JOC Article

Total Synthesis of Pancratistatin Relying on the [3,3]-Sigmatropic Rearrangement

Hyojin Ko,[†] Eunkyung Kim,[†] Jae Eun Park,[†] Deukjoon Kim,[‡] and Sanghee Kim*[,†,‡]

Natural Products Research Institute, College of Pharmacy, Seoul National University, 28 Yungun, Jongro, Seoul 110-460, Korea, and College of Pharmacy, Seoul National University, San 56-1, Shilim, Kwanak, Seoul 151-742, Korea

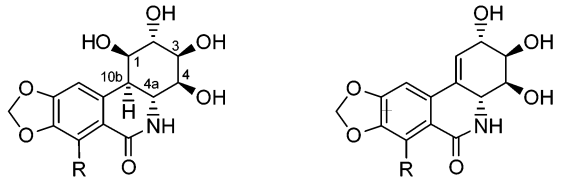
pennkim@snu.ac.kr

Received September 18, 2003

A new total synthesis of the antitumor alkaloid, pancratistatin (**1**), has been accomplished from readily available starting materials. Claisen rearrangement of the racemic dihydropyranethylene **17** was employed to construct the A and C rings with the appropriate stereochemistry. In addition, the Ireland−Claisen rearrangement of the enantiomerically pure **9** followed by ring-closing metathesis provided the important intermediate **24**, thus implying that our approach could yield the enantioselective synthesis of (+)-pancratistatin. With the appropriately functionalized cyclohexene **24**, stereo- and regiocontrolled functional group interchanges, such as iodolactonization, dihydroxylations, and a cyclic sulfate elimination reaction, facilitated the production of the target natural product.

Introduction

In 1984, Pettit and co-workers reported the isolation and structure of the highly oxygenated phenanthridone alkaloid designated (+)-pancratistatin (**1**, Figure 1).[1] This alkaloid exhibits high levels of in vitro and in vivo cancer cell growth inhibitory activity and antiviral activity.[2] Pancratistatin possesses six contiguous stereogenic centers in the C ring of a phenanthridone skeleton and a trans-fused BC ring junction. Subsequently, its unique structural features coupled with its low natural abundance and promising pharmacological profiles have prompted impressive synthetic efforts to date from a number of laboratories. The first total synthesis of the racemate was reported by Danishefsky in 1989,[3] and the first enantioselective synthesis of the natural enantiomer was recorded by Hudlicky in 1995.[4] In the same year, Trost presented an enantioselective synthesis with a high overall yield.[5] Since then, Haseltine,[6] Magnus,[7] and Rigby[8] have also presented new synthetic routes for (+)-pancratistatin. Recently, Pettit achieved the synthesis of (+)-**1** from the more abundant alkaloid (+)-narciclasine (**2**, Figure 1).[9]



R = OH, pancratistatin (**1**)
R = H, 7-deoxypancratistatin (**3**)

R = OH, narciclasine (**2**)
R = H, lycoricidine (**4**)

FIGURE 1. Structures of pancratistatin (**1**), narciclasine (**2**), 7-deoxypancratistatin (**3**), and lycoricidine (**4**).

Despite the numerous synthetic approaches for the synthesis of **1** and its congeners,[10] such as narciclasine (**2**), 7-deoxypancratistatin (**3**), and lycoricidine (**4**), the members of this phenanthridone alkaloid family remain particularly attractive targets for organic synthesis. In this paper,[11] we describe full details of the stereocon-

* To whom correspondence should be addressed. Tel: 82-2-740-8913. Fax: 82-2-762-8322.
[†] Natural Products Research Institute.
[‡] College of Pharmacy.

(1) (a) Pettit, G. R.; Gaddamidi V.; Cragg G. M.; Herald D. L.; Sagawa Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1693. (b) Pettit, G. R.; Gaddamidi V.; Cragg G. M. *J. Nat. Prod.* **1984**, *47*, 1018.

(2) (a) Pettit, G. R.; Gaddamidi, V.; Herald, D. L.; Singh, S. B.; Cragg, G. M.; Schmidt, J. M.; Boettner, F. E.; Williams, M.; Sagawa, Y. *J. Nat. Prod.* **1986**, *49*, 995. (b) Gabrielsen, B.; Monath, T. P.; Huggins, J. W.; Kevauver, D. F.; Pettit, G. R.; Groszek, G.; Holingshead, M.; Kirsi, J. J.; Shannon, W. M.; Schubert, E. M.; DaRe, J.; Ugarkar, B.; Ussery, M. A.; Phelan, M. J. *J. Nat. Prod.* **1992**, *55*, 1569. (c) Gabrielsen, B.; Monath, T. P.; Huggins, J. W.; Kirsi, J. J.; Holingshead, M.; Shannon, W. M.; Pettit. G. R. In *Natural Products as Antiviral Agents*; Chu, C. K., Cutler, H. G., Eds.; Plenum: New York, 1992; pp 121−135.

(3) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829.

(4) Tian, X.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643.

(5) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143.

(6) Doyle, T. J.; Hendrix, M.; VanDerveer, D.; Javanmard, S.; Haseltine, J. *Tetrahedron* **1997**, *53*, 11153.

(7) (a) Magnus, P.; Sebhat, I. K. *J. Am. Chem. Soc.* **1998**, *120*, 5341. (b) Magnus, P.; Sebhat, I. K. *Tetrahedron* **1998**, *54*, 15509.

(8) (a) Rigby, J. H.; Mateo, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 12655. (b) Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. *J. Am. Chem. Soc.* **2000**, *122*, 6624.

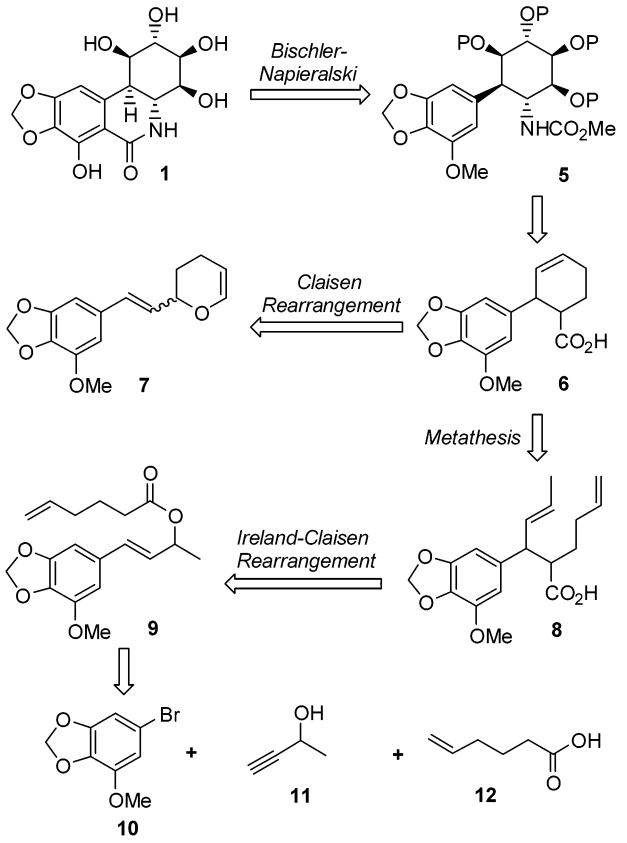
(9) Pettit, G. R.; Melody, N.; Herald, D. *J. Org. Chem.* **2001**, *66*, 2583.

(10) For a good review with citations, see: (a) Rinner, U.; Siengalewicz, P.; Hudlicky, T. *Org. Lett.* **2002**, *4*, 115. (b) Hudlicky, T.; Rinner, U.; Gonzalez, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T. A.; Pettit, G. R. *J. Org. Chem.* **2002**, *67*, 8726.

(11) Part of this work has been published in preliminary form, see: Kim, S.; Ko, H.; Kim, E.; Kim, D. *Org. Lett.* **2002**, *4*, 1343.

10.1021/jo035371n CCC: $27.50
Published on Web 12/12/2003

SCHEME 1. Retrosynthetic Analysis of Pancratistatin (1)

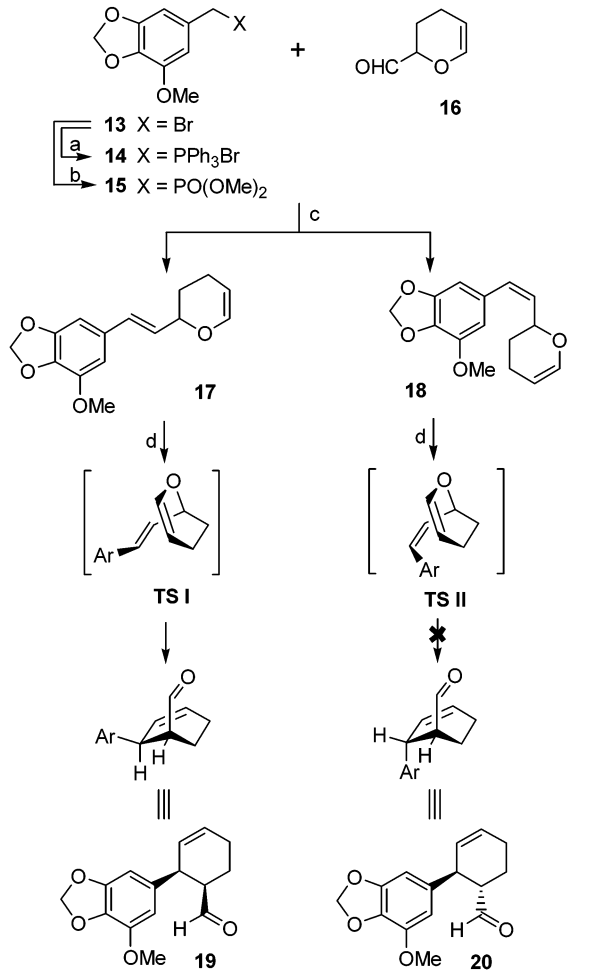


trolled total synthesis of pancratistatin (**1**), which are unique as compared to other previous syntheses.

Results and Discussion

The initial strategy of our synthesis is presented in Scheme 1. The B ring of the phenanthridone skeleton would be constructed at a relatively late stage of the synthesis by employing the Bischler−Napieralski reaction,[12] analogous to that of Magnus et al.[7] We envisioned that the requisite cyclization precursor **5**, which contains all six of the stereocenters in the C ring, could be stereoselectively synthesized from the simple disubstituted cyclohexene **6**. The presence of a γ,δ-unsaturated carbonyl unit in compound **6** suggested the use of a Claisen rearrangement of 3,4-dihydro-2*H*-pyranylethylene **7**.[13] At this transformation, the relative stereochemistry of two substituents of the cyclohexene ring could be controlled by the choice of the olefin configuration. The dihydropyranylethylene **7** could be assembled from a commercially available acrolein dimer, using a Wittig-type reaction. On the other hand, the cyclohexene ring of **6** could also come from the diene **8** via ring-closing metathesis. We envisaged the diene **8** could be obtained from an allylic ester **9** using an Ireland−Claisen rearrangement in which the stereochemical outcome of **8** was significantly influenced by the reaction conditions. Further analysis indicated that the readily available starting materials **10** and **12**, together with the commercially available 3-butyn-2-ol (**11**) as a chiral source, should be ideal synthetic precursors for the Ireland−Claisen rearrangement substrate **9**.

SCHEME 2[a]



[a] Reagents and conditions: (a) PPh_3, benzene, reflux 8 h, 83%; (b) $P(OMe)_3$, toluene, sealed tube 180 °C, 2 h, 99%; (c) **14**, **16**, *n*-BuLi, THF, −10 °C to rt, 1 h, 72% as a mixture of **17** and **18** (1:2.6); or **14**, **16**, KOH, 18-C-6, CH_2Cl_2, rt, 8 h, 85% as a mixture of **17** and **18** (1:4.6); or **15**, **16**, LHMDS, THF, −78 °C to rt, 22 h, 60% (92% based on the recovered starting material) as a single isomer of **17**; (d) toluene, sealed tube, 250 °C, 20 h, 78%.

Our approach commenced with the preparation of the known phosphonium bromide **14**[14] from the known bromide **13**,[15a] as shown in Scheme 2. The bromide **13** was readily prepared from commercially available methyl gallate via a conventional four-step sequence, following the published procedure.[15] Treatment of the obtained phosphonium bromide **14** with *n*-BuLi in THF at −10 °C formed the ylide, and then the addition of the commercially available acrolein dimer **16** (1.1 equiv) provided a mixture of olefins **18** and **17** in 72% yield with a *Z*/*E* ratio of 2.6:1. Employing a modified Wittig reaction[16] between **14** and **16** (1.1 equiv), in the presence of freshly

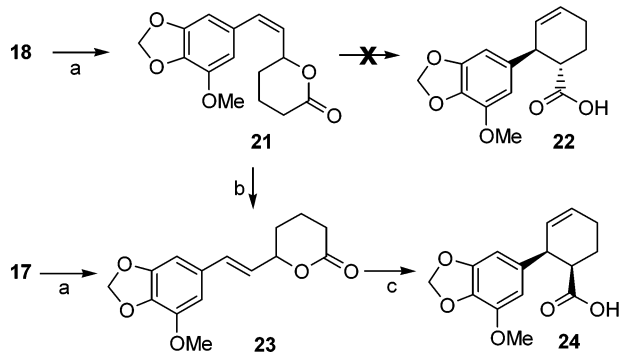
(12) (a) Banwell, M. G.; Cowden, C. J.; Gable, R. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3515. (b) Fodor, G.; Nagibandi, S. *Tetrahedron* **1980**, *36*, 1279.

(13) Büchi, G.; Powell, J. E., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 3126.

(14) Pettit, G. R.; Singh, S. B.; Boyd, M. R.; Hamel, E.; Pettit, R. K.; Schmidt, J. M.; Hogan, F. *J. Med. Chem.* **1995**, *38*, 1666.

(15) (a) Lalami, K.; Dhal, R.; Brown, E. *Heterocycles* **1988**, *27*, 1131. (b) For an efficient preparation of the corresponding alcohol from methyl gallate, see: Pettit, G. R.; Singh, S. B. *Can. J. Chem.* **1987**, *65*, 2390.

SCHEME 3[a]



[a] Reagents and conditions: (a) (i) *p*-TsOH, THF/H_2O, 20 h, (ii) PCC, MS 4 Å, CH_2Cl_2, 8 h, 80%; (b) CSA, CH_2Cl_2, 20 h, 98%; (c) (i) LHMDS, TBSCl, HMPA, THF, −78 °C to rt, 5 h, (ii) benzene, reflux, 23 h, (iii) THF/H_2O (3/1), 5 h, 70%.

powdered KOH and a catalytic amount of 18-crown-6 in CH_2Cl_2 at room temperature, also gave the *cis*-olefin **18** and its *trans* isomer **17** with a *Z*/*E* ratio of 4.6:1 in 85% yield. The yield and *Z*/*E* ratio with these reaction conditions were higher than those produced by the reaction described above, thus yielding more of the *cis* isomer **18**, which would give the *trans*-disubstituted cyclohexene **20** after a Claisen rearrangement.

Without further optimization, we investigated the feasibility of a Claisen rearrangement of dihydropyranethylenes **18** and **17**. Heating the cis isomer at 250 °C in a sealed tube did not provide any noticeable rearranged product, and increasing the temperature higher than 300 °C resulted only in the formation of polymeric materials. However, *trans*-dihydropyranethylene **17** (250 °C in a sealed tube) cleanly provided the *cis*-disubstituted cyclohexene **19** as a single isomer in 78% yield. As discussed by Büchi,[13] this rearrangement must proceed through a boatlike transition state, as depicted in TS I and II (Scheme 2). The transition state of the trans isomer **17** (TS I) leads to the 1,2-*cis*-disubstituted cyclohexene **19** in a stereospecific manner. On the other hand, the transition state of the cis isomer **18** (TS II), which leads to the *trans*-disubstituted cyclohexene **20**, suffers from the severe nonbonded interactions between the *cis*-oriented bulky aromatic ring (Ar) and the hydrogen atoms of the dihydropyran ring, retarding the rate of rearrangement.

To obtain a *trans*-disubstituted cyclohexene, we turned our attention to the vinyl lactones **21** and **23** as alternative precursors (Scheme 3). The Claisen rearrangement of lactonic enolates, compared to dihydropyrans, reportedly occurs under remarkably mild conditions.[17] Therefore, we expected that the rearrangement of *cis*-vinyl lactone **21** could be achieved, despite the severe nonbonded interactions. The required *cis*-vinyl lactone **21** was easily prepared from the corresponding *cis*-dihydropyranethylene **18** by oxidation with PCC in 80% yield.

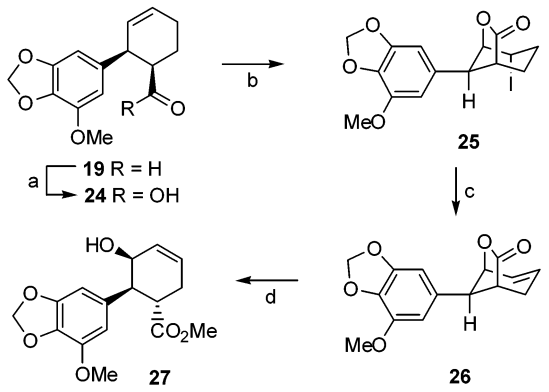
With compound **21** in hand, we then employed the cyclomutative variation of the Ireland ester enolate Claisen rearrangement[17,18] of **21** to gain the *trans*-disubstituted cyclohexene **22**. Unfortunately, all of our attempts with various silylating reagents, bases, and additives[18] yielded either unreacted starting material or its silyl ketene acetal intermediate. However, when the *trans*-vinyl lactone **23** was employed, the rearrangement was accomplished efficiently to give the *cis*-disubstituted cyclohexene **24**. Deprotonation of **23** (LHMDS/HMPA/THF) followed by trapping with TBSCl afforded the corresponding silyl ketene acetal, and rearrangement of the resulting crude material in refluxing benzene led, after hydrolysis of the silyl ester in aqueous THF, to the formation of **24** as the only identifiable product in 70% overall yield.[19] Access to the *trans*-vinyl lactone **23** was secured by applying the PCC oxidation to *trans*-dihydropyranethylene **17**, as in the preparation of **21**. Alternatively, it could be prepared from its cis isomer **21** by acid-catalyzed isomerization (CSA, CH_2Cl_2) at room temperature in an excellent yield (98%).

Through this work, in agreement with the observation by Büchi,[13] we felt that dihydropyranethylene and vinyl lactone, with a *cis*-oriented substituent on the aliphatic double bond, would not undergo the Claisen rearrangement under tolerable reaction conditions. As a result, we decided to utilize a Claisen rearrangement of the trans isomers for the total synthesis of pancratistatin. For brevity and efficiency, the *trans*-dihydropyranethylene **17** would be a more desirable intermediate than the *trans*-vinyl lactone **23**. This issue prompted us to investigate the selective synthesis of **17**. To our satisfaction, employing the Horner−Wadsworth−Emmons reaction between phosphonate **15** (Scheme 2) and acrolein dimer **16** (1.1 equiv) in the presence of LHMDS in THF afforded the desired (*E*)-olefin **17** with very high stereoselectivity in 60% yield (92% yield based on the recovered starting material). Only trace amounts (<1%) of the corresponding (*Z*)-olefin **18** were detected in the crude ^{1}H NMR spectra. The requisite phosphonate **15** was prepared from the bromide **13** with excess trimethyl phosphite in 99% yield.[20]

With a facile route to the large-scale preparation of the *cis*-disubstituted cyclohexene **19**, our study focused on the selective introduction of the stereocenters in the C ring (Scheme 4). First, the aldehyde group of **19** was oxidized with $NaClO_2$ to the corresponding carboxylic acid **24** (90% yield), which had been synthesized by a different route (Scheme 3). Iodolactonization of **24** under two-phase conditions, followed by treatment of the resulting iodolactone **25** with DBU in refluxing benzene, led to the formation of the bicyclic lactone **26** with an overall yield of 79%.[21] Methanolysis of the lactone **26** with NaOMe at room temperature for 18 h afforded an inseparable equilibrium mixture (ca. 1:1 ratio) of hydroxy ester **27** and its C-4a epimer (pancratistatin numbering). However, when the methanolysis was carried out in refluxing methanol for 20 h, epimerization of the methoxycarbonyl

(16) Bellucci, G.; Chiappe, C.; Lo Moro, G. *Tetrahedron Lett.* **1996**, *37*, 4225.
(17) Danishefsky, S.; Funk, R. L.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 6889.
(18) (a) Danishefsky, S.; Tsuzuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 6891. (b) Turos E.; Audia, J. E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 8231. (c) Corey, E. J.; Guzman-Perez, A.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1997**, *119*, 11769.
(19) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 478.
(20) Jawad, A.; Jacques, C.; Ingrid, H.-K.; Christian H.; Hugues, M.; Robert, G. R. *J. Med. Chem.* **2000**, *43*, 560.
(21) Kobayashi, S.; Kamiyama, K. Ohno, M. *J. Org. Chem.* **1990**, *55*, 1169.

SCHEME 4[a]



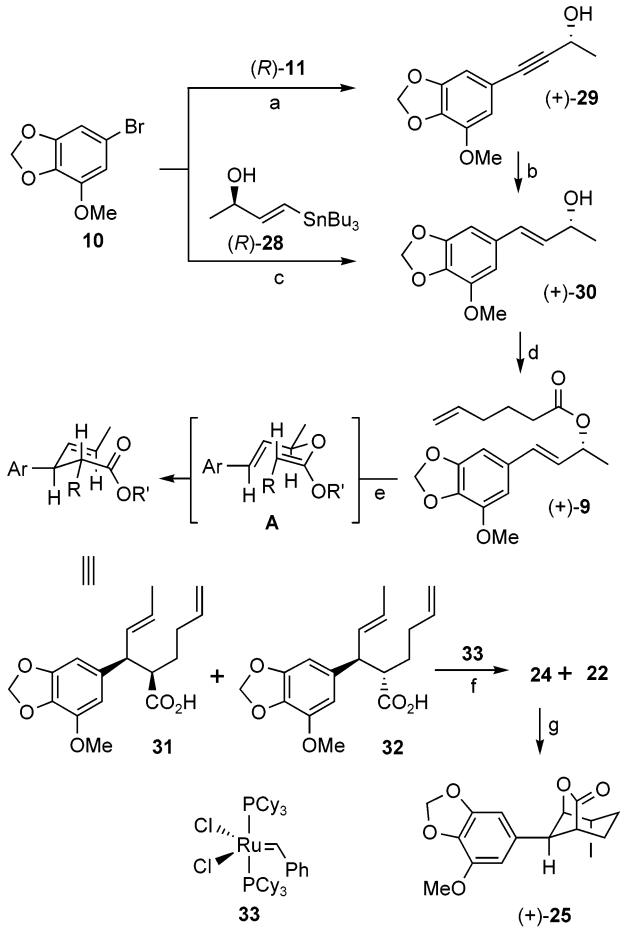
[a] Reagents and conditions: (a) 2-methyl-2-butene, $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, 0 °C to rt, 18 h, 90%; (b) KI_3, $NaHCO_3$, H_2O, CH_2Cl_2, 20 h, 99%; (c) DBU, benzene, reflux, 8 h, 80%; (d) NaOMe, MeOH, reflux, 20 h, 93%.

group was accomplished very cleanly to give **27** as the only identifiable product in 93% yield.

With the ultimate aim of achieving the enantioselective total synthesis of (+)-pancratistatin, we also studied the efficient synthesis of the appropriately functionalized cyclohexanes in their enantiomerically pure forms (Scheme 5). This synthesis began by preparing the known aryl bromide **10**[22] from the commercially available 5-bromo-3-methoxysalicylaldehyde, via a two-step sequence according to the published procedure.[7b] The resulting aryl bromide **10** was subjected to a palladium-catalyzed Sonogashira coupling reaction[23] with the commercially available, enantiomerically pure (*R*)-3-butyn-2-ol ((*R*)-**11**), in the presence of Et_3N and CuI, to yield the optically active propargylic alcohol (+)-**29** in high yield (80%). In this case, however, the reaction was very sluggish and required a large excess of (*R*)-**11** (6 equiv) for completion. Reduction of the triple bond in (+)-**29** with $LiAlH_4$ in THF stereoselectively provided the (*E*)-allylic alcohol (+)-**30** in 75% yield. However, the high cost of the enantiomerically pure (*R*)-**11** limited the utilization of this pathway. Another attractive route for the synthesis of (+)-**30** was the utilization of the chiral building block (*R*)-**28**, (*R*)-(*E*)-4-(tributylstannanyl)but-3-en-2-ol, for which we recently reported an efficient enzymatic preparation method.[24] To our delight, the Stille coupling[25] of aryl bromide **10** with a slight excess of vinylstannane (*R*)-**28** (>99% ee, 1.2 equiv), mediated by $Pd(PPh_3)_4$, successfully gave the (*E*)-allylic alcohol (+)-**30** in 84% yield.

Acylation of the resulting secondary alcohol (+)-**30** with the commercially available 5-hexenoic acid **12** under Steglich's DCC coupling conditions[26] provided (+)-**9** (93%), which was subjected to the Ireland ester enolate Claisen rearrangement.[19,27] Best results were obtained when (+)-**9** was exposed to LDA and TBSCl in 20%

SCHEME 5[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, MS 4 Å, 2 days, 80%; (b) LAH, THF, −78 °C to rt, 2 h, 75%; (c) $Pd(PPh_3)_4$, DMF, 65 °C, 24 h, 84%; (d) **12**, DCC, DMAP, CH_2Cl_2, 93%; (e) LDA, HMPA, THF, TBSCl, −78 °C to rt, 77% as a mixture of **31** and **32** (6:1); (f) **33**, CH_2Cl_2, 91% as a mixture of **24** and **22** (6:1); (g) KI_3, $NaHCO_3$, H_2O, CH_2Cl_2, 20 h, 76%.

HMPA/THF at −78 °C, with gradual warming to room temperature to promote the rearrangement. After an acidic workup, this reaction predominantly afforded the desired acid **31**, along with a minor amount of the stereoisomer **32**,[28] in 77% combined yield and 6:1 selectivity, as shown in Scheme 5. The relative stereochemistry of the newly generated stereocenters of **31** was established by its conversion to (+)-**25**, and this stereochemical outcome can be rationalized by invoking Ireland's chairlike transition state[27d] geometry, as shown in **A**.

The ring-closing metathesis of the inseparable mixture of **31** and **32** with Grubbs's catalyst[29] **33** in CH_2Cl_2 at room temperature produced the inseparable disubstituted cyclohexenes **24** and **22**, in 91% combined yield. Iodolactonization of a mixture of **24** and **22**, under the

(22) Shirasaka, T.; Takuma, Y.; Imaki, N. *Synth. Commun.* **1990**, *20*, 1223.

(23) (a) Sonogashira, K.; Thoda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Morita, S.; Otsubo, K.; Matsubara, J.; Ohtani, T.; Uchida, M. *Tetrahedron: Asymmetry* **1995**, *6*, 245.

(24) Lee, T.; Kim, S. *Tetrahedron: Asymmetry* **2003**, *14*, 1951.

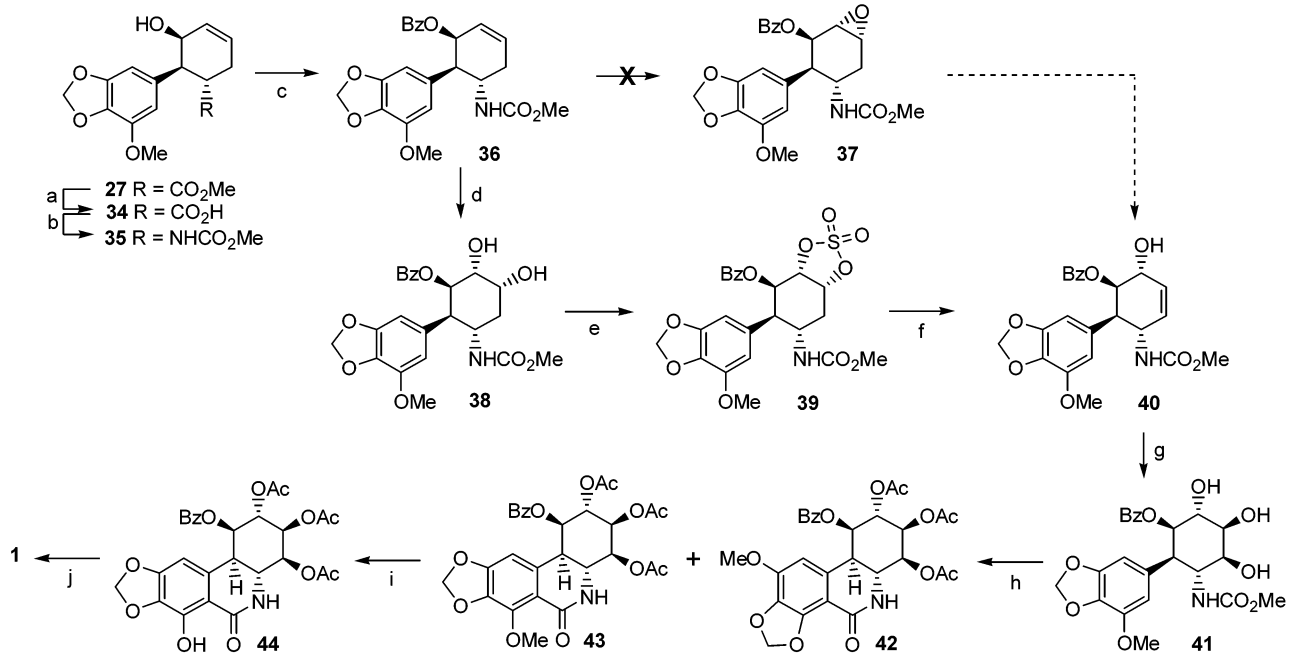
(25) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Geoffrey T. C.; Peter, T. C. *Tetrahedron* **1994**, *50*, 3213.

(26) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 52.

(27) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (c) Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279. (d) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650.

(28) When (+)-**9** was exposed to LDA and TBSCl in THF at −78 °C with warming to room temperature, the only detectable stereoisomer was the acid **32** (<30%).

SCHEME 6[a]



[a] Reagents and conditions: (a) 1 N LiOH, THF, rt, 18 h, 99%; (b) (i) DPPA, Et_3N, toluene, reflux, 15 h, (ii) NaOMe, MeOH, reflux, 0.5 h, 82%; (c) BzCl, Et_3N, DMAP, CH_2Cl_2, rt, 15 h, 99%; (d) OsO_4, NMO, THF/H_2O, rt, 20 h, 96%; (e) (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, (ii) Oxone, $RuCl_3 \cdot 3H_2O$, EtOAc/CH_3CN/H_2O, rt, 2 h, 83%; (f) DBU, toluene, reflux, 2 h, then H_2SO_4, H_2O/THF, rt, 4 h, 67%; (g) OsO_4, NMO, THF/H_2O, rt, 27 h, 88%; (h) (i) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 1 h, 77%, (ii) Tf_2O, DMAP, CH_2Cl_2, 0 °C to 5 °C, 22 h, 78% as a mixture of **43** and **42** (7:1); (i) BBr_3, CH_2Cl_2, −78 to 0 °C, 1 h, 65%; (j) NaOMe, MeOH, THF, rt, 4 h, 83%.

same conditions used previously (Scheme 4), provided the iodolactone (+)-**25** (76%) and unreacted **22** (13%), which were now separable. The ^1H and ^{13}C NMR spectroscopic data of (+)-**25** (>99% ee by chiral HPLC analysis) were identical to those of the racemate synthesized by a different route.

Although this enantioselective pathway provided a shorter synthetic route to the intermediate **24** with a reasonably high overall yield, as compared to the racemic synthesis, it was operationally more difficult for scale-up than the racemic pathway and yielded an inseparable mixture of diastereomers during the Ireland−Claisen rearrangement. These issues led us to utilize the racemic route to complete the total synthesis of pancratistatin.

With multigram quantities of **27** in hand, we began the second stage of our synthesis of pancratistatin by converting the ester functional group of **27** to the amine (Scheme 6). To this end, saponification of the methyl ester **27** with LiOH was followed by a modified Curtius rearrangement[30] of the resulting acid **34** with diphenylphosphoryl azide in refluxing toluene, to give a rather stable isocyanate intermediate. This required further treatment with NaOMe/MeOH to generate the corresponding carbamate **35** in 82% overall yield.

Initially, we explored the functional group transformation of the $\Delta^{2,3}$-olefin of **35** to the C-2α hydroxy $\Delta^{3,4}$-olefin of **40** by employing a sequential stereoselective epoxidation/regioselective rearrangement of epoxide to allylic alcohol process.[31] At this stage, it was necessary to protect the free hydroxyl group of **35** to selectively install the C-2 hydroxyl group on the α-face. This was accomplished by treating compound **35** with benzoyl chloride to furnish **36** in 99% yield. Attempted epoxidations of **36** to **37** with various reagents, such as *m*-CPBA and dioxiranes, were not successful and provided only decomposed materials, presumably due, in part, to the electron-rich nature of the aromatic ring. However, dihydroxylation of the $\Delta^{2,3}$-olefin with OsO_4 did occur on the desired α-face of the molecule to produce diol **38** in an excellent yield (96%). Thus, we decided to use **38** as an intermediate for this transformation. To our delight, the regioselective elimination of the C-3 hydroxyl group of the diol **38**, to generate the requisite $\Delta^{3,4}$ unsaturation, could be achieved by employing the cyclic sulfate elimination reaction.[32] Treatment of diol **38** with thionyl chloride followed by oxidation with $RuCl_3 \cdot 3H_2O$/Oxone[33] provided the corresponding cyclic sulfate **39** in 83% yield. The reaction of cyclic sulfate **39** with DBU in refluxing toluene[32a] led, after acidic workup, to the formation of the desired allylic alcohol **40** (67% yield). Finally, routine *cis*-dihydroxylation of **40** with OsO_4 afforded the single isomer **41** in 88% yield, thereby completing the functionalization of the C

(29) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. (b) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887.

(30) (a) Shin, K. J.; Moon, H. R.; George, C.; Marquez, V. E. *J. Org. Chem.* **2000**, *65*, 2172. (b) Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. *J. Org. Chem.* **1999**, *64*, 6411.

(31) For a good review of this transformation, see: Smith, J. G. *Synthesis* **1984**, 629.

(32) For the elimination reaction of an α-nonactivated cyclic sulfate, see: (a) Winkler, J. D.; Kim, S.; Harrison, S.; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc.* **1999**, *121*, 296. (b) Kim, C. U.; Lew, W.; Williams, M. A.; Wu, H.; Zhang, L.; Chen, X.; Escarpe, P. A.; Mendel, D. B.; Laver, W. G.; Stevens, R. C. *J. Med. Chem.* **1998**, *41*, 2451. (c) Schaub, C.; Müller, B.; Schmidt, R. R. *Eur. J. Org. Chem.* **2000**, 1745.

(33) Robins, M. J.; Lewandowska, E.; Wnuk, S. F. *J. Org. Chem.* **1998**, *63*, 7375.

ring of pancratistatin. The structural assignment made for this compound was strongly supported by its relevant ^{1}H NMR coupling patterns and by comparing the ^{1}H NMR spectral data of the derived tetraacetate with those reported by Magnus.[7]

Efforts were next directed toward the Bischler−Napieralski cyclization to introduce the B ring. The remaining steps to pancratistatin required protection of the hydroxyl groups, formation of the final lactam B ring, and protecting group removal. These steps were accomplished by employing reaction conditions analogous to those of Magnus et al.[7] Peracetylation of **41** (77%) was followed by Banwell's modified Bischler−Napieralski cyclization,[7,12] which predominantly provided the desired product **43**, along with a minor amount of the regioisomer **42**, in 78% combined yield and 7:1 regioselectivity. Treatment of the inseparable mixture of **43** and **42** with BBr_3, to remove the C-7 methyl group protection, yielded **44** (65%) and unreacted **42**, which were now separable.[34] Finally, simple removal of the protecting groups with NaOMe/MeOH afforded (±)-**1** in 83% yield, of which ^{1}H and ^{13}C NMR spectral data were in good agreement with those reported.[1,3−10]

In conclusion, we have accomplished the stereoselective total synthesis of (±)-pancratistatin in 17 steps with an overall yield of 5.8% from readily available starting material **13**. We have also developed an efficient synthetic pathway to the important intermediate **24** in enantiomerically pure form, thus showing that our approach could yield the enantioselective synthesis of (+)-pancratistatin. Several aspects of our approach differ significantly from other previous efforts. First, we utilized the Claisen rearrangement/Ireland−Claisen rearrangement as a key step to construct the A and C rings with the appropriate stereochemistry. In addition, the problem of installing six contiguous stereogenic centers in the C ring was successfully addressed in our approach, primarily due to the use of a cyclic sulfate elimination reaction.

Experimental Section

General Remarks. All chemicals were reagent grade and used as purchased. All reactions were performed under an inert atmosphere of dry argon or nitrogen using distilled dry solvents. Reactions were monitored by TLC analysis. Flash column chromatography was carried out on silica gel (230−400 mesh). Melting points are uncorrected. Optical rotations were measured using sodium light (D line 589.3 nm).

(7-Methoxybenzo[1,3]dioxol-5-ylmethyl)phosphonic Acid Dimethyl Ester (15). A mixture of bromide **13**[15] (90 mg, 0.37 mmol), trimethyl phosphite (0.5 mL, 4.24 mmol), and toluene (0.5 mL) in a sealed tube was heated at 180 °C in an oil bath for 2 h. After the mixture was cooled, the excess trimethyl phosphite was removed in vacuo. Purification of the residue by short flash column chromatography on silica gel (eluent: EtOAc) gave 94 mg (99%) of **15** as colorless oil: IR (film) ν_{max} 1633.9, 1510.4, 1452.5, 1435.2, 1358.0, 1319.4, 1244.2, 1196.0, 1134.3, 1093.7, 1033.9 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.02 (d, J = 21.3 Hz, 2H), 3.640 (d, J = 10.8 Hz, 3H), 3.644 (d, J = 10.8 Hz, 3H), 3.84 (s, 3H), 5.90 (s, 2H), 6.41−6.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.6, 33.5, 52.7 (d, J_{cp} = 6.8 Hz), 56.4, 101.3, 104.0 (d, J_{cp} = 6.5 Hz), 109.0 (d, J_{cp} = 7.4 Hz), 125.0 (d, J_{cp} = 9.1 Hz), 134.2 (d, J_{cp} = 3.7 Hz), 143.4 (d, J_{cp} = 3.2 Hz), 148.8 (d, J_{cp} = 3.2 Hz); MS-EI *m*/*z* (rel int) 274 (M$^+$, 42), 165 (100); HRMS-EI (calcd for $C_{11}H_{15}O_6P$) 274.0606, found 274.0609.

(*E*)-6-[2-(3,4-Dihydro-2*H*-pyran-2-yl)vinyl]-4-methoxybenzo[1,3]dioxole (17). To a solution of phosphonate **15** (300 mg, 1.16 mmol) in THF (4 mL) was added LHMDS (2.0 mL, 1.0 M in THF) at −78 °C. After this mixture was warmed to 0 °C over 1 h, acrolein dimer **16** (134 mg, 1.27 mmol) in THF (2 mL) was added slowly. The resulting mixture was allowed to warm to room temperature and stirred for 22 h. The reaction was quenched with brine (6 mL) and extracted with EtOAc (15 mL × 2). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 10:1) to give the desired compound **17** (181 mg, 60%; 92% based on the recovered starting material) as colorless oil, along with a recovered starting material **15** (105 mg): IR (film) ν_{max} 2924.4, 2853.0, 1736.1, 1626.1, 1508.5, 1450.6, 1429.4, 1356.1, 1319.4, 1261.6, 1240.3, 1197.9, 1136.2, 1091.8, 1045.5 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.64−1.77 (m, 1H), 1.88−2.08 (m, 3H), 3.83 (s, 3H), 4.39 (dddd, J = 8.4, 4.8, 2.1, 0.9 Hz, 1H), 4.67 (dddd, J = 4.5, 2.7, 2.7, 1.2 Hz, 1H), 5.89 (s, 2H), 6.04 (dd, J = 15.9, 6.3 Hz, 1H), 6.36 (dt, J = 6.3, 1.8 Hz, 1H), 6.45 (dd, J = 15.9, 1.2 Hz, 1H), 6.48 (d, J = 1.5 Hz, 1H), 6.56 (d, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.4, 28.3, 56.5, 75.2, 100.1, 100.5, 101.5, 106.7, 127.8, 130.6, 131.6, 143.4, 143.5, 149.0, 149.4; MS-EI *m*/*z* (rel int) 260 (M$^+$, 62), 203 (100), 204 (96), 165 (92); HRMS-EI (calcd for $C_{15}H_{16}O_4$) 260.1049, found 260.1045.

2-(7-Methoxybenzo[1,3]dioxol-5-yl)cyclohex-3-enecarbaldehyde (19). Dihydropyranethylene **17** (2.98 g, 10 mmol) was dissolved in toluene (150 mL). This solution was transferred to a sealed tube, degassed with N_2 gas, and heated at 250 °C in a sand bath for 20 h. The reaction mixture was cooled to room temperature, evaporated, and purified by column chromatography on silica gel (hexane/EtOAc = 10:1) to give aldehyde **19** (2.26 g, 78%) as a yellowish solid: mp 78−79 °C; IR (KBr) ν_{max} 1711.0, 1633.9, 1512.3, 1452.5, 1431.3, 1358.0, 1317.5, 1194.0, 1151.6, 1122.7, 1093.7, 1043.6 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.82−1.89 (m, 2H), 2.07−2.32 (m, 2H), 2.72 (dddd, J = 8.1, 6.0, 6.0, 2.4 Hz, 1H), 3.85−3.90 (m, 1H), 3.87 (s, 3H), 5.77 (dddd, J = 9.9, 4.5, 2.4, 1.8 Hz, 1H), 5.93 (s, 2H), 5.95−6.00 (m, 1H), 6.36 (d, J = 1.5 Hz, 1H), 6.41 (dd, J = 1.5, 0.3 Hz, 1H), 9.52 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.7, 23.5, 41.4, 50.8, 56.7, 101.4, 103.4, 109.0, 127.9, 128.7, 134.2, 134.6, 143.3, 148.9, 204.6; MS-EI *m*/*z* (rel int) 260 (M$^+$, 100), 232 (92), 203 (78), 178 (49), 173 (46), 152 (76); HRMS-EI (calcd for $C_{15}H_{16}O_4$) 260.1049, found 260.1040.

2-(7-Methoxybenzo[1,3]dioxol-5-yl)cyclohex-3-enecarboxylic Acid (24). From **19**: To a solution of aldehyde **19** (1.54 g, 5.9 mmol) in *t*-BuOH−H_2O (1:1, 20 mL) were added 2-methyl-2-butene (60 mL, 2.0 M in THF), $NaClO_2$ (3.2 g, 35.4 mmol), and NaH_2PO_4·$2H_2O$ (1.5 g, 17.7 mmol) at 0 °C. The reaction mixture was stirred for 18 h at room temperature. It was concentrated until THF was removed and extracted with EtOAc (25 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The subsequent residue was treated with hexane/EtOAc (5:1, 20 mL). After it was stirred for 1 h, the generated white solids were filtered, washed with hexane/EtOAc (7:1, 10 mL) twice and dried in vacuo to give carboxylic acid **24** (1.47 g, 90%) as a white solid: mp 181−182 °C; IR (KBr) ν_{max} 2926.3, 1695.6, 1631.9, 1512.3, 1452.5, 1433.2, 1359.9, 1317.5, 1263.5, 1240.3, 1184.4, 1120.7, 1093.7, 1045.5 cm^{-1}; ^{1}H NMR (pyridine-d_5, 300 MHz) δ 1.95−2.19 (m, 4H), 3.06 (m, 1H), 3.68 (s, 3H), 4.09 (t, J = 4.5 Hz, 1H), 5.81 (m, 1H), 5.84 (d, J = 1.2 Hz, 1H), 5.85 (d, J = 1.2 Hz, 1H), 5.89−5.93 (m, 1H), 6.82 (d, J = 1.2 Hz, 1H), 6.83 (d, J = 1.2 Hz, 1H); ^{13}C NMR (pyridine-d_5, 75 MHz) δ 19.7, 25.2, 43.0, 45.7, 56.5, 101.6, 104.5, 110.7, 128.5, 128.9, 134.7, 135.9, 143.6, 149.1, 176.0; MS-EI *m*/*z* (rel int) 276 (M$^+$, 100), 230 (50), 204 (86), 203 (90), 173 (40), 152 (30); HRMS-EI (calcd for $C_{15}H_{16}O_5$) 276.0998, found 276.0987.

(34) This reaction was patterned after a similar step in the Magnus synthesis.[7]

4-Iodo-8-(7-methoxbenzo[1,3]dioxol-5-yl)-6-oxabicyclo-[3.2.1]octan-7-one (25). To a solution of carboxylic acid **24** (863 mg, 3.12 mmol) in CH_2Cl_2 (10 mL) were added 1 N $NaHCO_3$ solution (15 mL) and aqueous KI_3 solution (40 mL, KI: 24.3 g, 36.5 mmol, I_2: 12.1 g, 16.5 mmol) at room temperature. The mixture was stirred for 20 h and poured into saturated aqueous $Na_2S_2O_3$ solution. This reaction mixture was extracted with EtOAc (50 mL × 2), and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 1:1) to give the iodolactone **25** (1.24 g, 99%) as colorless oil: IR (film) ν_{max} 1784.3, 1633.9, 1512.3, 1452.5, 1325.2, 1122.7, 1091.8, 1045.5, 958.7 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.91−2.12 (m, 3H), 2.31−2.45 (m, 1H), 2.78 (br s, 1H), 3.83 (s, 3H), 4.01 (s, 1H), 4.58 (t, J = 4.8 Hz, 1H), 4.72 (d, J = 4.2 Hz, 1H), 5.89 (s, 2H), 6.29 (d, J = 1.5 Hz, 1H), 6.37 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.4, 24.5, 29.1, 45.0, 50.3, 56.8, 85.3, 100.9, 101.6, 106.4, 133.8, 134.6, 143.8, 149.5, 177.1; MS-EI *m/z* (rel int) 402 (M^+, 100), 403 (17) 165 (21); HRMS-EI (calcd for $C_{15}H_{15}IO_5$) 401.9964, found 401.9948.

8-(7-Methoxybenzo[1,3]dioxol-5-yl)-6-oxabicyclo[3.2.1]-oct-3-en-7-one (26). The iodolactone **25** (1.24 g, 3.08 mmol) was dissolved in benzene (20 mL) and added DBU (0.5 mL, 3.34 mmol). The mixture was heated to reflux for 8 h and then cooled to room temperature. The precipitate was filtered off and filterate was diluted with EtOAc. This solution was washed with 1 N HCl aqueous solution and brine, dried over Na_2SO_4, and evaporated. The subsequent residue was treated with hexane/EtOAc (2:1, 10 mL). After 2 min, it gave rise to precipitate and solidified. After it was stirred for 1 h, the generated white solids were filtered, washed with hexane/EtOAc (3:1, 5 mL) twice, and dried in vacuo to give **26** (668 mg, 80%) as a white solid: mp 142−144 °C; IR (KBr) υ_{max} 1765.0, 1633.9, 1516.2, 1460.3, 1433.3, 1371.5, 1327.1, 1250.0, 1199.8, 1147.8, 1130.4, 1093.7, 1041.7 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.54 (m, 1H), 2.65 (m, 1H), 2.94 (br s, 1H), 3.38 (s, 1H), 3.81 (s, 3H), 4.69 (dt, J = 5.7, 0.9 Hz, 1H), 5.83−5.86 (m, 1H), 5.88 (s, 2H), 6.26−6.32 (m, 1H), 6.33 (d, J = 1.5 Hz, 1H), 6.38 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.9, 44.8, 50.6, 56.7, 78.0, 101.1, 101.5, 106.5, 130.1, 130.5, 134.1, 134.6, 143.8, 149.4, 178.5; MS-EI *m/z* (rel int) 274 (92), 246 (60), 178 (100); HRMS-EI (calcd for $C_{15}H_{14}O_5$) 274.0841, found 274.0852.

5-Hydroxy-6-(7-methoxybenzo[1,3]dioxol-5-yl)cyclohex-3-enecarboxylic Acid Methyl Ester (27). The mixture of olefinic lactone **26** (1.49 g, 5.43 mmol) and NaOMe/MeOH (55 mL, 0.5 M in MeOH) was heated to reflux for 20 h and then cooled to room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (25 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was purified by column chromatography on silica gel (hexane/EtOAc = 3:2) to give **27** as yellowish oil (1.55 g, 93%): IR (film) ν_{max} 3520.4, 1732.2, 1633.9, 1510.4, 1433.2, 1315.6, 1194.0, 1138.1, 1091.8, 1043.6 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48 (d, J = 3.6 Hz, 1H), 2.34 (m, 1H), 2.52 (m, 1H), 3.07 (dd, J = 12.3, 3.3 Hz, 1H), 3.22 (ddd, J = 12.3, 10.8, 5.1 Hz, 1H), 3.53 (s, 3H), 3.89 (s, 3H), 4.11 (br s, 1H), 5.94−5.97 (m, 4H), 6.44 (d, J = 1.5 Hz, 1H), 6.48 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.1, 38.9, 48.3, 51.5, 56.4, 66.6, 101.3, 102.5, 107.8, 127.5, 128.7, 134.1, 134.4, 143.4, 148.8, 175.4; MS-EI *m/z* (rel int) 306 (M^+, 7), 236 (100), 205 (20); HRMS-EI (calcd for $C_{16}H_{18}O_6$) 306.1103, found 306.1104.

(*R*)-4-(7-Methoxybenzo[1,3]dioxol-5-yl)but-3-yn-2-ol ((+)-29). To the predried mixture of bromide **10** (70 mg, 0.3 mmol), copper iodide (6 mg, 0.03 mmol), dichlorobis(triphenylphosphine)palladium(II) (21 mg, 0.03 mmol), and molecular sieves 4 Å (200 mg) were added triethylamine (3 mL) and (*R*)-(+)-3-butyn-2-ol ((*R*)-**11**) (0.048 mL, 0.6 mmol). The mixture was heated to 60 °C for 24 h, and then (*R*)-**11** (0.048 mL, 0.6 mmol) was added again. After the reaction mixture was heated for 12 h, additional (*R*)-**11** (0.048 mL, 0.6 mmol) was added once more for completion. The mixture was cooled to room temperature and filtrated through Celite. The filtrate was purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 20:1) to produce (+)-**29** (54 mg, 80%) as yellowish oil: $[\alpha]^{33}_D$ = +1.59 (*c* 2.5, $CHCl_3$); IR (film) ν_{max} 1624.2, 1506.5, 1448.7, 1429.4, 1352.2 1311.7, 1211.4, 1157.4, 1107.2, 1047.4 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.52 (d, J = 6.6 Hz, 3H), 2.27 (br s, 1H), 3.86 (s, 3H), 4.72 (q, J = 6.6 Hz, 1H), 5.96 (s, 2H), 6.58 (d, J = 1.2 Hz, 1H), 6.62 (d, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.4, 56.5, 58.8, 83.9, 89.3, 101.7, 105.9, 111.7, 116.0, 136.1, 143.4, 148.5; MS-EI *m/z* (rel int) 220 (M^+, 99), 205 (80), 175 (60), 147 (63), 119 (100); HRMS-EI (calcd for $C_{12}H_{12}O_4$) 220.0736, found 220.0730.

(*R*)-4-(7-Methoxybenzo[1,3]dioxol-5-yl)but-3-en-2-ol ((+)-30). From (+)-**29**: To a solution of (+)-**29** (290 mg, 1.3 mmol) in THF (5 mL) at −78 °C was slowly added LAH (2.8 mL, 1.0 M in Et_2O). The reaction mixture was allowed to warm to room temperature for 2 h. H_2O (0.08 mL), 10% aqueous NaOH solution (0.08 mL), and H_2O (0.25 mL) were added in order to the mixture. This resulting mixture was filtrated through a glass funnel packed with Celite. The filtrate was extracted with EtOAc twice, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 4:1) to give (+)-**30** (220 mg, 75%) as a colorless oil.

From **10**: To a solution of (*R*)-**28**[24] (1.3 g, 3.6 mmol) in DMF (10 mL) were added aryl bromide **10** (566 mg, 2.45 mmol) and $Pd(PPh_3)_4$ (283 mg, 0.25 mmol) under N_2 atmosphere. The mixture was heated to 65 °C for 24 h. After the mixture was cooled to room temperature, it was washed with 10% aqueous KF solution and extracted with EtOAc four times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 3:1) to give the desired compound (+)-**30** (460 mg, 84%) as colorless oil: $[\alpha]^{20}_D$ = +91.2 (*c* 3.4, $CHCl_3$); IR (film) ν_{max} 3379.6, 1626.1, 1510.4, 1450.6, 1431.3, 1356.1, 1321.4, 1238.4, 1197.9, 1136.2, 1091.8, 1045.5, 964.5 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.34 (d, J = 6.6 Hz, 3H), 1.94 (br s, 1H), 3.88 (s, 3H), 4.44 (ddq, J = 6.6, 0.9, 6.3 Hz, 1H), 5.94 (s, 2H), 6.08 (dd, J = 15.6, 6.3 Hz, 1H), 6.42 (d, J = 16.2 Hz, 1H), 6.51 (d, J = 1.5 Hz, 1H), 6.58 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.4, 56.5, 68.7, 100.0, 101.4, 106.6, 129.0, 131.6, 132.3, 134.9, 143.5, 149.0; MS-EI *m/z* (rel int) 222 (M^+, 92), 179 (100), 165 (48), 149 (38); HRMS-EI (calcd for $C_{12}H_{14}O_4$) 222.0892, found 222.0895.

(*R*)-Hex-5-enoic Acid 3-(7-Methoxybenzo[1,3]dioxol-5-yl)-1-methylallyl Ester ((+)-9). To a solution of (+)-**30** (1.05 g, 4.7 mmol) in CH_2Cl_2 (12 mL) were added hexenoic acid **12** (0.67 mL, 5.6 mmol), DMAP (0.17 g, 1.4 mmol), and DCC (1.36 g, 6.6 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature followed by dilution with hexane. The generated white precipitate was removed by filtration through Celite. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 15:1) to give (+)-**9** (1.4 g, 93%) as a colorless oil: $[\alpha]^{20}_D$ = +89.9 (*c* 3.6, $CHCl_3$); IR (film) ν_{max} 1730.3, 1626.1, 1510.4, 1450.6, 1431.3, 1358.0, 1319.4, 1242.3, 1199.8, 1138.1, 1093.7, 1043.6 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.38 (d, J = 6.6 Hz, 3H), 1.73 (m, 2H), 2.09 (m, 2H), 2.32 (t, J = 7.5 Hz, 2H), 3.89 (s, 3H), 4.95−5.05 (m, 2H), 5.55 (ddq, J = 6.9, 0.9, 6.6 Hz, 1H), 5.77 (dddd, J = 17.1, 10.2, 6.6, 6.6 Hz, 1H), 5.95 (s, 2H), 6.51 (dd, J = 15.9, 6.9 Hz, 1H), 6.47 (d, J = 15.6 Hz, 1H), 6.52 (d, J = 1.5 Hz, 1H), 6.60 (d, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.4, 24.0, 33.0, 33.8, 56.5, 70.7, 100.0, 101.5, 106.9, 115.3, 127.6, 131.2, 131.3, 135.1, 137.6, 143.5, 149.1, 172.7; MS-EI *m/z* (rel int) 318 (M^+, 75), 319 (17), 222 (100), 221 (64), 205 (88), 179 (70), 175 (90); HRMS-EI (calcd for $C_{18}H_{22}O_5$) 318.1467, found 318.1468.

(2*RS*,3*S*)-2-But-3-enyl-3-(7-methoxybenzo[1,3]dioxol-5-yl)hex-4-enoic Acid ((2*R*,3*S*)-31 and (2*S*,3*S*)-32). To a stirred solution of (+)-**9** (300 mg, 0.94 mmol) in THF (11 mL) and HMPA (4.4 mL) was added TBSCl (213 mg, 1.4 mmol) in

THF (3 mL). After the mixture was cooled to −78 °C, LDA (3.8 mL, 0.5 M in THF) was slowly added. The reaction mixture was slowly warmed to room temperature and stirred for 15 h. It was acidified to pH 2−3 with 1 N HCl aqueous solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 3:1) to give inseparable **31** and **32** (232 mg, 77%) as colorless oil. ^{1}H NMR analysis of crude reaction mixture indicated a 6:1 mixture of two stereoisomers **31** and **32**, respectively: IR (film) ν_{max} 2937.9, 1705.2, 1633.9, 1510.4, 1452.5, 1433.2 cm^{-1}; ^{1}H NMR of a major **31** ($CDCl_3$, 300 MHz) δ 1.28−1.39 (m, 1H), 1.51−1.59 (m, 1H), 1.61 (d, J = 5.2 Hz, 3H), 1.88−2.11 (m, 2H), 2.64 (ddd, J = 10.8, 10.8, 3.6 Hz, 1H), 3.28 (dd, J = 10.5, 7.8 Hz, 1H), 3.90 (s, 3H), 4.92−5.01 (m, 2H), 5.45−5.74 (m, 3H), 5.94 (s, 2H), 6.33 (d, J = 1.2 Hz, 1H), 6.37 (d, J = 1.5 Hz, 1H); ^{13}C NMR of a major **31** ($CDCl_3$, 75 MHz) δ 17.8, 29.7, 31.5, 51.3, 52.1, 56.6, 101.3, 101.5, 107.4, 115.4, 126.7, 131.8, 133.8, 136.5, 137.3, 143.6, 149.1, 181.2; MS-EI m/z (rel int) 318 (M^+, 17), 205 (100), 175 (92), 147 (31); HRMS-EI (calcd for $C_{18}H_{22}O_5$) 318.1467, found 318.1464.

(1*RS*,2*S*)-2-(7-Methoxybenzo[1,3]dioxol-5-yl)cyclohex-3-enecarboxylic Acid ((1*R*,2*S*)-24 and (1*S*,2*S*)-22). To a solution of the inseparable mixture of **31** and **32** (100 mg, 0.31 mmol) in CH_2Cl_2 was added Grubbs's catalyst **33** (12.8 mg, 0.016 mmol). The reaction mixture was stirred for 1 h at room temperature and concentrated. The crude residue was purified by column chromatography on silica gel (hexane/EtOAc = 5:2) to give **22** and desired compound **24** (79 mg, 91%) as white solids. ^{1}H NMR analysis of clude reaction mixture indicated a 1:6 mixture of two stereoisomers **22** and **24**, respectively.

(1*R*,4*R*,5*S*,8*R*)-4-Iodo-8-(7-methoxybenzo[1,3]dioxol-5-yl)-6-oxabicyclo[3.2.1]octan-7-one ((+)-25). To a solution of carboxylic acid **24** and **22** (88.5 mg, 0.32 mmol) in CH_2Cl_2 (2 mL) were added 1 N $NaHCO_3$ aqueous solution (1.5 mL) and KI_3 aqueous solution (4 mL, KI:2.5 g, 37 mmol, I_2:1.1 g, 16 mmol) at room temperature. The mixture was stirred for 20 h and poured into saturated aqueous $Na_2S_2O_3$ solution. This reaction mixture was extracted with EtOAc (10 mL × 2). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 1:1) to separate the iodolactone (+)-**25** (98 mg, 76%) as colorless oil and unreacted compound **22**. The enantiopurity was determined by chiral HPLC analysis (CHIRALCEL OD-H, hexane/2-propanol (99.5:0.5, v/v), flow rate: 0.5 mL/min, retention time: 44.7 min (+)-isomer, detected at 254 nm): $[\alpha]^{20}_D$ = +69.3 (c 2.0, $CHCl_3$).

5-Hydroxy-6-(7-methoxybenzo[1,3]dioxol-5-yl)cyclohex-3-enecarboxylic Acid (34). To a solution of ester **27** (1.0 g, 3.26 mmol) in THF (15 mL) was added 1 N LiOH aqueous solution (20 mL). After being stirred at room temperature for 18 h, the solution was acidified to pH 2 with 1 N HCl aqueous solution. It was diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc (25 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 3:2) to give **34** (952 mg, 99%) as a white solid: mp 195 °C dec; IR (KBr) ν_{max} 3468.3, 1726.5, 1633.9, 1512.3, 1450.6, 1433.2, 1186.3, 1143.9, 1099.5, 1039.7 cm^{-1}; ^{1}H NMR (pyridine-d_5, 300 MHz) δ 2.74 (m, 2H), 3.44 (dd, J = 12.3, 3.6 Hz, 1H), 3.74 (s, 3H), 3.82 (ddd, J = 12.0, 9.0, 6.9 Hz, 1H), 4.46 (t, J = 4.5 Hz, 1H), 5.77 (d, J = 1.2 Hz, 1H), 5.78 (d, J = 1.2 Hz, 1H), 5.91−5.97 (m, 1H), 6.22−6.29 (m, 1H), 6.97 (d, J = 1.2 Hz, 1H), 7.08 (d, J = 1.2 Hz, 1H); ^{13}C NMR (pyridine-d_5, 75 MHz) δ 31.3, 40.7, 49.6, 56.5, 67.0, 101.3, 104.0, 109.9, 127.4, 130.7, 134.2, 137.5, 143.7, 149.1, 178.0; MS-EI m/z (rel int) 292 (M^+, 15), 274 (34), 244 (68), 222 (100), 178 (33); HRMS-EI (calcd for $C_{15}H_{16}O_6$) 292.0947, found 292.0946.

[5-Hydroxy-6-(7-methoxybenzo[1,3]dioxol-5-yl)cyclohex-3-enyl]carbamic Acid Methyl Ester (35). The mixture of carboxylic acid **34** (1.04 g, 3.6 mmol), triethylamine (1.49 mL, 10.7 mmol), and diphenylphosphoryl azide (2.3 mL, 10.6 mmol) in toluene (42 mL) was stirred at room temperature for 20 min until the solution was clear. This reaction mixture was heated slowly to reflux for 15 h and cooled to room temperature. Then the mixture was diluted with EtOAc. It was washed with saturated aqueous NH_4Cl solution and brine and dried over Na_2SO_4. This crude product was evaporated and chromatographed on a silica gel column (hexane/EtOAc = 3:2) to give isocyanate intermediate (IR 2442, 1691 cm^{-1}). This intermediate was dissolved in MeOH (40 mL), and NaOMe (0.33 mg, 6.1 mmol) was added. The reaction mixture was heated to reflux for 30 min and then cooled to room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and diluted with EtOAc. It was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by column chromatography (hexane/EtOAc = 3:2) to give colorless syrup **35** (938 mg, 82%): IR (film) ν_{max} 3321.7, 1699.4, 1512.3, 1286.6, 1134.3, 1059.0 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.95 (m, 1H), 2.71 (dt, J = 17.4, 4.2 Hz, 1H), 2.79 (dd, J = 12.0, 3.3 Hz, 1H), 3.52 (br s, 3H), 3.81 (s, 3H), 4.12 (t, J = 3.3 Hz, 1H), 4.23 (br s, 1H), 4.39 (br d, J = 8.1 Hz, 1H), 5.84 (dt, J = 4.5, 1.8 Hz, 2H), 5.88 (s, 2H), 6.40−6.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.3, 44.0, 51.1, 51.2, 55.6, 67.7, 100.4, 102.2, 107.5, 126.7, 128.2, 131.6, 133.4, 142.7, 148.1, 155.6; MS-EI m/z (rel int) 321 (M^+, 4), 251 (48), 228 (100), 219 (32), 127 (27); HRMS-EI (calcd for $C_{16}H_{19}NO_6$) 321.1212, found 321.1212.

Benzoic Acid 6-(7-Methoxybenzo[1,3]dioxol-5-yl)-5-methoxycarbonylaminocyclohex-2-enyl Ester (36). To a solution of methyl ester **35** (677 mg, 2.11 mmol) in dry CH_2Cl_2 (30 mL) was added DMAP (77 mg, 0.63 mmol), triethylamine (0.88 mL, 6.31 mmol), and benzoyl chloride (0.47 mL, 4.05 mmol). The reaction mixture was stirred at room temperature for 15 h. Then, it was diluted with EtOAc and washed with 1 N HCl and saturated aqueous $NaHCO_3$ solution. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (hexane/EtOAc = 3:2) to give **36** (893 mg, 99%) as colorless oil: IR (film) ν_{max} 1711.0, 1535.5, 1340.7, 1269.3, 1111.1, 1057.1 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.05 (dd, J = 18.9, 9.6 Hz, 1H), 2.81 (dt, J = 17.7, 3.6 Hz, 1H), 2.99 (dd, J = 12.0, 3.6 Hz, 1H), 3.53 (br s, 3H), 3.55 (s, 3H), 4.52 (br s, 2H), 5.56 (t, J = 3.9 Hz, 1H), 5.78 (d, J = 1.5 Hz, 1H), 5.80 (d, J = 1.5 Hz, 1H), 5.82−5.94 (m, 2H), 6.39 (s, 2H), 7.31−7.37 (m, 2H), 7.43−7.49 (m, 1H), 7.89−7.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.2, 45.9, 50.2, 52.1, 56.1, 70.9, 101.3, 103.5, 108.2, 124.9, 128.3, 129.5, 130.1, 131.1, 131.6, 132.9, 134.3, 143.3, 148.6, 156.6, 165.3; MS-EI m/z (rel int) 425 (M^+, 5), 251 (26), 228 (100), 219 (23); HRMS-EI (calcd for $C_{23}H_{23}NO_7$) 425.1475, found 425.1485.

Benzoic Acid 2,3-Dihydroxy-6-(7-methoxybenzo[1,3]-dioxol-5-yl)-5-methoxycarbonylaminocyclohexyl Ester (38). To a solution of **36** (220 mg, 0.52 mmol) in THF (4 mL) was added *N*-methylmorpholine *N*-oxide (91 mg, 0.77 mmol) in H_2O (1 mL) and OsO_4 (0.2 mL, 4% in H_2O). The reaction mixture was stirred at room temperature for 20 h. The reaction was quenched with saturated aqueous $NaHSO_3$ solution and extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. This crude product was chromatographed on silica gel column (hexane/EtOAc = 2:3) to give colorless syrup **38** (228 mg, 96%): IR (film) ν_{max} 3373.8, 1693.7, 1635.8, 1537.4, 1452.5, 1280.9, 1111.1, 1066.7, 1026.2 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.85 (dd, J = 12.3, 2.4 Hz, 1H), 2.35−2.40 (m, 1H), 2.77 (br s, 1H), 3.18 (dd, J = 12.0, 2.7 Hz, 1H), 3.42 (br s, 1H), 3.57 (s, 6H), 4.15 (m, 2H), 4.39 (m, 1H), 4.79 (d, J = 8.4 Hz, 1H), 5.42 (t, J = 3.0 Hz, 1H), 5.83 (d, J = 1.5 Hz, 1H), 5.85 (d, J = 1.5 Hz, 1H), 6.42 (m, 2H), 7.41−7.46 (m, 2H), 7.54−7.60 (m, 1H), 7.96−8.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.7, 46.1. 47.0, 52.1, 56.1, 67.4, 69.2, 76.1, 101.2, 103.1, 107.7, 128.6, 129.3, 129.6, 131.9, 133.5, 134.2, 143.3,

148.6, 156.6, 165.1; MS-EI *m/z* (rel int) 459 (M^+, 1), 244 (12), 228 (43), 122 (100); HRMS-EI (calcd for $C_{23}H_{25}NO_9$) 459.1529, found 459.1517.

Benzoic Acid 5-(7-Methoxybenzo[1,3]dioxol-5-yl)-6-methoxycarbonylamino-2,2-dioxohexahydro-2λ^6-benzo-[1,3,2]dioxathiol-4-yl Ester (39). Triethylamine (0.17 mL, 1.22 mmol) and thionyl chloride (55 μL, 0.75 mmol) were added to a solution of ester **38** (230 mg, 0.50 mmol) in CH_2Cl_2 (6 mL) at 0 °C. After 30 min, this reaction mixture was added to H_2O (6 mL) and extracted with EtOAc (15 mL × 2). The combined organic layers were dried over Na_2SO_4 and concentrated. This crude cyclic sulfite was dried in vacuo for 3 h and dissolved in CH_3CN/EtOAc/H_2O (6 mL, 2:1:1). To the resulting solution were added $RuCl_3 \cdot 3H_2O$ (2 mg, 9.6 μmol) and Oxone (870 mg, 1.4 mmol). After the reaction mixture was stirred at room temperature for 2 h, it was diluted with EtOAc and washed with saturated $NaHSO_3$ solution. The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography on silica gel (hexane/EtOAc = 3:2) to give cyclic sulfate **39** (216 mg, 83%) as a colorless syrup: IR (film) ν_{max} 1716.8, 1635.8, 1514.3, 1452.5, 1392.7, 1265.4, 1211.4 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.28 (dt, J = 14.1, 9.3 Hz, 1H), 2.89 (dt, J = 14.1, 6.0 Hz, 1H), 3.17 (dd, J = 11.4, 2.1 Hz, 1H), 3.62 (s, 6H), 4.46−4.60 (m, 2H), 5.09 (dd, J = 4.8, 2.7 Hz, 1H), 5.26 (ddd, J = 11.1, 9.6, 6.0 Hz, 1H), 5.71 (t, J = 2.7 Hz, 1H), 5.89 (d, J = 1.5 Hz, 1H), 5.91 (d, J = 1.2 Hz, 1H), 6.39 (d, J = 1.5 Hz, 1H), 6.44 (d, J = 1.5 Hz, 1H), 7.47−7.52 (m, 2H), 7.61−7.67 (m, 1H), 7.97−8.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.7, 33.8, 44.9, 46.2, 52.4, 56.2, 70.7, 77.9, 80.1, 101.6, 102.8, 107.8, 128.2, 128.6 128.9, 129.3, 129.8, 134.2, 143.7, 149.2, 164.1; MS-EI *m/z* (rel int) 527 (M^+, 2), 253 (31), 112 (52), 105 (100); HRMS-EI (calcd for $C_{23}H_{23}NO_{11}S$) 521.0992, found 521.09827.

Benzoic Acid 2-Hydroxy-6-(7-methoxybenzo[1,3]dioxol-5-yl)-5-methoxycarbonylaminocyclohex-3-enyl Ester (40). A mixture of cyclic sulfate **39** (140 mg, 0.27 mmol) and DBU (0.1 mL, 0.67 mmol) in toluene (5 mL) was heated to reflux for 2 h. After the reaction mixture was cooled to room temperature, to it were added 10% aqueous H_2SO_4 solution (0.5 mL) and THF (4.5 mL). It was stirred for 4 h at room temperature, and then the reaction mixture was diluted with EtOAc. It was washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give allylic alcohol **40** (79.4 mg, 67%) as a colorless oil: IR (film) ν_{max} 3364.2, 1705.2, 1635.8, 1514.3, 1452.5, 1269.3 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 3.41 (dd, J = 10.8, 1.8 Hz, 1H), 3.51 (s, 3H), 3.63 (s, 3H), 4.15 (m, 1H), 4.69 (d, J = 5.1 Hz, 1H), 4.93 (t, J = 9.6 Hz, 1H), 5.27 (br s, 1H), 5.83−5.88 (m, 3H), 5.95 (dd, J = 10.2, 1.8 Hz, 1H), 6.38 (d, J = 9.3 Hz, 1H), 6.50 (d, J = 1.2 Hz, 1H), 6.60 (d, J = 0.9 Hz, 1H), 7.50−7.57 (m, 2H), 7.62−7.68 (m, 1H), 8.02−8.05 (m, 2H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 45.1, 49.2, 51.9, 56.4, 65.9, 78.3, 102.0, 103.2, 108.9, 128.0, 129.5, 130.2, 130.3, 131.0, 133.9, 134.1, 135.1, 144.2, 149.7, 157.5, 165.7; MS-EI *m/z* (rel int) 441 (M^+, 9), 298 (33), 244 (87), 228 (31), 105 (100); HRMS-EI (calcd for $C_{23}H_{23}NO_8$) 441.1424, found 441.1414.

Benzoic Acid 2,3,4-Trihydroxy-6-(7-methoxybenzo[1,3]-dioxol-5-yl)-5-methoxycarbonylaminocyclohexyl Ester (41). To a solution of allylic alcohol **40** (40 mg, 91 μmol) in THF (2 mL) was added *N*-methylmorpholine *N*-oxide (16 mg, 0.14 mmol) in H_2O (0.5 mL) and OsO_4 (0.2 mL, 4% in H_2O). The reaction mixture was stirred at room temperature for 27 h. The reaction was quenched with saturated aqueous $NaHSO_3$ solution and extracted with EtOAc (10 mL × 5). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. This crude product was chromatographed on a silica gel column in EtOAc to give triol **41** (37.9 mg, 88%) as a colorless oil: IR (film) ν_{max} 3366.1, 1699.4, 1635.8, 1539.3, 1512.3, 1452.5, 1273.1 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 3.45 (s, 3H), 3.49 (d, J = 2.7 Hz, 1H), 3.53 (d, J = 2.4 Hz, 1H), 3.58 (s, 3H), 3.77 (br d, J = 7.2 Hz, 1H), 4.01 (m, 1H), 4.15 (br s, 1H), 4.21 (dd, J = 6.3, 3.3 Hz, 1H), 4.71 (dd, J = 21.9, 10.2 Hz, 1H), 4.80 (d, J = 3.9 Hz, 1H), 5.20 (m, 1H), 5.82 (dd, J = 2.7, 1.2 Hz, 2H), 6.10 (br d, J = 9.6 Hz, 1H), 6.45 (d, J = 1.5 Hz, 1H), 6.62 (br s, 1H), 7.47−7.53 (m, 2H), 7.59−7.64 (m, 1H), 8.07−8.10 (m, 2H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 47.0, 51.0, 51.7, 56.2, 70.3, 72.7, 74.4, 77.5, 101.8, 103.9, 109.2, 129.3, 129.5, 130.4, 131.6, 133.7, 134.3, 144.0, 149.2, 158.3, 165.6; MS-EI *m/z* (rel int) 475 (M^+, 5), 260 (48), 232 (35), 207 (31), 105 (100); HRMS-EI (calcd for $C_{23}H_{25}NO_{10}$) 475.1478, found 475.1498.

Benzoic Acid 2,3,4-Triacetoxy-7-methoxy-6-oxo-1,2,3,4,-4a,5,6,11b-octahydro[1,3]dioxolo[4,5-*j*]phenanthridin-1-yl Ester (42 and 43). To a mixture of triol **41** (36 mg, 76 μmol), pyridine (0.2 mL, 2.5 mmol), and DMAP (5 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) was added Ac_2O (0.1 mL, 1.1 mmol). After being stirred at room temperature for 1 h, the reaction mixture was evaporated and purified by column chromatography on silica gel in hexane/EtOAc (1:1) to yield triacetate (35 mg, 77%). To a stirred solution of the resulting triacetate (19 mg, 32 μmol) and DMAP (20 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added trifluoromethanesulfonic anhydride (45 μL, 0.27 mmol). After the resulting mixture was stirred at 5 °C for 22 h, it was poured into saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with 0.5 M HCl solution and brine, dried over Na_2SO_4, and concentrated. This mixture was dissolved in THF (2 mL) and 2 M HCl (0.2 mL) and stirred at room temperature for 5 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatograpyh on silica gel (hexane/EtOAc = 1:5) to give an inseparable mixture of **43** and **42** (14 mg, 78%, 7:1) as a white solid: IR (film) ν_{max} 1749.6, 1658.9, 1257.7 cm^{-1}; ^1H NMR of a major **43** ($CDCl_3$, 300 MHz) δ 1.81 (s, 3H), 2.09 (s, 3H), 2.20 (s, 3H), 3.49 (dd, J = 12.9, 1.8 Hz, 1H), 4.05 (s, 3H), 4.37 (dd, J = 12.6, 10.8 Hz, 1H), 5.23 (dd, J = 10.8, 3.3 Hz, 1H), 5.34 (t, J = 3.0 Hz, 1H), 5.50 (t, J = 3.0 Hz, 1H), 5.80 (m, 1H), 5.94 (s, 2H), 6.40 (m, 1H), 6.42 (s, 1H), 7.40−7.45 (m, 2H), 7.55−7.61 (m, 1H), 7.98−8.01 (m, 2H); MS-EI *m/z* (rel int) 569 (M^+, 16), 344 (22), 284 (32), 260 (16), 105 (100); HRMS-EI (calcd for $C_{28}H_{27}NO_{12}$) 569.1533, found 569.1527.

Benzoic Acid 2,3,4-Triacetoxy-7-hydroxy-6-oxo-1,2,3,4,-4a,5,6,11b-octahydro[1,3]dioxolo[4,5-*j*]phenanthridin-1-yl Ester (44). To a solution of **42** and **43** (13 mg, 0.023 mmol) in CH_2Cl_2 (2 mL) at −78 °C was added BBr_3 (60 μL, 1 M in CH_2Cl_2, 0.06 mmol). The reaction mixture was warmed to 0 °C and stirred for 30 min. Then, 10% NH_4OH aqueous solution (2 mL) was added at 0 °C. After being stirred for 20 min, the reaction mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give unreacted **42** and the desired compound **44** (7.2 mg, 65%) as white solid: mp 152 °C dec; IR (film) ν_{max} 1755.4, 1674.4, 1624.2, 1601.1, 1464.1, 1369.6, 1340.7, 1271.2, 1234.6 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.83 (s, 3H), 2.11 (s, 3H), 2.20 (s, 3H), 3.56 (ddd, J = 13.2, 2.7, 0.9 Hz, 1H), 4.47 (dd, J = 13.2, 10.8 Hz, 1H), 5.25 (dd, J = 10.8, 3.6 Hz, 1H), 5.36 (t, J = 3.0 Hz, 1H), 5.52 (t, J = 3.0 Hz, 1H), 5.82 (br s, 1H), 5.97 (d, J = 1.5 Hz, 1H), 6.01 (d, J = 1.5 Hz, 1H), 6.22 (br s, 1H), 6.30 (d, J = 0.9 Hz, 1H), 7.40−7.46 (m, 2H), 7.56−7.62 (m, 1H), 8.00−8.02 (m, 2H), 12.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.4, 20.7, 20.8, 39.5, 48.6, 66.4, 66.8, 67.6, 71.6, 96.8, 102.4, 107.2, 128.5, 128.8, 130.0, 131.5, 133.5, 133.8, 146.6, 149.4, 153.3, 164.9, 168.2, 169.1, 170.0; MS-EI *m/z* (rel int) 555 (M^+, 40), 274 (94), 105 (100); HRMS-EI (calcd for $C_{27}H_{25}NO_{12}$) 555.1377, found 555.1378.

(±)-Pancratistatin (1). To a solution of **44** (7.2 mg, 13 μmol) in THF (2 mL) was added NaOMe (0.4 mL, 0.5 M in MeOH). After being stirred at room temperature for 4 h, the

reaction was quenched with saturated aqueous NH_4Cl solution (2 mL). This mixture was extracted with EtOAc (10 mL × 7) and the combined organic layers were dried over Na_2SO_4, concentrated, and purified by column chromatography on silica gel (EtOAc/MeOH = 15:1) to give (±)-pancratistatin (3.5 mg, 83%) as a white solid: mp 263−264 °C dec; IR (KBr) υ_{max} 3420.1, 1672.4, 1628.1, 1468.0, 1358.0, 1084.1, 1047.4 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.96 (d, J = 10.8 Hz, 1H), 3.66−3.72 (m, 2H), 3.84 (m, 1H), 3.95 (dd, J = 7.2, 3.6 Hz, 1H), 4.27 (m, 1H), 4.82 (d, J = 7.5 Hz, 1H), 5.05 (d, J = 5.7 Hz, 1H), 5.08 (d, J = 5.7 Hz, 1H), 5.36 (d, J = 4.2 Hz, 1H), 6.02 (d, J = 0.9 Hz, 1H), 6.05 (d, J = 1.2 Hz, 1H), 6.48 (d, J = 0 0.9 Hz, 1H), 7.51 (br s, 1H), 13.06 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 29.2, 50.7, 68.7, 70.2, 70.4, 73.5, 97.9, 101.9, 107.7, 131.9, 135.9, 145.6, 152.2, 169.7; MS-EI m/z (rel int) 325 (M^+, 100), 247 (49), 206 (67), 205 (68); HRMS-EI (calcd for $C_{14}H_{15}NO_8$) 325.0798, found 325.0784.

Acknowledgment. This work was supported by a grant (1999-2-21500-001-3) from the Basic Research Program of the Korea Science & Engineering Foundation.

Supporting Information Available: Experimental procedures for the syntheses of **18**, **21**, **23**, and **24**; copies of ^1H NMR and ^{13}C NMR spectra of compounds **1**, **9**, **17**, **19**, **23**−**26**, **34**, **36**, **40**, **41**, and **44**, as well as mixtures of **22** and **24**, **31** and **32**; chiral HPLC analysis data of (+)-**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035371N