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A Convergent Synthesis of (+)-Pancratistatin Based on Intramolecular Electrophilic Aromatic Substitution†

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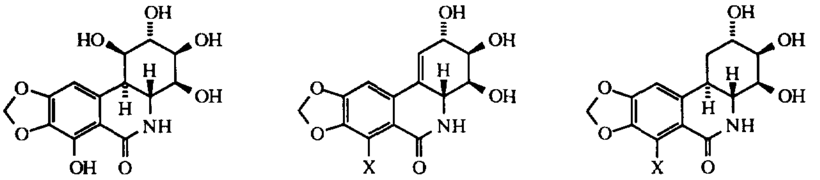
Abstract: A convergent formal synthesis of (+)-pancratistatin (1) is reported. Specifically, an optically active adduct of piperonyl bromide and acetonated conduritol A was converted to a late-stage intermediate from the Danishefsky-Lee synthesis of 1. The carbon skeleton was established via intramolecular electrophilic aromatic substitution within the piperonylated conduritol. Some competitive cationic rearrangement was observed in this operation, being dependent on the degree to which a 2-substituent in the piperonyl domain favors attack ipso to the piperonyl benzylic carbon.

INTRODUCTION AND SYNTHETIC STRATEGY

(+)-Pancratistatin (**1**) was originally isolated in 1984 by Pettit et al. from *Pancratium littorale*.[1] These workers determined the molecular structure via single-crystal x-ray diffraction performed on pancratistatin's monomethyl ether. They were also the first to describe pancratistatin's antitumor activity (38-106% life extension/0.75-12.5 mg/kg dose against murine P388 lymphocytic leukemia, P.S. system; 53-84% extension/0.38-3.0 mg/kg against murine M5076 ovary sarcoma). Pettit et al. optimized their isolation procedure to obtain a 0.039% yield of **1** based on wet plant weight.[1b] Other *Amaryllidaceae* constituents that show strong anticancer activity include narciclasine (**2**) which inhibits the growth of murine Ehrlich carcinoma and human HeLa and $\mathrm{HEP_{II}}$ carcinomas[2] and dihydronarciclasine (**4**) which inhibits murine P-388 lymphocytic leukemia with an $\mathrm{ED_{50}}$ of 0.0032 mg/mL.[3] The 7-deoxy analogs lycoricidine (**3**) and dihydrolycoricidine (**5**) are also active. When tested against the NCI human tumor cell line panel, all five natural products showed mean panel $\mathrm{GI_{50}}$ values within the 10-150 nM range.[4] They also showed very similar patterns of differential cell selectivity within the 60-line panel, with particular activity against NSC brain, lung, colon, and renal lines.



1 Pancratistatin

2 Narciclasine (X = OH)
3 Lycoricidine (X = H)

4 Dihydronarciclasine (X = OH)
5 Dihydrolycoricidine (X = H)

Figure 1. Pancratistatin and Some Relevant *Amaryllidaceae* Alkaloids.

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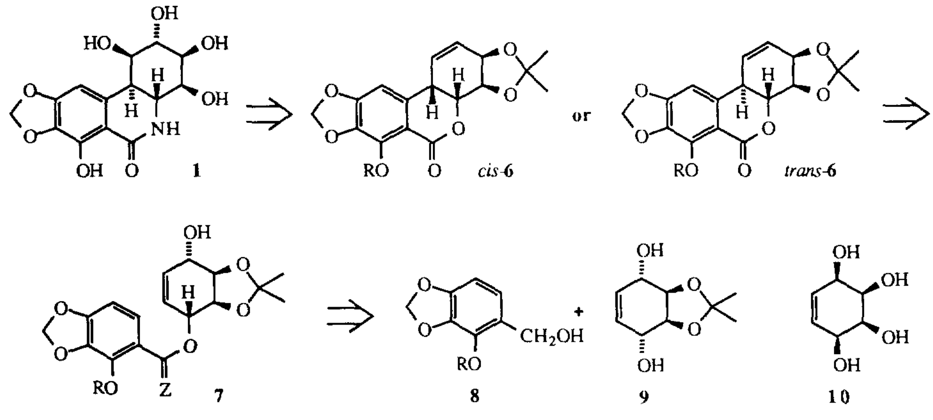
†This paper is dedicated to Professor Samuel Danishefsky in gratitude for his inspiring scientific frontiersmanship.

The selectivity profile of **1-5** does not correlate well with that of any established antitumor agents.[4] The molecular-level mechanism of action of narciclasine has been studied intensively. Narciclasine is an inhibitor of protein elongation specific for eukaryotic organisms.[5,6] Cross-resistance studies on *Saccharomyces cerevisia* located the receptor on the 60S subunit of the ribosome.[7] This evidence was supported by direct binding studies using tritium-labelled narciclasine.[6] The unusual mode of action of narciclasine is likely shared by its relatives since all have similar potencies and cell selectivities. That this mode complements those of established therapeutic agents implies new possibilities in combination drug therapies if the family is sufficiently non-toxic.

Work concerning fully synthetic routes to these alkaloids is valuable for the broader access it provides to analogs. Pancratistatin has been in pre-clinical development, but because of its surprisingly low solubility in water (53 mg/mL),[8] it cannot be formulated for *in vivo* administration at practical concentrations. The National Cancer Institute has been seeking analogs with improved solubility for evaluation.[9] New deoxygenated and epimeric versions of pancratistatin would provide further details on the structure-activity relationship of the family. Some may also emerge with therapeutic potential in their own right.

Certainly not for lack of interest (!),[10-13] the only reported synthesis of pancratistatin until 1995 was that of Danishefsky and Lee in 1989.[10a] Among the most noteworthy results in that synthesis were 1) the enhancement of reactivity in a halolactonization by use of a vinylogous stannyl urethane as nucleophile, and 2) the regio- and stereoselective installation of pancratistatin's nitrogen via an imidation and subsequent Overman rearrangement performed on a densely functionalized allylic alcohol. The sequence as a whole addressed stereospecifically pancratistatin's distinctive feature of six contiguous chiral centers.

We too saw pancratistatin as a target having potential medical significance, all the more worthy for the strategic challenge of its aminocyclitol domain.[14] Our analysis of **1** is given in abbreviated form in Scheme 1. Lactones *cis*- and *trans*-**6** represent protected precursors of **1** requiring the introduction of the amide nitrogen and two hydroxyls. A special appeal of *cis*-**6** lay in its close relationship to late-stage Danishefsky-Lee intermediates (vide infra). This lactone implied a secure end game. Isomeric *trans*-**6** on the other hand offered an unusually accommodating installation of the C1,C2-diol of **1**: electronically preferred *trans*-diaxial opening of *either* α- or β-oxide of the alkene of *trans*-**6** would correctly deliver the C1β,C2α configuration.[15] Either lactone, *cis*-**6** or *trans*-**6**, signified a convenient system entry if it could be assembled asymmetrically from a functionalized piperonol (e.g., **8**) and a conduritol (e.g., **9**). A key determinant of efficiency in the overall strategy would be the stereoselectivity of the internal allylic substitution **7** → **6**. Ratios of *cis*-**6**/*trans*-**6** near parity would not be optimal, but a good selectivity for either isomer would neatly accommodate our plan. As for the kinetic aspect of **7** → **6**, we expected to achieve sufficient reactivity by the rational variation of R, Z, and the leaving group.

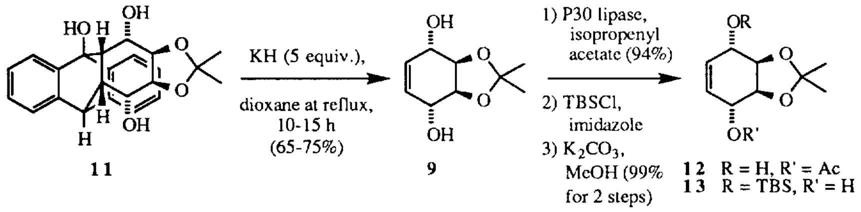


Scheme 1.

In a less abridged analysis of **1**, we considered approaches similar to that just described but requiring differently configured conduritols. Conduritol D (**10**) was a particularly attractive alternative. In our early experiments, we found that conduritol A acetonide (**9**) was readily available by adapting a synthesis devised by Knapp.[16] Our adaptation allowed for the generation of several grams of **9** per batch and required only one chromatographic purification. Parallel attempts to obtain conduritol D in quantity, however, were met with stolid molecular resistance.[17] The A-type stereochemistry therefore came to predominate in our tactical projections.

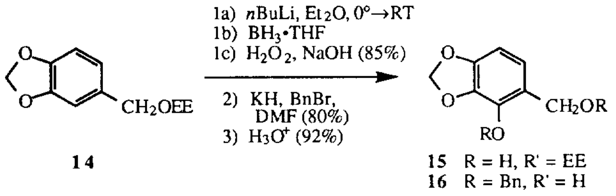
DISCUSSION OF RESULTS

The sequence to **9** and its asymmetric derivatives is outlined in Scheme 2. We had followed the shrewd protocol devised by Knapp for generating acetonide **11** stereoselectively from anthrone and benzoquinone.[16] This same acetonide had been further protected by Knapp, then made to undergo an anionically accelerated retro-Diels-Alder reaction, and was finally partially deprotected to deliver **9**. Rutledge found that an unaccelerated retro-DA could be run successfully on an unprotected anthracene/benzoquinone derivative,[18] but this proved unamenable to scale-up in our hands. Fortunately, we found **11** itself to be a fit candidate for accelerated retro-DA, ceding **9** directly. We employed Johnson's sequence for desymmetrization: enzymatic acetylation supplied **12** which was successively silylated and deacetylated to furnish **13** in 93% overall yield from **9**.[19]



Scheme 2.

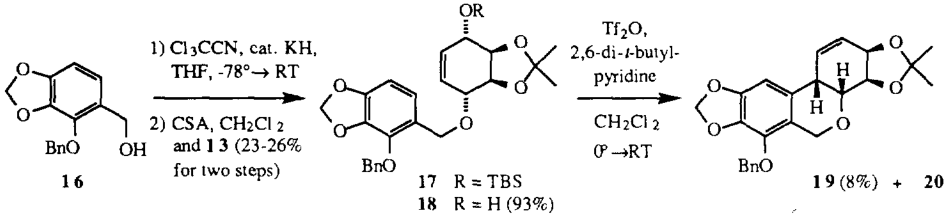
The prototype of our aromatic component was also realized straightforwardly. We hoped to incorporate the pancratistatin C7-oxygen at an early stage of our synthesis through the capacity of piperonyl ethers for efficient, regioselective lithiation.[20] We expected a properly metalated ether to convert smoothly to the corresponding phenol via the arylborohydride.[21] As depicted in Scheme 3, 1-ethoxyethyl-protected piperonol (**14**) was metalated by treatment with *n*-BuLi in diethyl ether. The aryllithium species reacted with borane, presumably to provide the borohydride which was in turn cleaved with basic peroxide. Phenol **15** was benzylated and the EE group was removed to yield **16** in very good overall yield.



Scheme 3.

We were now able to explore our key strategic operation, the fusion of piperonol and conduritol. Little trouble was anticipated with regard to an initial tethering of the two components. However, we favored the conduction of the ensuing cyclization (**7** → **6**, Scheme 1) as an electrophilic aromatic substitution, so the nature of the tether could affect the cyclization rate to a great extent. An ether linkage was the logical first choice in terms of its activating, *o,p*-directing character and post-cyclization oxidizability. Trichloroacetimidate methodology allowed us to execute a mildly successful coupling of piperonol **16** and allylic alcohol **13** (Scheme 4).[22] Other methods of activating the piperonol component did not lead to detectable amounts of coupled product. We attribute this behavior to an overly destabilizing effect of the benzyloxy group in the piperonyl unit upon activation, perhaps leading to polymerization, since we could never isolate the activated species. Yields obtained via the trichloroacetimidate were adequate for investigating the subsequent cyclization. Ether **17** was desilylated to give alcohol **18**.

Initial attempts at closing the central ring (**18**→**19**) relied on palladium-catalyzed π-allyl alkylation chemistry. Because intermolecular examples of that reaction typically exhibit a high net retention of facial stereochemistry in the electrophilic component (when relevant),[23] it seemed an ideal means of approach to purely *cis*-fused product. The acetate of **18** was indeed found capable of such chemistry but only as an electrophile. It could be condensed intermolecularly with potassium phthalimide, for example. In the absence of an external nucleophile, however, no cyclization product was apparent prior to substrate decomposition. We were able to induce the cyclization of **18** through the creation of a more potent leaving group at low temperature. Specifically, exposure of **18** to trifluoromethanesulfonic anhydride and 2,6-di-*tert*-butylpyridine (CH_2Cl_2, 0°→RT) generated a major product in 50% yield that appeared to be the expected **19** from its spectral data. The ^{1}H-^{1}H coupling evident in the NMR spectrum of this product was consistent with the anticipated cis ring fusion, but a single crystal x-ray analysis was carried out for corroboration. The initially perplexing result is shown in Figure 2.



Scheme 4.

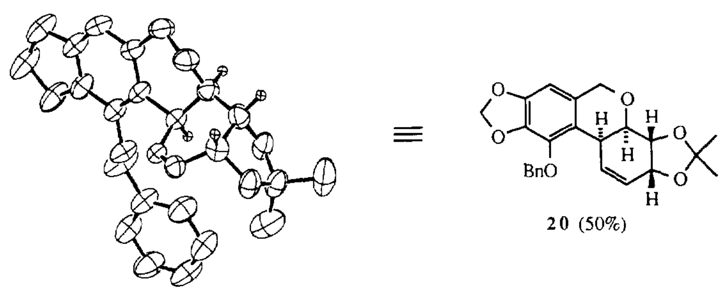
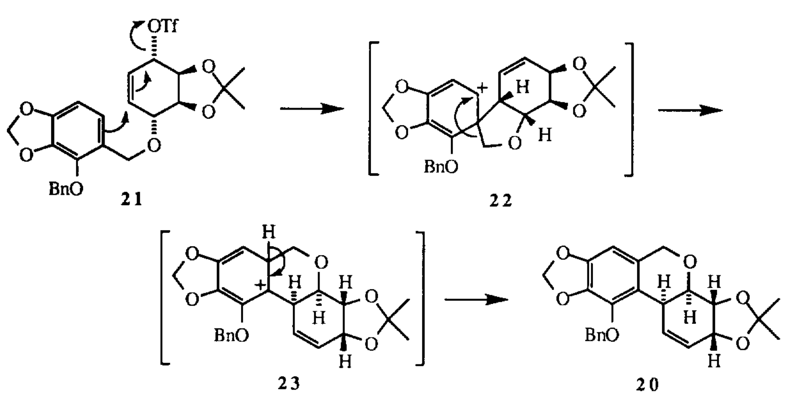


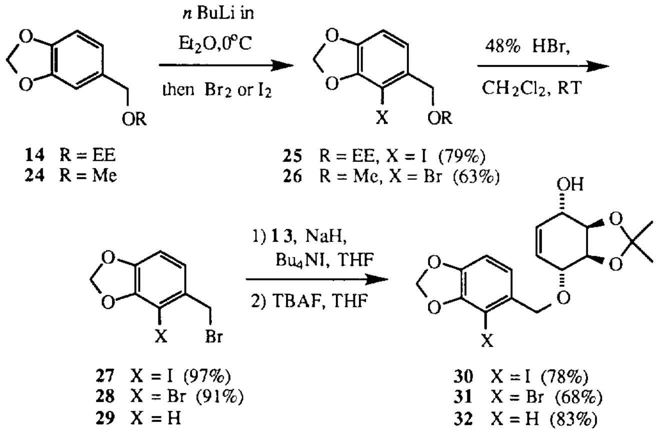
Figure 2.

The observed order of substituents on the aromatic nucleus in **20** can only be explained by a rearrangement in the cyclization step. A reasonable mechanistic pathway bridging **18** and **20** is offered in Scheme 5. Attack by the arene ring is proposed to occur from the most resonantly activated position (ipso to the tethering element) in an S_N2' or S_N1' mode to attain **22**.[24] A subsequent 1,2-shift of the alkoxymethyl substituent in **22** gives **23**. We note that a partial positive charge on the migrating carbon can be resonantly stabilized by its bonded oxygen.[25] A final deprotonation affords **20**. The desired pentacycle **19** was also isolable (8% yield) from the triflation of **18**. The identity of **19** was confirmed by chemical correlation.[26]



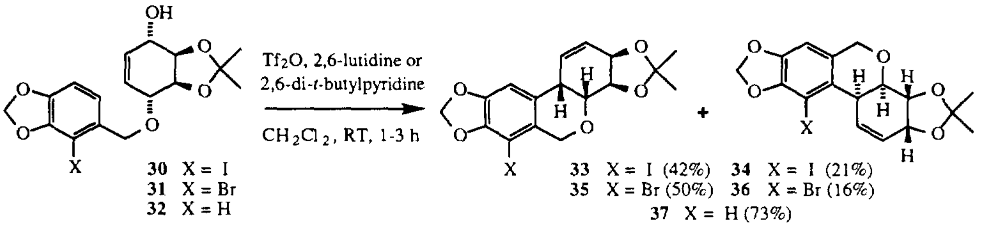
Scheme 5.

Confident in our mechanistic interpretation, we moved to improve our fortune by variation of the substituent at the aromatic C2-position. We needed an atom or group that would activate C6, or at least not activate C1, but which could also be easily recast as a phenolic hydroxyl after negotiating the cyclization. Bromine and iodine were well-behaved choices up through the Williamson reaction and so were given the most attention. This sequence to the cyclization substrates is shown in Scheme 6. Piperonyl bromide also worked well in the etherification. It is significant that **27** and **28** were stable as isolated compounds, and as alkylating agents they represented great improvement over the earlier imidate chemistry. We inferred the complete retention of absolute stereochemistry in the conversion of **12** → **13** → **30-32** by ^{1}H NMR studies using **30-32** purified only by silica gel chromatography, their non-enzymatically prepared racemic forms, and the shift reagent Eu(hfc)$_3$.[27] At concentrations that showed excellent spectral resolution of the enantiomeric pair of each of the three racemates, the 300 MHz data indicated the presence of only a single enantiomer in each optically active sample.



Scheme 6.

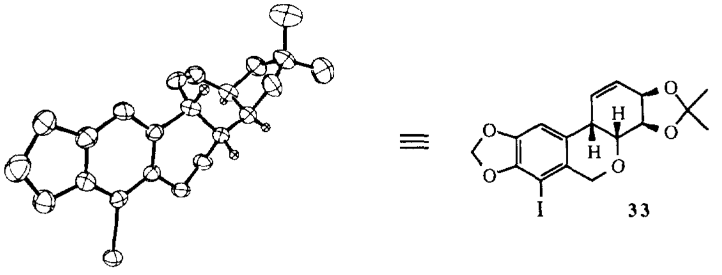
Ethers **30-31** suffered cyclization under triflating conditions as detailed in Scheme 7. In the cases of **30** and **31**, rearrangement was still a significantly populated pathway (see **34** and **36**). Ether **32** gave a 73% yield of pentacycle **37**, some of which may have arisen by rearrangement. The assigned relative stereochemistry of **33** was supported by a crystallographic analysis as was its absolute configuration (Figure 3). The structure assignments for **33**, **35**, and **37** were confirmed by chemical correlation (vide infra).



30 X = I
31 X = Br
32 X = H

33 X = I (42%) **34** X = I (21%)
35 X = Br (50%) **36** X = Br (16%)
37 X = H (73%)

Scheme 7.

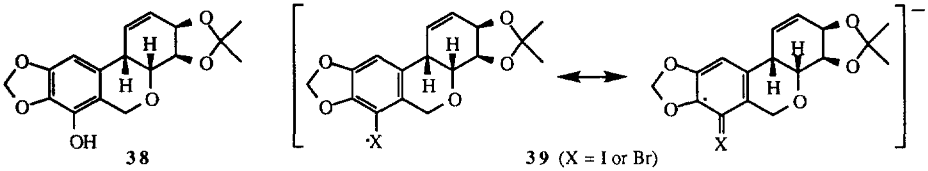


33

Figure 3.

With sufficient material in hand at this point, we postponed the optimization of the cyclizations and explored instead the advancement of properly constituted **33** and **35**. Attempts to oxidize those pentacycles to the corresponding lactones were wholly unsuccessful. A recourse to metal/halogen exchange followed by sequential treatment with borane and sodium hydroperoxide did give rise to phenol **38** (Figure 4), but very inconsistently and rarely in good yield. The chief side-product, and in some trials the major product, was **37**. We attribute this facile net reduction of **33**/**35** to an inefficiency of metal/halogen exchange on the oxygenated arene nucleus. The mechanism of metal/halogen exchange on aryl iodides is believed to involve single-electron transfer (SET).[28] If SET is truly operating, **33** would give rise to radical anion **39** (Figure 4). Because **39** can stabilize its surplus charge both inductively and resonantly by virtue of the dioxole oxygens, its mean lifetime may allow extensive dissociation from the radical partner (e.g., *t*-Bu·). After dissociation, a release of iodide and abstraction of a hydrogen from solvent would account for the reduction product **37**. Aryl bromides do not normally show evidence of the SET mechanism in metal/halogen exchange,[29] but a relative stability of **39** or its preceding transition state may sponsor an exception in the case of **35**.

Given the inauspicious tendencies of **33** and **35**, we turned more serious attention to the prospects offered by **37**. This congener had been obtained in the best overall yield for the three-step sequence of Williamson reaction, desilylation, and cyclization (61%). If the aromatic ring proved oxidizable at the necessary position, **37** could represent the preferred channel for further progress. Attempts to functionalize the aromatic ring of **37** itself did not succeed. We also tested the corresponding lactone (prepared from **37** by exposure to CrO_3 and sodium acetate in CH_2Cl_2/AcOH) under conditions intended to effect directed metalation of the arene, but this too was unprofitable. A breakthrough was made by adapting the tactics that had delivered **25** and **26**. Benzylic oxidation

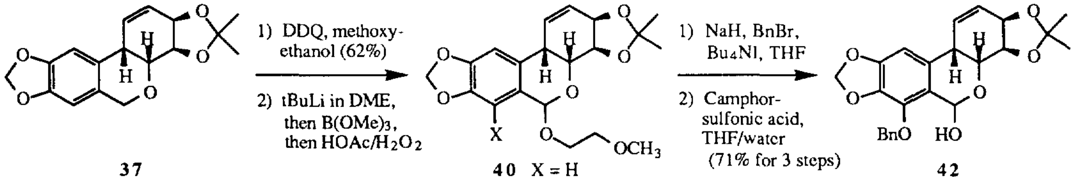


38

39 (X = I or Br)

Figure 4.

of **37** in the presence of methoxyethanol furnished a diastereomerically pure mixed acetal (**40**, Scheme 8).[30] It was hoped that the installed appendage would direct metalation in the desired manner, and this indeed took place. Trials employing DME as the solvent provided moderate but consistent yields of **41**, with the balance of material recovered as unreacted **40**. The oxidized material was best isolated after benzylation of the new hydroxyl and hydrolysis of the acetal, i.e., as lactol **42**.



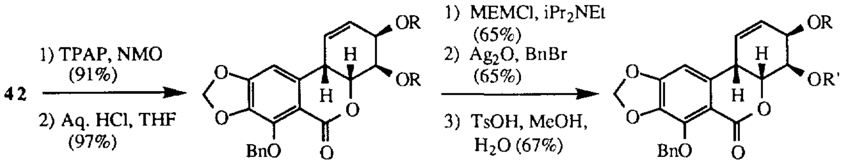
37

40 X = H
41 X = OH

42

Scheme 8.

Lactol **42** possesses the same relevant connectivity and stereochemistry as the late-stage Danishefsky-Lee intermediate **47** (Scheme 9), converted to pancratistatin by those workers in six steps.[10a] We proceeded to carry out the transformations that would bridge **42** and **47** and thereby accomplish a formal synthesis of **1**. Thus TPAP-catalyzed oxidation[31] of **42** followed by ketal hydrolysis yielded lactone-diol **44**. The remaining steps consisted of a regioselective protection of the allylic hydroxyl of **44**, benzylation of the remaining hydroxyl, and a final hydrolysis of the MEM ether. The infrared, ^1H NMR, and mass spectral data obtained for **47** were entirely consistent with those reported by Danishefsky and Lee, verifying a formal synthesis of pancratistatin.



43 R,R = $C(CH_3)_2$
44 R = H

45 R = MEM, R' = H
46 R = MEM, R' = Bn
47 R = H, R' = Bn

Scheme 9.

In summary, a new convergent route to pancratistatin has been established. Our approach combined with that of Danishefsky offers a distinctive avenue to analogs of **1** that may comprise or suggest effective therapeutic agents. We also emphasize that oxygenated, heterocycle-fused arenes represent a common theme among natural product structures. The observations we have made regarding appropriate tactics and their timing in the construction of the pancratistatin nucleus should therefore prove valuable to future investigators.

EXPERIMENTAL SECTION

Materials and Methods. Moisture- and/or atmosphere-sensitive reactions were maintained under a slight positive pressure of dry nitrogen. Tetrahydrofuran, ether, and 1,2-dimethoxyethane were distilled from sodium/benzophenone. Methylene chloride and *N,N*-dimethylformamide were dried over 3Å molecular sieves. Reagent chemicals were purchased from Aldrich Chemical Company, Milwaukee, WI, and used without further purification. P30 lipase was purchased from Amano Pharmaceutical Company. Reactions were monitored by thin layer chromatography using silica gel on glass (250 µm thickness, 5-17 µm particle size, 60 Å pore size) from Aldrich Chemical Company, Milwaukee, WI. Flash chromatography was performed using 40 µm silica gel from J. T. Baker. Melting points were determined on a Meltemp apparatus from Laboratory Devices and are uncorrected. Infrared spectra were recorded on a Nicolet 520 FT-IR spectrometer. The 300 MHz ^{1}H NMR spectra were recorded on a Varian Gemini 300 FT-NMR spectrometer. High resolution mass spectra were recorded on a VG Instruments 70-SE mass spectrometer by Mr. David E. Bostwick and Ms. Sarah J. Shealy of the Georgia Institute of Technology. Single crystal x-ray diffraction structural analyses were performed on a Syntex diffractometer by Dr. Donald VanDerveer of the Georgia Institute of Technology. Microanalyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ.

Conduritol A acetonide (**9**). Triol **11**[16] (1.00 g, 2.63 mmol) was slowly added as a solid to a suspension of KH (527 mg, 132 mmol) in dioxane (50 mL). The resulting suspension was stirred at reflux for 28 h. The reaction mixture was cooled to 0°C. A solution of ethanol (3 mL) in THF (18 mL) was added to the reaction mixture, followed by potassium acetate (1.0 g). Acetic acid (1.3 mL) was added and the reaction allowed to stir for 1 h while warming to room temperature. The reaction mixture was concentrated and chloroform (250 mL) was then added. The resulting mixture was filtered through a pad of celite and the filtrate was concentrated. The residue was chromatographed with EtOAc:hexanes (1:1). Product-containing fractions were combined and concentrated. The residue was crystallized from methylene chloride:hexanes (1:1) to give 340 mg (69%) of **9** as white prisms: mp 102-103°C ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.91 (app s, 2H), 4.22 (app s, 4H), 2.72 (app s, 2H), 1.46 (s, 3H), 1.37 (s, 3H); IR (KBr): 3413, 3338, 2983, 2942, 2915, 2867, 1653, 1571, 1380, 1271, 1210, 1175, 1080, 1060, 889 cm^{-1}; HRMS (CI, 5.3V): (M+H) *m/e* 187.0970; calculated for $C_9H_{15}O_4$, 187.0974. Elemental Analysis: Found: C, 57.97; H, 7.74. Calculated for $C_9H_{14}O_4$: C, 58.05; H, 7.58.

Conduritol A acetonide monoacetate (**12**). Conduritol A acetonide (**9**) (342 mg, 1.84 mmol), Amano P-30 lipase (680 mg), and isopropenyl acetate (2.4 mL) were stirred in a 50° sand bath for 49 h. The reaction mixture was filtered through a fine fritted funnel and the residue washed with CH_2Cl_2. The solvent was evaporated and the residual liquid (products and isopropenyl acetate) was applied to a column of silica gel and eluted with ethyl acetate:hexanes (3:7). Product-containing fractions were combined and concentrated to give 393 mg (94%) of **12** as colorless prisms: mp 93-94°C; $[\alpha]_D^{25}$ = -38.2° (*c* = 2.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.89 (dd, J = 2.5 Hz, 10 Hz, 1H), 5.69 (dd, J = 2.5 Hz, 10 Hz, 1H), 5.23 (m, 1H), 4.31 (m, 1H), 4.25 (m, 1H), 4.16 (m, 1H), 2.28 (d, J = 5 Hz, 1H), 2.14 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H); IR (KBr): 3453, 2989, 2938, 1744, 1374, 1237, 1068 cm^{-1}; HRMS (CI, 5.5V): *m/e* (M+H) 229.1055; calculated for $C_{11}H_{17}O_5$, 229.1076. Elemental Analysis: Found: C, 57.77; H, 7.13. Calculated for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07.

Conduritol A acetonide mono-TBS-ether (**13**). Conduritol A acetonide monoacetate (**12**, 61.6 mg, 0.270 mmol), *tert*-butyldimethylsilyl chloride (115 mg, 0.763 mmol), imidazole (46 mg, 0.68 mmol), and DMF (1.0 mL) were stirred at room temperature for 20 h. The reaction mixture was poured into ether (30 mL) and washed with saturated sodium bicarbonate solution, water, and brine. The ether phase was dried over sodium sulfate and concentrated to give 92.5 mg (100%) of the silyl ether as a colorless oil. $[\alpha]_D^{25}$ = -7.0° (*c* = 3.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.73 (dd, J = 2.4 Hz, 10.1 Hz, 1H), 5.55 (dd, J = 2.4 Hz, 10.1 Hz, 1H), 5.17 (m, 1H), 4.24 - 4.19 (m, 2H), 4.11 -4.06 (m, 1H), 2.14 (s, 3H), 1.47 (s, 3H), 1.36 (s, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); IR (neat): 2964, 2931, 2858, 1748, 1373, 1235, 1118, 1068, 838, 423 cm^{-1}; HRMS (EI, 5.6V): *m/e* (M+H) 343.1941; calculated for $C_{17}H_{31}O_5Si$, 343.1941.

A mixture of this oil (92.5 mg, 0.270 mmol), K_2CO_3 (50 mg), and methanol (2.4 mL) was stirred at room temperature for 15 min. The reaction mixture was poured into ether (30 mL) and washed successively with saturated sodium bicarbonate solution (50 mL), water (50 mL), and brine (50 mL). The organic phase was dried over sodium sulfate and concentrated to give 80.4 mg (99%) of **13** as a colorless oil. $[\alpha]_D^{25}$ = +36.1° (*c* = 3.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.10 (dd, J = 4.3 Hz, 9.9 Hz, 1H), 5.97 (dd, J = 4.3 Hz, 9.9 Hz, 1H), 4.37-4.28 (m, 2H), 4.22 (m, 1H), 4.13 (m, 1H), 2.81 (d, J = 8.5 Hz, 1H), 1.39 (s, 3H), 1.34 (s, 3H), 0.90 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); IR (neat): 3453, 2958, 2930, 2858, 1384, 1255, 1212, 1162, 1063, 889, 839, 777 cm^{-1}; HRMS (CI, 1.2V): *m/e* (M+H) 301.1841; calculated for $C_{15}H_{29}O_4Si$, 301.1835.

4-Hydroxy-5-(1-ethoxyethyl)oxymethyl-1,3-benzodioxolane (**15**). A solution of *n*-butyllithium in hexanes (2.18 mL, 2.5M, 5.5 mmol) was slowly added at 0°C to a solution of **14** (1.05 g, 4.69 mmol) in 9 mL of ether. The resulting solution was stirred for 1.5 h at 0°C, then allowed to warm to room temperature. Borane in THF (9.46 mL, 1.0M, 9.5 mmol) was added and stirring continued for 1.5 h. The solution was then cooled to 0°C and carefully quenched with aqueous NaOH (10%, 1 mL) followed after 5 min by NaOH solution (10%, 4 mL) and hydrogen peroxide solution (15%, 8 mL). Stirring was continued for 40 min at 0°C. Ether (25 mL) was added and the mixture was quickly extracted with sodium hydroxide solution (10%, 4 x 15 mL). The combined aqueous phases were extracted two times with ether, KOAc was added (2.5 g), and the solution was neutralized at 0°C with 33% H_2SO_4. The preciptated product was extracted into EtOAc and washed successively with saturated aqueous $NaHCO_3$, water (2x), and brine. Drying over sodium sulfate and concentration gave 963 mg (85.6%) of **15** as an oil. This material was sufficiently pure for further transformations. Spectroscopically pure material could be obtained by chromatography on silica ($CHCl_3$, Et_2O, Et_3N, 90:10:0.5): ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 6.56 (d, J = 8.1 Hz, 1H), 5.92 (s, 2H), 4.83 (q, J = 5.2 Hz, 1H), 4.70 (d, J = 11.8 Hz, 1H), 4.56 (d, J = 11.8 Hz, 1H), 3.58 (m, 2H), 1.32 (d, J = 5.2 Hz, 3H), 1.23 (app t, J = 7.1 Hz, 3H); IR (neat): 3600-3100, 2981, 2884, 1484, 1264, 1057, 921 cm^{-1}; MS (EI): *m/e* 240.2 (0.8), 150.1 (100), 92.1 (17.1), 73.1 (40.0), 45.0 (62.5); HRMS (EI): *m/e* 240.0990; calculated for $C_{12}H_{16}O_5$, 240.0997.

4-Phenylmethoxy-5-hydroxymethyl-1,3-benzodioxolane (**16**). A solution of **15** (650 mg, 2.71 mmol) in DMF (5 mL) was slowly added to a flask containing potassium hydride (130 mg, 3.25 mmol) at room temperature. After 10 min, benzyl bromide (0.40 mL, 3.3 mmol) was added dropwise over 5 min. The resulting mixture was stirred at room temperature for 2 h. The reaction was added to water (70 mL) and extracted with methylene chloride (25 mL). The organic phase was washed successively with 10% sodium hydroxide solution, water, and brine. The organic phase was then dried over sodium sulfate and concentrated. The residue was applied to a column of silica gel and eluted with ethyl acetate:hexanes (1:4). Product-containing fractions were combined and concentrated to give 716 mg (80%) of product as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$): δ 7.46-7.32 (m, 5H), 6.85 (d, J = 8.3 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 5.95 (app s, 2H), 5.27 (app s, 2H), 4.77 (q, J = 5.3 Hz, 1H), 4.50 (ABq, J = 11.1 Hz, Δυ = 37 Hz, 2H), 3.65 - 3.57 (m, 1H), 3.49 - 3.43 (m, 1H), 1.32 (d, J = 5.3 Hz, 3H), 1.16 (app t, J = 7 Hz, 3H); IR (neat): 2983, 2883, 1630, 1469, 1380, 1261, 1137, 1064 cm^{-1}; HRMS (EI, 3.8V): *m/e* 330.1431; calculated for $C_{19}H_{22}O_5$, 330.1467.

A mixture of this oil (231 mg, 0.701 mmol), THF (1.2 mL), and 0.5*N* HCl (1.2 mL) was stirred at room temperature for 7.25 h. The reaction mixture was poured into saturated sodium bicarbonate solution (30 mL) and extracted with methylene chloride (40 mL). The organic phase was washed with brine, dried over sodium sulfate, and concentrated to give 165 mg (92%) of **16** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$): δ 7.44-7.33 (m, 5H), 6.75 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 5.96 (s, 2H), 5.31 (s, 2H), 4.54 (s, 2H), 1.98 (br s, 1H); IR (neat): 3566, 3390, 3032, 2884,1630, 1607, 1468, 1381, 1258, 1065, 805, 736, 700, 466 cm^{-1}; HRMS (CI, 1.4V): *m/e* 258.0895; calculated for $C_{15}H_{14}O_4$, 258.0892.

TBS ether **17**. A solution of **16** (41.6 mg, 0.161 mmol) in THF (1 mL) was cannulated into a flask containing potassium hydride (6.0 mg, 0.15 mmol) and THF (2 mL) at room temperature. The cannula and transfer flask were rinsed with THF (2 x 0.5 mL) and the rinsings transferred to the reaction flask. The reaction mixture was stirred at room temperature for 10 min and then cooled to -78°C. Trichloroacetonitrile (0.018 mL, 0.18 mmol) was added to the reaction dropwise over 20 sec. The resulting mixture was allowed to stir at -78°C for 1 h. The reaction mixture was concentrated (not quite to dryness) after which petroleum ether (2.5 mL) and methanol (2 drops) were added to the residue. The mixture was filtered and the solution was applied to a column of silica gel and the product eluted with ethyl acetate/triethylamine/hexanes (15:2:83). Product-containing fractions were combined and concentrated to give trichloroacetimidate (50.7 mg) as a yellow oil. The trichloroacetimidate was dissolved in methylene chloride (1.5 mL) and the resulting solution was cooled to 0°C. A solution of camphorsulfonic acid (2.2 mg, 0.013 mmol) and conduritol **13** (41.2 mg, 0.137 mmol) in methylene chloride (1 mL) was cannulated into the imidate solution at 0°C. The cannula and transfer flask were rinsed with methylene chloride (3 x 0.5 mL). The reaction mixture was allowed to stir at 0°C for 20 min and then allowed to stir at room temperature for 34 h. Triethylamine (3 drops) was added to quench the reaction. The reaction mixture was applied directly to a column of silica gel and eluted with ethyl acetate/triethylamine/hexanes (5:1:44). Product-containing fractions were combined and concentrated to give ether **17** (22.4 mg, 26% based on **16**) as a slightly yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.31 (m, 5H), 6.92 (d, J = 8.0 Hz, 1H), 6.54 (d, J = 8.0 Hz, 1H), 5.95 (app s, 2H), 5.71-5.57 (m, 2H), 5.27 (app s, 2H), 4.65 (ABq, J = 11.4 Hz, $\Delta\upsilon$ = 43.1 Hz, 2H), 4.20-4.15 (m, 1H), 4.08-4.05 (m, 1H), 3.97-3.93 (m, 2H), 1.45 (s, 3H), 1.31 (s, 3H), 0.92 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); IR (neat on KBr): 2954, 2929, 2857, 1631, 1469, 1381, 1257, 1213, 1100, 1066, 885, 837 cm^{-1}; HRMS (CI, 2.9V): *m/e* 540.2567; calculated for $C_{30}H_{40}O_7Si$, 540.2543.

Allylic alcohol **18**. Tetrabutylammonium fluoride (1.0M solution in tetrahydrofuran, 0.43 mL, 0.43 mmol) was added to a solution of **17** (67 mg, 0.12 mmol) in tetrahydrofuran (2.4 mL). The resulting mixture was stirred at room temperature for 5.5 h. The reaction was transferred to a separatory funnel with ether (20 mL) and washed successively with saturated sodium bicarbonate solution (50 mL), water (50 mL), and brine (50 mL). The organic phase was dried over sodium sulfate and concentrated. The residue was applied to a column of silica gel and eluted with ethyl acetate/hexanes (2:3). Product-containing fractions were combined and concentrated to give alcohol **18** (49 mg, 93%) as a waxy white solid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.32 (m, 5H), 6.84 (d, J = 8.0 Hz, 1H), 6.53 (d, J = 8.0 Hz, 1H), 5.98-5.91 (m, 4H), 5.28 (app s, 2H), 4.57 (ABq, J=11.0 Hz, $\Delta\upsilon$ = 22.6 Hz, 2H), 4.40-4.36 (m, 1H), 4.20-4.16 (m, 1H), 4.09-4.08 (m, 1H), 4.00 (app s, 1H), 2.65 (br s, 1H), 1.40 (s, 3H), 1.30 (s, 3H); IR (KBr): 3448, 2986, 2892, 1630, 1468, 1379, 1261, 1212, 1064 cm^{-1}; HRMS (EI, 1.0V): *m/e* 426.1654; calculated for $C_{24}H_{26}O_7$, 426.1679.

Benzyloxypentacycles **19** *and* **20**. Trifluoromethanesulfonic anhydride (0.04 mL, 0.24 mmol) was added dropwise over 30 min to a solution of **18** (15.0 mg, 0.035 mmol) and 2,6-di-*tert*-butylpyridine (0.08 mL, 0.36 mmol) in methylene chloride (4 mL) at 0°C. The cold bath was removed and the reaction was allowed to warm to room temperature while stirring for 30 min. The reaction was transferred to a separatory funnel with CH_2Cl_2 (20 mL) and washed successively with saturated sodium bicarbonate solution (30 mL), water (20 mL), and brine (20 mL). The organic phase was dried over sodium sulfate, concentrated, and applied to a column of silica gel. The products were eluted with ether/hexanes (1:4). The major product (**20**, 7.1 mg, 50%) was crystallized from ethyl acetate/hexanes (1:4) as white prisms: mp 81-83°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.38 (m, 5H), 6.22 (s, 1H), 5.93 (d, J = 3.0 Hz, 2H), 5.62 (m, 2H), 5.32 (ABq, J = 15.0 Hz, $\Delta\upsilon$ = 30.0 Hz, 2H), 4.71 (app s, 2H), 4.63-4.61 (m, 1H), 4.45-4.42 (m, 1H), 4.11-4.08 (m, 1H), 3.60 (app s, 1H), (1.46 (s, 3H), 1.41 (s, 3H); IR (KBr): 2930, 2875, 1740, 1650, 1465, 1460, 1280, 1110, 1050 cm^{-1}; HRMS (CI, 0.13V) *m/e* 408.1551; calculated for $C_{24}H_{24}O_6$, 408.1573. Elemental Analysis: Found: C, 70.31; H, 5.90. Calculated for $C_{24}H_{24}O_6$: C, 70.56; H, 5.92.

The minor product (**19**, 1.1 mg, 8%) was obtained as a colorless glass: ^1H NMR (300 MHz, $CDCl_3$): δ 7.37-7.32 (m, 5H), 6.48 (s, 1H), 5.93-5.92 (m, 2H), 5.64 (app s, 2H), 5.31-5.20 (m, 2H), 4.72 (ABq, J = 15.4 Hz, Δυ = 47.4 Hz, 2H), 4.63-4.60 (m, 1H), 4.43-4.40 (m, 1H), 3.29-3.28 (m, 1H), 1.45 (s, 3H), 1.41 (s, 3H); IR (KBr): 2982, 2912, 1627, 1478, 1380, 1238, 1223, 1119, 1066, 1040, 735 cm^{-1}; HRMS (EI, 1.7V): *m/e* 408.1548; calculated for $C_{24}H_{24}O_6$, 408.1573.

4-Iodo-5-(1-ethoxy)ethoxymethyl-1,3-benzodioxolane (**25**). *n*-Butyllithium (2.5M, 2.0 mL, 5.0 mmol) was added dropwise over 15 min to a solution of **14** (1.0 g, 4.5 mmol) in ether (10 mL) at 0°C. The reaction was allowed to stir for 1 h at 0°C. The reaction was then cooled to -78°C. A solution of iodine (1.4 g, 5.4 mmol) in ether (15 mL) was added dropwise over 20 min at -78°C. The cold bath was removed and the reaction allowed to warm to room temperature over 30 min. The reaction was poured into saturated sodium bicarbonate solution (50 mL) and extracted with ether. The organic phase was washed with brine (30 mL), and then dried over sodium sulfate and concentrated. The residue was applied to a column of silica gel and eluted with ethyl acetate:hexanes (1:9) to give 1.1 g (79%) of **25** as a slightly yellow oil: ^1H NMR (300 MHz, $CDCl_3$): δ 6.94 (d, J = 7.9 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 6.04 (app s, 2H), 4.86 (q, J = 5.4 Hz, 1H), 4.53 (ABq, J = 11.8 Hz, Δυ = 42 Hz, 2H), 3.73-3.68 (m, 1H), 3.58-3.53 (m, 1H), 1.40 (d, J = 5.4 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H); IR (neat): 2979, 2895, 1612, 1502, 1454, 1385, 1329, 1253, 1142, 1101, 1059, 934, 884, 802 cm^{-1}; HRMS (EI, 4.1V): *m/e* 350.0026; calculated for $C_{12}H_{15}IO_4$, 350.0015.

4-Iodo-5-bromomethyl-1,3-benzodioxolane (**27**). Hydrobromic acid (48%, 15 mL) was added to a solution of **25** (1.75 g, 4.99 mmol) in CH_2Cl_2 (20 mL). The resulting two-phase mixture was vigorously stirred at room temperature for 5 h. The reaction mixture was transferred to a separatory funnel containing methylene chloride (30 mL) and the aqueous layer (more dense) was drained off. The organic phase was washed successively with saturated $NaHCO_3$ solution (2 x 50 mL), water (50 mL), brine (50 mL), and then dried over sodium sulfate and concentrated. The product was crystallized from acetone:hexane (2:1) to give 1.49 g (97%) of product as white needles: mp 127-128°C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.02 (d, J = 8.1 Hz, 1 H), 6.74 (d, J = 8.1 Hz, 1 H), 6.07 (s, 2H), 4.60 (s, 2H); IR (deposited film on KBr): 2899, 1608, 1458, 1258, 1246, 1202, 1047, 933, 817, 642 cm^{-1}; HRMS (EI, 4.8V): *m/e* 339.8584; calculated for $C_8H_6BrIO_2$, 339.8596. Elemental Analysis: Found: C, 28.05; H, 1.77; I, 37.18; Br, 23.15. Calculated for $C_8H_6BrIO_2$: C, 28.18; H, 1.77; I, 37.22; Br, 23.44.

4-Bromo-5-methoxymethyl-1,3-benzodioxolane (**26**). *n*-Butyllithium (2.5M, 32.9 mL, 82 mmol) was added dropwise over 20 min to a solution of **24** (9.77 g, 58.8 mmol) in ether (140 mL) at 0°C. The reaction was allowed to stir for 1.5 h at 0°C. The ice bath was removed and the reaction allowed to warm for 20 min. The reaction was then cooled to -78°C. Bromine (4.24 mL, 13.2 g, 82.3 mmol) was added dropwise over 20 min at -78°C. The cold bath was removed and the reaction allowed to warm to room temperature over 50 min. The reaction was poured into saturated sodium bicarbonate solution (150 mL) and extracted successively with ether (300 mL) and ethyl acetate (50 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (200 mL), water (200 mL), and brine (200 mL), then dried over sodium sulfate and concentrated. The residue was chromatographed using ethyl acetate:hexanes (1:19) to give 9.12 g (63%) of **26** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$): δ 6.92 (d, J = 7.9 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 6.05 (s, 2H), 4.45 (s, 2H), 3.42 (s, 3H); IR (neat): 2980, 2919, 2896, 2876, 2807, 1618, 1497, 1466, 1451, 1388, 1261, 1245, 1227, 1090, 1049, 937, 816, 789 cm^{-1}; HRMS (EI, 3.4V): *m/e* 243.9759; calculated for $C_9H_9BrO_3$, 243.9735. Elemental Analysis: Found: C, 44.14; H, 3.71. Calculated for $C_9H_9BrO_3$: C, 44.11; H, 3.70.

4-Bromo-5-bromomethyl-1,3-benzodioxolane (**28**). Hydrobromic acid (48%, 2 mL) was added to a solution of **26** (140.1 mg, 0.572 mmol) in methylene chloride (2 mL). The resulting two-phase mixture was vigorously stirred at room temperature for 4 h. The reaction mixture was transferred to a separatory funnel and the aqueous layer (more dense) was drained off. The organic phase was washed successively with saturated sodium bicarbonate solution (30 mL), brine (30 mL), and then dried over sodium sulfate and concentrated. The product was crystallized from acetone:hexanes (2:1) to give 153.0 mg (91%) of **28** as white needles: mp 136-138°C ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99 (d, J = 8.1 Hz, 1 H), 6.74 (d, J = 8.1 Hz, 1 H), 6.08 (s, 2H), 4.59 (s, 2H); IR (KBr): 3030, 3006, 2979, 2916, 2789, 1613, 1497, 1464, 1451, 1348, 1249, 1211, 1051, 935, 813, 642, 546, 467 cm^{-1}; HRMS (EI, 2.4V): *m/e* 291.8731; calculated for $C_8H_6Br_2O_2$, 291.8735. Elemental Analysis: Found: C, 32.42; H, 2.04; Br, 54.26. Calculated for $C_8H_3Br_2O_2$: C, 32.69; H, 2.06; Br, 54.37.

Allylic alcohol **30**. A solution of **13** (349 mg, 1.16 mmol) in dry THF (5 mL) was added dropwise to a suspension of NaH (55.8 mg, 2.30 mmol) and Bu_4NI (92.0 mg, 0.25 mmol) in THF (15 mL) at room temperature. After 5 min, a solution of **27** (434 mg, 1.40 mmol) in THF (5 mL) was added dropwise at room temperature. The resulting mixture was allowed to stir at room temperature for 16.5 h. Aqueous sodium hydroxide (10%, 5 mL) was added and the reaction was stirred for 30 min. The reaction mixture was transferred to a separatory funnel and extracted with ether (70 mL). The organic phase was washed with saturated sodium bicarbonate solution (40 mL), water (40 mL), and brine (40 mL), then dried over sodium sulfate and concentrated. The residue was applied to a column of silica gel and eluted with ether:hexanes (1:19) to give 550 mg (84%) of product as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01 (d, J = 7.8 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.04 (app s, 2H), 5.95-5.64 (m, 2H), 4.67 (ABq, J = 11.8 Hz, $\Delta\upsilon$ = 43 Hz, 2H), 4.28-4.24 (m, 1H), 4.13-4.11 (m, 1H), 4.10-3.99 (m, 2H), 1.49 (s, 3H), 1.38 (s, 3H), 0.92 (s, 9H) 0.12 (s, 3H), 0.11 (s, 3H); IR (neat): 2929, 2856, 1459, 1381, 1249, 1111, 1050, 885, 822, 778 cm^{-1}; HRMS (EI, 6.9V): (M-15) *m/e* 545.0832; calculated for $C_{22}H_{33}IO_6Si$, 545.0856.

A solution of TBAF (1.0 M, 2.9 mL, 2.9 mmol) was added to a solution of this adduct (550 mg, 0.981 mmol) in THF (6 mL). The solution was allowed to stir at room temperature for 5 h. The reaction mixture was extracted with ether (80 mL). The organic phase was washed successively with saturated sodium bicarbonate solution (30 mL), water (2 x 30 mL), and brine (30 mL), and then dried over sodium sulfate and concentrated. The residue was applied to a column of silica gel and eluted with ethyl acetate:hexanes (1:1) to give 410 mg (93%) of **30** as a viscous colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.04 (app s, 2H), 5.97-5.96 (m, 2H), 4.64 (ABq, J = 11.6 Hz, $\Delta\upsilon$ = 28 Hz, 2H), 4.46-4.42 (m, 1H), 4.23-4.18 (m, 1H), 4.19 (m, 1H), 4.07-4.05 (m, 1H), 2.74 (br s, 1H), 1.46 (s, 3H), 1.38 (s, 3H); IR (neat): 3448, 2985, 2902, 1458, 1375, 1259, 1048, 932, 872 cm^{-1}; HRMS (EI, 6.1V): *m/e* 446.0203; calculated for $C_{17}H_{19}IO_6$, 446.0226.

Allylic alcohol **31**. A solution of **13** (1.044 g, 3.47 mmol) in dry THF (20 mL) was added dropwise to a suspension of NaH (125 mg, 5.21 mmol) and Bu_4NI (123 mg, 0.333 mmol) in THF (20 mL) at room temperature. After 5 min, a solution of **28** (1.27 g, 4.33 mmol) in THF (20 mL) was added dropwise at room temperature. The resulting mixture was allowed to stir at room temperature for 16.5 h. The reaction mixture was transferred to a separatory funnel and extracted with ether (100 mL). The organic phase was washed with saturated ammonium chloride solution (50 mL), water (50 mL), and brine (50 mL), dried over sodium sulfate and concentrated. The residue was applied to a column of silica gel and eluted with ethyl acetate:hexanes (1:9) to give 1.55 g (87%) of product as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.03 (d, J = 8.1 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.04 (s, 2H), 5.76-5.64 (m, 2H), 4.72 (ABq, J = 12.0 Hz, $\Delta\upsilon$ = 39 Hz, 2H), 4.26-4.21 (m, 1H), 4.13-4.11 (m, 1H), 4.10-3.97 (m, 2H), 1.48 (s, 3H), 1.37 (s, 3H), 0.92 (s, 9H) 0.12 (s, 3H), 0.11 (s, 3H); IR (neat): 2987, 2955, 2857, 1617, 1501, 1467, 1382, 1249, 1212, 1106, 1052, 939, 906, 838, 779 cm^{-1}; HRMS (EI, 5.5V): *m/e* 512.1243; calculated for $C_{23}H_{33}BrO_6Si$, 512.1230.

A solution of TBAF (1.0 M, 2.94 mL, 2.94 mmol) was added to a solution of this adduct (1.201 g, 3.01 mmol) in THF (14 mL). The solution was allowed to stir at room temperature for 4 h. The reaction mixture was extracted with ether (60 mL). The organic phase was washed successively with saturated sodium bicarbonate solution (40 mL), water (40 mL), and brine (40 mL), and then dried over sodium sulfate and concentrated to give 894 mg (96%) of **31** as a viscous colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.05 (app s, 2H), 6.04-5.96 (m, 2H), 4.68 (ABq, J = 11.8 Hz, Δυ = 26 Hz, 2H), 4.46-4.42 (m, 1H), 4.24-4.20 (m, 1H), 4.17-4.13 (m, 1H), 4.05-4.04 (m, 1H), 2.48 (d, J = 6.8 Hz, 1H), 1.45 (s, 3H), 1.37 (s, 3H); IR (neat): 3446, 2986, 2908, 1616, 1500, 1466, 1380, 1246, 1212, 1050, 936, 876 cm^{-1}; HRMS (EI, 1.9V): *m/e* 398.0379; calculated for $C_{17}H_{19}BrO_6$, 398.0365.

Allylic alcohol **32**. A solution of **13** (1.972 g, 6.56 mmol) in dry THF (5 mL) was added dropwise to a suspension of NaH and Bu_4NI in THF (10 mL) at room temperature. After 5 min, a solution of piperonyl bromide (1.83 g, 8.52 mmol) in THF (5 mL) was added. The mixture was stirred for 16.5 h. Sodium hydroxide solution (10%, 5 mL) was then added and the reaction stirred for 30 min. The mixture was poured into a separatory funnel and extracted with ether (70 mL). The organic phase was washed with saturated $NaHCO_3$ solution (40 mL), water (40 mL), and brine (40 mL), dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel, eluting with ether:hexanes (1:19) to give 2.58 g (91%) of the ether as a colorless oil: $[\alpha]_D^{25} = -1.8°$ (*c* = 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92-6.76 (m, 3H), 5.95 (app s, 2H), 5.69-5.66 (m, 2H), 4.64 (ABq, J = 11.7 Hz, Δυ = 35 Hz, 2H), 4.22-4.17 (m, 1H), 4.10-4.08 (m, 1H), 4.02-3.98 (m, 1H), 3.94-3.92 (m, 1H), 1.46 (s, 3H), 1.36 (s, 3H), 0.91 (s, 9H) 0.12 (s, 3H), 0.10 (s, 3H); IR (neat): 2954, 2930, 2888, 2857, 1504, 1446, 1383, 1252, 1212, 1101, 1042, 885, 838, 779 cm^{-1}; MS (CI, 6.1V): *m/e* 435.3 (M^+, 40), 319.2 (40), 301.2 (20), 283.2 (40) 269.1 (60), 225.2 (60), 135.1 (100).

A THF solution of Bu_4NF (1.0M, 5.8 mL, 5.8 mmol) was added to the ether (844 mg, 1.94 mmol) in THF (15 mL). The solution was allowed to stir at room temperature for 1.5 h. The reaction mixture was extracted with ether (100 mL). The organic phase was washed successively with saturated $NaHCO_3$ solution (40 mL), water (40 mL), and brine (40 mL), then dried over sodium sulfate. Concentration gave 620 mg (99%) of **32** as a colorless glass: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.88-6.76 (m, 3H), 6.03-5.94 (m, 3H), 4.53 (ABq, J = 11.5 Hz, Δυ = 19 Hz, 2H), 4.41-4.37 (m, 1H), 4.23-4.19 (m, 1H), 4.16-4.12 (m, 1H), 4.02-3.99 (m, 1H), 2.53 (d, J = 6.6 Hz, 1H), 1.44 (s, 3H), 1.37 (s, 3H); IR (KBr): 3365, 2987, 2933, 1512, 1501, 1443, 1381, 1250, 1238, 1072, 1039, 879 cm^{-1}; HRMS (EI, 2.6V): *m/e* 320.1284; calculated for $C_{17}H_{20}O_6$, 320.1260.

Iodopentacycles **33** *and* **34**. Trifluoromethanesulfonic anhydride (0.19 mL, 0.56 mmol) was added dropwise over 3.5 h to a solution of **30** (105 mg, 0.236 mmol) and 2,6-lutidine (0.27 mL, 2.3 mmol) in dry CH_2Cl_2 (4.7 mL) at room temperature. Thin layer chromatography (1:4 ethyl acetate:hexanes) showed the reaction to be complete immediately. Saturated sodium bicarbonate solution (3 mL) was added to the reaction mixture. The mixture was allowed to stir at room temperature for 5 min. The reaction mixture was then transferred to a separatory funnel with methylene chloride (30 mL). The organic phase was washed successively with saturated sodium bicarbonate solution (10 mL), water (10 mL), and brine (10 mL), dried over Na_2SO_4 and concentrated. The residual oil was applied to a column of silica gel and eluted with ether/hexanes (3:17) to give **33** (42 mg, 42%) as a solid that could be crystallized from methylene chloride as colorless prisms: mp >195°C dec.; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (s, 1H), 6.03 (d, J = 5.5 Hz, 2H), 5.71-5.59 (m, 2H), 4.63-4.61 (m, 1H), 4.61 (ABq, J = 15 Hz, Δυ = 60 Hz, 2H), 4.46-4.43 (m, 1H), 4.17-4.15 (m, 1H), 3.28 (app s, 1H), 1.46 (s, 3H), 1.42 (s, 3H); IR (KBr): 2987, 2927, 2901, 2853, 1606, 1499, 1462, 1383, 1244, 1217, 1120, 1072, 1042, 1027, 938, 722 cm^{-1}; HRMS (EI, 1.2V): *m/e* 428.0140; calculated for $C_{17}H_{17}IO_5$, 428.0121. Elemental Analysis: Found: C, 47.44; H, 3.89; I, 29.50. Calculated for $C_{17}H_{17}IO_5$: C, 47.68; H, 4.00; I, 29.64.

Pentacycle **34** (21 mg, 21%) was also obtained as a colorless solid that crystallized from methylene chloride: mp >400°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.43 (s, 1H), 6.03 (app s, 2H), 5.75-5.62 (m, 2H), 4.72 (app s, 2H), 4.67-4.63 (m, 1H), 4.47-4.44 (m, 1H), 4.19-4.16 (m, 1H), 3.49-3.47 (m, 1H), 1.50 (s, 3H), 1.43 (s, 3H); IR (KBr): 2980, 2931, 2904, 2863, 2820, 1611, 1464, 1420, 1383, 1259, 1209, 1121, 1062, 1031, 941, 856 cm^{-1}; HRMS (EI, 1.3V): *m/e* 428.0148; calculated for $C_{17}H_{17}IO_5$, 428.0121.

***Bromopentacycles* 35 *and* 36.** Trifluoromethanesulfonic anhydride (0.22 mL, 1.31 mmol) was added dropwise over 1.75 h to a solution of **31** (148 mg, 0.372 mmol) and 2,6-lutidine (0.43 mL, 3.7 mmol) in dry CH_2Cl_2 (10 mL) at room temperature. Thin layer chromatography (1:4 ethyl acetate:hexanes) showed the reaction to be complete immediately. Saturated $NaHCO_3$ solution (3 mL) was added to the mixture. The mixture was allowed to stir at room temperature for 5 min. The reaction mixture was then transferred to a separatory funnel with methylene chloride (60 mL). The organic phase was washed successively with saturated sodium bicarbonate solution (60 mL), water (30 mL), and brine (30mL), dried over sodium sulfate and concentrated. The residual oil was applied to a column of silica gel and eluted with ether/hexanes (3:17) to give the two pentacycles:

35 (70 mg, 50%), as a solid that crystallized from methylene chloride as colorless prisms: mp 225-227°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (s, 1H), 6.03 (d, J = 2.8 Hz, 2H), 5.71-5.58 (m, 2H), 4.63-4.61 (m, 1H), 4.71 (ABq, J = 15 Hz, $\Delta\upsilon$ = 72 Hz, 2H), 4.46-4.43 (m, 1H), 4.17-4.16 (m, 1H), 3.32 (app s, 1H), 1.45 (s, 3H), 1.42 (s, 3H); IR (KBr): 3052, 3044, 2980, 2908, 1610, 1498, 1469, 1383, 1352, 1256, 1216, 1131, 1064, 1027, 933, 889, 862, 839, 736 cm^{-1}; HRMS (EI, 4.4V): *m/e* 380.0203; calculated for $C_{17}H_{17}BrO_5$, 380.0259. Elemental Analysis: Found: C, 53.58; H, 4.46. Calculated for $C_{17}H_{17}BrO_5$: C, 53.56; H, 4.49.

36 (22 mg, 16%), as a colorless glass: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.44 (s, 1H), 6.03 (app s, 2H), 5.74-5.64 (m, 2H), 4.74 (app s, 2H), 4.66-4.63 (m, 1H), 4.46-4.44 (m, 1H), 4.18-4.15 (m, 1H), 3.59 (app s, 1H), 1.48 (s, 3H), 1.43 (s, 3H); IR (KBr): 2984, 2894, 1612, 1470, 1260, 1212, 1121, 1032, 942, 859 cm^{-1}; HRMS (EI, 1.6V): *m/e* 380.0259; calculated for $C_{17}H_{17}BrO_5$, 380.0280.

Pentacycle **37**. A solution of **32** (135 mg, 0.42 mmol) in CH_2Cl_2 (5 mL) was cannulated into a solution of trifluoromethanesulfonic anhydride (0.11 mL, 0.65 mmol) and 2,6-di-*tert*-butylpyridine (0.95 mL, 4.2 mmol) in CH_2Cl_2 (8 mL) over 15 min. The cannula and transfer flask were rinsed with CH_2Cl_2 (2 mL). The resulting mixture was allowed to stir at room temperature for 1.75 h. Saturated sodium bicarbonate solution (3 mL) was added to the reaction mixture. The mixture was allowed to stir at room temperature for 5 min. The reaction mixture was then transferred to a separatory funnel with methylene chloride (60 mL). The organic phase was washed successively with saturated sodium bicarbonate solution (60 mL), water (30 mL), and brine (30 mL), dried over sodium sulfate and concentrated. The residual oil was applied to a column of silica gel and eluted with ether/hexanes (3:17) to give **37** (93 mg, 73%) as a solid that could be crystallized from methylene chloride to give white needles: mp 123-125°C; $[\alpha]_D^{25}$ = -194° (*c* = 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (s, 1H), 6.46 (s, 1H), 5.94 (app s, 2H), 5.66-5.61 (m, 2H), 4.74 (d, J = 2.8 Hz, 2H), 4.64-4.61 (m, 1H), 4.44-4.41 (m, 1H), 4.22-4.19 (m, 1H), 3.33 (app s, 1H), 1.46 (s, 3H), 1.42 (s, 3H); IR (KBr): 2984, 2894, 1612, 1470, 1260, 1212, 1121, 1032, 942, 859 cm^{-1}; HRMS (EI, 1.8V): *m/e* 302.1182; calculated for $C_{17}H_{18}O_5$, 302.1154. Elemental Analysis: Found: C, 67.56; H, 5.83. Calculated for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00.

Acetal **40**. A solution of 2-methoxyethanol (0.42 mL, 5.3 mmol) and **37** (214 mg, 0.707 mmol) in CH_2Cl_2 (3 mL) was degassed with a stream of dry nitrogen for 2 min. Approximately twenty 3Å molecular sieves (4-8 mesh) were added and the mixture was stirred for 30 min. 2,3-Dichloro-5,6-dicyanoquinone (244 mg, 1.08 mmol) was added and the mixture was stirred at room temperature for 26 h. The mixture was applied to a pad of neutral alumina in a fritted funnel and the product was eluted with methylene chloride (50 mL) followed by ether (50 mL) and then ethyl acetate (100 mL). The eluant was concentrated onto neutral alumina. The alumina-adsorbed product was applied to a column of silica gel and the product was eluted with ethyl acetate/triethylamine/hexanes (5:1:14). Product-containing fractions were combined and concentrated to give **40** (166 mg, 62%) as a colorless glass: $[\alpha]_D^{25}$ = -238° (*c* = 3.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (s, 1H), 6.71 (s, 1H), 5.94 (d, J = 8.2 Hz, 2H), 5.69-5.54 (m, 2H), 5.50 (s, 1H), 4.70-4.69 (m, 1H), 4.64-4.62 (m, 1H), 4.43-4.40 (m, 1H), 3.98-3.93 (m, 1H), 3.85-3.78 (m, 1H), 3.64-3.61 (m, 2H), 3.41 (s, 3H), 3.28 (app s, 1H), 1.45 (s, 3H), 1.43 (s, 3H); IR (film on KBr): 2984, 2928, 2888, 1504, 1370, 1260, 1114, 1037, 944, 862 cm^{-1}; HRMS (EI, 1.9V): *m/e* 376.1521; calculated for $C_{20}H_{24}O_7$, 376.1522.

Lactol **42**. A solution of acetal **40** (101 mg, 0.268 mmol) in dry dimethoxyethane (2 mL) was deoxygenated with a stream of dry nitrogen for 3 min at room temperature. The solution was then cooled to -78°C. *t*-Butyllithium (1.5 M in pentane, 0.23 mL, 0.35 mmol) was added to the reaction flask dropwise over 1 min. The reaction mixture was allowed to stir at -78°C for 45 min. Freshly distilled trimethyl borate (0.12 mL, 1.1 mmol) was added at -78°C and the reaction was allowed to stir for 10 min. The cold bath was replaced by a dry ice/CCl_4 bath and the reaction was allowed to stir at -25°C for 80 min. The cold bath was then replaced by an ice bath and the reaction allowed to stir at 0°C for 10 min. The ice bath was then removed and the reaction was allowed to warm for 10 min. A solution of 36% acetic anhydride in acetic acid (0.28 mL) was added to the reaction mixture followed immediately by 30% hydrogen peroxide solution (0.9 mL). The resulting mixture was allowed to stir at room temperature for 1 h. The reaction mixture was transferred to a separatory funnel with ether (20 mL). The organic phase was washed with 10% ferrous ammonium sulfate solution saturated with ammonium sulfate (3 x 10 mL), followed by water (2 x 10 mL). The organic phase was then extracted with 10% sodium hydroxide solution (2 x 20 mL). The organic phase was dried over sodium sulfate and concentrated to give unreacted **40** (38.2 mg, 38%). The aqueous extract was neutralized with glacial acetic acid to give a white precipitate. The precipitate and aqueous solution were transferred to a separatory funnel and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried over sodium sulfate and concentrated to give a light yellow, viscous oil (62.9 mg). This oil was dissolved in tetrahydrofuran (2 mL) and the resulting solution was cannulated into a flask containing sodium hydride (14.4 mg, 0.600 mmol). The cannula and transfer flask were rinsed with tetrahydrofuran (2 x 1 mL). Benzyl bromide (0.12 mL, 1.01 mmol) was added followed by tetrabutylammonium iodide (12.5 mg, 0.0338 mmol). The resulting mixture was allowed to stir at room temperature for 5.5 h. The mixture was transferred to a separatory funnel with ether (20 mL). The organic phase was washed with saturated ammonium chloride solution (10 mL) and water (2 x 10 mL), then concentrated to give a viscous oil that was dissolved in tetrahydrofuran (5 mL) and water (2 mL). Camphorsulfonic acid (55 mg) was added and the mixture was allowed to stir at room temperature for 18 h. The reaction mixture was transferred to a separatory funnel with ethyl acetate (20 mL) and washed with saturated sodium bicarbonate solution (10 mL), water (10 mL), and brine (10 mL). The organic phase was dried over sodium sulfate and concentrated. The residue was applied to a column of silica gel and the product eluted with ether/methylene chloride (1:19). Product-containing fractions were combined and concentrated to give lactol **42** (50.1 mg, 71% based on recovered **40**) as a white solid: $[\alpha]_D^{25}$ = -194° (c = 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.32 (m, 5H), 6.49 (s, 1H), 6.04 (d, J = 3.8 Hz, 1H), 5.95 (app s, 2H), 5.67-5.51 (m, 2H), 5.31 (ABq, J = 11.7 Hz, $\Delta\upsilon$ = 19.1 Hz, 2H), 4.85-4.84 (m, 1H), 4.60-4.57 (m, 1H), 4.44-4.40 (m, 1H), 3.28 (app s, 1H), 2.85 (d, J = 3.8 Hz, 1H), 1.45 (s, 3H), 1.41 (s, 3H); IR (film on KBr): 3374, 2909, 1621, 1477, 1376, 1219, 1102, 1046, 977 cm^{-1}; HRMS (EI, 2.7V): *m/e* 424.1539; calculated for $C_{24}H_{24}O_7$, 424.1522.

Lactone **43**. Lactol **42** (17.7 mg, 0.0417 mmol) was dissolved in CH_2Cl_2 (2 mL). *N*-methylmorpholine-*N*-oxide (11.6 mg, 0.099 mmol) was added to the solution followed by tetrapropylammonium perruthenate (1.0 mg, 0.0028 mmol). The resulting mixture was allowed to stir at room temperature for 1 h. The reaction mixture was transferred to a separatory funnel with methylene chloride (15 mL) and washed successively with saturated sodium sulfite solution (15 mL), brine (15 mL), and saturated cupric sulfate solution (15 mL). The organic phase was then dried over sodium sulfate and concentrated. The residue was applied to a column of silica gel and eluted with ether/methylene chloride (1:49). Product-containing fractions were combined and concentrated to give **43** (16.0 mg, 91%) as a colorless glass: $[\alpha]_D^{25}$ = -269° (c = 0.34, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.56-7.29 (m, 5H), 6.53 (s, 1H), 6.06 (d, J = 1.4 Hz, 1H), 6.02 (d, J=1.4 Hz, 1H) 5.85-5.80 (m, 1H), 5.50-5.46 (m, 1H), 5.34 (ABq, J = 11.4 Hz, $\Delta\upsilon$ = 17.9 Hz, 2H), 4.86-4.83 (m, 1H), 4.75-4.72 (m, 1H), 4.54-4.50 (m, 1H), 3.55-3.54 (m, 1H), 1.45 (s, 3H), 1.42 (s, 3H); IR (film on KBr): 2986, 2917, 1725, 1615, 1477, 1372, 1277, 1236, 1125, 1046 cm^{-1}; HRMS (EI, 3.8V): *m/e* 422.1353; calculated for $C_{24}H_{22}O_7$, 422.1366.

Diol **44**. Aqueous HCl (3*N*, 1.0 mL) was added to a mixture of lactone **43** (28.3 mg, 0.0669 mmol) and THF (1 mL). The mixture was allowed to stir at room temperature for 44 h. The mixture was transferred to a separatory funnel and ethyl acetate (30 mL) was added. The organic phase was washed successively with saturated sodium bicarbonate solution (20 mL), water (20 mL), and brine (20 mL) and then dried over sodium sulfate. The solution was concentrated, applied to a column of silica gel, and the product eluted with ether. Product-containing fractions were combined and concentrated to give the diol (24.8 mg, 97%) as a colorless glass: $[\alpha]_D^{25}$ = -126° (c = 1.1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.55-7.30 (m, 5H), 6.53 (s, 1H), 6.06 (d, J = 1.5 Hz, 1H), 6.02 (d, J=1.5 Hz, 1H), 5.74-5.69 (m, 2H), 5.57-5.53 (m, 1H), 5.33 (ABq, J = 11.4 Hz, $\Delta\upsilon$ = 16 Hz, 2H), 4.86-4.82 (m, 1H), 4.61-4.59 (m, 1H), 4.32-4.30 (m, 1H), 3.70-3.68 (m, 1H), 3.07 (d, J = 6.5 Hz, 1H), 3.00 (d, J = 2.2 Hz, 1H); IR (film on KBr): 3392, 2915, 1718, 1615, 1477, 1371, 1262, 1112, 1059, 1040, 940, 733, 698 cm^{-1}; HRMS (EI, 5.6V): *m/e* 382.1070; calculated for $C_{21}H_{18}O_7$, 382.1053.

MEM ether **45**. 2-Methoxyethoxymethyl chloride (0.007 mL, 0.058 mmol) was added to a solution of diol **44** (14.9 mg, 0.039 mmol) and *N*-ethyldiisopropyl amine (0.07 mL, 0.4 mmol) in methylene chloride (2 mL). The mixture was allowed to stir at room temperature for 16 h. Additional 2-methoxyethoxymethyl chloride (0.01 mL, 0.09 mmol) was added and the reaction was allowed to stir at room temperature for 30 min. The reaction mixture was transferred to a separatory funnel and ether (20 mL) was added. The solution was washed successively with saturated sodium bicarbonate solution (10 mL), water (10 mL), and brine (10 mL), then dried over sodium sulfate. The solution was concentrated and chromatographed with ether/methylene chloride (7:3). Product-containing fractions were combined and concentrated to give **45** (11.9 mg, 65%) as a colorless glass: $[\alpha]_D^{25}$ = -163° (c = 0.31, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.56-7.31 (m, 5H), 6.52 (s, 1H), 6.03 (ABq, J = 1.4 Hz, $\Delta\upsilon$ = 12 Hz, 2H), 5.71-5.67 (m, 1H), 5.55-5.50 (m, 1H), 5.33 (ABq, J = 11.5 Hz, $\Delta\upsilon$ = 18 Hz, 2H), 4.89 (app s, 2H), 4.82-4.78 (m, 1H), 4.50-4.45 (m, 1H), 4.02 (d, J = 3.2 Hz, 1H), 3.96-3.88 (m, 1H), 3.76-3.58 (m, 4H), 3.41 (s, 3H); IR (film on KBr): 3431, 2919, 2851, 1721, 1615, 1477, 1369, 1250, 1109, 1063 cm^{-1}; HRMS (FAB, 0.596V): *m/e* 471.1649 (M+H); calculated for $C_{25}H_{27}O_9$, 471.1655.

Benzyl ether **46**. Silver(I) oxide (24 mg, 0.10 mmol) was added to a solution of alcohol **45** (7.1 mg, 0.015 mmol) in benzyl bromide (0.5 mL). The mixture was allowed to stir at room temperature for 14.5 h. Additional silver(I) oxide (44 mg, 0.19 mmol) was added and the mixture was allowed to stir at room temperature for 24 h. The reaction mixture was applied directly to a column of silica gel and the product was eluted with ether/methylene chloride (1:9). Product-containing fractions were combined and concentrated to give **46** (5.5 mg, 65%) as a colorless glass: $[\alpha]_D^{25}$ = -229° (c = 0.16, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.55-7.29 (m, 10H), 6.51 (s, 1H), 6.02 (ABq, J = 1.4 Hz, $\Delta\upsilon$ = 12 Hz, 2H), 5.83-5.78 (m, 1H), 5.56-5.50 (m, 1H), 5.31 (ABq, J = 11.4 Hz, $\Delta\upsilon$ = 18 Hz, 2H), 4.84 (app s, 2H), 4.78 (ABq, J = 12.2 Hz, $\Delta\upsilon$ = 54 Hz, 2H), 4.65-4.63 (m, 2H), 4.18-4.16 (m, 1H), 3.80-3.71 (m, 2H), 3.66-3.63 (m, 1H), 3.59-3.55 (m, 2H), 3.40 (s, 3H); IR (film on KBr): 2917, 2885, 1722, 1616, 1476, 1370, 1261, 1123, 1045 cm^{-1}; HRMS (FAB, 8.7V): *m/e* 561.2161 (M+H); calculated for $C_{32}H_{33}O_9$, 561.2125.

Alcohol **47**. *p*-Toluenesulfonic acid monohydrate (22 mg, 0.12 mmol) was added to a solution of **46** (5.4 mg, 0.0096 mmol) in methanol (1.5 mL). The reaction flask was placed in a 40°C sand bath and the mixture was stirred for 3 h. The mixture was transferred to a separatory funnel and ethyl acetate (10 mL) was added. The solution was washed successively with saturated sodium bicarbonate solution (20 mL), water (20 mL), and brine (20 mL), then dried over sodium sulfate. The solution was concentrated, applied to a column of silica gel, and the product eluted with acetone/methylene chloride/hexanes (3:5:12). Product-containing fractions were combined and concentrated to give **47** (3.1 mg, 67%) as a colorless glass: $[\alpha]_D^{25}$ = -74.3° (c = 0.14, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.56-7.29 (m, 10H), 6.51 (s, 1H), 6.03 (ABq, J = 1.4 Hz, $\Delta\upsilon$ = 13.2 Hz, 2H), 5.76-5.73 (m, 1H), 5.49-5.45 (m, 1H), 5.31 (ABq, J = 11.4 Hz, $\Delta\upsilon$ = 11.2 Hz, 2H), 4.74-4.72 (m, 1H), 4.73 (ABq, J = 12.2 Hz, $\Delta\upsilon$ = 8.2 Hz, 2H), 4.55-4.52 (m, 1H), 4.14-4.11 (m, 1H), 3.57-3.55 (m, 1H), 2.42 (d, J = 11.3 Hz, 1H); IR (film on KBr): 3381, 2922, 1718, 1616, 1384, 1150, 1142, 1093, 1045 cm^{-1}; HRMS (EI, 0.666V): *m/e* 472.1487; calculated for $C_{28}H_{24}O_7$, 472.1522.

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REFERENCES AND NOTES

1. (a) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M. *J. Nat. Prod.* **1984**, *47*, 1018-1020. (b) Pettit, G. R.; Gaddamidi, V.; Herald, D. L.; Singh, S. B.; Cragg, G. M.; Schmidt, J. M. *J. Nat. Prod.* **1986**, *46*, 995-1002. (c) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M.; Herald, D. L.; Sagawa, Y. *J. Chem. Soc. Chem. Commun.* **1984**, 1693-1694. Isolation of 7-deoxy- and 2-*O*-β-D-glucosyl pancratistatin: (d) Ghosal, S.; Singh, S.; Kumar, Y.; Srivastava, R. S. *Phytochemistry* **1989**, *28*, 611-613.
2. (a) Okamoto, T.; Torii, Y.; Isogai, Y. *Chem. Pharm. Bull.* **1968**, *16*, 1860-1864. (b) Mondon, A.; Krohn, K. *Chem. Ber.* **1975**, *108*, 445-463.
3. Pettit, G. R.; Cragg, G. M.; Singh, S. B.; Duke, J. A.; Doubek, D. L. *J. Nat. Prod.* **1990**, *53*, 176-178.
4. Pettit, G. R.; Pettit III, G. R.; Backhaus, R. A.; Boyd, M. R.; Meerow, A. W. *J. Nat. Prod.* **1993**, *56*, 1682-1687.
5. (a) Barbacid, M.; Vazquez, D. *J. Mol. Biol.* **1974**, *84*, 603-623. (b) Carrasco, L.; Fresno, M.; Vazquez, D. *FEBS Lett.* **1975**, *52*, 236-239. (c) Jiminez, A.; Sanchez, L.; Vazquez, D. *FEBS Lett.* **1975**, *55*, 53-56.
6. Baez, A.; Angoso, M.; Alonso, G.; Vazquez, D. *Biochimie* **1977**, *59*, 751-753.
7. Jiminez, A.; Sanchez, L.; Vazquez, D. *FEBS Lett.* **1975**, *60*, 66-69.
8. *NCI Investigational Drugs. Chemical Information*, National Institutes of Health, 1988, pp. 273-275.
9. Dr. Gordon M. Cragg, Natural Products Branch, NCI, Frederick Cancer Research and Development Center (personal communication).
10. Syntheses of **1**: (a) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829-4837. (b) Tian, X.; Hudlicky, T.; Königsberger, K *J. Am. Chem. Soc.* **1995**, *117*, 3643-3644. (c) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143-10144.
11. Synthetic approaches to **1**: (a) Clark, R. D.; Jahangir; Souchet, M.; Kern, J. R. *J. Chem. Soc., Chem. Commun.* **1989**, 930-931. (b) Clark, R. D.; Souchet, M. *Tetrahedron Lett.* **1990**, *31*, 193-196. (c) Thompson, R. C.; Kallmerten, J. *J. Org. Chem.* **1990**, *55*, 6076-6078. (d) Lopes, R. S. C.; Lopes, C. C.; Heathcock, C. H. *Tetrahedron Lett.* **1992**, *33*, 6775-6778. (e) Angle, S. R.; Louie, M. S. *Tetrahedron Lett.* **1993**, *34*, 4751-4754. (f) Park, T. K.; Danishefsky, S. J. *Tetrahedron Lett.* **1995**, *36*, 195-196. (g) Rigby, J. H.; Gupta, V. *Synlett* **1995**, 547-548. (h) Gauthier, Jr., D. R.; Bender, S. L. *Tetrahedron Lett.* **1996**, *37*, 13-16.
12. Syntheses of 7-deoxypancratistatin: (a) Ohta, D.; Kimoto, S. *Chem. Pharm. Bull.* **1976**, *24*, 2977-2984. (b) Paulsen, H.; Stubbe, M. *Tetrahedron Lett.* **1982**, *23*, 3171-3174; *Liebig's Ann. Chem.* **1983**, 535-556. (c) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289-7290.
13. Others have described convergent syntheses of (+)-lycoricidine (**3**). Each of these syntheses have united aromatic and cyclitol components by an intramolecular Heck coupling. See: (a) Chida, N.; Ohtsuka, M.;

Ogawa, S. *Tetrahedron Lett.* **1991**, *32*, 4525-4528; *J. Org. Chem.* **1993**, *58*, 4441-4447. (b) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694-9696. (c) Su, L.; Johnson, C. R. Thirty-third National Organic Chemistry Symposium, Bozeman, Montana, June, 1993, abstract #A-119. See also: (d) McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4823-4832.

14. For earlier communication of this work, see: (a) Doyle, T. J.; Hendrix, M.; Haseltine, J. *Tetrahedron Lett.* **1994**, *35*, 8295-8298. (b) Doyle, T. J.; VanDerveer, D.; Haseltine, J. *Tetrahedron Lett.* **1995**, *36*, 6197-6200.
15. Weinreb executed a similar stereochemically divergent/convergent tactic in the actinobolin sytem. See: Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1985**, *107*, 7790.
16. Knapp, S.; Ornaf, R. M.; Rodriques, K. E. *J. Am. Chem. Soc.* **1983**, *105*, 5494-5495.
17. We were unable to reproduce the bis-acetonation of *epi*-inositol following the procedure of Angyal and Gilham. See Angyal, S. J.; Gilham, P. T. *J. Chem. Soc.* **1958**, 375-379.
18. Cambie, R. C.; Renner, N. D.; Rutledge, P. S.; Woodgate, P. D. *Syn. Commun.* **1989**, *19*, 537-546.
19. (a) Johnson, C. R.; Plé, P. A.; Adams, J. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1006-1007. (b) Dumortier, L.; Liu, P.; Dobbelaere, S.; Van der Eycken, J.; Vandewalle, M. *Synlett* **1992**, 243-245.
20. Napolitano, E.; Giannone, E.; Fiaschi, R.; Marsili, A. *J. Org. Chem.* **1983**, *48*, 3653-3657.
21. Thorpe, F. G.; Pickles, G. M.; Podesta, J. C. *J. Organomet. Chem.* **1977**, *128*, 305-312.
22. For a similar example, see: Liu, P.; Vandewalle, M. *Tetrahedron Lett.* **1993**, *34*, 3625-3628.
23. (a) Trost, B. M.; Verhoeven, T. R. J. Org. Chem. **1976**, *41*, 3215-3216. (b) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2591-2594. (c) Oppolzer, W.; Gaudin, J.-M.; Birkinshaw, T. N. *Tetrahedron Lett.* **1988**, *29*, 4705-4708. (d) Johnson, C. R.; Senanayake, C. H. *J. Org. Chem.* **1989**, *54*, 735-736 and references therein. (e) Deardorff, D. R.; Linde II, R. G.; Martin, A. M.; Shulman, M. J. *J. Org. Chem.* **1989**, *54*, 2759-2762.
24. For a discussion of spirocyclizations involving phenonium ions, see: (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; 3rd ed., Harper and Row, Inc.: New York. 1987; pp. 434-448. For electronically similar cyclizations directed by oxygen substituents, see: (b) Lombardo, L.; Mander, L. N.; Turner, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6626-6628. (c) Nicolaou, K. C.; Zipkin, R. E. *Angew. Chem., Intl. Ed. Engl.* **1981**, *20*, 785-786.
25. A similar influence operates in the solvolysis of alkoxymethyl halides. See: (a) Streitweiser, A. Jr. *Solvolytic Displacement Reactions;* McGraw-Hill: New York. 1962; pp. 102-103. Another analogy can be found in the rearrangement of 3,3-disubstituted indolenines to 2,3-disubstituted indoles. The migrations involved here can be directed by oxygen or nitrogen. See: (b) Jackson, A. H.; Smith, A. E. *Tetrahedron* **1968**, *24*, 403-413. (c) Jackson, A. H.; Smith, P. *Tetrahedron* **1968**, *24*, 2227-2239. (d) Biswas, K. M.; Jackson, A. H. *Tetrahedron* **1969**, *25*, 227-241.
26. Pentacycle **19** was prepared alternatively by the benzylation of phenol **38** derived by metal/halogen exchange performed on **33**.
27. See Goering, H. L.; Eikenberry, J. N.; Koermer, G. S. *J. Am. Chem. Soc.* **1971**, *93*, 5913-5914 for the introduction of this technique.
28. (a) Ward, H. R.; Lawler, R. G.; Cooper, R. A. *J. Am. Chem. Soc.* **1969**, *91*, 746-748. (b) Lepley, A. R.; Landau, R. L. *J. Am. Chem. Soc.* **1969**, *91*, 748-749.
29. Rogers, H. R.; Houk, J. *J. Am. Chem. Soc.* **1982**, *104*, 522-525.
30. Xu, Y.-C.; Lebeau, E.; Gillard, J. W.; Attardo, G. *Tetrahedron Lett.* **1993**, *34*, 3841-3844.
31. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. P. *J. Chem. Soc., Chem. Commun.* **1987**, 1625-1626.

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