Total Synthesis of (±)-Pancratistatin

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Abstract: The total synthesis of the antitumor title compound has been accomplished. Among the key steps was an iodolactonization of a cyclohexadiene bearing a neighboring carboxamido group mediated by an ortho-stannylated phenol (see **16** → **17**). A series of cis vicinal functionalization reactions were used to control stereochemistry. The scheme was applicable as a consequence of an intervening Overman rearrangement of a highly functionalized allylic imidate (see **35** → **36**).

Background

Pancratistatin, a phenanthridone alkaloid, was isolated by Pettit and co-workers[1,2] from the root of the plant *Pancratium littorale* Jacq., native to Hawaii. They showed it to have structure **1** (Figure 1). From the same phytochemical source were obtained the previously known anhydro and anhydrodeoxy congeners narciclasine (**2**) and lycoricidine (**3**).[3] Interest in pancratistatin is heightened by its particularly promising activity in several anticancer test systems administered by the National Cancer Institute. In protocols where test (T) to control (C) survival ratios of 180 are taken to be indicative of promising activity, pancratistatin has registered T:C values as high as 206. In comparative evaluations, prancratistatin has exhibited significantly greater activity than either **2** or **3**.[4]

At the present writing, there is no substantive information bearing on the mechanism of the antineoplastic action of pancratistatin. However, considerable research has gone into defining the origin of the similar but less pronounced behavior of its congener narciclasine.[5] These studies have indicated that the mechanism of action of narciclasine involves the inhibition of the growth of eukaryotic cells by the disruption of protein biosynthesis. The inhibition for narciclasine has been demonstrated both in cell-free and in intact cells. It has been concluded that narciclasine inhibits the binding of tRNA to the peptidal transferase center of the 60S ribosomal subunit.[5a] Since narciclasine inhibits the binding of another peptidal biosynthesis inhibitor, anisomycin, the binding sites of anisomycin and narciclasine may well be the same.[5a] Of course, the extent to which the findings concerning narcisclasine are pertinent to the more potent pancratistatin remains to be determined.

In this paper we describe the first total synthesis of pancratistatin.[6] Although this goal has not been previously accomplished, it should be noted than an analogous synthesis of a 7-deoxy system was completed by both Ohta[7] and by Paulsen[8] during the course of their syntheses of lycoricidine (**2**). In each case, the previous workers passed through an intermediate, which was a derivatized version of 7-deoxypancratistatin. In each case dehydration of a C_1 alcohol was involved in reaching their goal system.

Thus, in principle, either the Ohta or the Paulsen synthesis could be restructured to include the 7-hydroxyl required for pancratistatin. The inclusion of such an additional oxygen center in the required precursor would be one of the significant issues in a total synthesis of either narciclasine or pancratistatin. It was our purpose to develop an entirely new approach—one which would probe the feasibility of certain oxidation reactions on systems which were close to aromaticity. The realization of stereoselective oxidative addition reactions to double bonds, while avoiding dehydrogenations or dehydrations leading to aromatic rings, was a major challenge to our plan (vide infra). Of course, the strategy would have to embrace inclusion of an additional C_7 oxygen.

We note that the methodology which we describe below could also be directed toward a total synthesis of narciclasine. However, the more potent biological activity of pancratistatin and its lesser availability from natural sources, not to speak of its greater structural complexity, render it the more attractive target. Indeed, the possibility of reaching pancratistatin through a partial synthesis from naturally occurring narciclasine is now a matter of some interest to our laboratory.

Synthetic Strategy

We note that the C-ring of pancratistatin contains six stereogenic carbon centers. *It was our hope to reduce the construction of the synthesis of this C-ring to a set of reactions in which the elaboration of vicinal cis relationships is to be expected.* We first examined the structure i and noted a set of relationships between carbons 1 and 2, carbons 3 and 4, and carbons 4a and 10b which are trans, cis, and trans, respectively (Figure 2). It was assumed that the C_{4a} amino group would be introduced relatively late in the synthesis and that the benzenoid A-ring would be engaged with the C_1 oxygen in the form of a lactone. This notion is represented in structure ii wherein the relationships between carbon sets 10b-1, 2-3, and 4-4a are cis-trans-trans, respectively. A significant simplification at the conceptual level arises from removal of the C_3 and C_4 oxygen groups with installation (in a retrosynthetic sense) of a double bond between these atoms. In the forward sense, there would thus be required a vicinal cis oxygenation of the 3-4 double bond in going from hypothetical intermediate type iii to ii. In analyzing structure iii, another cis relationship becomes apparent, namely, that between the α-disposed oxygen and amino substituents at C_2 and C_{4a}, respectively.

Another simplification at the conceptual level arises from the possibility that the C_{4a} α-amino group of structure iii might in fact have arisen from a suprafacial allylic transposition of a C_3 α-hydroxyl function. In that event, a new C_2-C_3 cis relationship

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(2) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M. *J. Nat. Prod.* **1984**, *47*, 1018.
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(5) (a) Carrasco, L.; Fresno, M.; Vazquez, D. *FEBS Lett.* **1975**, *52*, 236. (b) Jimenez, A.; Sanchez, L.; Vazquez, D. *FEBS Lett.* **1975**, *55*, 53. (c) Mondon, A.; Krohn, K. *Chem. Ber.* **1975**, *108*, 445.
(6) The full account of this work is found in the Ph.D. Thesis of J. Y. Lee, Yale University, 1989.
(7) (a) Ohta, S.; Kimoto, S. *Chem. Pharm. Bull.* **1976**, *24*, 2969. (b) Ohta, S.; Kimoto, S. *Chem. Pharm. Bull.* **1976**, *24*, 2977.
(8) (a) Paulsen, H.; Stubbe, M. *Tetrahedron Lett.* **1982**, 3171. (b) Paulsen, H.; Stubbe, M. *Liebigs Ann. Chem.* **1983**, 535.

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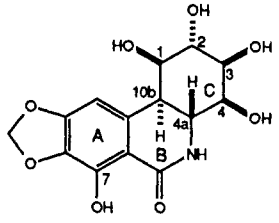
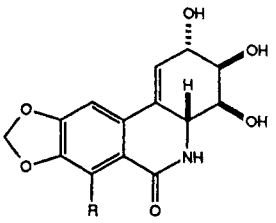


1 pancratistatin



2 R = OH, narciclasine
3 R = H, lycoricidine

Figure 1.

emerges in compound iv. This analysis led back to hypothetical precursor v. It would be necessary to achieve a cis hydroxylation of v selectively at the C_2–C_3 double bond to pave the way for the suprafacial hydroxy to amino allylic transposition, implicit in the relationship of structures iv and iii. A plausible precursor to structure v would be the prototype system vi. Transformation vi to v would involve a halolactonization reaction followed by an elimination. An attractive feature of this formulation was that the C_{10b}–C_1 cis relationship would be established in the context of the sequence.[9] This conception in turn led back to aldehyde vii, which was perceived to be the precursor of the cyclohexadiene ring in structure vi.

While it did not prove possible to reduce to reality the program set forth herein in full detail (see formation of **18a** from **18**), the overall construct was a valuable matrix to organize our experiments, which culminated in a total synthesis of pancratistatin. The synthesis of aldehyde type vii emerged as a crucial subgoal. It was with experiments directed to that end that we began.

Results

The specific compound corresponding to prototype system vii, which we identified as a target, was compound **10**. As will become apparent, the aldehyde function would be employed to build a conjugated butadiene residue (see compound **12**), which would in turn be used to reach compound prototype system vi.

The starting material for the effort was pyrogallol (**4**) (Figure 3). Reaction of compound **4** with triethyl orthoformate afforded the orthoester **5**.[10] The free hydroxyl group was carbamoylated through the action of diethylcarbamoyl chloride. Compound **5** was available in 86% yield. The orthoester was cleaved to provide the monocarbamoyl derivative **6** (86%). The vicinal hydroxyl groups were now engaged[11] in the form of a methylenedioxy linkage via the reaction of **6** with potassium carbonate and methylene bromide (in the presence of CuO in dimethylformamide). Compound **7** was obtained in 70% yield.

Our efforts now focussed on conversion of the trisubstituted aromatic system **7** into a tetrasubstituted variation. In the event, treatment of compound **7** with *sec*-butyllithium at −78 °C in tetrahydrofuran followed by warming to ambient temperature promoted rearrangement according to the precedents of Snieckus.[12] Unfortunately, the yield of the resultant **8** did not exceed 60%.[13]

It was now convenient to protect the hydroxyl group of **8** as its OTBS derivative. This was indeed accomplished through the action of TBDMSCl in the presence of imidazole in methylene chloride. At this stage the ortho lithiation of compound **9** was accomplished. Reaction of this lithium derivative with dimethylformamide produced the desired aldehyde **10** in 70% yield.

Elaboration of the arylbutadiene moiety could now begin. Reaction of **10** with allylmagnesium bromide in ether at −78 °C afforded (92%) alcohol **11** (Figure 4). Activation of the alcohol function was accomplished with mesyl chloride. Elimination of the homoallylic mesylate was induced by treatment with DBU. Diene **12** was thus obtained in 54% overall yield.

Reaction of diene **12** with the known acetylenic dienophile equivalent **13**,[14] occurred smoothly in chloroform to afford adduct **14** in 96% yield. Treatment of compound **14** with tri-*n*-butyltin hydride gave rise to cyclohexadiene **15** (see prototype system vi).

Attempts to achieve halolactonization by reaction of compound **15** with a variety of halogenating agents were unsuccessful.[6] It was reasoned that such reactions would be easier if some of the repulsion between the large OTBS group and the diethylimminium function were alleviated. Such repulsion would be particularly serious in the hypothetical intermediate **15a**. Accordingly, compound **15** was treated with tetra-*n*-butylammonium fluoride. Phenol **16** was produced in 80% yield.

Even this compound proved to be quite sluggish in terms of fostering the needed halolactonization. *We now turned to stannylation of the phenolic function as an approach toward increasing the effective nucleophilicity of the carboxamido linkage.*[15] The rationale arose from the known tendency of stannylation of an oxygen function to increase its nucleophilicity.[16]

In practice, treatment of compound **16** with bis(tributyltin) oxide in toluene followed by the reaction of the resulting stannyl ether with iodine dissolved in THF indeed provided lactone **17** in 67% yield. Thus, the "X-functionalization"[17] of the cyclohexadiene had now been accomplished, and the cis stereochemical relationship between the C_{10a} and C_1 functions had been installed. The phenolic hydroxyl group was protected as its benzylic ether via the reaction of **17** with silver oxide and benzyl bromide in DMF. The yield for this transformation was 85%.

Attentions were now directed toward conversion of iodolactone **18** to the prototype system v. Unfortunately, attempts to accomplish this transformation by elimination of HI from **18** with bases under various conditions were unsuccessful owing to the great tendency of this system (v, P = Bn) to undergo very rapid conversion to acid **18a**.

It as therefore necessary to protect the array against aromatization. This was accomplished by reaction of compound **18** with osmium tetraoxide in the presence of NMO. There was thus obtained a 90% yield of the diol iodolactone **19** (Figure 5). Clearly, recourse to this hydroxylation reaction constituted a tactical retreat from the most concise version of our original plan. Ultimately, there would be required the reductive removal of the C_4–C_{4a} heterofunctions with reinstallization of a double bond between those centers. Nonetheless, it was appropriate to rigorously establish the stereochemistry in this series. Toward that end we returned to phenol **17**. Osmylation of this compound afforded compound **19a**, which upon triacetylation gave rise to compound **19b**. That this compound **19b** corresponds to the structure formulated was established by an X-ray crystallographic determination.[18]

Before installation of the C_2–C_3 functionality, it was necessary to prepare for regiospecific reductive elimination of the heteroatoms between C_4 and C_{4a}. Toward this end, compound **20** was treated with 2-acetoxyisobutyryl bromide in a Moffatt-like transformation.[19,20] The hope was to convert **20** to an acetoxy compound of the type **21** or **21a**. In such a fashion the vicinal heterofunctionality at C_4–C_{4a} would be distinguished from the

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(10) Dietl, F.; Gierer, G.; Merz, A. *Synthesis* **1985**, 626.
(11) Tomita, M.; Aoyagi, Y. *Chem. Pharm. Bull.* **1968**, *16*, 523.
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(13) One of the side products was the phenol of **7**, in which the carbamate group had been cleaved.
(14) (a) Ono, N.; Kamimura, A.; Kaji, A. *Tetrahedron Lett.* **1986**, 1595. (b) Ono, N.; Kamimura, A.; Kaji, A. *J. Org. Chem.* **1986**, *51*, 2139.
(15) See: Poller, R. C. In *Comprehensive Organic Chemistry*; Barton, D. F. R. S., Sir; Ollis, W. D., Eds.; Pergamon Press: Oxford, England, 1979; Vol. 3, pp 1073–1095.
(16) For a review on stannylenes, see: David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.
(17) See: Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, pp 411–454.
(18) The details of the X-ray structure determination of compound **19b** and the structural parameters are found in the Ph.D. Thesis of J. Y. Lee, Yale University, 1989. We acknowledge Gayle Schulte at Yale Instrument Center for this determination.
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(20) Robins, M. J.; Hansske, F.; Low, N. H.; Park, J. I. *Tetrahedron Lett.* **1984**, 367.

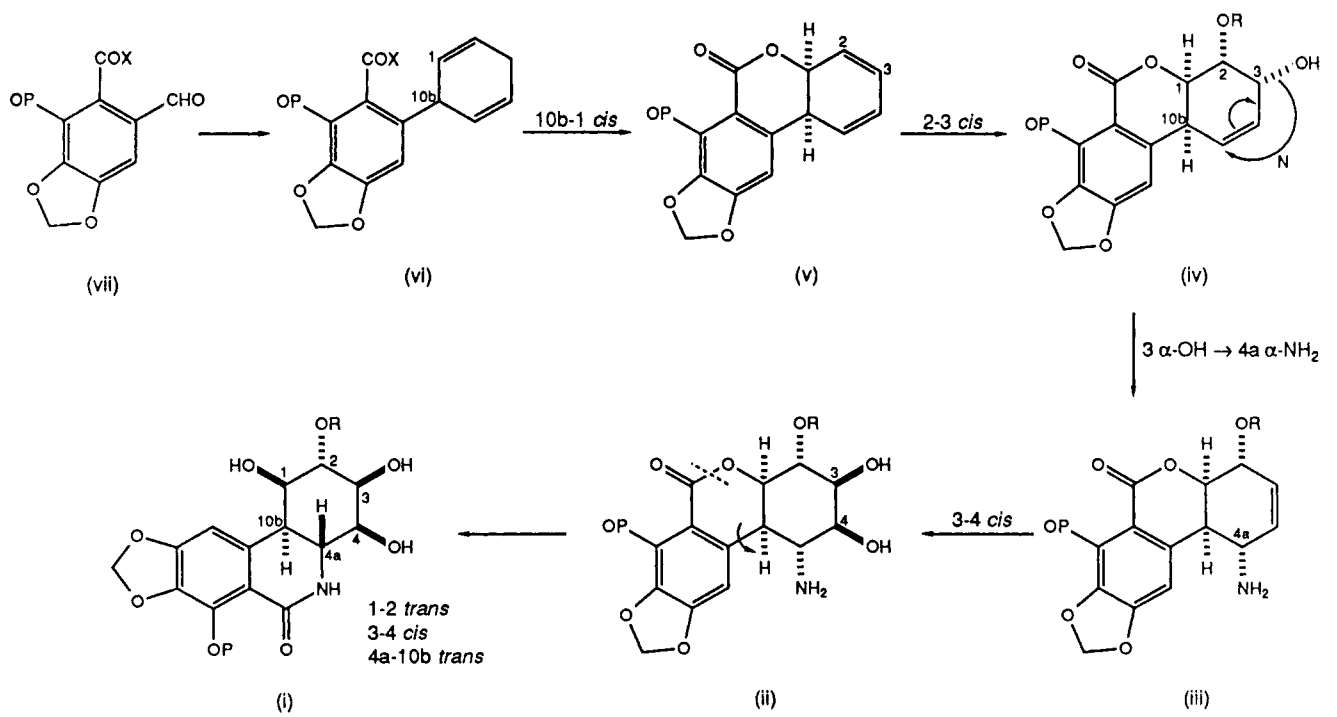

Figure 2.

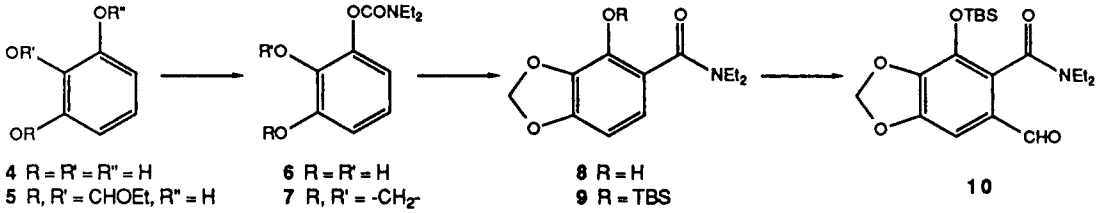

Figure 3.

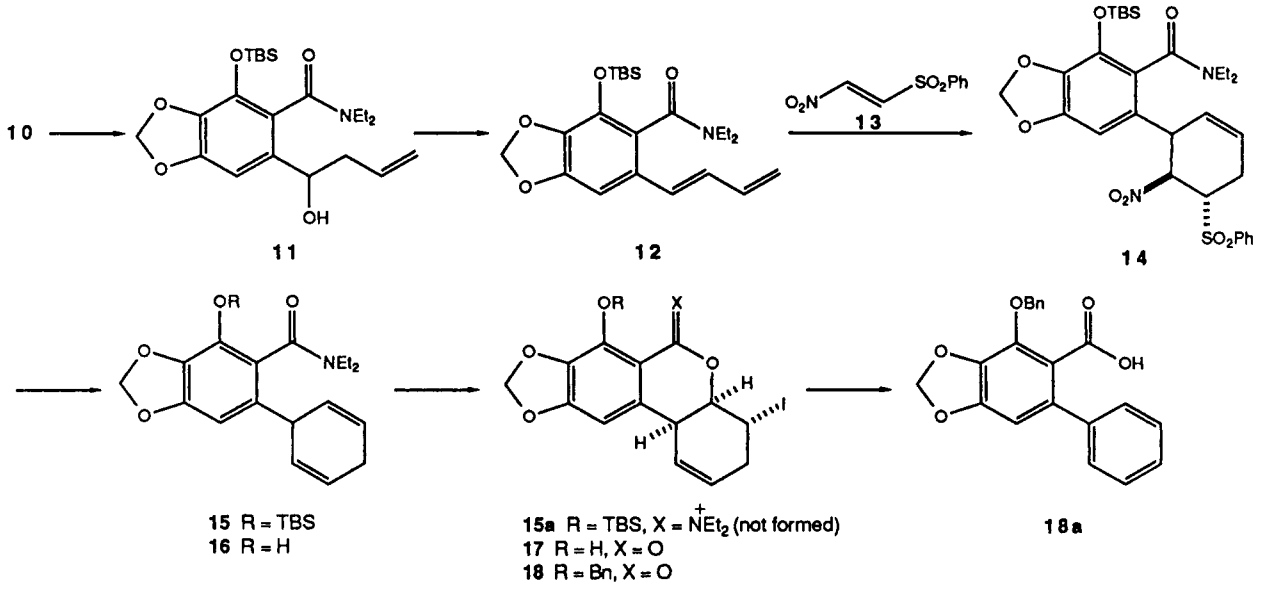

Figure 4.

vicinal diol functionality soon to be introduced at carbons 2 and 3 (vide infra). Unfortunately, this reaction proved to be somewhat complicated. Although the bromacetate **21** was obtained (63%), the process gave rise to a significant amount (25%) of the allylic isomer **22**. Only the former compound was useful for subsequent development.

Given the presence of the cis fusion between C_{10b} and C_1, augmented by a β-bromine substituent at C_4, it was not surprising to find that hydroxylation of the C_2–C_3 double bond did indeed occur on the α-face of the molecule to produce diol **23**. For the first time a hexasubstituted C-ring had been elaborated. Moreover, treatment of this compound with zinc dust furnished the desired enediol **24**. *As envisioned, the reductive elimination was selective for the trans vicinal bromoacetate relative to the trans vicinal bromohydrin.*

We now focused on realization of a suprafacial allylic transposition of the C_3 α-hydroxyl group to install the required C_{4a} α-amino precursor.[21] Contemplating an Overman rearrangement

to accomplish this goal,[22] we treated diol **24** with trichloroacetonitrile. Of the two hydroxy functions, it was expected that the one at C_3 would be most reactive and that imidate formation would occur at this center (see structure **28**). In practice there was produced not an imidate but the cyclic orthoamide **25** as a mixture of diastereomers. Interestingly, the two compounds could be separated by careful chromatography on silica gel. The NMR spectra at 250 MHz of the two substances were virtually identical except for slightly differing chemical shifts. The spectra of both compounds were lacking a resonance at δ 8.5 which would have been suggestive of an imidate N–H proton. The infrared spectra of both compounds exhibited weak absorption bands between 3300 and 3500 cm^{-1}, indicative of primary amines.

It was hoped that orthoamide formation would not per se block our intended plan. It seemed reasonable to suppose that these orthoamides **25a** and **25b** would be in equilibrium with the required imidate **28** and that the latter would indeed undergo Overman rearrangement. There was precedent for such a possibility from the work of Vyas and co-workers (cf. transformation **26** to **27**).[23]

In practice, however, all attempts to achieve the Overman rearrangement of compounds **25** in an attempt to reach compound **30** were unsuccessful. That the orthoamides **25** were apparently undergoing conversion to an imidate was suggested by the fact that the individual isomers **25a** and **25b** underwent equilibration to the same mixture upon thermolysis in *tert*-butylbenzene. This curious result could be interpreted in two ways. One possibility was that the orthoamide only opened to produce imidate **29** and the required imidate **28** was not being produced. Alternatively, it could be argued that **28** was indeed being produced but that the rate of its reclosure to **25** was much greater than the rate of its rearrangement to the desired **30**. In any case the formation of orthoamides **25** was effectively closing off the much-needed Overman[22] allylic–imidate rearrangement. In order to deal with this problem, it would be necessary to install a blocking group at the C_3 hydroxyl function. In this way orthoamide formation would be blocked.

Toward this goal, compound **23** was treated with bis(di-*n*-butyltin) oxide. The resultant stannylene reacted with *p*-methoxybenzyl bromide in the presence of nBu_4NI at 80 °C to afford **31** in 84% yield (Figure 6).[16] The remaining C_3 hydroxyl group was now protected as its benzyl ether through the agency of benzyl bromide in the presence of Ag_2O in DMF. There was thus obtained a 95% yield of compound **32**. The PMB blocking group was now selectively removed by the reaction of **32** with DDQ in methylene chloride followed by aqueous workup.[24] The monoalcohol **33** was thus available in 75% yield. Treatment of **33** with zinc dust provided **34** (81%). As before (cf. **23** → **24**), the trans-related bromo–acetoxyl functions suffered reductive elimination in preference to the trans-related vicinal bromohydrin.

Treatment of compound **34** with sodium hydride in the presence of trichloroacetonitrile in THF afforded a 74% yield of imidate **35** (Figure 7). Unfortunately, we were unable to drive this reaction to completion, and approximately 20% recovered **34** always accompanied the formation of **35**. Fortunately, the two compounds were amenable to chromatographic purification on silica gel, and the former could be recycled.

Some difficulties were now encountered in forcing the Overman rearrangement to conclusion. The best results were obtained by pyrolysis of imidate **35** in neat form at 100–105 °C under a high vacuum for 1 h. A 56% yield of the rearrangement product **36** was obtained. The stage was appropriate for installation of the C_3–C_4 vicinal hydroxyl substituents. Once again we turned to an osmium tetraoxide hydroxylation protocol in the expectation that the α-heterofunctions at C_2 and C_{4a} would ensure attack of the C_3–C_4 double bond from its β-face. This expectation was fully borne out (vide infra).

Reaction of compound **36** with catalytic osmium tetraoxide/NMO did indeed produce the diol. That this substance was properly formulated as compound **37** was established by its diacetylation product. The vicinal coupling constants of this compound were fully consistent with the proposed structure shown as **38**.

Armed with this information, we returned to compound **37**. Treatment of this compound with potassium carbonate in methanol generated what was believed to be the amino acid **39**. This substance could be cyclized with DCC in methylene chloride to produce an 82% yield of the C_3, C_7 dibenzyl ether (**40**) of (±)-pancrastistatin. Finally, the reduction of the latter with $Pd(OH)_2/C$ and hydrogen[25] in ethyl acetate served to cleave the two benzyl protecting groups. There was thus obtained a 90% yield of (±)-pancratistatin (**1**). *The chromatographic mobility and infrared and 490-MHz spectra of the fully synthetic product were identical with those obtained from an authentic specimen sample.*[26] *The total synthesis of* (±)-*pancratistatin* (*1*) *had clearly been achieved.*

Conclusions

While the total synthesis of pancratistatin had been accomplished in a stereospecific way, there were several weak steps that eroded the efficiency of the total effort. A disappointing yield was obtained in the rearrangement of **7** → **8**. The Moffatt transposition (**20** → **21**) was accompanied by the formation of a nonusable allylic isomer, **22**. The orthoamide problem (see compound **25**) required an elaborate blocking maneuver to regiospecifically distinguish the C_3 hydroxyl group for imidate rearrangement. Nonetheless the scheme indicates the merit of original retrosynthetic analysis wherein all stereochemical issues could be solved by a series of vicinal cis functionalization reactions of double bonds. This work still leaves much room for creative chemistry in furnishing a more practical route to the much desired pancratistatin either by total or by partial synthesis.

Experimental Section

2-Ethoxy-1,3-benzodioxol-4-ol (5). In a 2-L flask equipped with a 50-cm Vigreaux column and distillation head, pyrogallol **4** (100 g, 0.793 mol), $CH(OEt)_3$ (158 mL, 0.95 mol), and a catalytic amount (5 g) of Amberlyst-15 were suspended in 1 L of benzene. The reaction mixture was heated at reflux with azeotropic removal of benzene/ethanol for 12 h. The reaction mixture was cooled, filtered over Celite, and rinsed with benzene. The filtrate was removed in vacuo, and the residue was filtered through 600 g of silica gel with 10% EtOAc/hexane, yielding 117 g (86%) of orthoester **5** as a colorless oil: ^1H NMR ($CDCl_3$, 90 MHz) δ 6.8 (s, 1 H), 6.35–6.65 (m, 3 H), 5.4 (s, 1 H), 3.7 (q, J = 7 Hz, 2 H), 1.23 (t, J = 7 Hz, 3 H); IR (film) 3410, 2979, 1638, 1476, 1341, 1130, 896, 762 cm^{-1}; MS (EI, 20 eV) m/e 182 (60.3), 137 (98.7), 126 (100), 108 (40.5), 80 (38).

1,2-Dihydroxyphenyl Diethylcarbamate (6). To a dry 1-L flask under N_2 was added NaH (31 g, 60% dispersion in mineral oil, 0.77 mol) and washed with hexane. It was suspended in THF (400 mL) and cooled to 0 °C. Alcohol **5** (117 g, 0.642 mol) was dissolved in THF (100 mL) and canulated into the suspension of NaH slowly. After the fizzling had stopped, Et_2NCOCl (83.5 mL, 0.659 mol) and DMAP (3.9 g, 0.032 mol) were added and slowly warmed to room temperature. The reaction was monitored by TLC (20% EtOAc/hexane). Upon completion of the reaction 20 h), the mixture was cooled to 0 °C and was quenched by slow addition of H_2O. THF was removed in vacuo, and the residue was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the resulting residue was dissolved in MeOH (300 mL). A catalytic amount (7 g) of *p*-TsOH was added, and the mixture was stirred for 4 h. The reaction was quenched with saturated $NaHCO_3$, and MeOH was removed in vacuo. The residue was extracted with EtOAc (3 × 70 mL), and the combined organic layers were washed with brine

(21) Attempts to achieve the required transformation through displacement reaction with various nitrogen nucleophiles using (π-allyl)palladium chemistry via the cyclic carbonate of **24** were unsuccessful.[6]

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(23) Vyas, D. M.; Chiang, Y.; Doyle, T. W. *J. Org. Chem.* **1984**, *49*, 2037.

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(25) Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663.

(26) The natural pancratistatin was provided by Dr. Pettit at Arizona State University and Dr. Suffness at the National Cancer Institute.

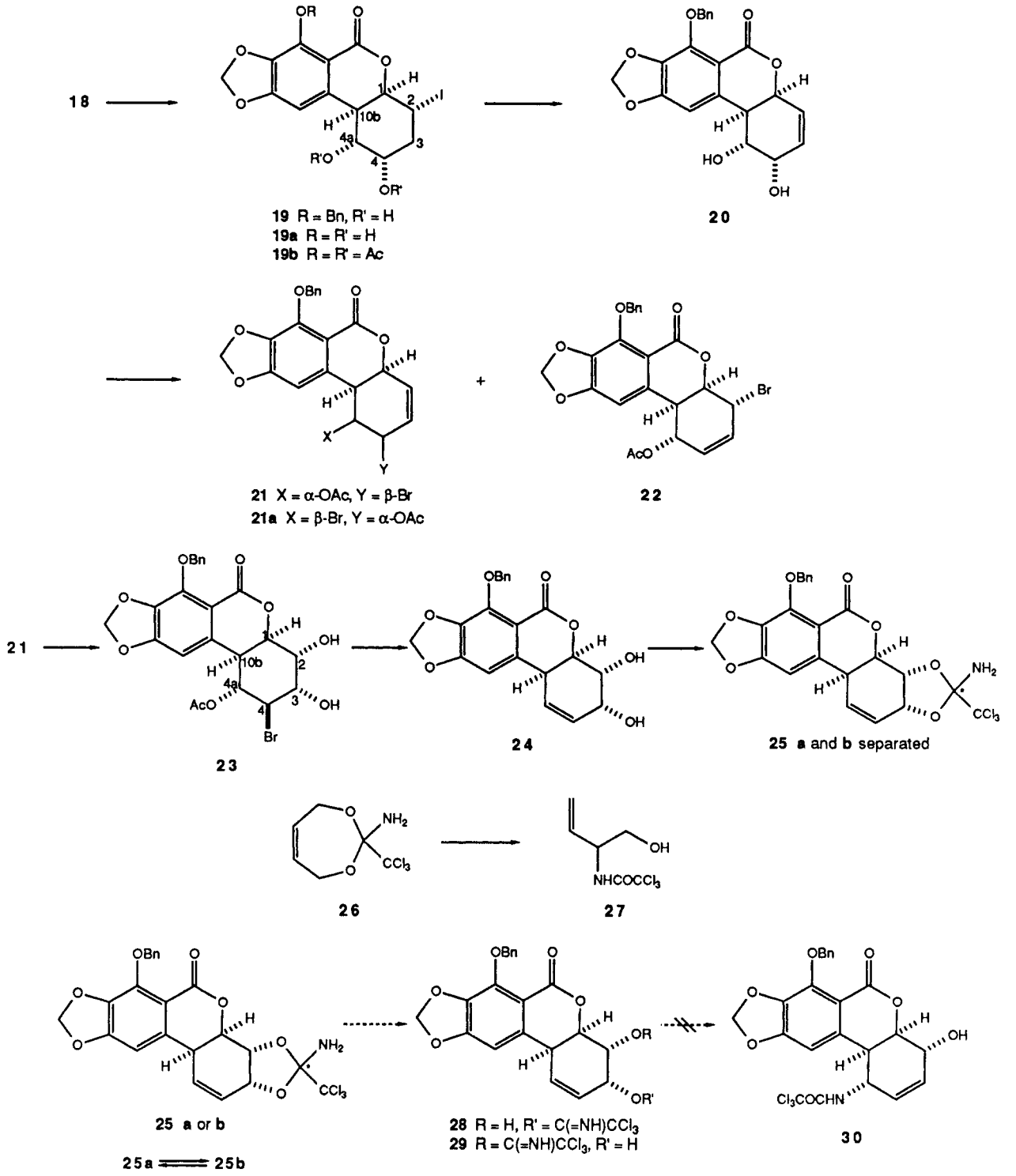
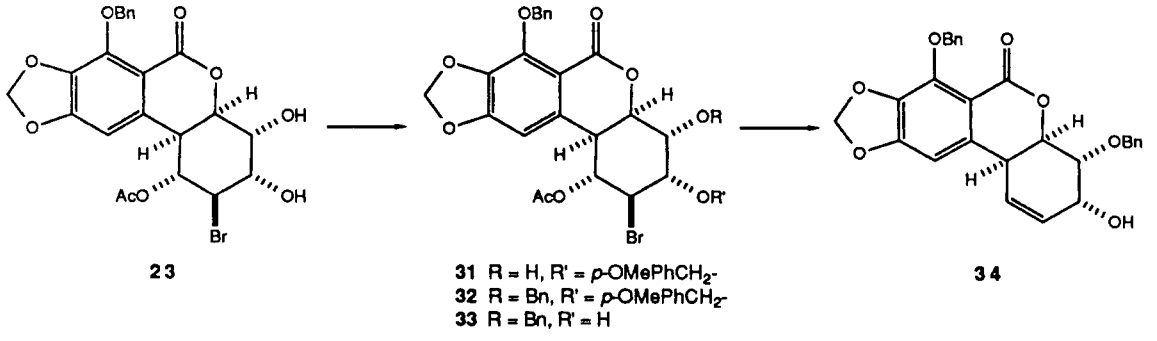


Figure 5.



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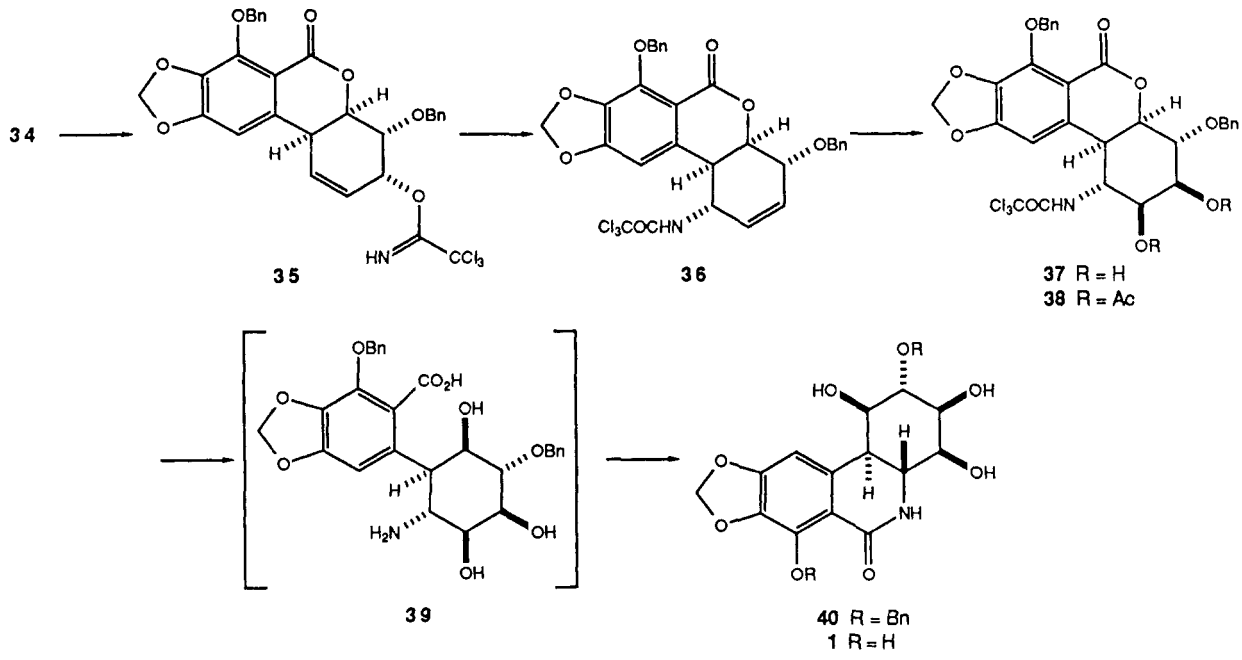

Figure 7.

and dried over $MgSO_4$. The product was purified by flash chromatography, 25% EtOAc/hexane, which yielded 123.8 g (86%) of carbamate **6** as a solid: mp 102–104 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.9–6.4 (m, 3 H), 3.52–3.34 (m, 4 H), 2.35 (br d, 2 H), 1.32–1.20 (m, 6 H); IR (film) 3310, 2974, 1682, 1604, 1469, 1423, 1275, 1217, 1158, 1055, 990 cm^{-1}; MS (EI, 20 eV) *m/e* 225 (9.5), 126 (1.0), 100 (100), 72 (38). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.61; H, 6.89; N, 6.01.

4-[(Diethylcarbamyl)oxy]-1,3-benzodioxole (7). In a dry 2-L flask equipped with a reflux condenser under N_2, **6** (123.8 g, 0.55 mol) was dissolved in DMF (1 L). To this was added K_2CO_3 (152 g, 1.1 mol), CH_2Br_2 (77.2 mL, 1.1 mol), and CuO (4.4 g, 0.1 mol), and the mixture was heated at reflux for 1.5 h. The cooled mixture was filtered over Celite and rinsed with EtOAc. The filtrate was diluted with H_2O (2 L) and extracted with EtOAc (5 × 500 mL). The combined organic layers were washed with H_2O (2 × 100 mL) and brine and dried over $MgSO_4$. Purification by flash chromatography, 10% EtOAc/hexane, afforded 91.7 g (70%) of **7** as an oil: ^1H NMR ($CDCl_3$, 250 MHz) δ 6.82–6.64 (m, 3 H), 5.96 (s, 2 H), 3.46–3.34 (m, 4 H), 1.27–1.19 (m, 6 H); IR (film) 2955, 1720, 1629, 1460, 1245, 1057, 921, 745 cm^{-1}; MS (EI, 20 eV) *m/e* 237 (34.2), 137 (10.5), 100 (100), 72 (55.3).

***N,N*-Diethyl-4-hydroxy-1,3-benzodioxole-5-carboxamide (8).** In a dry 1-L RB flask, carbamate **7** (10.4 g, 43.8 mmol) was dissolved in THF (450 mL) and cooled to −78 °C. To this was added TMEDA (8.6 mL, 57 mmol) and *sec*-BuLi (44 mL, 1.3 M in cyclohexane, 57 mmol), respectively. The reaction mixture was slowly warmed to room temperature and stirred overnight. The mixture was quenched with saturated NH_4Cl, and THF was removed in vacuo. The residue was dissolved in EtOAc and H_2O and extracted with EtOAc (4 × 100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Purification by flash chromatography, 30% EtOAc/hexane, provided 6.0 g (58%) of amide **8**: ^1H NMR ($CDCl_3$, 250 MHz) δ 9.98 (br s, 1 H), 6.83 (d, J = 8.2 Hz, 1 H), 6.39 (d, J = 8.2 Hz, 1 H), 6.0 (s, 2 H), 3.5 (q, J = 7.1 Hz, 4 H), 1.25 (t, J = 7.1 Hz, 6 H); IR (film) 3200, 2967, 1635, 1582, 1458, 1373, 1275, 1053, 910 cm^{-1}; MS (EI, 20 eV) *m/e* 237 (100), 220 (11.8), 165 (92), 137 (4.6).

***N,N*-Diethyl-4-[(*tert*-butyldimethylsilyl)oxy]-1,3-benzodioxole-5-carboxamide (9).** The solution of **8** (21 g, 88 mmol) in CH_2Cl_2 (220 mL) was cooled to 0 °C, and to this was added imidazole (7.2 g, 0.106 mol) and TBSCl (15.8 g, 0.102 mol), respectively. After fizzling had ceased, the ice bath was removed, and the reaction mixture was stirred at room temperature until the reaction was complete (30 min, TLC monitoring). The mixture was filtered over Celite, and the residue was rinsed with CH_2Cl_2. The filtrate was washed with saturated $NaHCO_3$ and brine and then dried over Na_2SO_4. Purification by flash chromatography, 20% EtOAc/hexane, yielded 26.7 g (86%) of **9**: ^1H NMR ($CDCl_3$, 250 MHz) δ 6.68 (d, J = 8.0 Hz, 1 H), 6.49 (d, J = 8.0 Hz, 1 H), 5.92 (br s, 2 H), 3.55–3.1 (m, 4 H), 1.22 (t, J = 7.1 Hz, 3 H), 1.01 (t, J = 7.1 Hz, 3 H), 0.95 (s, 9 H), 0.20 (br s, 6 H); IR (film) 2922, 2851, 1628, 1468, 1421, 1267, 1060, 835, 782 cm^{-1}; MS (EI, 20 eV) *m/e* 351 (0.1), 336 (4.9), 294 (100), 220 (2.5).

***N,N*-Diethyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-formyl-1,3-benzodioxole-5-carboxamide (10).** In a dry 1-L flask, **9** (8.03 g, 22.8 mmol) was dissolved in THF (450 mL), and it was cooled to −78 °C. To this was added TMEDA (4.14 mL, 27.4 mmol) and *sec*-BuLi (21 mL, 1.3 M in cyclohexane, 27.4 mmol), respectively, and the resulting deep red mixture was stirred at −78 °C for 1 h. Dry DMF (5.3 mL, 68.5 mmol) was added to the reaction mixture, and it was slowly warmed to room temperature overnight. The reaction was quenched by the addition of saturated NH_4Cl, followed by the removal of THF in vacuo. The resulting residue was dissolved in EtOAc and H_2O, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Purification by flash chromatography, 20% EtOAc/hexane, afforded 6.05 g (70%) of aldehyde **10** as a solid: mp 76–78 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 9.78 (s, 1 H), 7.09 (s, 1 H), 6.06 (ABq, J = 1.3 Hz, $\Delta\nu$ = 3.8 Hz, 2 H), 3.9–3.1 (m, 4 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.04 (t, J = 7.1 Hz, 3 H), 0.96 (s, 9 H), 0.25 (s, 3 H), 0.21 (s, 3 H); IR (film) 2924, 2851, 1690, 1629, 1604, 1471, 1398, 1294, 1221, 1087, 832, 777 cm^{-1}; MS (EI, 20 eV) *m/e* 379 (0.1), 364 (2.4), 322 (100), 264 (1.1), 251 (14.0); HRMS calculated for $C_{18}H_{29}NO_4Si$ 352.1944, found 352.1921.

***N,N*-Diethyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-(1-hydroxy-3-butenyl)-1,3-benzodioxole-5-carboxamide (11).** To a solution of allylmagnesium bromide (44.2 mL, 1.0 M solution in Et_2O, 44.2 mmol) in Et_2O (100 mL) at −78 °C was added dropwise aldehyde **10** (14 g, 36.8 mmol) dissolved in Et_2O (50 mL). After the reaction was complete (TLC monitoring), it was quenched with saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, and the solvent was evaporated in vacuo. Purification by flash chromatography, 20% EtOAc/hexane, afforded 14.4 g (92%) of alcohol **11** as a mixture of amide rotamers: ^1H NMR ($CDCl_3$, 250 MHz) δ 6.68 and 6.67 (2 s, 1 H), 6.05–5.70 (m, 3 H), 5.20–5.0 (m, 2 H), 4.52–4.42 (m, 1 H), 3.87–2.88 (m, 4 H), 2.78–2.24 (m, 2 H), 1.30–1.04 (m, 6 H), 0.95 (s, 9 H), 0.24–0.16 (3 s, 6 H); IR (film) 3400, 2920, 1614, 1465, 1420, 1362, 1285, 1220, 1084, 1032, 838, 780 cm^{-1}; MS (EI, 20 eV) *m/e* 421 (5.0), 364 (78.2), 322 (15.7), 307 (100), 294 (20.0). Anal. Calcd for $C_{22}H_{35}NO_5Si$: C, 62.67; H, 8.37; N, 3.32. Found: C, 62.66; H, 8.35; N, 3.31.

***N,N*-Diethyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-(1,3-butadienyl)-1,3-benzodioxole-5-carboxamide (12).** Alcohol **11** (12.3 g, 29.17 mmol) was dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C. To this solution was added Et_3N (6.1 mL, 43.76 mmol) and methanesulfonyl chloride (2.71 mL, 35.01 mmol), respectively; then, the ice bath was removed. After all alcohol **11** had reacted (TLC monitoring), DBU (4.4 mL, 29.17 mmol) was added to the reaction mixture. In addition, 2 × 3 mL of DBU was added over the course of 24 h. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ (2 × 20 mL) and brine. It was dried over Na_2SO_4, and the solvent was evaporated in vacuo. Purification by flash chromatography, 10% EtOAc/hexane, yielded 6.3 g (54%) of diene **12** as a white solid: mp 104–106 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.76 (s, 1 H), 6.62 (dd, J = 15.6 and 10.1 Hz, 1 H),

6.49–6.34 (m, 2 H), 5.94 (ABq, J = 1.3 Hz, $\Delta\nu$ = 8.4 Hz, 2 H), 5.28 (dd, J = 16.9 and 1.4 Hz, 1 H), 5.13 (dd, J = 10.5 and 1.4 Hz, 1 H), 3.87–3.06 (m, 4 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.02 (t, J = 7.1 Hz, 3 H), 0.95 (s, 9 H), 0.24 (s, 3 H), 0.20 (s, 3 H); IR (film) 2933, 2862, 1629, 1603, 1469, 1417, 1290, 1085, 1021, 836, 778 cm^{-1}; MS (EI, 20 eV) m/e 403 (7.3), 346 (100), 331 (1.5), 303 (1.1), 290 (3.5), 275 (4.2), 260 (1.0), 217 (1.0).

***N,N*-Diethyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-[5-(phenylsulfonyl)-6-nitro-2-cyclohexen-1-yl]-1,3-benzodioxole-5-carboxamide (14).** Diene **12** (6.29 g, 15.58 mmol) and the dienophile **13**[14] (4 g, 18.7 mmol) were suspended in $CHCl_3$ (16 mL) and heated at reflux for 12 h. The cooled, homogeneous reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography, directly, 20% EtOAc/hexane followed by 30% EtOAc/hexane, which afforded 9.25 g (96%) of cycloadduct **14** as a mixture of amide rotamers: ^1H NMR ($CDCl_3$, 250 MHz) δ 8.13–7.58 (m, 5 H), 6.30 and 6.22 (2 s, 1 H), 6.08–5.43 (m, 5 H), 4.36–2.55 (m, 8 H), 1.4–1.02 (m, 6 H), 0.99 (2 s, 9 H), 0.25, 0.23, and 0.18 (3 s, 6 H); IR (film) 2903, 1619, 1549, 1467, 1416, 1360, 1290, 1246, 1144, 1088, 1030, 834, 784, 683 cm^{-1}; MS (EI, 20 eV) m/e 601 (M − 15, 1.9), 559 (100), 512 (6.4), 428 (16.6), 417 (30.3), 372 (40.7), 355 (45.4), 299 (4.1), 100 (3.0); HRMS calculated for $C_{30}H_{40}N_2OSSi$ 617.2354, found 617.2369.

***N,N*-Diethyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-(2,5-cyclohexadien-1-yl)-1,3-benzodioxole-5-carboxamide (15).** To the solution of **14** (9.19 g, 14.9 mmol) in toluene (35 mL) was added AIBN (2.45 g, 14.9 mmol) and Bu_3SnH (12 mL, 44.7 mmol), and the mixture was heated at reflux for 3 h. After being cooled down to room temperature, the mixture was directly loaded on a column packed with hexane as solvent. It was first eluted with 1 L of hexane followed by 5% EtOAc/hexane to afford 4.6 g (72%) of cyclohexadiene **15**: ^1H NMR ($CDCl_3$, 250 MHz) δ 6.45 (s, 2 H), 5.89 (ABq, J = 1.4 Hz, $\Delta\nu$ = 13.5 Hz, 2 H), 5.90–5.56 (m, 4 H), 3.85–3.76 and 3.30–3.17 (m, 5 H), 2.75–2.70 (m, 2 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.08 (t, J = 7.1 Hz, 3 H), 0.95 (s, 9 H), 0.24 (s, 3 H), 0.20 (s, 3 H); IR (film) 2934, 1625, 1467, 1416, 1359, 1284, 1246, 1220, 1087, 1037, 936, 834, 777 cm^{-1}; MS (EI, 20 eV) m/e 429 (61.9), 412 (33.7), 372 (46.2), 355 (100), 299 (41.5), 269 (6.0), 241 (3.2), 100 (3.3).

***N,N*-Diethyl-4-hydroxy-6-(2,5-cyclohexadien-1-yl)-1,3-benzodioxole-5-carboxamide (16).** Cyclohexadiene **15** (4.6 g, 10.71 mmol) was dissolved in THF (30 mL) and cooled to 0 °C. To this was added $Bu_4N^+F^-$ (11.7 mL, 1.1 M in THF, 12.85 mmol) dropwise. The reaction was complete in 5 min (TLC monitoring). The ice bath was removed, and the mixture was poured into H_2O (50 mL). It was extracted with EtOAc (4 × 20 mL), and the extract was washed with brine and dried over $MgSO_4$. Purification by flash chromatography, 2% MeOH/CH_2Cl_2, yielded 2.66 g (79%) of **16** as a white solid: mp 197 °C dec; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.91 (br s, 1 H), 6.32 (s, 1 H), 5.75 (br s, 6 H), 3.83–3.76 (m, 1 H), 3.41 (br s, 4 H), 2.73–2.70 (m, 2 H), 1.19 (br s, 6 H); IR (film) 3200, 2960, 1628, 1596, 1465, 1419, 1354, 1217, 1073, 1027, 903, 707 cm^{-1}; MS (EI, 20 eV) m/e 315 (44.3), 314 (M − 1, 100), 242 (25.9), 241 (27.7), 212 (4.5), 184 (7.8), 183 (7.1), 165 (2.3), 164 (2.1), 128 (2.2), 100 (8.6). Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.51; H, 6.87; N, 4.39.

[(±)-(4α,4aα,11bα)]-3,4,4a,11b-Tetrahydro-4-iodo-7-hydroxy-6*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-6-one (17). To the suspension of phenol **16** (174 mg, 0.552 mmol) in dry toluene (1.5 mL) was added $(Bu_3Sn)_2O$ (141 μL, 0.276 mol), which made the mixture homogeneous. Powdered 3-Å molecular sieves were added to absorb H_2O produced, and the mixture was stirred for 2 h. I_2 (560 mg, 2.208 mmol) was dissolved in THF (1.5 mL), added to the reaction mixture, and stirred at room temperature for 30 h. Saturated $Na_2S_2O_3$ was added until the I_2 color had disappeared, and the aqueous layer was extracted with EtOAc (4 × 3 mL). The combined extracts were washed with brine and dried over $MgSO_4$. Purification by flash chromatography, eluting first with 1 L of hexane followed by 10% EtOAc/hexane, afforded 143 mg (67%) of iodolactone **17** as a white solid: mp 177–179 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.46 (s, 1 H), 6.09 (s, 2 H), 5.75–5.69 (m, 1 H), 5.52–5.46 (m, 1 H), 4.93–4.90 (m, 1 H), 4.62–4.58 (m, 1 H), 4.09–4.07 (m, 1 H), 3.39–3.29 (m, 1 H), 2.72–2.62 (m, 1 H); IR (film) 3110, 2916, 1673, 1507, 1488, 1452, 1341, 1267, 1138, 1089, 1027, 929 cm^{-1}; MS (EI, 20 eV) m/e 386 (100), 269 (25.2), 241 (7.3), 213 (10.7), 193 (8.5), 183 (13.7), 149 (10.8), 129 (9.0), 71 (6.6).

[(±)-(4α,4aα,11bα)]-3,4,4a,11b-Tetrahydro-4-iodo-7-(phenylmethoxy)-6*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-6-one (18). To the solution of phenol **17** (29.2 mg, 0.075 mmol) in DMF (700 μL) was added Ag_2O (52.6 mg, 0.227 mmol) and benzyl bromide (27 μL, 0.227 mmol). The mixture was stirred for 2 h at room temperature, filtered over Celite, and rinsed with EtOAc (3 mL). The filtrate was washed with H_2O (2 × 1 mL) and brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the crude product was purified by flash chromatography using 20% EtOAc/hexane, yielding 32 mg (85%) of **18** as a solid: mp 190–193 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.57–7.30 (m, 5 H), 6.57 (s, 1 H), 6.04 (ABq, J = 1 Hz, $\Delta\nu$ = 9.8 Hz, 2 H), 5.75–5.69 (m, 1 H), 5.52–5.48 (m, 1 H), 5.34 (ABq, J = 11.4 Hz, $\Delta\nu$ = 9.5 Hz, 2 H), 4.77–4.74 (m, 1 H), 4.58–4.54 (m, 1 H), 4.01–4.00 (m, 1 H), 3.46–3.38 (m, 1 H), 2.70–2.61 (m, 1 H); IR (film) 2912, 1712, 1608, 1466, 1368, 1251, 1239, 1097, 1029 cm^{-1}; MS (EI, 20 eV) m/e 476 (4.6), 331 (22.1), 253 (1.6), 225 (2.7), 128 (1.5), 105 (1.9), 91 (100).

[(±)-(1α,2α,4aα,4aα,11bα)]-1,2,3,4,4a,11b-Hexahydro-1,2-dihydroxy-4-iodo-7-(phenylmethoxy)-6*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-6-one (19). Iodolactone **18** (700 mg, 1.47 mmol) was dissolved in a minimum amount of CH_2Cl_2 and diluted with THF (15 mL). To this was added *N*-methylmorpholine *N*-oxide (NMO) (300 mg, 2.94 mmol), and H_2O was added dropwise until NMO was dissolved. The OsO_4 solution (1.87 mL, 0.196 M in THF, 0.367 mmol) was added to the mixture, and it was stirred at room temperature for 20 h. The reaction was quenched with 10% $NaHSO_3$ and extracted with EtOAc several times. The combined organic layers were washed with brine and dried over $MgSO_4$. Purification by flash chromatography, 40% acetone/hexane, yielded 673.8 mg (90%) of diol **19** as a solid: mp 177–180 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.55–7.30 (m, 5 H), 6.61 (s, 1 H), 6.03 (ABq, J = 1.4 Hz, $\Delta\nu$ = 9.4 Hz, 2 H), 5.34 (ABq, J = 11.5 Hz, $\Delta\nu$ = 10 Hz, 2 H), 4.84–4.81 (m, 1 H), 4.40 (br s, 1 H), 4.27 (br s, 1 H), 3.79–3.72 (m, 1 H), 3.47 (dd, J = 10.2 and 2.5 Hz, 1 H), 2.74–2.49 (m, 4 H); IR (film) 3446, 2896, 1700, 1610, 1500, 1468, 1358, 1242, 1113, 1073, 1022, 899, 725 cm^{-1}; MS (EI, 20 eV) m/e 510, 420, 365, 347, 329, 275, 240, 91; HRMS calculated for $C_{21}H_{19}O_7I$ 511.0254, found 511.0261.

[(±)-(1α,2α,4aα,11bα)]-1,2,4a,11b-Tetrahydro-1,2-dihydroxy-7-(phenylmethoxy)-6*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-6-one (20). Diol **19** (673 mg, 1.3 mmol) was solvated in dry benzene (13 mL), and to this was added DBU (207 μL, 1.38 mmol). The reaction mixture as heated at reflux for 1.5 h. The cooled mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated $NaHCO_3$ and brine. The solvent was dried over $MgSO_4$ and removed in vacuo. Purification by flash chromatography, 45% acetone/hexane, afforded 440 mg (88%) of **20**: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.52–7.28 (m, 5 H), 6.55 (s, 1 H), 6.13 (dd, J = 9.8 and 5.0 Hz, 1 H), 6.03 (dd, J = 9.8 and 5.0 Hz, 1 H), 5.98 (d, J = 1.0 Hz, 1 H), 5.92 (d, J = 1.0 Hz, 1 H), 5.25 (s, 2 H), 4.87 (dd, J = 4.2 and 3.7 Hz, 1 H), 4.25–4.20 (m, 1 H), 3.96–3.88 (m, 1 H), 3.27 (d, J = 3.5 Hz, 1 H), 3.21 (d, J = 6.8 Hz, 1 H), 3.06 (dd, J = 11.1 and 3.5 Hz, 1 H); IR (film) 3405, 3039, 2897, 1708, 1689, 1605, 1502, 1470, 1367, 1303, 1252, 1091, 1027, 943, 866, 731, cm^{-1}; MS (EI, 20 eV) m/e 382 (2.6), 346 (13.8), 302 (2.2), 269 (2.0), 240 (29.9), 191 (6.7), 91 (100).

[(±)-(1α,2β,4aα,11bα)]-1,2,4a,11b-Tetrahydro-1-acetoxy-2-bromo-7-(phenylmethoxy)-6*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-6-one (21) and [(±)-(1α,4α,4aα,11bα)]-1,4,4a,11b-Tetrahydro-1-acetoxy-4-bromo-7-(phenylmethoxy)-6*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-6-one (22). The solution of diol **20** (440 mg, 1.15 mmol) in dry CH_3CN (12 mL) was cooled to 0 °C, and to this was added 2-acetoxyisobutyryl bromide[19] (481 mg, 2.3 mmol) dropwise. The reaction was complete in 5 min (TLC monitoring). The mixture was warmed to room temperature and was quenched by the slow addition of saturated $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Purification by flash chromatography, 20% EtOAc/hexane followed by 30% EtOAc/hexane, yielded 356 mg of **21** and 138.7 mg of **22** as solids (88%): mp 156–159 °C (**21**), 144–147 °C (**22**). For **21**: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.57–7.30 (m, 5 H), 6.42 (s, 1 H), 6.21 (dd, J = 9.9 and 2.1 Hz, 1 H), 6.0 (dd, J = 9.9 and 2.1 Hz, 1 H), 6.02 (ABq, J = 1.2 Hz, $\Delta\nu$ = 9.0 Hz, 2 H), 5.58 (dd, J = 11.6 and 8.8 Hz, 1 H), 5.34 (ABq, J = 11.3 Hz, $\Delta\nu$ = 16.2 Hz, 2 H), 4.94–4.90 (m, 1 H), 4.75–4.71 (m, 1 H), 2.90 (dd, J = 11.6 and 3.4 Hz, 1 H), 2.02 (s, 3 H); IR (film) 3036, 2908, 1736, 1718, 1609, 1474, 1365, 1307, 1243, 1217, 1120, 1082, 1037, 928, 786, 735 cm^{-1}; MS (EI, 20 eV) m/e 488 (1.4), 486 (1.3), 347 (3.2), 329 (37.8), 256 (4.9), 241 (39.6), 212 (2.6), 183 (2.6), 91 (100). For **22**: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.58–7.32 (m, 5 H), 6.53 (s, 1 H), 6.07 (d, J = 0.5 Hz, 1 H), 6.05 (d, J = 0.5 Hz, 1 H), 6.09–6.03 (m, 1 H), 5.86 (dd, J = 10.2 and 1.9 Hz, 1 H), 5.47–5.43 (m, 1 H), 5.37 (ABq, J = 11.5 Hz, $\Delta\nu$ = 12.0 Hz, 2 H), 4.86 (br s, 1 H), 4.78–4.76 (m, 1 H), 3.38 (dd, J = 9.4 and 2.3 Hz, 1 H), 2.09 (s, 3 H); IR (film) 3042, 2913, 1738, 1732, 1607, 1501, 1472, 1366, 1301, 1254, 1230, 1101, 1042, 1013, 901, 778, 736 cm^{-1}; MS (EI, 20 eV) m/e 488 (1.9), 486 (1.9), 347 (3.7), 329 (22.9), 256 (1.9), 241 (8.9), 212 (1.4), 91 (100); HRMS calculated for $C_{23}H_{19}O_7Br$ 489.0372, found 489.0404.

[(±)-(1α,2β,3α,4α,4aα,11bα)]-1,2,3,4,4a,11b-Hexahydro-3,4-dihydroxy-1-acetoxy-2-bromo-7-(phenylmethoxy)-6*H*-[1,3]benzodioxolo-[5,6-*c*][1]benzopyran-2-one (23). The solution of **21** (523 mg, 1.07 mmol) in a minimum amount of CH_2Cl_2 was diluted with THF (6 mL). To this was added *N*-methylmorpholine *N*-oxide (NMO) (217 mg, 2.14 mmol),

and H_2O was added dropwise until all NMO was dissolved. OsO_4 in THF (1.36 mL, 0.157 M, 0.214 mmol) was added to the mixture, and it was stirred at room temperature for 12 h. The reaction was quenched with 10% $NaHSO_3$ and extracted with EtOAc several times. The combined organic layers were washed with brine and dried over $MgSO_4$ and then purified by flash chromatography using 3% $MeOH/CH_2Cl_2$. Since the residue was insoluble in this solvent system, it was dissolved in 10% $MeOH/CH_2Cl_2$ followed by the addition of ca. 3 g of silica gel. The solvent was evaporated in vacuo and pumped on high vacuum. The resulting silica gel, impregnated with the crude product, was loaded onto a column packed with 3% $MeOH/CH_2Cl_2$ and chromatographed to afford 494 mg (88%) of diol **23** as a solid: mp 221 °C dec; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.51–7.30 (m, 5 H), 6.38 (s, 1 H), 6.0 (ABq, J = 1.4 Hz, $\Delta\nu$ = 7.5 Hz, 2 H), 5.31 (ABq, J = 11.4 Hz, $\Delta\nu$ = 12.6 Hz, 2 H), 5.23 (dd, J = 10.5 and 10.5 Hz, 1 H), 4.58 (dd, J = 3.2 and 3.2 Hz, 1 H), 4.26 (dd, J = 10.5 and 10.5 Hz, 1 H), 4.19 (dd, J = 3.2 and 3.2 Hz, 1 H), 4.12 (dd, J = 10.5 and 2.9 Hz, 1 H), 3.09 (dd, J = 10.7 and 2.9 Hz, 1 H), 2.02 (s, 3 H); IR (film) 3499, 2913, 1733, 1695, 1600, 1478, 1370, 1332, 1249, 1236, 1083, 1045, 873 cm^{-1}; MS (EI, 20 eV) m/e 522 (2.8), 520 (2.8), 381 (2.4), 363 (3.4), 345 (4.9), 291 (1.5), 273 (1.7), 257 (3.4), 245 (1.3), 229 (1.9), 207 (1.3), 91 (100).

[(±)-(3α,4α,4aα,11bα)]-3,4,4a,11b-Tetrahydro-3,4-dihydroxy-7-(phenylmethoxy)]-6*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-6-one (24). To the solution of **23** (45 mg, 0.086 mmol) in CH_2Cl_2 (1 mL with 100 μL of MeOH) was added AcOH (200 μL, 3.44 mmol) and Zn (dust) (56 mg, 0.86 mmol), and the mixture was heated at reflux for 9 h. More Zn (50 mg) was necessary for the completion of the reaction. The cooled mixture was diluted with H_2O (1 mL) and extracted with EtOAc (3 × 1 mL). The organic layer was washed with brine and dried over $MgSO_4$. Purification by flash chromatography, 60% EtOAc/hexane, yielded 30 mg (91%) of **24**: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.52–7.30 (m, 5 H), 6.50 (s, 1 H), 6.0 (br d, J ≈ 8.7 Hz, 1 H), 5.70 (br d, J = 10.2 Hz, 1 H), 5.49 (br d, J = 10.2 Hz, 1 H), 5.29 (ABq, J = 11.4 Hz, $\Delta\nu$ = 13.2 Hz, 2 H), 4.81–4.78 (m, 1 H), 4.58 (br s, 1 H), 4.29–4.25 (m, 1 H), 3.66 (br s, 1 H); IR (film) 3300, 3016, 2896, 1709, 1609, 1470, 1364, 1251, 1105, 1039, 932, 893, 833 cm^{-1}.

Orthoamide 25. To a suspension of NaH (0.2 mg 60% dispersion in mineral oil, 5.86 μmol) in THF (200 μL) was added **24** (22.4 mg, 0.0586 mmol) dissolved in THF (100 μL), and the mixture was cooled to 0 °C. In a separate flask CCl_3CN (5.9 μL, 0.058 mmol) in THF (300 μL) was cooled to 0 °C, and to this was canulated the alkoxide solution of **24**. The mixture was slowly warmed to room temperature, and the solvent was evaporated in vacuo. The residue was chromatographed with 30% EtOAc/hexane to yield 26.3 mg (85%) of **25** as a 2:1 mixture of isomers. For the major isomer: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.57–7.31 (m, 5 H), 6.53 (s, 1 H), 6.06 (ABq, J = 1.0 Hz, $\Delta\nu$ = 9.5 Hz, 2 H), 5.90 (dt, J = 10 and 3.3 Hz, 1 H), 5.60 (br d, J = 10 Hz, 1 H), 5.37 (ABq, J = 9.2 Hz, $\Delta\nu$ = 9.6 Hz, 2 H), 5.11–5.07 (m, 1 H), 5.08–5.02 (m, 1 H), 4.94–4.91 (m, 1 H), 3.61 (br s, 1 H), 2.60 (s, 2 H); IR (film) 3424, 3344, 2901, 1720, 1612, 1504, 1464, 1370, 1296, 1228, 1167, 1107, 1046, 905, 831, 804 cm^{-1}; MS (EI, 20 eV) m/e 527 (2.9), 329 (1.0), 256 (8.0), 241 (2.1), 212 (2.1), 91 (100). For the minor isomer: ^1H NMR ($CDCl_3$, 250 MHz), same as that of the major isomer, except slightly different chemical shifts; IR and MS, same pattern as major isomer.

[(±)-(1α,2β,3α,4α,4aα,11bα)]-1,2,3,4,4a,11b-Hexahydro-4-hydroxy-1-acetoxy-2-bromo-3-[(4-methoxyphenyl)methoxy]-7-(phenylmethoxy)-6*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-6-one (31). The diol **23** (490 mg, 0.94 mmol) was solvated in dry toluene (24 mL), and to this was added Bu_2SnO (281 mg, 1.128 mmol) and 3-Å molecular sieves. The reaction mixture was heated at reflux for 1 h and cooled to room temperature, and *p*-methoxybenzyl bromide (283 mg, 1.41 mmol) and $Bu_4N^+I^-$ (35 mg, 0.094 mmol) were added. This mixture was heated at ca. 80 °C until the reaction was complete (3.5 h, TLC monitoring). The cooled mixture was directly loaded onto a column packed with 35% EtOAc/hexane and chromatographed to yield 510 mg (84%) of **31** as a single regioisomer: mp 194 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.56–6.92 (m, 9 H), 6.39 (s, 1 H), 6.02 (ABq, J = 1.3 Hz, $\Delta\nu$ = 8.8 Hz, 2 H), 5.34 (ABq, J = 11.3 Hz, $\Delta\nu$ = 14.8 Hz, 2 H), 5.31–5.27 (m, 1 H), 4.72 (ABq, J = 10.6 Hz, $\Delta\nu$ = 39.8 Hz, 2 H), 4.64–4.61 (m, 1 H), 4.27 (dd, J = 10.6 and 10.6 Hz, 1 H), 4.22–4.19 (m, 1 H), 4.06 (dd, J = 10.6 and 3.0 Hz, 1 H), 3.83 (s, 3 H), 3.08 (dd, J = 10.7 and 2.7 Hz, 1 H), 2.75 (d, J = 1.3 Hz, 1 H), 2.05 (s, 3 H); IR (film) 3463, 2904, 1748, 1722, 1605, 1514, 1475, 1358, 1241, 1218, 1091, 1046, 877, 728 cm^{-1}; MS (EI, 20 eV) m/e 642 (1.8), 640 (1.8), 363 (1.1), 345 (1.3), 303 (1.0), 273 (4.3), 245 (1.6), 211 (47.8), 121 (100), 91 (36.2); HRMS calculated for $C_{31}H_{29}O_{10}Br$ 641.1021, found 641.1017.

[(±)-(1α,2β,3α,4α,4aα,11bα)]-1,2,3,4,4a,11b-Hexahydro-1-acetoxy-2-bromo-3-[(4-methoxyphenyl)methoxy]-4,7-bis(phenylmethoxy)-6*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-6-one (32). To the solution of alcohol **31** (213 mg, 0.332 mmol) in DMF (4 mL) was added Ag_2O (770 mg, 3.32 mmol) and benzyl bromide (395 μL, 3.32 mmol). The mixture was stirred at room temperature for 16 h (TLC monitoring), diluted with CH_2Cl_2 (10 mL), and filtered through Celite. The organic layer was washed with H_2O (3 × 5 mL) and brine and then dried over $MgSO_4$. The crude product was purified by flash chromatography, 25% EtOAc/hexane, to afford 231 mg (95%) of **32** as a solid: mp 159–160 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.57–6.92 (m, 14 H), 6.38 (s, 1 H), 6.02 (ABq, J = 1.3 Hz, $\Delta\nu$ = 8.8 Hz, 2 H), 5.34 (ABq, J = 11.3 Hz, $\Delta\nu$ = 15.9 Hz, 2 H), 5.30 (dd, J = 10.6 and 10.6 Hz, 1 H), 4.86–4.41 (m, 6 H), 4.08–4.01 (m, 2 H), 3.84 (s, 3 H), 3.07 (dd, J = 10.6 and 2.8 Hz, 1 H), 2.06 (s, 3 H); IR (film) 3034, 2910, 1753, 1722, 1605, 1506, 1475, 1363, 1240, 1209, 1097, 1042, 738 cm^{-1}; MS (EI, 20 eV) m/e (0.2), 730 (0.2), 641 (0.5), 639 (0.5), 611 (0.5), 609 (0.5), 355 (1.2), 353 (1.5), 301 (1.7), 273 (3.1), 257 (1.7), 245 (2.7), 227 (2.8), 211 (23.2), 181 (5.6), 137 (3.5), 121 (100), 91 (72.2).

[(±)-(1α,2β,3α,4α,4aα,11bα)]-1,2,3,4,4a,11b-Hexahydro-3-hydroxy-1-acetoxy-2-bromo-4,7-bis(phenylmethoxy)-6*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-6-one (33). To the solution of **32** (231 mg, 0.316 mmol) dissolved in CH_2Cl_2 (3.2 mL) and H_2O (320 μL) was added DDQ (108 mg, 0.474 mmol), and the reaction mixture was stirred for 3.5 h (TLC monitoring) at room temperature; 10% $NaHSO_3$ (1 mL) was added to the mixture, and it was extracted with EtOAc (3 × 4 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The product was purified by flash chromatography, 30% EtOAc/hexane, to yield 145 mg (75%) of alcohol **33** as a solid: mp 212–214 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.56–7.31 (m, 10 H), 6.39 (s, 1 H), 6.02 (ABq, J = 1.4 Hz, $\Delta\nu$ = 8.9 Hz, 2 H), 5.33 (ABq, J = 11.3 Hz, $\Delta\nu$ = 14.9 Hz, 2 H), 5.31–5.24 (m, 1 H), 4.78 (ABq, J = 11.5 Hz, $\Delta\nu$ = 38.8 Hz, 2 H), 4.56 (dd, J = 3.2 and 3.2 Hz, 1 H), 4.38–4.22 (m, 2 H), 4.15–4.12 (m, 1 H), 3.06 (dd, J = 10.6 and 2.8 Hz, 1 H), 2.61 (d, J = 5.8 Hz, 1 H), 2.06 (s, 3 H); IR (film) 3414, 3046, 2915, 1749, 1718, 1606, 1469, 1363, 1238, 1213, 1095, 1045, 877, 733 cm^{-1}; MS (EI, 20 eV) m/e 612 (1.8), 610 (1.6), 521 (1.0), 345 (1.8), 291 (1.0), 181 (6.3), 105 (1.4), 91 (100).

[(±)-(3α,4α,4aα,11bα)]-3,4,4a,11b-Tetrahydro-3-hydroxy-4,7-bis-(phenylmethoxy)-6*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-6-one (34). To the solution of alcohol **33** (144 mg, 0.236 mmol) in CH_2Cl_2 (3 mL) was added Zn (dust) (618 mg, 9.45 mmol), glacial acetic cid (541 μL, 9.45 mmol), and H_2O (100 μL). The mixture was heated at reflux, and the reaction progress was monitored by TLC (2 days). More Zn (600 gm) was needed for the completion of the reaction. Upon completion, the mixture was diluted with H_2O (1 mL) and neutralized with a few drops of saturated $NaHCO_3$. It was extracted with EtOAc (4 × 2 mL), and the combined organic layers were washed with brine and dried over $MgSO_4$. Purification by flash chromatography, 30% EtOAc/hexane, afforded 90 mg (81%) of allylic alcohol **34**: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.57–7.29 (m, 10 H), 6.51 (s, 1 H), 6.03 (ABq, J = 1.3 Hz, $\Delta\nu$ = 10.7 Hz, 2 H), 5.77–5.71 (m, 1 H), 5.50–5.44 (m, 1 H), 5.32 (ABq, J = 11.3 Hz, $\Delta\nu$ = 10.9 Hz, 2 H), 4.76–4.73 (m, 1 H), 4.73 (ABq, J = 11.6 Hz, $\Delta\nu$ = 8.0 Hz, 2 H), 4.57–4.52 (m, 1 H), 4.15–4.11 (m, 1 H), 3.58–3.55 (m, 1 H), 2.46 (d, J = 11.1 Hz, 1 H); IR (film) 3447, 3022, 2907, 1711, 1608, 1467, 1364, 1254, 1229, 1113, 1036, 734, 689 cm^{-1}; MS (EI, 20 eV) m/e 472 (1.7), 381 (5.5), 363 (1.3), 257 (1.1), 240 (2.6), 229 (1.5), 181 (3.6), 91 (100); HRMS calculated for $C_{28}H_{24}O_7$ 473.1601, found 473.1583.

[(±)-(3α,4α,4aα,11bα)]-3,4,4a,11b-Tetrahydro-4,7-bis(phenylmethoxy)-3-[(2,2,2-trichloroethanimidoyl)oxy]-6*H*-[1,3]benzodioxolo[5,6-*c*]-[1]benzopyran-6-one (35). In a dry 10-mL RB flask, NaH (2.1 mg, 60% dispersion in mineral oil, 0.053 mmol) was placed and washed with pentane. To this was added THF (800 μL) and the mixture was cooled to 0 °C. The solution of **34** (50 mg, 0.105 mmol) in THF (200 μL) was canulated to the suspension of NaH in THF and stirred for 5 min. To this alkoxide solution was added CCl_3CN (53 μL, 0.53 mmol) dropwise, and the mixture was slowly warmed to room temperature over a 2-h period. The solvent was removed in vacuo, and the crude product was chromatographed without work-up, 20% EtOAc/hexane, to yield 48 mg (74%) of imidate **35**. The starting alcohol **34** (10 mg) was recovered with 30% EtOAc/hexane (92% yield based on the recovered starting material): ^1H NMR ($CDCl_3$, 250 MHz) δ 8.51 (s, 1 H), 7.56–7.30 (m, 10 H), 6.52 (s, 1 H), 6.03 (ABq, J = 1.2 Hz, $\Delta\nu$ = 11.6 Hz, 2 H), 5.92–5.84 (m, 2 H), 5.68–5.62 (m, 1 H), 5.33 (ABq, J = 11.4 Hz, $\Delta\nu$ = 12.5 Hz, 2 H), 4.82 (ABq, J = 11.8 Hz, $\Delta\nu$ = 70.1 Hz, 2 H), 4.69–4.65 (m, 1 H), 4.52–4.48 (m, 1 H), 3.74–3.72 (m, 1 H); IR (film) 3328, 3042, 2918, 1717, 1661, 1605, 1468, 1362, 1282, 1250, 1130, 1039, 784 cm^{-1}; MS (EI, 20 eV) m/e 454 (M − 162, 1.9), 363 (8.4), 346 (2.2), 313 (1.7), 257 (3.1), 236 (3.1), 181 (3.2), 149 (2.1), 129 (4.2), 91 (100).

[(±)-(1α,4α,4aα,11bα)]-1,4,4a,11b-Tetrahydro-4,7-bis(phenylmethoxy)-1-[(2,2,2-trichloroacetyl)amino]-6*H*-[1,3]benzodioxolo[5,6-*c*][1]-benzopyran-6-one (36). The imidate **35** (19.8 mg, 0.032 mmol) was placed in a 15-mL RB flask and heated to 100–105 °C under a high vacuum (0.05–0.1 mmHg) for 1.2 h. After cooling to room temperature,

the vacuum was released, and the product was isolated by flash chromatography (20% EtOAc/hexane) to yield 11.2 mg (56%) of the amide **36** as a solid: mp 186–187 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.59–7.31 (m, 10 H), 6.73 (d, J = 9.3 Hz, 1 H), 6.44 (s, 1 H), 6.10–6.03 (m, 1 H), 6.02 (ABq, J = 1.3 Hz, $\Delta\nu$ = 11.8 Hz, 2 H), 5.90 (dd, J = 10.3 and 1.7 Hz, 1 H), 5.37 (ABq, J = 11.4 Hz, $\Delta\nu$ = 13.8 Hz, 2 H), 4.70–4.68 (m, 1 H), 4.66 (ABq, J = 11.6 Hz, $\Delta\nu$ = 9.0 Hz, 2 H), 4.54–4.46 (m, 1 H), 4.12–4.10 (m, 1 H), 3.0 (dd, J = 9.9 and 2.4 Hz, 1 H); IR (film) 3303, 3038, 2915, 1703, 1611, 1512, 1469, 1358, 1248, 1094, 1020, 823, 731 cm^{-1}; exact mass MS (FAB, thioglycerol) calculated for $C_{30}H_{24}Cl_3NO_7$ 616.06985 (m + 1), observed 616.06685 (m + 1).

[(±)-(1α,2β,3β,4α,4aα,11bα)]-1,2,3,4,4a,11b-Hexahydro-2,3-dihydroxy-4,7-bis(phenylmethoxy)-1-[(2,2,2-trichloroacetyl)amino]-6*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-6-one (37). To the solution of amide **36** (27 mg, 0.044 mmol) in THF (300 μL) was added *N*-methylmorphine *N*-oxide (NMO) (8.9 mg, 0.088 mmol), and H_2O was added dropwise until all NMO had dissolved (2 drops). OsO_4 in THF (140 μL, 0.157 M, 0.022 mmol) was added to the mixture, and it was stirred for 45 h (TLC monitoring) at room temperature. It was quenched with 10% $NaHSO_3$ and extracted with EtOAc (4 × 2 mL). The combined extracts were washed with brine and dried over $MgSO_4$, and the solvent was evaporated in vacuo. The following procedure was used for the purification. The crude product was dissolved in 10% MeOH/CH_2Cl_2 to which ca. 100 mg of silica gel was added. The solvent was completely removed in vacuo, and the resulting silica gel, impregnated with the crude product, was loaded onto a column packed with 2% MeOH/CH_2Cl_2 and chromatographed. This gave 21.4 mg (75%) of the diol **37** as a solid: mp 202–206 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.48–7.26 (m, 10 H), 6.43 (s, 1 H), 5.97 (d, J = 1.3 Hz, 1 H), 5.89 (d, J = 1.3 Hz, 1 H), 5.29 (ABq, J = 11.4 Hz, $\Delta\nu$ = 12.8 Hz, 2 H), 4.61 (ABq, J = 11.7 Hz, $\Delta\nu$ = 16.2 Hz, 2 H), 4.59–4.57 (m, 1 H), 4.22–4.21 (m, 1 H), 4.13–3.96 (m, 3 H), 3.31 (dd, J = 10.9 and 2.8 Hz, 1 H); IR (film) 3304, 3039, 2910, 1710, 1698, 1611, 1469, 1288, 1250, 1088 cm^{-1}; exact mass MS (FAB, thioglycerol) calculated for $C_{30}H_{26}Cl_3NO_9$ 650.07531 (m + 1), observed 650.0762 (m + 1).

[(±)-(1β,2α,3β,4β,4aβ,11bα)]-1,3,4,4a,5,11b-Hexahydro-1,3,4-trihydroxy-2,7-bis(phenylmethoxy)[1,3]dioxolo[4,5-*j*]phenanthridin-6-(2*H*)-one (40). To the solution of diol amide **37** (10 mg, 0.0154 mmol) in dry MeOH/CH_2Cl_2 (5:2, 350 μL) was added anhydrous K_2CO_3 (21.2 mg, 0.154 mmol), and the mixture was refluxed for 8 h for complete hydrolysis (TLC monitoring). It was cooled to room temperature and neutralized with Amberlite IR-120. The ionic resin was filtered, and the solvent was evaporated in vacuo. The resulting residue was dissolved in CH_2Cl_2 (300 μL), and to this was added DCC (4.8 mg, 0.023 mmol). After the reaction was complete (5 min, TLC monitoring), the solvent was evaporated in vacuo. The residue was purified by flash chromatography, 3% MeOH/CH_2Cl_2, to afford 6.4 mg (82%) of lactam **40** as a solid: mp 98–100 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.10 (br s, 1 H), 7.51–7.20 (m, 1 H), 6.66 (s, 1 H), 5.94 (s, 2 H), 5.23 (ABq, J = 11.2 Hz, $\Delta\nu$ = 11.7 Hz, 2 H), 4.59 (ABq, J = 11.8 Hz, $\Delta\nu$ = 11.6 Hz, 2 H), 4.45 (br s, 1 H), 4.20 (br s, 1 H), 4.03 (dd, J = 3.1 and 3.1 Hz, 1 H), 3.99–3.76 (m, 2 H), 3.09 (d, J = 13.2 Hz, 1 H); IR (film) 3320, 2924, 1641, 1603, 1465, 1330, 1275, 1219, 1075, 1035, 730 cm^{-1}; MS (EI, 20 eV) m/e 505 (4.9), 415 (24.2), 288 (2.6), 260 (7.7), 247 (30.1), 231 (11.1), 218 (15.3), 190 (5.1), 108 (12.8), 91 (100).

Pancratistatin or [(±)-(1β,2α,3β,4β,4aβ,11bα)]-1,3,4,4a,5,11b-Hexahydro-1,2,3,4,7-pentahydroxy[1,3]dioxolo[4,5-*j*]phenanthridin-6-(2*H*)-one (1). In a 25-mL two-neck RB flask equipped with a balloon filled with H_2, compound **40** (6.4 mg, 0.0127 mmol) was suspended in EtOAc (300 μL), and to this was added $Pd(OH)_2/C$ (40 mg). The flask was evacuated and filled with H_2 twice by use of high vacuum and liquid N_2. The reaction was complete in 30 min (TLC monitoring). The mixture was filtered through Celite and rinsed with 10% MeOH/CH_2Cl_2. The solvent was evaporated in vacuo, and the product was purified by flash chromatography, 10% MeOH/CH_2Cl_2, according to the method used for compound **37** (DMF was used to dissolve the crude). This yielded 3.7 mg (90%) of pancratistatin as a white solid: started to decompose at 212 °C; ^{1}H NMR (DMSO-d_6, 490 MHz) δ 13.05 (br s, 1 H), 7.54 (br s, 1 H), 6.47 (s, 1 H), 6.03 (br d, J = 11.2 Hz, 2 H), 5.40 (d, J = 3.9 Hz, 1 H), 5.17 (d, J = 6.2 Hz, 1 H), 5.11 (d, J = 5.6 Hz, 1 H), 4.86 (d, J = 7.6 Hz, 1 H), 4.28–4.27 (m, 1 H), 3.96–3.95 (m, 1 H), 3.86–3.85 (m, 1 H), 3.74–3.76 (m, 2 H), 2.96 (br d, J = 12.9 Hz, 1 H); IR (KBr) 3321, 2914, 1675, 1616, 1464, 1330, 1082, 1050, 1019, 993, 821, 764 cm^{-1}; exact mass MS (FAB, thioglycerol) calculated for $C_{14}H_{15}NO_8$ 326.0876 (m + 1), observed 326.0889 (m + 1).

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