8.0 Hz, 1 H), 4.15 (m, 3 H), 4.02 (m, 1H), 3.60 (m, 4 H), 1.38 (s, 3 H), 1.28 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 131.6, 130.0, 109.4, 79.60, 8.0, 69.2, 52.6, 51.4, 27.2, 25.0; HMRS (CI) calcd for $C_{11}H_{19}NO_5$: 244.1184; Found 244.1145. Anal. Calcd for $C_{11}H_{18}NO_5 \cdot {}^1/_2H_2O$: C; 52.17; H, 7.11; N, 5.53. Found: C, 52.10; H, 6.78; N, 5.33.

(1*R*,2*R*,3*R*,6*S*)-6-(*N*-Carbomethoxy)amino)-1,2-*O*-isopropylidenecyclohex-4-ene-1,2,3-triol ((+)-17) and (1*S*,2*S*,3*S*,6*R*)-6-(*N*-Carebomethoxy)amino-1,2-*O*-isopropylidene-3-acetylcyclohex-4-ene-1,2-diol (33). Acetylation product **31** (2.0 g, 7.0 mol) was suspended in 0.1 M phosphate buffer (50 mL, pH = 7.0, T = 25 °C) and treated with PPL Sigma Type II crude lipase (200 mg). The mixture was stirred at room temperature, keeping the pH of the solution constant by addition of 1 N aq NaOH (4.5 mL of 1 N NaOH was added over 9 h). The reaction mixture was purified by flash chromatography (hexanes/ethyl acetate 2:1), affording 0.60 g (35%) of (+)-**15** and 0.80 g of **33** (40%). mp: 98−100 °C; R_f 0.68 (hexanes/ethyl acetate, 1:2) $[\alpha]^{25}_D$ +25 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.86 (d, J = 7.0 Hz, 1 H), 5.80 (d J = 7.0 Hz, 1 H), 5.22 (m, 1 H), 5.00 (bs, 1 H), 4.28 (m, 1 H), 4.19 (m, 2 H), 3.65 (s, 3 H), 2.02 (s, 3 H), 1.42 (s, 3 H), 1.30 (s, 3 H)^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 158.0, 131.0, 127.8, 109.3, 76.3, 76.0, 70.8, 52.3, 50.5, 26.9, 24.9, 21.1; HRMS calcd for $C_{13}H_{20}NO_6$ 286.1290, found 286.1292. Anal. Calcd for $C_{13}H_{20}NO_6$: C, 54.54; H, 6.66; N, 4.89. Found: C, 54.41; H, 6.45; N, 4.83.

Methyl (1*S*,4*S*,5*R*,6*S*)-4,5-(Isopropylidenedioxy)-7-azobicyclo[4.1.0]hept-2-ene-7-carboxylate (32). To a solution of alcohol (+)-**15** (2.22 g, 9.0 mmol) in freshly distilled THF (100 mL) was added PPh_3 (4.74 g) followed by DEAD (2.35 g, 13.5 mmol). The reaction mixture was stirred at room temperature until total consumption of starting material (20 h). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (hexanes/ethyl acetate 3:2), affording compound **32** (1.24 g, 60%); R_f 0.57 (hexanes/ethyl acetate, 3:2). $[\alpha]^{28}_D$ +92 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz $CDCl_3$) δ 6.07 (m, 1 H), 5.74 (dd, J = 10.0, 1.6 Hz, 1 H), 4.82 (d, J = 7.0 Hz, 1 H), 4.45 (t, J = 7.0 Hz, 1 H), 3.74 (s, 3 H), 3.05 (d, J = 4.9 Hz, 1H), 2.98 (t, J = 5.0 Hz, 1 H), 1.41 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 130.9, 122.5, 110.4, 70.9, 70.0, 53.8, 34.5, 33.1, 27.8, 26.1.

Methyl *N*-[(1*S*,2*S*,5*S*,6*R*)-2-(1,3)-Benzodioxol-5-yl)-5,6-(isopropylidenedioxy)cyclohex-3-en-1-yl]carbamate (35). To a solution of 5-bromo-1,3-benzodioxole **34** (12.3 mL, 53.2 mmol) in freshly distilled THF (500 mL) was added 2.5M *n*-BuLi in hexanes (21.3 mL) at −78 °C. The reaction mixture was stirred for 60 min at −78 °C before CuCN (2.39 g, 26 mmol) was added. After 90 min at −78 °C, aziridine **32** (3.0 g, 13 mmol) in THF (50 mL) was added followed by $BF_3 \cdot Et_2O$ (0.8 mL). After 3 h, the mixture was allowed to warm to room temperature. Saturated aq NH_4Cl (150 mL) was added, the layers were separated, and the aqueous phase was extracted with ethyl acetate (4 × 100 mL). The combined organic layers were dried over $MgSO_4$, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (hexanes/ethyl acetate, 4:1) to give carbamate **35** (0.936 g, 20%) as a white solid. R_f 0.31 (hexanes/ethyl acetate, 3:2); mp 189−190 °C (hexanes/ethyl acetate); $[\alpha]^{28}_D$ −81.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (d, J = 8.0 Hz, 1 H), 6.67 (d, J = 1.8 Hz, 1 H), 6.62 (dd, J = 8.0, 2.0 Hz, 1 H), 5.97 (m, 1 H), 5.94 (m, 1 H), 5.90 (m, 1 H), 4.68 (t, J = 5.0 Hz, 1 H), 4.60 (bs, 1 H), 4.40 (bs, 1 H), 3.54 (s, 3 H), 3.40 (m, 1 H), 1.54 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 147.0, 146.0, 136.0, 132.0, 123.5, 121.5, 109.0, 108.4, 108.2, 101.0, 76.4, 72.4, 57.0, 51.0, 45.0, 28.2, 25.9.

Methyl *N*-[(1*S*,2*R*,5*S*,6*R*)-2-(1,3-Benzodioxol-5-yl)-5,6-dihydroxycyclohex-3-en-1-yl]carbamate (36). To a solution of **35** (300 mg, 9.74 mmol) in 20 mL of methanol was added a spatula tip of Dowex-50W. The reaction mixture was allowed to stir at room temperature for 20 h (total consumption of starting material), the resin was removed by filtration, and the solvent was removed under reduced pressure affording 260 mg of compound **36** (95%) as white solid. R_f 0.34 (chloroform/methanol, 8:1). Mp 190−202 °C (ethyl acetate/methanol); $[\alpha]^{28}_D$ −105.3 (*c* 0.8, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 6.70 (m, 3 H), 5.98 (m, 3 H), 5.70 (dd, J = 9.5, 2.1 Hz, 1 H), 4.61 (s, 1 H), 4.27 (s, 1 H), 3.81 (m, 1 H), 3.60 (s, 3 H), 3.27 (m, 1 H); ^{13}C NMR (75 MHz, CD_3OD) δ 159.8, 149.0, 147.8, 137.2, 134.9, 127.8, 122.7, 109.6, 108.8, 102.1, 73.4, 67.9, 56.1, 52.3, 50.2.

Methyl *N*-[(1*S*,2*S*,3*S*,4*S*,5*R*,6*R*)-2-(1,3-Benzodioxol-5-yl)-5,6-dihydroxy-3,4-epoxycyclohex-1-yl]carbamate (37). To a solution of olefin **36** (250 mg, 0.81 mmol) in benzene (20 mL) were added $VO(acac)_2$ (18 mg, 0.065 mmol) and 5 M *t*-BuOOH (1.0 mL). The reaction mixture was heated at 70 °C for 5 h (total consumption of starting material). After the solution was cooled to room temperature, the solvent was removed under reduced pressure and the residue purified by flash column chromatography (chloroform/methanol, 8:1) to afford epoxide **37** (175 mg, 67%) as white solid. R_f 0.28 (chloroform/methanol, 8:1); mp 193−195 °C (chloroform/methanol); $[\alpha]^{28}_D$ −65.8 (*c* 0.8, MeOH); ^{1}H NMR (300 MHz, CD_3OD); 6.96 (d, J = 8.0 Hz, 1 H), 6.80 (d, J = 8.1 Hz, 1 H), 6.72 (d, J = 8.0 Hz, 1 H) 5.90 (s, 2 H), 4.25 (t, J = 5.0 Hz, 1 H), 3.78 (t, J = 10.0 Hz,), 3.46 (s, 3 H), 3.38 (m, 3 H), 3.08 (d, J = 10.9 Hz, 1 H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.0, 150.0, 148.3, 135.2, 123.5, 109.0, 108.7, 102.3, 73.2, 68.0, 60.0, 54.4, 52.3, 51.9, 48.3.

Methyl *N*-[(1*S*,2*S*,3*S*,4*R*,5*R*,6*R*)-2-(1,3-Benzodioxol-5-yl)-3,4,5,6-tetrahydroxycyclohexyl]carbamate (38). To a solution of epoxide **37** (170 mg, 0.49 mmol) in 5 mL of water was added sodium benzoate (5 mg, 0.034 mmol). The mixture was heated at 100 °C until total consumption of the starting material (8 d). The solution was cooled to room temperature, the water was removed in vacuo, and the residue was purified by flash column chromatography (chloroform/methanol, 6:1), affording aryl aminocyclitol **38** (130 mg, 80%) as white solid: R_f 0.20 (chloroform/methanol, 8:1); mp 190−202 °C (ethyl acetate/methanol); $[\alpha]^{28}_D$ +1.69 (*c* 0.95, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 6.90 (s, 1 H), 6.77 (dd, J = 8.0, 1.8 Hz, 1 H), 6.70 (d, J = 8.0 Hz, 1 H), 5.85 (m, 2 H) 4.30 (m, 1 H), 4.00 (m, 2 H) 3.75 (m, 2 H), 3.50 (s, 3 H), 3.30 (s, 1 H), 3.18 (dd, J = 12.0, 2.0 Hz, 1 H); ^{13}C NMR (75 MHz, CD_3OD) δ 159.9, 148.6, 147.5, 134.9, 123.7, 110.9, 108.6, 102.0, 76.0, 73.5, 73.4, 71.8, 52.3, 51.3, 48.3.

Methyl *N*-[(1*S*,2*S*,3*S*,4*R*,5*R*,6*R*)-2-(1,3-Benzodioxol-5-yl)-3,4,5,6-tetraacetoxycyclohexyl]carbamate (39). To a solution of aryl aminocyclitol **38** (50 mg, 0.15 mmol) in pyridine (1.0 mL) was added acetic anhydride (1.0 mL). The reaction mixture was stirred at room temperature for 16 h (total consumption of starting material). The solvent was removed in vacuo and the residue purified by flash column chromatography (hexanes/ethyl acetate, 1:1) to afford tetraacetate **39** (60 mg, 82%) as white solid; R_f 0.41 (hexanes/ethyl acetate 2:3); mp 108−111 °C (hexanes/ethyl acetate); $[\alpha]^{28}_D$ −13.9 (*c* 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (m, 3H), 5.93 (s, 2H), 5.35 (s, 1H), 5.09 (m, 2H), 4.70 (m, 1H), 4.40 (bd, 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 (75 MHz, $CDCl_3$) δ 170.5, 169.3, 168.8, 168.3, 156.6, 147.7, 147.0, 129.6, 122.2, 109.1, 108.2, 101.0, 72.1, 71.1, 68.7, 68.1, 52.2, 48.1, 47.2, 20.8, 20.6.

(1*S*,2*R*,3*R*,4*R*,4a*S*,11*S*)-1,2,3,4-Tetraacetoxy-1,2,3,4,4a,-11-hexahydro-1,3-dioxolo[4,5-*j*]phenanthridin-6(2*H*)-one (40). To a solution of tetraacetate **39** (33 mg, 0.65 mmol) in CH_2Cl_2 (3 mL) were added trifluoromethanesulfonic anhydride (60 mg, 0.216 mmol) and DMAP (24 mg, 0.195 mmol). The reaction mixture was stirred at 5 °C for 18 h (total consumption of starting material), and then the solvent was removed in vacuo. THF (2 mL) and 2 N aq HCl (0.2 mL) were added, and the mixture was stirred at room temperature for

6 h. The mixture was quenched with saturated $NaHCO_3$, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over $MgSO_4$, the solvent removed under reduced pressure, and the residue purified by flash column chromatography (hexanes/ethyl acetate, 1:1) to afford the desired compound **40** (20 mg, 61%) as white solid. R_f 0.48 (hexanes/ethyl acetate, 1:2) mp 231−237 °C (hexanes/ethyl acetate); $[\alpha]^{28}_D$ −73.4 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1 H), 6.56 (s, 1 H), 6.3 (bs, 1 H) 6.02 (d, J = 8.8 Hz, 2 H), 5.57 (t, J = 2.9 Hz, 1 H), 5.47 (t, J = 2.9 Hz, 1 H), 5.22 (t, J = 2.9 Hz, 1 H), 5.19 (d, J = 3.1 Hz, 1 H), 4.29 (dd, J = 12.8, 11.1 Hz, 1 H), 3.45 (dd, J = 13.4, 2.7 Hz, 1 H) 2.15 (s, 3 H), 2.09 (s, 3 H), 2.07 (s, 3 H), 2.03 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 170.0, 165.0, 151.7, 147.0, 131.0, 123.3, 108.5, 103.7, 101.9, 71.3 67.7, 66.4, 66.3, 48.2, 39.7, 20.8, 20.7, 20.6.

***ent*-7-Deoxypancratistatin (*ent*-4).** To a suspension of K_2CO_3 (50 mg) in methanol (5 mL) was added compound **40** (10 mg, 0.014 mmol). The reaction mixture was stirred at room temperature until total consumption of the starting material (15 h), and then the precipitate was removed by filtration. The solvent was removed in vacuo affording *ent*-deoxypancratistatin (12 mg, 72%) as white solid; R_f 0.29; (chloroform/methanol, 4:1); mp 304−307 °C. $[\alpha]^{28}_D$ −75.7 (*c* 0.8, DMF); ^{1}H NMR (500 MHz,DMSO-d_6) δ 7.31 (s, 1 H), 6.90 (s, 1 H), 6.83 (s, 1 H), 6.04 (s, 2 H), 5.36 (d, J = 4 Hz, 1 H), 5.05 (m, 2 H), 4.77 (d, J = 7.5 Hz, 1 H), 4.31 (m, 1H), 3.97 (q, J = 4.0 Hz, 1 H), 3.84 (m, 1 H), 3.73 (m, 2 H), 2.98 (d, J = 12.0 Hz, 1H).

(1*S*,2*R*,3*R*,4*R*,5*S*,6*S*)-3,4-(Isopropylidenedioxy)-5,6-dihydroxy-7-(4′-methylphenylsulfonyl)-7-azabicyclo[4.1.0]heptane (54). To a solution of aziridine **46** (500 mg, 1.56 mmol) in a mixture of ethyl acetate (7 mL) and acetonitrile (7 mL) was added a solution of $NaIO_4$ (500 mg, 2.34 mmol) and $RuCl_3 \cdot H_2O$ (32 mg, 0.16 mmol) in water (5 mL) at 0−5 °C. After 15 s, the reaction was quenched by addition of 30% aq $Na_2S_2O_3$ (15 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic phase was dried over Na_2SO_4 and filtered through a plug of silica gel before the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexanes/ethyl acetate 3:1), affording diol **54** (472 mg, 85%) as white crystals. R_f 0.28 (hexanes/ethyl acetate, 1:1); mp 166−168 °C (hexanes/ethyl acetate); $[\alpha]^{26}_D$ +6.6 (*c* 1.1, $CHCl_3$); IR ν 3367, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.4 Hz, 2 H), 7.39 (d, J = 8.4 Hz, 2 H), 4.42 (s, 2 H), 4.13 (m, 1 H), 3.98 (m, 1 H), 3.34 (dt, J = 6.9, 1.5 Hz, 1 H), 3.28 (dt, J = 6.9, 1.1 Hz, 1 H), 2.47 (s, 3 H), 1.42 (s, 3 H), 1.32 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 133.8, 130.4, 128.2, 110.2, 69.5, 68.4, 62.1, 45.5, 43.4, 27.5, 25.1, 22.0; HRMS (FAB) calcd for $C_{16}H_{22}NO_6S$ 356.1168, found 356.1166. Anal. Calcd for $C_{16}H_{21}NO_6S$: C, 54.07; H, 5.96. Found: C, 54.04; H, 5.97.

(1*S*,2*R*,3*R*,4*S*,5*R*,6*S*)-3,4-(Isopropylidenedioxy)-5,6-O-sulfuryl-7-(4′-methylphenylsulfonyl)-7-azabicyclo[4.1.0]heptane (55). To a solution of diol **54** (100 mg, 0.28 mmol) in dry CH_2Cl_2 (5 mL) were added triethylamine (317 mL, 228 mg; 2.25 mmol) and 1.0 M sulfuryl chloride in methylene chloride (0.85 mL, 0.85 mmol) at 0−5 °C. After addition, the reaction mixture was warmed to room temperature and stirred until total consumption of the starting material (2 h). The mixture was diluted with CH_2Cl_2 (30 mL) and extracted with water (2 × 20 mL). The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude product **55** was sufficiently pure for the next reaction. R_f 0.45 (hexanes/ethyl acetate, 3:1); mp 208−210 °C (hexanes/ethyl acetate); $[\alpha]^{24}_D$ −51.8 (*c* 1.0, $CHCl_3$); IR ν 1597, 1212, 1165 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.2 Hz, 2 H), 7.35 (d, J = 8.2 Hz, 2 H), 5.25 (dd, J = 6.1, 3.8 Hz, 1 H), 5.01 (d, J = 6.1 Hz, 1 H), 4.62 (d, J = 5.6 Hz, 1 H), 4.54 (d, J = 4.1 Hz, 1 H), 3.53 (d, 6.4 Hz, 1 H), 3.38 (dd, J = 5.8, 4.1 Hz, 1 H), 2.46 (s, 3 H), 1.43 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 133.5, 130.0, 128.7, 110.8, 76.7, 76.0, 72.7, 69.1, 41.7, 38.0, 27.5, 25.2, 22.0; HRMS (CI) calcd for $C_{16}H_{20}O_8NS_2$: 418.0630. Found: 418.0639. Anal. Calcd for $C_{16}H_{19}NO_8S_2$: C, 46.04; H, 4.59. Found: C, 46.18; H. 4.49.

(1*S*,2*R*,3*R*,4*S*,5*S*,6*S*)-3,4-(Isopropylidenedioxy)-5-hydroxy-6-benzoyl-7-(4′-methylphenylsulfonyl)-7-azabicyclo-[4.1.0]heptane (56a). To a solution of cyclic sulfate **55** (3.20 g, 7.66 mmol) in dry DMF (20 mL) was added ammonium benzoate (2.69 g, 19.2 mmol). The reaction mixture was heated at 70 °C for 2 h (total consumption of starting material). The reaction mixture was cooled to 40 °C, and the DMF was removed under reduced pressure. The residue was suspended in THF (100 mL), and 4 drops of H_2O and H_2SO_4 was added. The resulting mixture was stirred for 1 h before it was quenched with saturated aq $NaHCO_3$ (150 mL) and then diluted with CH_2Cl_2 (100 mL). The organic phase was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic layer was dried over Na_2SO_4, the solvent was removed in vacuo, and the compound was purified by flash column chromatography (hexanes/ethyl acetate, 5:1), affording ester **56a** (3.16 g, 90%). R_f 0.26 (hexanes/ethyl acetate, 3:1); $[\alpha]^{30}_D$ +41.6 (*c* 0.98, $CHCl_3$); IR ν 3494, 1723, 1599 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.0 Hz, 2 H), 7.85 (d, J = 8.3 Hz, 2 H), 7.59 (t, J = 7.4 Hz, 1 H), 7.45 (t, J = 7.7 Hz, 2 H), 7.40 (d, J = 7.9 Hz, 2 H), 5.12 (d, J = 5.4 Hz, 1 H), 4.56 (d, J = 6.1 Hz, 1 H), 4.19 (t, J = 5.7 Hz, 1 H), 3.96 (dd, J = 8.1, 5.4 Hz, 1 H), 3.33 (s, 1 H), 2.73 (d, J = 8.4 Hz, 1 H), 2.48 (s, 3 H), 1.52 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 145.7, 134.0, 133.7, 130.4, 130.1, 129.4, 128.7, 128.3, 110.2, 75.2, 70.5, 68.4, 68.1, 41.5, 39.7, 27.7, 25.3, 21.9; HRMS (FAB) calcd for $C_{23}H_{26}O_7NS$ 460.1430, found 460.1441. Anal. Calcd for $C_{23}H_{25}NO_7S$: C, 60.12; H 5.48. Found: C, 60.54; H, 5.59.

(1*S*,2*R*,3*R*,4*S*,5*S*,6*S*)-3,4-(Isopropylidenedioxy)-5-[(*tert*-butyldimethylsilyl)oxy]-6-benzoyl-7-(4′-methylphenylsulfonyl)-7-azabicyclo[4.1.0]heptane (57). To a solution of alcohol **56a** (1.66 g, 3.35 mmol) in dry DMF (8 mL) were added imidazole (1.14 g, 16.8 mmol) and TBSCl (2.53 g, 16.8 mmol). The solution was stirred at room temperature for 12 h (total consumption of starting material). The reaction was quenched with water (10 mL), and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the product was isolated by flash column chromatography (hexanes/ethyl acetate, 9:1), yielding **57** (1.63 g, 85%) as colorless oil. R_f 0.47 (hexanes/ethyl acetate, 5:1); $[\alpha]^{26}_D$ +20.9 (*c* 1.2, $CHCl_3$); IR ν 1725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 7.3 Hz, 2 H), 7.85 (d, J = 8.3 Hz, 2 H), 7.59 (t, J = 7.4 Hz, 1 H), 7.45 (t, J = 7.7 Hz, 2 H), 7.37 (d, J = 8.5 Hz, 2 H), 4.92 (m, 1 H), 4.52 (m, 1 H), 3.91 (d, J = 5.9 Hz, 1 H), 3.33 (d, J = 6.4 Hz, 1 H), 3.10 (d, J = 6.4 Hz, 1 H), 2.46 (s, 3 H), 1.54 (s, 3 H), 1.36 (s, 3 H), 0.91 (s, 9 H), 0.74 (s, 6 H), 0.09 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 145.2, 134.7, 133.7, 130.2, 130.0, 129.7, 128.7, 128.3, 110.0, 77.5, 71.7, 71.2, 70.5, 43.1, 39.1, 28.3, 26.1, 26.0, 25.9, 25.8, 22.0, 18.2, −4.4, −4.7; HRMS (FAB) calcd for $C_{29}H_{40}O_7NSSi$ 574.2295, found 574.2293. Anal. Calcd for $C_{29}H_{39}NO_7SSi$: C, 60.71; H 6.85. Found: C, 60.63; H, 6.98.

(1*S*,2*R*,3*R*,4*S*,5*S*,6*S*)-3,4-(Isopropylidenedioxy)-5-[(*tert*-butyldimethylsilyl)oxy]-6-hydroxy-7-(4′-methylphenylsulfonyl)-7-azabicyclo[4.1.0]heptane (59). To a solution of benzyl ester **57** (2.12 g, 3.70 mmol) in THF (80 mL) was added 5.5 M methanolic sodium methoxide (3.36 mL, 18.5 mmol). The reaction mixture was stirred for 10 min (total consumption of starting material) before it was quenched with aqueous NH_4Cl (200 mL) and extracted with ethyl acetate (3 × 150 mL). The combined organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was purifed by flash column chromatogaphy (hexanes/ethyl acetate, 7:1), affording 1.28 g of alcohol **59** (74%) as colorless oil. R_f 0.23 (hexanes/ethyl acetate, 5:1); $[\alpha]^{26}_D$ −5.76 (*c* 1.1, $CHCl_3$); IR ν 3515, 1463, 1382, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, J = 8.4 Hz, 2 H), 7.32 (dd, J = 8.5, 0.6 Hz, 2 H), 4.35 (d, J = 5.3 Hz, 1 H), 3.97 (t, J = 5.3 Hz, 1 H), 3.89

(dt, J = 4.8, 0.8 Hz, 1 H), 3.69 (ddd, J = 9.2, 4.3, 1.6 Hz, 1 H), 3.19 (d, J = 6.7 Hz, 1 H), 3.04 (d, J = 6.7 Hz, 1 H), 2.75 (d, J = 9.0 Hz, 1 H), 2.44 (s, 3 H), 1.49 (s, 3 H), 1.33 (s, 3 H), 0.82 (s, 9 H), 0.05 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.9, 134.9, 129.9, 128.2, 109.7, 76.1, 71.2, 70.3, 68.0, 42.3, 39.2, 28.1, 25.8, 25.8, 21.9, 18.1, −4.7, −4.8; HRMS (FAB) calcd for $C_{22}H_{36}O_6NSSi$ 470.2033, found 470.2020. Anal. Calcd for $C_{22}H_{35}NO_6SSi$: C, 56.26; H 7.51. Found: C, 56.19; H, 7.42.

(1*R*,2*R*,3*S*,4*S*,5*S*,6*R*)-4,5-(Isopropylidenedioxy)-3-[(*tert*-butyldimethylsil)oxy]-6-*N*-(3′,4′-dimethoxymethylbenzyl)-*N*(4′-methylphenylsulfonyl)-7-oxabicyclo[4.1.0]heptane (64). To a solution of alcohol **59** (100 mg, 0.21 mmol) in dry THF (15 mL) at −78 °C was added *t*-BuLi (1.6 M in hexanes; 133 mL, 0.21 mmol). The solution was stirred for 10 min before it was slowly warmed to −30 °C. Piperonyl bromide (55 mg; 0.26 mmol) and a catalytic amount of NBu_4I were added, and two-thirds of the solvent was removed under reduced pressure. The solution was stirred for additional 2 h and slowly warmed to room temperature. After 48 h the reaction was quenched with 20 mL saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography affording ether **64** (84 mg, 0.14 mmol, 68%). R_f 0.53 (hexanes/ethyl acetate, 3:1); $[\alpha]^{30}_D$ −9.3 (*c* 2.2, $CHCl_3$); IR ν, 1598 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8.3 Hz, 2 H), 7.28 (d, J = 8.06 Hz, 2 H), 6.89 (d, J = 1.7 Hz, 1 H), 6.81 (dd, J = 8.1, 1.7 Hz, 1 H), 6.70 (d, J = 7.8 Hz, 1 H), 5.93 (s, 2 H), 4.42 (d, J = 15.9 Hz, 1 H), 4.26 (d, J = 15.6 Hz, 1 H), 4.20 (dd, J = 7.9, 5.5 Hz, 1 H), 4.01 (dt, J = 5.1, 2.3 Hz, 1 H), 3.88 (dd, J = 4.7, 2.7 Hz, 1 H), 3.10 (t, J = 3.5 Hz, 1 H), 3.02 (t, J = 3.2 Hz, 1 H), 2.43 (s, 3 H), 1.33 (s, 3 H), 1.16 (s, 3 H), 0.86 (s, 9 H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.1, 147.3, 143.8, 137.5, 131.1, 129.8, 127.7, 121.8, 109.0, 109.0, 108.2, 101.3, 78.7, 77.4, 74.1, 70.6, 58.9, 55.5, 53.3, 50.2, 29.9, 26.9, 26.0, 24.4, 21.8, 18.3, 1.2, −4.6, −4.8; HRMS (FAB) calcd for $C_{30}H_{42}O_8NSSi$ 604.2400, found 604.2392. Anal. Calcd for $C_{30}H_{41}NO_8SSi$: C, 59.68; H 6.84. Found: C, 59.78; H, 6.84.

(1*R*,2*S*,3*S*,4*S*,4a*R*,10b*S*)-1,3,4,4a,11b-Hexahydro-1-hydroxy-2-[(*tert*-butyldimethylsilyl)oxy]-3,4-isoproylidenedioxy-5-*N*-(4′methyl-phenylsulfonyl)-[1,3]dioxolo[4,5-*j*]-phenanthridin (66). To a solution of epoxide **64** (58.7 mg, 0.10 mmol) in dry CH_2Cl_2 (10 mL) at −30 °C were added a 1.0 M solution of $(CH_3)_2AlCl$ (100 mL, 0.10 mmol). The reaction mixture was stirred at −30 °C for 1 h before it was allowed to warm to 0 °C over about a period of 1 h and then quenched with water (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic phase was dried over Na_2SO_4, the solvent was removed in vacuo, and the residue subjected to flash column chromatography (hexanes/ethyl acetate, 9:1), affording **66** (40.2 mg, 68%) as colorless oil. R_f 0.57 (hexanes/ethyl acetate, 2:1); $[\alpha]^{26}_D$ −33.5 (*c* 1.1, $CHCl_3$); IR ν 3561, 1486 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 8.3 Hz, 2 H), 7.09 (d, J = 8.0 Hz, 2 H), 7.06 (s, 1 H), 6.34 (s, 1 H), 5.81 (dd, J = 8.7, 1.4 Hz, 2 H), 4.49 (d, J = 17.3 Hz, 1 H), 4.30 (dd, J = 10.5, 7.9 Hz, 1 H), 4.21 (d, J = 17.4 Hz, 1 H), 4.11 (dd, J = 10.3, 6.9 Hz, 1 H), 3.93 (t, J = 6.7 Hz, 1 H), 3.82 (dd, J = 10.7, 6.4 Hz, 1 H), 3.37 (dd, J = 10.8, 7.7 Hz, 1H), 2.95 (t, J = 7.7 Hz, 1H), 2.28 (s, 3H), 1.45 (s, 3 H), 1.22 (s, 3 H), 0.85 (s, 9 H), 0.20 (s, 3 H), 0.19 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 146.5, 143.4, 137.6, 129.6, 129.1, 127.5, 124.1, 110.6, 108.6, 105.3, 101.2, 79.0, 75.1, 74.7, 71.8, 52.2, 42.6, 39.9, 27.5, 26.1, 25.3, 21.7, 18.3, −4.0, −4.8; HRMS (EI) calcd for $C_{30}H_{42}O_8NSSi$ 604.2400, found 604.2409. Anal. Calcd for $C_{30}H_{41}NO_8SSi$: C, 59.68; H 6.84. Found: C, 60.36; H, 6.98.

(1*R*,2*S*,3*S*,4*S*,4a*R*,10b*S*)-1,3,4,4a,11b-Hexahydro-1-methoxymethyl-2[(*tert*-butyldimethylsilyl)oxy]-3,4-isoproylidenedioxy-5-*N*-(4′methyl-phenylsulfonyl)-[1,3]dioxolo[4,5-*j*]phenanthridin (67). To a solution of alcohol **66** (20 mg, 0.033 mmol) in 0.5 mL of Hünig's base was added at room temperature methoxymethyl chloride (100 mL, 0.85 mmol). The solution was stirred for 12 h (total consumption of starting material). The reaction was quenched with water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL), the combined organic phase was dried over Na_2SO_4, the solvent was removed in vacuo, and the residue was purified by flash column chromatography (hexanes/ethyl acetate, 5:1), affording compound **67** as colorless oil (21 mg, 97%). R_f 0.35 (hexanes/ethyl acetate, 3:1); $[\alpha]^{25}_D$ +5.9 (*c* 0.85, $CHCl_3$); IR ν 1487, 1244 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.2 Hz, 2 H), 7.20 (d, J = 7.9 Hz, 2 H), 7.11 (s, 1 H), 6.40 (s, 1 H), 5.88 (s, 2 H), 4.92 (d, J = 7.0 Hz, 1 H), 4.63 (d, J = 7.0 Hz, 1 H), 4.59 (d, J = 17.0 Hz, 1 H), 4.38 (m, 1 H), 4.30 (d, J = 18.4 Hz, 1 H), 4.23 (d, J = 7.9 Hz, 1 H), 3.95 (m, 2 H), 3.79 (t, J = 6.7 Hz, 1 H), 3.24 (s, 3 H), 3.16 (t, J = 5.7 Hz, 1 H), 2.24(s, 3H), 1.50 (s, 3 H), 1.26 (s, 3 H), 0.88 (s, 9 H), 0.15 (s, 3 H), 0.12 (s, 3 H);^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 146.4, 143.4, 137.0, 129.5, 128.3, 127.9, 124.9, 109.5, 108.4, 106.0, 101.2, 97.9, 79.8, 78.5, 75.4, 72.9, 56.0, 53.0, 43.0, 41.4, 27.7, 26.1, 25.4, 21.7, 18.3, −4.1, −4.2; HRMS (FAB) calcd for $C_{32}H_{46}O_9NSiS$ 648.2663, found 648.2668.

(1*R*,2*S*,3*S*,4*S*,4a*R*,10b*S*)-1,3,4,4a,11b-Hexahydro-1-methoxymethyl-2[(*tert*-butyldimethylsilyl)oxy]-3,4-isoproylidenedioxy-5-*N*-(4′methylphenylsulfonyl)-[1,3]dioxolo[4,5-*j*]phenanthridin-6(2*H*)-one (68). To a suspension of **67** (25 mg, 0.039 mmol) in $CH_3CN/CCl_4/H_2O$ (2:2:3) were added $NaIO_4$ (66 mg;0.31 mmol) and a catalytic amount of $RuCl_3{\cdot}H_2O$. The reaction mixture was stirred at room temperature until total consumption of the starting material (30 min). The heterogeneous mixture was diluted with CH_2Cl_2 (40 mL) and filtered through a plug of silica gel before it was extracted with water (3 × 30 mL). The combined organic phase was dried over Na_2SO_4, the slightly greenish solution was filtered through silica, and the solvent was removed under reduced pressure. Flash column chromatography (hexanes/ethyl acetate, 5:1) of the residue provided **68** (14 mg, 50%) as pale yellow oil. R_f 0.30 (hexanes/ethyl acetate, 3:1); $[\alpha]^{25}_D$ +5.0 (*c* 1.0, $CHCl_3$); IR ν 1683, 1486, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 8.3 Hz, 2 H), 7.42 (s, 1 H), 7.29 (d, J = 8.1 Hz, 2 H), 7.19 (s, 1 H), 6.00 (dd, J = 4.9, 1.2 Hz, 2 H), 5.09 (dd, J = 9.5, 5.6 Hz, 1 H), 4.98 (d, J = 7.1 Hz, 1 H), 4.77 (d, J = 7.3 Hz, 1 H), 4.18 (dd, J = 6.6, 2.4 Hz, 1 H), 4.10 (m, 1 H), 3.80 (t, J = 7.0 Hz, 1 H), 3.69 (d, J = 3.9 Hz, 1 H), 3.44 (s, 3 H), 2.41 (s, 3 H), 1.63 (s, 3 H), 1.19 (s, 3 H), 0.88 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 152.8, 147.3, 144.6, 137.0, 135.1, 130.0, 129.0, 122.2, 109.9, 108.8, 106.4, 102.3, 97.6, 79.4, 78.3, 75.4, 73.9, 56.1, 54.9, 43.4, 27.4, 26.1, 25.2, 21.9, 18.4, −4.3; HRMS (FAB) calcd for $C_{32}H_{44}O_{10}NSSi$: 662.2455. Found 662.2495.

(1*R*,2*S*,3*S*,4*S*,4a*R*,10b*S*)-1,3,4,4a,11b-Hexahydro-1-methoxymethyl-2[(*tert*-butyldimethylsilyl)oxy]-3,4-isoproylidenedioxy-[1,3]dioxolo[4,5-*j*]phenanthridin-6(2*H*)-one (69). To a solution of **70** (30 mg, 0.045 mmol) in dry DME (5 mL) at −50 °C was added a 0.5 M Na/naphthalene in DME until a green color persisted (total sonsumption of starting material according to TLC). The solution was stirred for 10 min before the reaction was quenched with saturated aq NH_4Cl. The mixture was warmed to room temperature, diluted with water, and extracted with Et_2O (3 × 30 mL). The combined organic phase was dried over Na_2SO_4, the solvent was removed in vacuo, and the residue was purified by flash column chromatography affording compound **69** (12 mg, 0.024 mol, 52%) as pale yellow oil. R_f 0.35 (hexanes/ethyl acetate, 2:1); $[\alpha]^{25}_D$ +7.8 (1.0, $CHCl_3$); IR ν 3206, 1671, 1464, 1381 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1 H), 6.88 (s, 1 H), 6.43 (bs, 1 H), 6.01 (dd, J = 2.8, 1.2 Hz, 2 H), 4.55 (d, J = 6.2 Hz, 1 H), 4.39 (d, J = 6.4 Hz, 1 H), 4.20 (m, 3 H), 3.80 (dd, J = 8.9, 6.1 Hz, 1 H), 3.72 (t, J = 9.8 Hz, 1 H), 2.98 (d, J = 8.5 Hz, 1 H), 2.84 (s, 3 H), 1.57 (s, 3 H), 1.40 (s, 3 H), 0.89 (s, 9 H), 0.18 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.3, 151.1, 147.6, 135.4, 110.5, 109.4, 108.1, 101.9, 98.8, 80.6, 78.9, 76.4, 76.3, 56.4, 52.8, 41.3, 28.4, 26.5, 26.2, 18.4, −3.8, −4.2; HRMS (FAB) calcd for $C_{25}H_{37}O_8NSi$: 508.2367. Found 508.2348.

***epi*-7-Deoxypancratistatin (70).** To a solution of **69** (15 mg; 0.03 mmol) in methanol (1.5 mL) was added 3% HCl in methanol (0.5 mL). The reaction mixture was stirred until total consumption of the starting material (2 d). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography affording 7 mg of the epimer of the natural product (70%). R_f 0.1 (chloroform/methanol, 4:1); $[\alpha]^{25}_D$ +5.9 (0.49, MeOH); IR ν 3328, 1648, 1468, 1254 cm^{-1}; ^1H NMR (500 MHz, C_5D_5N) δ 9.09 (s, 1 H), 7.95 (s, 1 H), 7.24 (s, 1 H), 5.95 (s, 1 H), 5.86 (s, 1 H), 4.95 (t, J = 2.6 Hz, 1 H), 4.74 (t, J = 9.3 Hz, 1 H), 4.64 (dd, J = 9.6, 2.8 Hz, 1 H), 4.52 (t, J = 3.3 Hz, 1 H), 4.30 (t, J = 9.6 Hz, 1H), 3.65 (dd, J = 10.2, 3.7 Hz, 1 H); ^{13}C NMR (125 MHz, C_5D_5N) δ 164.6, 149.1, 146.3, 136.8, 122.8, 109.9, 106.6, 100.6, 74.2, 73.9, 71.6, 70.9, 55.6, 41.7; HRMS (EI pos) calcd. for $C_{14}H_{15}O_7N$ 309.0849, found 309.0875.

***N*-[(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-2-(1,3-Benzodioxol-5-yl)-3,4-dihydroxy-5,6-(isopropylidenedioxy)cyclohex-1-yl]-4-methylbenzenesulfonamide (73).** A solution of **71**[10b] (2.30 g, 5.19 mmol) in CH_3CN/EtOAc (1:1, 65 mL) at 0 °C was treated with a solution of $RuCl_3 \cdot H_2O$ (81 mg, 0.39 mmol) and $NaIO_4$ (1.66 g, 7.76 mmol) in H_2O (11 mL) and allowed to stir at 0 °C for 3 min. The reaction was quenched with 50% aq $Na_2S_2O_3$ (100 mL) and then warmed to room temperature. The organic and aqueous phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/ethyl acetate, 1:2) to afford diol **73** (1.87 g, 75%) as a white solid: R_f 0.14 (hexanes/ethyl acetate, 1:2); mp: 103−105 °C; $[\alpha]^{29}_D$ −27.1 (*c* 1.1, CH_3OH); IR (KBr) ν 3482, 1734, 1599, 1490 cm^{-1}; ^1H NMR (500 MHz, acetone) δ 7.49 (d, J = 8.2 Hz, 2 H), 7.21 (d, J = 8.2 Hz, 2 H), 6.59 (d, J = 1.7 Hz, 1 H), 6.58 (d, J = 8.0 Hz, 1 H), 6.52 (dd, J = 8.0, 1.6 Hz, 1 H), 6.34 (d, J = 9.6 Hz, 1 H), 5.94 (m, 2 H), 4.51 (m, 1 H), 4.32 (dd, J = 5.9, 2.9 Hz, 1 H), 4.21 (t, J = 6.1 Hz, 1 H), 4.02 (m, 1 H), 3.94 (ddd, J = 8.5, 6.0, 2.4 Hz, 1 H), 3.77 (td, J = 8.8, 6.3 Hz, 1 H), 3.67 (d, J = 5.8 Hz, 1 H), 2.83 (t, J = 8.8 Hz, 1 H), 2.40 (s, 3 H), 1.49 (s, 3 H), 1.28 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 146.2, 142.3, 140.3, 135.4, 129.1, 126.8, 122.3, 109.2, 108.6, 107.7, 100.9, 77.9, 77.5, 71.7, 71.0, 58.2, 50.1, 26.8, 24.7, 20.5; HRMS (FAB) calcd for $C_{23}H_{28}NO_8S$ 478.1536, found 478.1516. Anal. Calcd for $C_{23}H_{27}NO_8S$: C, 57.85; H, 5.70; N, 2.93. Found: C, 57.76; H, 5.79; N, 2.83.

Methyl *N*-[(1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-2-(1,3-Benzodioxol-5-yl)-3,4-dihydroxy-5,6-(isopropylidenedioxy)cyclohex-1-yl]carbamate (74). A solution of $RuCl_3 \cdot H_2O$ (81 mg, 0.39 mmol) and $NaIO_4$ (1.65 g, 7.71 mmol) in H_2O (10 mL) was added to a solution of **72**[10b] (1.79 g, 5.14 mmol) in CH_3CN/EtOAc (1:1, 50 mL) at 0 °C. The resulting solution was allowed to stir at 0 °C for 3 min before it was quenched with 50% aq $Na_2S_2O_3$ (50 mL). After separation of the organic and aqeous layers, the aqueous phase was extracted with ethyl acetate (3 × 75 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography (hexanes/ethyl acetate, 1:4) to furnish diol **74** (1.35 g, 69%) as a white solid: R_f 0.27 (hexanes/ethyl acetate, 1:4); mp: 115−117 °C; $[\alpha]^{29}_D$ −47.7 (*c* 1.0, $CHCl_3$); IR (KBr) ν 3398, 1702, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (d, J = 7.8 Hz, 1 H), 6.77 (d, J = 1.7 Hz, 1H), 6.70 (dd, J = 8.2, 1.4 Hz, 1 H), 5.96 (s, 2 H), 4.64 (bs, 1 H), 4.37 (dd, J = 5.3, 2.7 Hz, 1 H), 4.34 (q, J = 2.3 Hz, 1 H), 4.19 (m, 1 H), 4.02 (dt, J = 10.2, 2.9 Hz, 1 H), 3.90 (q, J = 9.7 Hz, 1 H), 3.53 (s, 3 H), 2.95 (t, J = 9.5 Hz, 1 H), 2.76 (m, 1 H), 1.87 (m, 1 H), 1.60 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 148.0, 146.9, 131.8, 122.2, 109.2, 108.6, 108.4, 101.0, 77.3, 76.7, 72.3, 69.5, 55.5, 52.0, 47.9, 27.8, 25.8; HRMS (FAB) calcd for $C_{18}H_{24}NO_8$ 383.1502, found 383.1500. Anal. Calcd for $C_{18}H_{23}NO_8$: C, 56.69; H, 6.08; N, 3.67. Found: C, 56.42; H, 6.18; N, 3.53.

***N*-[(1*R*,2*R*)-2-(1,3-Benzodioxol-5-yl)-3-hydroxy-1-(hydroxymethyl)propyl]-4-methylbenzenesulfonamide (75).** A solution of diol **73** (1.72 g, 3.60 mmol) in THF/H_2O/TFA (4:1:1, 30 mL) was stirred at room temperature for 17 h. After removal of the solvents by Kugelrohr distillation, the residue was dissolved in acetone/H_2O (3:2, 30 mL) and subsequently treated with $NaIO_4$ (2.13 g, 9.97 mmol) in H_2O (13 mL). The solution was stirred at room temperature for 4 h and then diluted with water (5 mL). Excess acetone was removed under reduced pressure, and the remaining solution was extracted with EtOAc (2 × 50 mL). The combined organic extract was dried over Na_2SO_4 and concentrated in vacuo. The solution in CH_3OH (120 mL) at 0 °C was treated with $NaBH_4$ (1.60 g, 42.3 mmol) and slowly warmed to room temperature. After stirring for 14 h, the solution was diluted with H_2O (20 mL) and excess methanol was removed under reduced pressure. The concentrate was extracted with EtOAc (2 × 60 mL), and the combined organic extract was dried over Na_2SO_4. Removal of the solvent under reduced pressure and purification of the residue by flash column chromatography (methylene chloride/acetone 3:2) gave tosylamide **75** (820 mg, 60%) as a white solid: R_f 0.61 (methylene chloride/acetone, 1:1); mp: 137−139 °C; $[\alpha]^{25}_D$ +50.7 (*c* 1.0, $CHCl_3$); IR (KBr) ν 3464, 3303, 2886, 1501 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.4 Hz, 2 H), 7.28 (d, J = 9.0 Hz, 2 H), 6.71 (d, J = 7.8 Hz, 1 H), 6.61−6.58 (m, 2 H), 5.94 (s, 2 H), 4.90 (d, J = 8.4 Hz, 1 H), 3.95 (dt, J = 9.9, 4.2 Hz, 1 H), 3.71−3.59 (m, 2 H), 3.53−3.40 (m, 2 H), 3.16 (m, 1 H), 2.92 (dt, J = 8.6, 5.0 Hz, 1 H), 2.63 (bs, 1 H), 2.41 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 146.8, 143.5, 137.0, 131.6, 129.6, 126.9, 121.6, 108.5, 108.4, 101.0, 62.9, 62.8, 55.9, 48.8, 21.5; HRMS (CI) calcd for $C_{18}H_{22}NO_6S$ 380.1168, found 380.1166. Anal. Calcd for $C_{18}H_{21}NO_6S$: C, 56.98; H, 5.58; N, 3.69. Found: C, 56.83; H, 5.52; N, 3.66.

Methyl *N*-[(1*R*,2*R*)-2-(1,3-Benzodioxol-5-yl)-3-hydroxy-1-(hydroxymethyl)propyl]carbamate (76). A solution of diol **74** (1.97 g, 5.17 mmol) in THF/H_2O/TFA (4:1:1, 45 mL) was stirred at room temperature for 16 h. The residue after removal of the solvents via Kugelrohr distillation was dissolved in acetone/H_2O (3:2, 40 mL) and the stirred mixture treated with a solution of $NaIO_4$ (3.73 g, 17.4 mmol) in H_2O (20 mL). After 4 h, the reaction mixture was diluted with H_2O (5 mL), and excess acetone was removed under reduced pressure. The concentrate was extracted with EtOAc (3 × 60 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue in CH_3OH (175 mL) at 0 °C was treated with $NaBH_4$ (2.43 g, 64.2 mmol) and was allowed to warm slowly to room temperature. After 20 h, the solution was diluted with H_2O (25 mL), and excess methanol was removed under reduced pressure. The concentrate was extracted with EtOAc (2 × 70 mL) and then dried over Na_2SO_4. Removal of the solvent under reduced pressure and purification of the residue by flash column chromatography (methylene chloride/acetone, 3:2) provided carbamate **76** (654 mg, 45%) as oil: R_f 0.36 (3:2 CH_2Cl_2/acetone) $[\alpha]^{26}_D$ −55.2 (*c* 1.0, $CHCl_3$); IR (neat) ν 3392, 1694, 1505 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, J = 8.0 Hz, 1 H), 6.69 (d, J = 1.1 Hz, 1 H), 6.64 (dd, J = 8.0, 1.5 Hz, 1 H), 5.95 (s, 2 H), 5.02 (d, J = 9.1 Hz, 1 H), 4.16 (sx, J = 4.7 Hz, 1 H), 3.82 (t, J = 4.8 Hz, 1 H), 3.75 (m, 1 H), 3.71 (s, 3 H), 3.68−3.61 (m, 2 H), 3.55 (dd, J = 11.6, 5.4 Hz, 1 H), 3.03 (dt, J = 9.6, 2.5 Hz, 1 H), 2.19 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 147.8, 146.7, 131.8, 121.6, 108.7, 108.4, 101.0, 63.4, 63.0, 52.9, 52.5, 48.8; HRMS (FAB) calcd for $C_{13}H_{18}NO_6$ 284.1134, found 284.1138. Anal. Calcd for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05. Found: C, 54.96; H, 5.99.

***N*-[(1*R*,2*R*)-2-(1,3-Benzodioxol-5-yl)-3-(*tert*-butoxycarbonyloxy)-1-(hydroxymethyl)propyl]-*N*-(*tert*-butoxycarbonyl)-4-methylbenzenesulfonamide (77).** To a stirred suspension of NaH (87 mg, 3.63 mmol) in THF (7 mL) at 0 °C was added diol **75** (425 mg, 1.12 mmol) in THF (7 mL). After 20 min di-*tert*-butyl dicarbonate (783 mg, 3.58 mmol) in THF (5 mL) was added dropwise, and the solution was allowed to warm slowly to room temperature. After 20 h, the reaction was quenched with H_2O, and the reaction mixture was extracted with ethyl acetate (3 × 35 mL). The combined

organic extracts were dried over $MgSO_4$, and solvent removed under reduced pressure. The remaining residue was purified via flash column chromatography (hexanes/ethyl acetate, 2:1) to afford **77** (540 mg, 83%) as a white solid: R_f 0.62 (hexanes/ethyl acetate, 1:1); mp 67−69 °C; $[\alpha]^{25}_D$ +18.1 (*c* 1.0, $CHCl_3$); IR (KBr) ν 3284, 1744, 1492 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.2 Hz, 2 H), 7.25 (d, J = 8.5 Hz, 2 H), 6.68 (d, J = 7.7 Hz, 1 H); 6.55−6.56 (m, 2 H), 5.90 (s, 2 H), 4.52 (bs, 1 H), 4.21 (dd, J = 11.0, 7.6 Hz, 1 H), 4.15 (dd, J = 11.0, 6.0 Hz, 1 H), 3.93−3.81 (m, 3 H); 3.13 (dd, J = 10.7, 7.1 Hz, 1 H); 2.40 (s, 3 H); 1.42 (s, 18 H); ^{13} C NMR (125 MHz, $CDCl_3$) δ 153.0, 152.8, 147.9, 147.1, 143.4, 137.4, 129.6, 129.5, 127.0, 121.9, 108.8, 108.5, 101.1, 82.6, 82.2, 66.4, 66.2, 52.7, 44.9, 27.7, 27.6, 21.5; HRMS (EI) calcd. for $C_{28}H_{37}NO_{10}S$ 579.2138, found 579.2128. Anal. Calcd for $C_{28}H_{37}NO_{10}S$: C, 58.02; H, 6.43; N, 2.42. Found: C, 57.75; H, 6.43; N, 2.33.

(2*R*,3*R*)-2-Amino-3-(1,3-Benzodioxol-5-yl)-butane-1,4-diol Hydrochloride (78). To a solution of diol **76** (198 mg, 0.70 mmol) in CH_3OH (6 mL) was added 10% aq KOH (4.5 mL), and the mixture was heated at reflux for 14 h. The reaction was allowed to cool to room temperature, and the reaction mixture was extracted with Et_2O (3 × 20 mL). The combined organic extract was dried over Na_2SO_4 and concentrated in vacuo. A solution of the remaining residue in CH_3OH (5 mL) was added to CH_3OH saturated with HCl at 0 °C, with stirring. After 5 min, the solvent was removed under reduced pressure. The residue was dissolved in 2-propanol and filtered into chilled Et_2O to precipitate amine hydrochloride **78** (149 mg, 82%) as a pale tan solid: $[\alpha]^{25}_D$ +59.0 (*c* 1.0, CH_3OH); IR (neat) ν 3416, 1631, 1504, 1490, cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 6.79 (s, 1 H), 6.73 (m, 2 H), 5.86 (s, 2 H), 4.24 (t, J = 8.5 Hz, 1 H), 4.13 (dd, J = 10.4, 6.3 Hz, 1 H), 3.85−3.78 (m, 2 H), 3.31 (td, J = 7.4, 4.6 Hz, 1 H); ^{13}C NMR (75 MHz, CD_3OD) d149.8, 148.6, 133.7, 122.1, 109.5, 108.7, 102.6, 75.8, 72.2, 59.8, 51.5; HRMS (CI) calcd for $C_{11}H_{16}NO_4$ (M + H − Cl) 226.1079, found 226.1082.

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