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A Short Route to Enantiomerically Pure Benzophenanthridinone Skeleton: Synthesis of Lactone Analogues of Narciclasine and Lycoricidine

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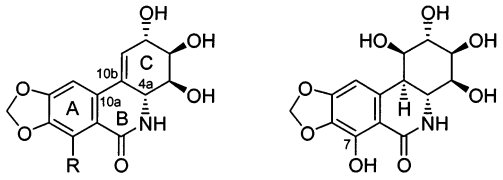
Condensation of functionalized *o*-toluamide anions on a carbohydrate-derived lactone, followed by intramolecular aldol cyclization, provides enantiomerically pure 2-arylcyclohexenones. Different approaches for the stereoselective transformation of the carbonyl group of these key intermediates into an amino group were unsuccessful. However 1,4-addition of thiolate and concomitant ring closure to isocoumarine provided a useful method for the transformation of the tertiary amide function. Opening of the isocoumarin with ammonia provided the corresponding amide and recovery of the enone system. Subsequent reductive amination of this cyclohexenone was found to depend on the nature of the protecting groups and led to the protected form of 4-*epi*- and -*iso*-narciclasine. Oxo analogues of narciclasine and *epi*-narciclasine and lycoricidine were also obtained after reduction of the enone and subsequent lactonization. They showed no biological activity as antitumor agents.

Introduction

Lycoricidine **1** and narciclasine **2** are alkaloids extracted from different daffodil bulbs (Figure 1).[1] In the 1970s, structural determination[2,3] showed that these inhibitors of protein synthesis[4] are highly oxygenated benzophenantridinone-type compounds. The antitumor activity of these compounds has been also investigated and seems to be related to the oxygenated cycle and to the tricyclic system. Compounds lacking this rigid arrangement failed to exhibit any biological properties.[5] More recently, a related compound pancratistatin **3**[6] and its 7-deoxy analogue[7] were isolated and exhibited very promising antitumor activity.[8] These intriguing and unique structures and the associated biological properties have triggered synthetic studies culminating with the syntheses of lycoricidine,[9] narciclasine,[3a,b,9m,n,10a−d] pancratistatin,[10d,11] and some derivatives thereof.[12] Synthetic studies toward the natural compounds[11h,13] and the



1 R = H Lycoricidine
2 R = OH Narciclasine
3 Pancratistatin

FIGURE 1. Structures of natural compounds.

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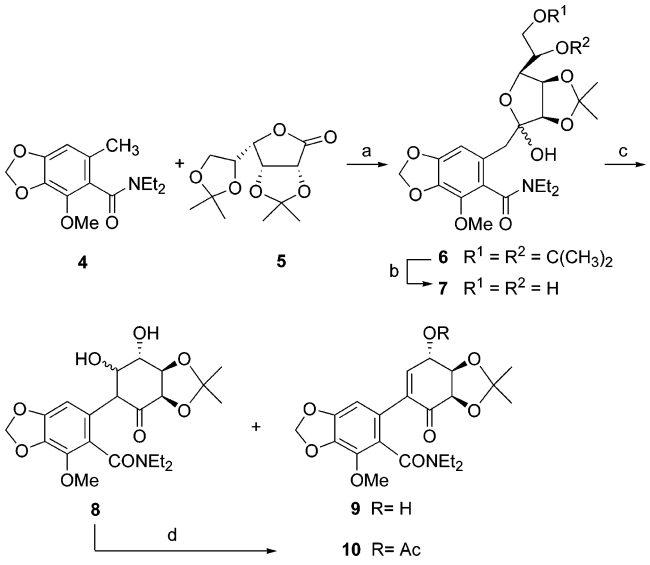
preparation of analogues have appeared over the years.[13b,14] In this context, we developed a program for the synthesis of analogues.[5,13h,15]

From a retrosynthetic point of view, two main approaches can be envisioned. In one approach, a convergent synthesis consisted of constructing two fragments representing the A and C cycles which must be coupled together to form the B ring. This approach implies the formation of the 10a−10b carbon−carbon bond, which is a crucial point of the synthesis. Heck reaction and other palladium-based bond-forming reactions,[16] radical cyclization,[9l,m,14d,g] photocyclization,[10d,13d] and others proved to be efficient for forming this bond.[11c−e] Our own work along these lines showed that this synthetic operation is strikingly dependent on the protecting groups present on the C ring.[17] For example, all attempts to construct the B ring by an intramolecular process including Heck reaction, radical cyclization, and others using benzyloxy groups at positions 2, 3, and 4 failed. Ring B construction can be achieved by coupling an aromatic anion easily produced by an orthometalation process to the appropriate precursor of the C ring.[9d,11b] This procedure needs an ortho directing group, obviously a tertiary amide, which proved reluctant to further transformations.[18]

SCHEME 1[a]



[a] Reagents and conditions: (a) ^{s}BuLi, THF, −78 °C; (b) AcOH, H_2O, 60 °C; (c) $NaIO_4$, MeOH, rt, then THF, Na_2CO_3, DBU, rt; (d) Ac_2O, pyridine, rt.

An alternate synthetic route would be the formation of the C ring from a suitable precursor in which the 10a−10b bond of the target would already be present. In this context, the use of benzylic anions would provide a good solution for the connection between the A ring and the chiral residue needed for the C ring construction. Here again, the use of a tertiary amide would be suitable for the formation of the benzylic anion, but the above-mentioned problems related to further transformations of the tertiary amide group also need to be solved efficiently.

Here, we describe the details of our investigations of this second strategy.[15] This led to a viable route to narciclasine derivatives suitable for biological evaluation. En route to the natural compounds, we also prepared the lactone analogues of narciclasine, lycoricidine, and their 4-*epi* derivatives for biological evaluation as antitumor agents.

Results

Our model compound for the A-ring was the pentasubstituted orthotoluamide **4** prepared according to a standard procedure.[15,19] The chiral part of the future C-ring was taken from the chiral pool, and D-gulonolactone was easily recognized as a suitable starting material[14d,g] because all of the chiral centers, with the correct configuration, are present in **5**.

Condensation of the lithium anion derived from **4** (*s*-BuLi, −78 °C) with **5** gave the expected lactol in 70% yield as a mixture of anomers **6** (Scheme 1). The extra carbon of the sugar residue was then excised by selective hydrolysis of one acetal ring followed by Malaprade

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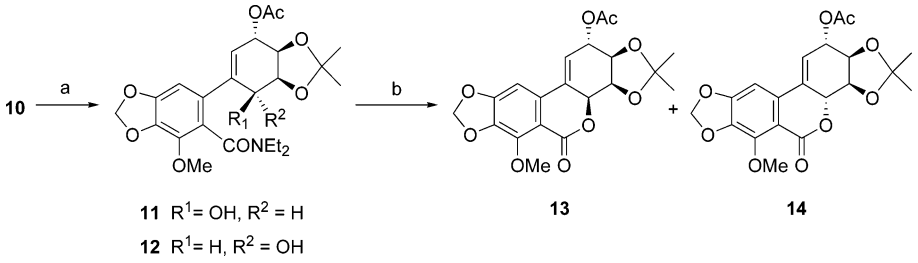
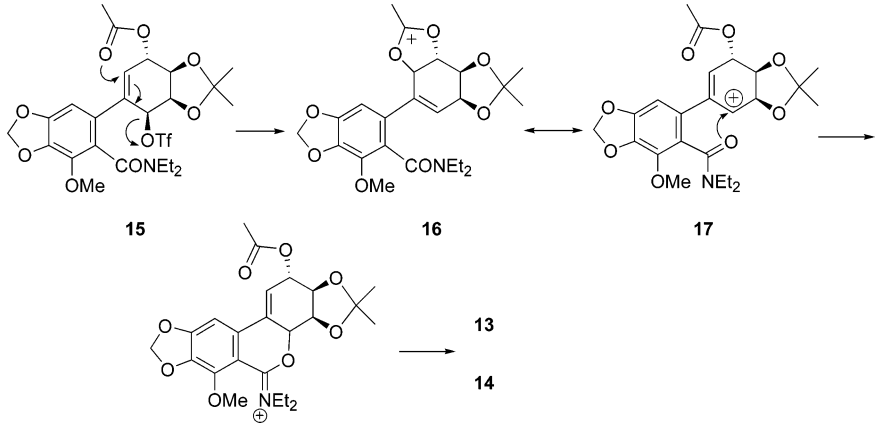
SCHEME 2[a]



[a] Reagents and conditions: (a) $NaBH_4$, $CeCl_3$, EtOH, rt; (b) Tf_2O, pyridine, −30 °C then NaN_3, DMF.

SCHEME 3[a]



[a] Postulated mechanism for the formation of lactones **13** and **14**.

cleavage of the resulting diol **7** to provide the corresponding aldehyde. This crude aldehyde was then involved in the Knoevenagel-type cyclization. Extensive experimentation led to efficient conditions (Na_2CO_3, DBU cat., THF) for this cyclization, giving a mixture of the aldol compound **8** (mixture of epimers) and cyclohexenone **9** in 70% yield. The purified mixture of **8** and **9** can be treated with acetic anhydride to give a single acetate **10**. This compound was actually a 1:2 mixture of atropoisomers in ^1H NMR due to a restricted rotation around the amide bond.

With compound **10** in hand, the reduction of the carbonyl group was next examined using Luche's conditions.[20] A mixture of two diastereoisomers **11** and **12** was obtained in a 1:1 ratio (Scheme 2). Alcohol **11** seemed to be an ideal substrate to study the introduction of the nitrogen atom at C-4a in the proper configuration using an S_N2-type reaction. Attempts to introduce an azido group using diphenylphosphoryl azide completely failed. This could be attributed to a severe crowding of the hydroxyl group preventing the initial formation of the expected oxyphosphonium salt. The use of a less sterically demanding activating group such as a triflate was investigated. Treatment of **11** with triflic anhydride in a CH_2Cl_2/pyridine mixture gave the corresponding triflate, immediately engaged in an S_N2 reaction with sodium azide. A 1:1 mixture of epimeric lactones **13** and **14** in equal amounts was isolated, and their structures were easily established by spectroscopy. The formation of these products should be explained by internal displacement of the triflate by the oxygen of the amide carbonyl to form the intermediate iminium salt hydrolyzed to the corresponding lactone on workup.[21] This mechanism explained well the formation of **14** with inversion of configuration at C-4a. However, this pathway did not account for the formation of **13**. A more likely mechanism accounting for the formation of both **13** and **14** would take into account the presence of the allylic acetate in the intermediate triflate **15**. Anchimeric assistance of the ester triggers the expulsion of the triflate yielding the intermediate dialkoxycarbenium ion **16** in equilibrium with the allylic cation **17** (Scheme 3).

The latter can undergo nucleophilic attack of the hard oxygen atom from both faces of the cycle to give **13** and **14**. The synthetic route described here had the merit to furnish an excellent solution to the problem of tertiary amide transformation. An indirect proof supporting the proposed mechanism could be obtained by the use of a nonparticipating protecting group at O-2. Starting from alcohol **9**, several ethers were tested such as MOM, MEM, and BOM. Bad results were observed in the introduction of these groups in basic medium, but tetrahydropyran formation proceeded well yielding **18** in 90% yield as a diastereoisomeric mixture (Scheme 4). Carbonyl reduction of **18** gave two alcohols **19** and **22**. The structure of these compounds was established after THP removal to give **20** and **23**, respectively. Formation of triflate **24** from **22** proceeded uneventfully, but attempts to substitute the triflate group with an azide group gave the corresponding lactone in poor yield. At low temperature in DMF, only formate **26** was formed in good yield. These results confirmed two important

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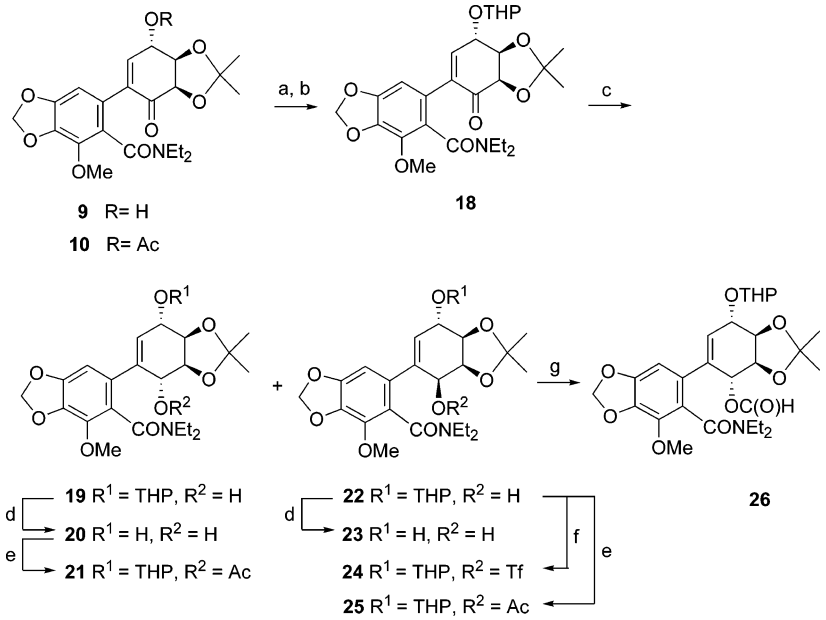
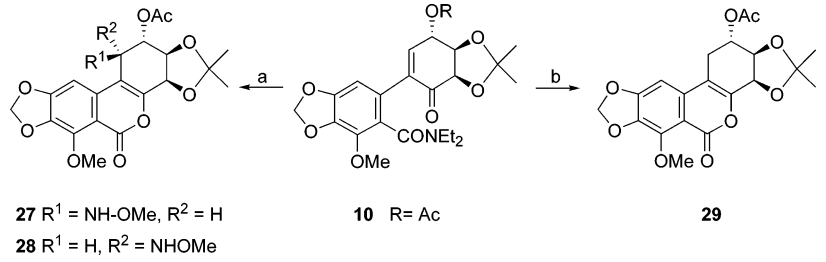
SCHEME 4[a]



[a] Reagents and conditions: (a) MeONa, MeOH, rt; (b) DHP, TsOH, rt; (c) $NaBH_4$, $CeCl_3$, EtOH, rt; (d) THF, Dowex H^+ resin; (e) Ac_2O, pyridine, 70 °C; (f) Tf_2O, CH_2Cl_2, pyridine, −30 °C; (g) from **22** Tf_2O, DMF, −30 °C, 1 h then NaN_3.

SCHEME 5[a]



[a] Reagents and conditions: (a) NH_2OMe, HCl, THF, reflux; (b) L-Selectride, THF, −30 °C.

points: the prominent role of the acetate group in **13** and the easy transformation of the unreactive tertiary amide function into a lactone. Furthermore, the steric hindrance around the C-4a atom, which impedes the approach of external nucleophiles on this position, was also confirmed. This led to the conclusion that internal nucleophilic displacement would be an acceptable solution to this issue.

Introduction of an azido group at C-4a of alcohols **19** and **22** using Murahashi's method was investigated.[22] Acetylation of **19** and **22** with acetic anhydride in pyridine at 70 °C in the presence of DMAP gave the corresponding acetates **21** and **25**, respectively. Treatment of either **21** or **25** with sodium azide in a water−THF mixture in the presence of $Pd(dba)_2$−$CHCl_3$ complex and bis[2(diphenylphosphino)ethyl]phenylphosphine failed to give any product. Again, the severe crowding of the 4a position whatever the absolute configuration was used to explain these failures. A further confirmation was also given by the rather drastic conditions needed to introduce the acetyl groups.

The introduction of the nitrogen function using the carbonyl group of the enone was next considered as an alternative, presumably nonstereoselective, route. Many attempts to prepare benzylimine from ketone **10** gave untractable mixtures. A more rewarding reaction was treatment of **10** with *O*-methylhydroxylamine hydrochloride, which did not provide the expected oxime but the two isocoumarins **27** and **28** upon heating (Scheme 5). This result opened a second way to an intramolecular chemical manipulation of the tertiary amide group. Moreover, it gave the possibility of achieving our goal by providing a way for the completion of the aminocyclitol synthesis. Judicious choice of the starting sugar is necessary to provide the correct configuration involved of the pancratistatin C ring.

All of the above results clearly showed that an excellent solution to the unavoidable chemical transformation of the tertiary amide group could be based on an intramolecular reaction. It was clear that nucleophilic attack by the oxygen atom led to an iminium species which was easily hydrolyzed to the lactone. Another way to achieve this goal should be the trapping of an enolate intermediate by the amide group, which would afford an isocoumarin. On this basis, reduction of the enone system of **10** with L-Selectride was carried out giving the isocou-

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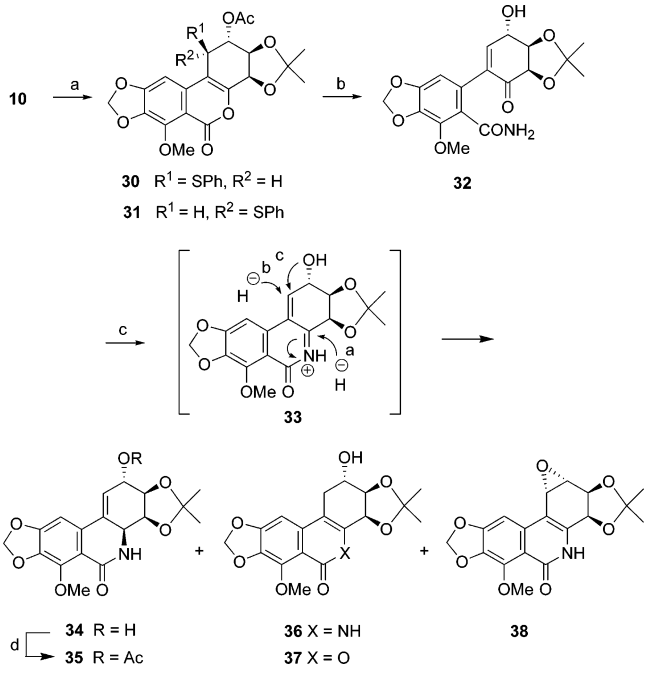
SCHEME 6[a]

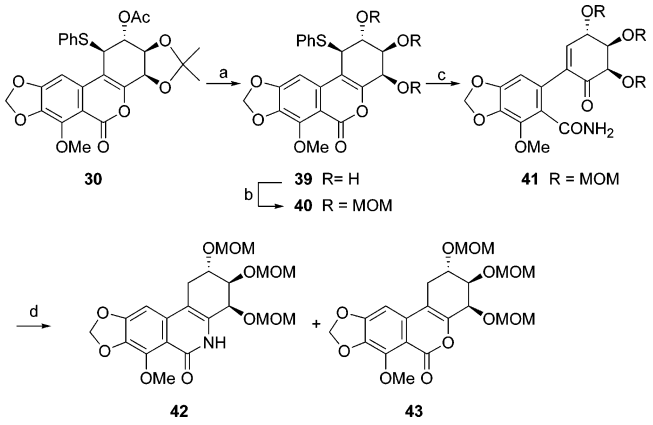


[a] Reagents and conditions: (a) PhSH, NEt_3, THF, reflux; (b) NH_3, MeOH, 0 °C then rt; (c) $NaBH_3CN$, HCO_2H, CH_3CN, reflux; (d) Ac_2O, pyridine, rt.

marin **29** in modest yield. A more efficient procedure for isocoumarine was found by using a powerful nucleophile such as thiophenol in the presence of triethylamine, which cleanly added to the double bond of **10** to provide the corresponding isocoumarin in 86% yield as a separable 4:1 mixture of two epimers **30** and **31** (Scheme 6). All attempts to prepare the tetraisoquinoline ring system by treatment of isocoumarins **29**, **30**, and **31** with benzylamine as described by Thompson and Kallmerten failed.[9f] Upon treatment of **30** with ammonia in methanol the amide **32** was formed. Thus, this two-step synthetic sequence led formally to the hydrolysis of the amide group and conversion to a primary amide group. Despite its length, the efficiency of the sequence was sufficient and allowed introduction of the amino group at C-4a. Obviously, reductive animation of the keto group of **32** using the primary amide function as the amine donor would afford a good solution. If the reductive amination of ketones is well precedented, the reductive amination of an enone is less documented and could be troublesome. Indeed, it was, as shown by treatment of **32** with sodium cyanoborohydride in acetonitrile in the presence of formic acid. Under these conditions, a mixture of four products was formed (8/10/2/1) which consisted of the 4a-*epi*-narciclasine derivative **34** and the isonarciclasine derivative **36** as the main product. Two minor compounds **38** and **37** were also isolated from the mixture. The structure of these compounds was established by ^1H NMR and mass spectrometry.

The *epi*-narciclasine derivative **34** was clearly a compound resulting from the expected reductive amination. Not unexpectedly, the reduction of the intermediate iminium derivative (path a) **33** occurs from the less hindered face placing the nitrogen cis to the isopropylidene ring. The structure of **34** was deduced from the

SCHEME 7[a]



[a] Reagents and conditions: (a) TFA, THF/H_2O, reflux; (b) MOMCl, iPr_2NEt, CH_2Cl_2, rt; (c) NH_3, MeOH, 0 °C then rt; (d) $NaBH_3CN$, HCO_2H, CH_3CN, reflux.

coupling constant between H-4 and H-4a of 6.5 Hz indicating a *cis* arrangement of these protons in the C-ring in a boat conformation.

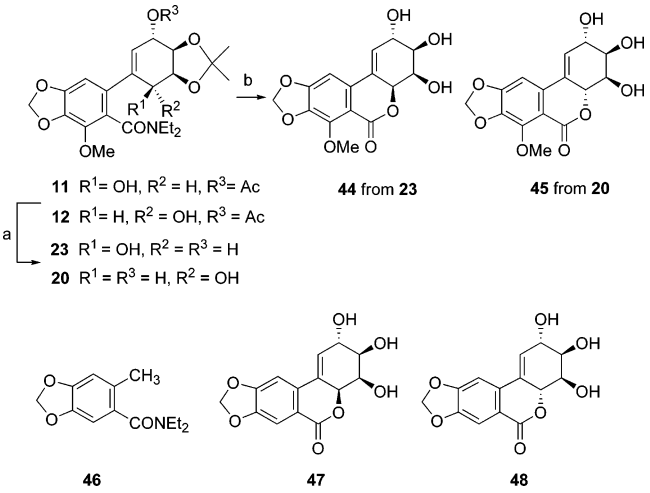
The structure of compound **36** was also deduced from its NMR spectrum which exhibited an allylic methylene signal. Moreover, comparison with known derivatives prepared by Krohn and Mondon from natural narciclasine supported our hypothesis.[3a,b] Finally, this compound was expected from a 1,4-reduction of the intermediate iminium **33** (path b). It is obvious that this reduction is favored over the "normal" pathway leading to **34** because of a possible steric hindrance in the hydride approach (path a) which does not exist in path b.

The formation of the intriguing structure **38** can be explained by the intramolecular addition of the hydroxyl group at C-2 on the activated double bond in **33** (path c). The formation of minute amounts of the isocoumarin **37** probably results from 1,4-reduction of the enone of **32** to give the corresponding enolate, which undergoes facile intramolecular lactonization.

From this first set of experiments it appeared that this synthetic sequence is probably one of the shortest routes to the benzophenantridinone skeleton described so far. However, in the context of a narciclasine total synthesis, this route suffered some drawbacks: the wrong stereochemistry obtained in the reduction of the iminium ion and the formation of byproducts. It was clear that **38** would no longer be formed using an OH-2-protected derivative of **32**. It could also be hypothesized that a more favorable and stereoselective reduction should be carried out on a less rigid cycle. This led us to examine a slightly different route using methoxymethyl ethers as protecting groups. Thus, compound **30** (major isomer) was treated with trifluoroacetic acid in a water/THF mixture to remove the acetate and the acetal group. The resulting triol **39** was treated with a large excess of MOMCl in the presence of diisopropylethylamine in dichloromethane giving **40** in 70% yield. As for **30**, treatment of **40** with ammonia gave the primary amide **41**. Finally, reductive amination of the latter gave in this case only two compounds in a 8/2 ratio, the isonarciclasine derivative **42** being the major one (Scheme 7).

From these results, it can be concluded that the stereoselective introduction of the nitrogen atom at C-4a

SCHEME 8[a]



[a] Reagents and conditions: (a) MeONa, MeOH, rt; (b) AcOH, H_2O 9/1, TFA, reflux.

remains difficult. It is clear that the protecting groups used here play an important role in the reductive amination reaction. Changing the isopropylidene acetal for the more bulky MOM group did affect dramatically the course of the reaction.

The easy formation of the lactone ring system from the tertiary amide led us to explore the synthesis of lactone analogues of narciclasine and lycoricidine. In the narciclasine series, we started from compounds **11** or **12**, deacetylated in the usual way to afford the corresponding alcohols **23** and **20** (Scheme 8). Attempts to cyclize these compounds under basic conditions proved difficult. Finally, it was found that treatment under acidic conditions led to the removal of the acetal protecting groups and promoted lactone formation in satisfactory yields.

The same sequence was used for the synthesis of a lycoricidine analogue starting from D-gulonolactone derivative **5** and the orthotoluamide derivative **46**.[23] Lactones **47** and **48** were thus obtained. The four lactones were assayed as antitumor agents against L1210 cell lines but none showed any significant biological activity.

Conclusion

In conclusion, we have developed a very short route to the benzophenanthridinone skeleton of Amaryllidaceae alkaloids using the *o*-toluamide anion condensation onto gulonolactone. The synthetic route described also makes use of a facile transformation of tertiary amide into lactone, thus solving the problem associated with these useful metalation-directing groups. This opens the way to iso-narciclasine and many other analogues of narciclasine. Lactone analogues of narciclasine and lycoricidine and their *epi* derivatives have also been obtained by this route, but no biological activities as antitumor agents were found for these analogues. Since we have shown before[5] that seco analogues of Amaryllidaceae alkaloids bearing the amide bond are not biologically active, we can now draw the conclusion that both the tricyclic system and the amide function at least are required for biological activity.

Experimental Section

1-Deoxy-1-[6-[(diethylamino)carbonyl]-7-methoxy-1,3-benzodioxol-5-yl]-3,4:6,7-bis-*O*-(1-methylethylidene)-*β*-D-*gulo*-2-heptulofuranose (6). A 1.1 M solution of *s*-BuLi in cyclohexane (30 mL) was slowly added to a −78 °C cooled solution of amide **4** (7 g, 26 mmol) in dry THF (400 mL). After the dark solution was stirred for 30 min at this temperature, a solution of lactone **5** (10 g, 38.7 mmol) was added. The mixture was stirred for 1 h at −78 °C and quenched by addition of a saturated aqueous ammonium chloride solution (120 mL). The solvent was removed in vacuo, and the residue was extracted with CH_2Cl_2 (3 × 250 mL). The organic phase was washed with 3 N HCl solution (20 mL) and water until neutral, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography with hexane/EtOAc (3:2) to give 14.2 g of **6** as a mixture of anomers in 70% yield: R_f 0.22 and 0.44 (hexane/EtOAc 3:2); mp 150−152 °C; IR ν_{max} 3220, 1650, 1370, 1390 cm^{-1}; ^1H NMR δ 0.98 (t, 3H, J = 7 Hz), 1.24 (t, 3H, J = 7 Hz), 1.33 (s, 3H), 1.40 (s, 3H), 1.45 (s, 3H), 1.50 (s, 3H), 2.82 (d, 1H, J = 14.5 Hz), 3.12 (m, 3H), 3.30 (d, 1H, J = 14.5 Hz), 3.69 (m, 1H, J = 8.5, 7.5 Hz), 3.98 (m, 4H), 4.11 (dd, 1H, J = 4.5, 8.5 Hz), 4.20 (dd, 1H, J = 6.5, 8.5 Hz), 4.31, (m, 2H, J = 5.5 Hz), 4.71 (dd, 1H, J = 5.5, 4.5 Hz), 5.90 (d, 1H, J = 1.5 Hz), 5.96 (d, 2H, J = 1.5 Hz), 6.90 (s, 1H); ^{13}C NMR δ 12.4, 13.9, 25.0, 25.1, 26.2, 26.7, 36.4, 39.8, 42.7, 59.6, 60.0, 76.1, 80.6, 80.8, 83.9, 101.3, 104.9, 106.2, 109.6, 112.6, 123.0, 129.3, 138.9, 150.0, 169.3. Anal. Calcd for $C_{26}H_{27}NO_{10}$: C, 59.66; H, 7.00; N, 2.68. Found: C, 59.86; H, 7.00; N, 2.78.

1-Deoxy-1-[6-[(diethylamino)carbonyl]-7-methoxy-1,3-benzodioxol-5-yl]-3,4-*O*-(1-methylethylidene)-*β*-D-*gulo*-2-heptulofuranose (7). To a stirred solution of hemiacetal **6** (10.14 g, 20 mmol) in THF (20 mL) was added an aqueous solution of acetic acid 3:7 v/v (300 mL). This mixture was heated at 60 °C. The reaction was monitored by TLC. After complete disappearance of starting material, the solvents were removed under vacuum, and the residue was codistilled several times with toluene (10 mL each time) to remove water. The residue was purified by column chromatography (hexane/EtOAc 1:4) to give **7** as a mixture of anomers (7.69 g, 90%): R_f 0.4 (EtOAc); mp 154−156 °C; $[\alpha]_D$ +3.17 (*c* 1.8, $CHCl_3$); IR ν_{max} 3334, 1650, 1173 cm^{-1}; ^1H NMR δ 1.29 (t, 3H, J = 7 Hz), 1.37 (s, 3H), 1.40 (t, 3H, J = 7 Hz), 1.55 (s, 3H), 2.45 (s, 1H), 2.67 (d, 1H, J = 14.5 Hz), 3.32 (m, 4H), 3.98 (s, 3H), 4.10 (m, 2H), 4.35 (d, 1H, J = 6 Hz), 4.85 (dd, 1H, J = 4, 6 Hz), 5.95 (m, 3H), 6.80 (2s, 2H); ^{13}C NMR δ 12.7, 14.0, 24.5, 26.0, 36.5, 39.8, 43.3, 60.1, 64.1, 70.8, 77.2, 81.4, 84.2, 101.5, 104.7, 104.9, 112.7, 123.0, 129.0, 134.6, 150.0, 169.4. Anal. Calcd for $C_{23}H_{33}NO_{10}$: C, 57.13; H, 6.88; N, 2.95. Found: C, 57.12; H, 6.86; N, 2.90.

(3′a*R*,7′*S*,7′a*R*)-*N*,*N*-Diethyl-3′a,4′,7′,7′a-tetrahydro-7′-hydroxy-7-methoxy-2′,2′-dimethyl-4′-oxo[5,5′-bi-1,3-benzodioxole]-6-carboxamide (9) and 2-Deoxy-2-[6-[(diethylamino)carbonyl]-7-methoxy-1,3-benzodioxol-5-yl]-5,6-*O*-(1-methylethylidene)-1-inosose (8). To a solution of diol **7** (465 mg, 1 mmol) in methanol (10 mL) was added, at room temperature, sodium periodate (278 mg, 1.3 mmol). The mixture was stirred for 1 h; after that time, no starting material was present (TLC monitoring with EtOAc). Methanol was removed in vacuo, and the residue was taken up in CH_2Cl_2 (100 mL). The organic phase was washed with water, dried, and concentrated. The resulting aldehyde was dissolved in anhydrous THF (20 mL). To this solution were added solid sodium carbonate (252 mg, 3 mmol) and one or two drops of DBU. The suspension turned red as the reaction proceeded. After 6 h, aqueous 3 N HCl was cautiously added to neutrality. The residue was extracted with diethyl ether (2 × 50 mL). The organic phase was washed, dried, and concentrated in vacuo.

(23) Khaldi, M.; Chrétien, F.; Chapleur, Y. *Bull. Soc. Chim. Fr.* **1996**, *133*, 7−13.

The residue was purified by column chromatography (hexane/EtOAc 2:3) to afford **8** (81 mg, 18%) and **9** (303 mg, 70%). Compound **8**: R_f 0.38 (EtOAc); $[\alpha]_D$ −29.1 (*c* 0.9 $CHCl_3$); IR ν_{max} 3400, 1740, 1600, 1380, 1390 cm^{-1}; ^1H NMR δ 0.80 (t, 3H, J = 7 Hz), 1.20 (t, 3H, J = 7 Hz), 1.35 (s, 3H), 1.50 (s, 3H), 3.1−3.7 (m, 4H), 3.98 (s, 3H), 4.20 (m, 1H), 4.46 (d, 1H, J = 6 Hz), 4.50 (t, 1H, J = 6 Hz), 4.73 (m, 2H), 5.98 (d, 2H, J = 1.5 Hz), 6.04 (s, 1H). Compound **8** was not further characterized but transformed into **10**. Standard acetylation (pyridine Ac_2O) and workup of the **9** and **8** mixture gave only acetate **10** in 92% yield. This compound was purified by column chromatography (hexane/EtOAc, 1:4) and isolated as a 34/66 mixture of atropoisomers A and B.

Compound **9**: R_f 0.51(EtOAc); mp 200 °C; $[\alpha]_D$ −39.3 (*c* 1,-$CHCl_3$); IR ν_{max} 3350, 1740, 1600, 1380, 1390 cm^{-1}; ^1H NMR δ 0.90 (t, 3H, J = 7 Hz), 1.30 (t, 3H, J = 7 Hz), 1.40 (s, 6H), 2.80−3.80 (m, 4H), 4.00 (s, 3H), 4.54 (m, 2H), 4.57 (dd, 1H, J = 3, 4 Hz), 5.98 (s, 2H), 6.28 (s, 0.33H, atropoisomer A), 6.45 (s, 0.66H, atropoisomer B), 6.81 (d, 0.33H, J = 3 Hz, atropoisomer A), 6.93 (d, 0.66H, J = 3 Hz, atropoisomer B); ^{13}C NMR δ 12.5, 13.5, 25.6, 27.3, 38.6, 43.3, 59.9, 66.4, 75.4, 78.9, 101.5, 105.0, 110.2, 126.3, 128.3, 136.2, 137.6, 139.4, 145.0, 149.5, 166.9, 193.7; EIMS (*m*/*z*) 433 $[M]^+$. Anal. Calcd for $C_{22}H_{33}NO_8$: C, 60.95; H, 6.28; N, 3.23. Found: C, 60.75; H, 6.17; N, 3.36.

(3′a*R*,7′*S*,7′a*R*)-*N*,*N*-Diethyl-7′-(acetyloxy)-3′a,4′,7′,7′a-tetrahydro-7-methoxy-2′,2′-dimethyl-4′-oxo[5,5′-bi-1,3-benzodioxole]-6-carboxamide (10): R_f 0.48 (EtOAc); $[\alpha]_D$ + 25.2 (*c* 1, $CHCl_3$); IR ν_{max} 1760, 1700, 1630, 1380 cm^{-1}; ^1H NMR δ 0.98 (t, 3H, J = 7 Hz), 1.10 (t, 3H, J = 7 Hz), 1.15 (s, 3H), 1.20 (s, 3H), 2.10 (s, 0.99, atropoisomer A), 2.18 (s, 2.1H, atropoisomer B), 2.95, 3.15, 3.25, 3.40, 3.75 (m, 4H), 3.98 (s, 0.99H, atropoisomer A), 4.00 (s, 2.1H, atropoisomer B), 4.60 (m, 2H), 5.63 (m, 1H, J = 3.5 Hz), 5.98 (s, 2H), 6.31 (s, 0.34H, atropoisomer A), 6.48 (s, 0.66H, atropoisomer B), 6.68 (d, 0.66H, J = 3 Hz, atropoisomer B), 6.83 (d, 0.34H, J = 3 Hz, atropoisomer B); ^{13}C NMR δ 12.5, 13.4, 20.6, 25.5, 26.9, 38.3, 42.9, 59.8, 68.8, 75.4, 76.4, 101.4, 104.8, 100.8, 122.8, 125.3, 127.1, 137.5, 139.3, 142.4, 148.8, 166.1 169.8. Anal. Calcd for $C_{24}H_{29}NO_9$: C, 60.61; H, 6.15; N, 2.95. Found: C, 60.32; H, 6.08; N, 2.71.

(3′a*R*,4′*S*,7′*S*,7′a*R*)-*N*,*N*-Diethyl-3′a,4′,7′,7′a-tetrahydro-,7′-acetyloxy-4′hydroxy-7-methoxy-2′,2′-dimethyl[5,5′-bi-1,3-benzodioxole]-6-carboxamide (11) and (3′a*R*,4′*R*,7′*S*,7′a*R*)-*N*,*N*-Diethyl-3′a,4′,7′,7′a-tetrahydro-,7′-acetyoxy-4′hydroxy-7-methoxy-2′,2′-dimethyl[5,5′-bi-1,3-benzodioxole]-6-carboxamide (12). To a solution of enone **10** (1 g, 2.1 mmol) in ethanol (6 mL) at 0 °C were added solid cerium chloride hydrate (823 mg, 2.1 mmol) and sodium borohydride (50 mg, 2.1 mmol). After the mixture was stirred for 15 min, a few drops of 3 N hydrochloric acid were added. Ethanol was removed in vacuo, and the residue was taken up in 100 mL of CH_2Cl_2. The organic phase was washed with water until neutral, dried, and concentrated under vacuum. The two isomers were separated by high-pressure column chromatography (hexane/EtOAc, 3:2) to give **11** (350 mg, 35%) and **12** (561 mg, 56%). Compound **11**: R_f 0.52 (EtOAc); $[\alpha]_D$ +106.5 (*c* 0.8, $CHCl_3$); IR ν_{max} 3419, 1737, 1609, 1471, 1373; ^1H NMR δ 1.02 (t, 3H, J = 7 Hz), 1.21 (t, 3H, J = 7 Hz), 1.35 (s, 3H), 1.48 (s, 3H), 2.00 (s, 3H), 3.10, 3.40, 3.60 (m, 4H), 3.98 (s, 0.99, atropoisomer A), 4.00 (s, 2.1H, atropoisomer B), 4.44 (dd, 1H, J = 2, 7 Hz), 4.56 (dd, 1H, J = 1.5, 3.5 Hz), 4.77 (dd, 1H, J = 7, 3.5 Hz), 5.05 (s, 1H), 5.19 (dd, 1H, J = 1.5, 6 Hz), 5.89 (dd, 1H), 5.94 (d, 1H, J = 2 Hz), 5.98 (d, 1H, J = 2 Hz), 6.40 (s, 1H); ^{13}C NMR δ 12.7, 13.5, 20.8, 24.4, 25.4, 39.3, 43.2, 59.9, 67.5, 68.5, 76.1, 77.2, 101.4, 104.9, 109.5, 120.9, 123.2, 131.4, 135.5, 138.7, 149.3, 149.7, 168.7, 169.8. Anal. Calcd for $C_{24}H_{31}NO_9$: C, 60.37; H, 6.54; N, 2.93. Found: C, 60.09; H, 6.32; N, 2.78. Compound **12**: R_f 0.73 (EtOAc); $[\alpha]_D$ +15.0 (*c* 1.1, $CHCl_3$); IR ν_{max} 3450, 1750, 1630, 1380 cm^{-1}; ^1H NMR δ 1.05 (t, 3H, J = 7 Hz), 1.10 (t, 3H, J = 7 Hz), 1.40 (s, 3H), 1.50 (s, 3H), 2.10 (s, 3H), 3.05 (q, 2H, J = 7 Hz), 3.20 (q, 2H), 3.50−3.60 (m, 2H), 3.98 (s, 2.H, 3H atropoisomer A), 4.00 (s, 1H, 3H atropoisomer B), 4.19 (dd, 1H, J = 2.5, 4.5 Hz), 4.23 (dd, 1H, J = 5.5, 7.5 Hz), 4.39 (dd, 1H, J = 4.5, 7.5 Hz), 5.21 (dd, 1H, J = 2.5, 5.5 Hz), 5.30 (s, 1H), 5.48 (t, 1H, J = 2.5 Hz), 5.98 (d, 1.3H, J = 2 Hz, atropoisomer A), 6.00 (d, 0.7H, J = 2 Hz, atropoisomer B), 6.30 (s, 0.7H, atropoisomer A), 6.40 (s, 0.3H, atropoisomer B); ^{13}C NMR δ 12.5, 13.7, 21.2, 24.9, 27.2, 39.1, 43.2, 60.0, 72.1, 73.7, 75.9, 79.0, 101.5, 104.8, 110.5, 121.9, 125.0, 131.9, 135.6, 138.9, 144.4, 149.9, 168.8, 170.68. Anal. Calcd for $C_{24}H_{31}NO_9$: C, 60.37; H, 6.54; N, 2.93. Found: C, 60.01; H, 6.20; N, 2.88.

[3a*R*-(3aα,3bα,12*β*,12aα)]-3a,3b,12,12a-Tetrahydro-12-acetyloxy-6-methoxy-2,2-dimethyl-2*H*-[1,3]benzodioxolo-[5,6-*c*]-1,3-dioxolo[4,5-*h*][1]benzopyran-5-one (13) and [3a*R*-(3aα,3b*β*,12*β*,12aα)]-3a,3b,12,12a-Tetrahydro-12acetyloxy-6-methoxy-2,2-dimethyl-2*H*-[1,3]benzodioxolo[5,6-*c*]-1,3-dioxolo[4,5-*h*][1]benzopyran-5-one (14). To a solution of allylic alcohol **11** or **12** (477 mg, 1 mmol) in anhydrous CH_2Cl_2 (10 mL) at −30 °C was added pyridine (0.6 mL) and then triflic anhydride (0.4 mL). After being stirred for 30 min at −30 °C, the solution was allowed to warm to room temperature for 2 h. The mixture was poured into chilled sodium bicarbonate solution. The compounds were extracted with dichloromethane (2 × 50 mL). The organic phase was washed with water, dried, and concentrated. High-pressure chromatography allowed separation of **14** (109 mg, 27%) and **13** (110 mg, 27%). Compound **13**: R_f 0.38 (hexane/EtOAc, 2:3); $[\alpha]_D$ + 3.69 (*c* 0.5, $CHCl_3$); mp 154 °C; IR ν_{max} 1725, 1708, 1483, 1373 cm^{-1}; ^1H NMR δ 1.28 (s, 3H), 1.39 (s, 3H), 2.05 (s, 3H), 4.10 (s, 3H), 4.53 (dd, 1H, J = 1.5, 6.5 Hz), 4.95 (dd, 1H, J = 3.5, 6.5 Hz), 5.33 (dd, 1H, J = 6.5, 1.5 Hz), 5.38 (dd, 1H, J = 3, 3.5 Hz), 6.04 (d, 2H, J = 4 Hz), 6.55 (dd, 1H, J = 3, 6.5 Hz), 6.92 (s, 1H); ^{13}C NMR δ 20.8, 24.7, 26.1, 60.9, 67.8, 73.9, 74.5, 75.7, 79.4, 102.3, 110.2, 110.5, 118.0, 131.8, 133.1, 139.5, 145.5, 153.6, 159.1, 169.9. Anal. Calcd for $C_{20}H_{20}O_9$: C, 59.40; H, 4.99. Found: C, 59.61; H, 5.19. Compound **14**: R_f 0.53 (hexane/EtOAc, 2:3); $[\alpha]_D$ +222.15 (*c* 0.72, $CHCl_3$); mp 198 °C; IR ν_{max} 1715, 1709, 1472, 1374 cm^{-1}; ^1H NMR δ 1.45 (s, 3H), 1.53 (s, 3H), 2.18 (s, 3H), 4.10 (s, 3H), 4.30 (dd, 1H, J = 6, 7 Hz), 4.62 (dd, 1H, J = 3.5, 7 Hz), 5.03 (t, 1H, J = 2 Hz), 5.50 (dt, 1H, J = 2.5, 2 Hz), 6.04 (d, 1H, J = 1 Hz), 6.08 (d, 1H, J = 1 Hz), 6.12 (dd, 1H, J = 2.5, 2.5 Hz), 6.75 (s, 1H); ^{13}C NMR δ 21.1, 25.6, 27.4, 60.7, 71.96, 73.9, 75.5, 76,5, 98.2, 102.3, 109.5, 110.2, 123.0, 129.9, 123.9, 138.7, 145.3, 153.8, 160.0, 170.5. Anal. Calcd for $C_{20}H_{20}O_9$: C, 59.40; H, 4.99. Found: C, 59.03; H, 4.75.

(3′a*R*,7′*S*,7′a*R*)-*N*,*N*-Diethyl-7′-tetrahydropyranyloxy-3′a,4′,7′,7′a-tetrahydro-7-methoxy-2′,2′-dimethyl-4′-oxo-[5,5′-bi-1,3-benzodioxole]-6-carboxamide (18). The starting compound could be alcohol **9**, but it was more useful to start from acetate **10** resulting from the cyclization−acetylation sequence of **7**. The acetate group of **10** was removed by conventional treatment with sodium methoxide in methanol. To a solution of **9** (1 g, 2.5 mmol) in dry CH_2Cl_2 (60 mL) were added dry dihydropyran (0.75 mL, 7.5 mmol) and PTSA (50 mg). The mixture was stirred for 4 h at room temperature and then diluted with CH_2Cl_2 (100 mL). Saturated aqueous sodium bicarbonate (5 mL) was added. The organic phase was washed with water, saturated ammonium chloride solution (10 mL), and water and dried. The residue was purified by column chromatography (hexane/EtOAc, 3:2) to provide **18** (1.1 g, 90%). This compound was a mixture of diastereoisomers, each isomer being present as a mixture of atropoisomers. Compound **18**: R_f 0.45 (hexane/EtOAc, 2:3); IR ν_{max} 1760, 1630, 1380 cm^{-1}; ^1H NMR δ 1.02 (t, 3H, J = 7 Hz), 1.14 (t, 3H, J = 7 Hz), 1.42−1.78 (m, 14H), 2.95−3.91 (m, 4H), 3.98 (s, 3H), 4.00 (s, 3H), 4.55−4.64 (m, 3H), 4.86 (m, 1H), 5.01 (m, 1H), 5.96 (s, 2H), 6.30, 6.32, 6.42, 6.49 (4s, 1H), 6.83, 6.95, 7.02 (3d, 1H, J = 3 Hz).

(3′a*R*,4′*R*,7′*S*,7′a*R*)-*N*,*N*-Diethyl-7′-acetyloxy-3′a,4′,7′,7′a-tetrahydro-7-methoxy-2′,2′-dimethyl-4′-hydroxy[5,5′-bi-1,3-benzodioxole]-6-carboxamide (20) and (3′a*R*,4′*S*,7′*S*,7′

a*R*)-*N*,*N*-Diethyl-7′-acetyloxy-3′a,4′,7′,7′a-tetrahydro-7-methoxy-2′,2′-dimethyl-4′-hydroxy[5,5′-bi-1,3-benzodioxole]-6-carboxamide (23). The mixture **18** was directly processed to enone reduction using the procedure already described for the preparation of **11** and **12**. Two compounds **19** and **22** were obtained in a 2/1 ratio. Here again, mixtures of isomers and atropoisomers were obtained. To ascertain the configuration at C4a, the THP group was removed according to the following procedure: to a solution of **19** or **22** (26 mg, 0.05 mmol) in anhydrous THF (5 mL) was added Dowex-H^+ resin (30 mg). This suspension was gently stirred at room temperature for 4 h. The resin was then filtered off, and the resulting solution was concentrated to give **20** or **23** (20 mg, 90%). It should be noted that the same compounds can be obtained from deacetylation of **11** and **12** by NH_3g in MeOH. Compound **20**: R_f 0.24 (EtOAc); $[\alpha]_D$ −16.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 1.05 (t, 3H, J = 7 Hz), 1.19 (m, 5H), 1.36 (s, 3H), 1.45 (s, 3H), 3.13−3.62 (m, 4H), 3.99 (s, 3H), 4.15−4.30 (m, 4H), 4.50 (dd, 1H, J = 7.5, 3 Hz), 4.64 (dd, 1H, J = 7.5, 3 Hz), 5.85−5.95 (m, 3H), 6.38 (s, 1H); ^{13}C NMR δ 12.6, 13.6, 24.4, 26.7, 39.1, 43.4, 59.9, 66.2, 69.8, 77.7, 79.0, 101.4, 104.5, 109.6, 121.8, 130.3, 133.9, 134.9, 138.8, 143.8, 149.7, 168.7. Anal. Calcd for $C_{22}H_{22}NO_8$: C, 60.65; H, 6.71; N, 3.22. Found: C, 60.81; H, 6.55; N, 3.09. Compound **23**: R_f 0.40 (EtOAc); $[\alpha]_D$ 23.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 1.07 (t, 3H, J = 7 Hz), 1.16 (t, 3H, J = 7 Hz), 1.36, 146 (2s, 4.5H, atropoisomer A), 1.37, 1.51 (2s, 1.5H, atropoisomer B), 3.15−3.30 (m, 3H), 3.66 (m, 3H), 3.96 (s, 3H), 4.27−4.35 (m, 2H), 4.45 (m, 1H), 4.57 (m, 1H), 5.85−5.94 (m, 3H), 6.45 (s, 0.75H, atropoisomer A), 6.47 (s, 0.25H, atropoisomer B); ^{13}C NMR δ 12.4, 12.4, 24.3, 26.4, 38.8, 43.1, 59.9, 68.2, 69.2, 76.2, 79.2, 101.3, 104.0, 109.9, 121.6, 131.9, 133.9, 135.4, 138.9, 142.8, 149.4, 168.2. Anal. Calcd for $C_{22}H_{22}NO_8$: C, 60.65; H, 6.71; N, 3.22. Found: C, 60.55; H, 6.76; N, 3.14.

(3′a*R*,4′*R*,7′*S*,7′a*R*)-*N*,*N*-Diethyl-7′-(tetrahydropyran-2-yloxy)-3′a,4′,7′,7′a-tetrahydro-7-methoxy-2′,2′-dimethyl-4′-acetyloxy[5,5′-bi-1,3-benzodioxole]-6-carboxamide (21) and (3′a*R*,4′*S*,7′*S*,7′a*R*)-*N*,*N*-Diethyl-7′-(tetrahydropyran-2-yloxy)-3′a,4′,7′,7′a-tetrahydro-7-methoxy-2′,2′-dimethyl-4′-acetyloxy[5,5′-bi-1,3-benzodioxole]-6-carboxamide (25). Standard acetylation of **19** or **22** using acetic anhydride in pyridine gave **21** and **25**, respectively, in 85% yield. For the above-described reasons, these mixtures of isomers were not fully characterized but used as such. Compound **21**: R_f 0.70 (hexane/EtOAc, 3:2); IR ν_{max} 1740, 1600, 1375 cm^{-1}; ^{1}H NMR δ 1.00−1.2 (m, 6H), 1.38−1.90 (m, 14H), 2.10 (m, 3H), 2.90−3.40 (m, 2H), 3.50−3.75 (m, 2H), 3.98−4.00 (3s, 3H), 4.30 (m, 1H), 4.45 (m, 1H), 6.65 (m, 1H), 4.80 (s, 0.5H, atropoisomer A), 5.0 (s, 0.5H, atropoisomer B), 5.78 (m, 1H), 5.98 (m, 2H), 6.10 (m, 0.5H, atropoisomer A), 6.35 (m, 0.5H, atropoisomer B), 6.50 (m, 1H). Compound **25**: R_f 0.62 (hexane/EtOAc, 3:2); IR ν_{max} 1745, 1605, 1380 cm^{-1}; ^{1}H NMR δ 1.05−1.20 (m, 6H), 1.38−1.70 (m, 14H), 1.90 (2s, 1.2H, atropoisomer A), 2.05 (2s, 1.8H, atropoisomer B), 3.10 (m, 2H), 3.50, (m, 2H), 3.98−4.00 (m, 3H), 4.15 (m, 1H), 4.35 (m, 1H), 4.80 (m, 0.4H, atropoisomer A), 5.0 (m, 0.6H, atropoisomer B), 5.53 (m, 1H), 5.8 (s, 1H), 5.95 (m, 2H), 6.05 (m, 0.4H, atropoisomer A), 6.15 (m, 0.6H, atropoisomer B), 6.45 (m, 1H).

(3′a*R*,4′*R*,7′*S*,7′a*R*)-*N*,*N*-Diethyl-7′-(tetrahydropyran-2-yloxy)-3′a,4′,7′,7′a-tetrahydro-7-methoxy-2′,2′-dimethyl-4′-formyloxy[5,5′-bi-1,3-benzodioxole]-6-carboxamide (26). Due to the presence of two diastereoisomers (THP) and atropoisomers, this compound was difficult to characterize completely, especially the ^{13}C NMR spectra: R_f 0.51 (hexane/EtOAc, 3:2); IR ν_{max} 1772, 1605, 1380 cm^{-1}; ^{1}H NMR δ 1.10−1.14 (m, 6H), 1.35−1.45 (m, 14H), 3.10 (m, 2H), 3.50 (m, 2H), 3.98 (s, 3H), 4.00 (s, 3H), 4.25−4.64 (m, 3H), 4.75 (m, 0.5H, atropoisomer.A), 4.95 (s, 0.5H, atropoisomer B), 5.7 (s, 0.5H, atropoisomer A), 5.8 (m, 0.5H, 1H), 5.96 (2s, 1H), 6.0 (2s, 1H), 6.05, 6.10 (2d, 0.5H, J = 3 Hz, atropoisomer A), 6.25, 6.30 (2d, 0.5H, J = 3 Hz atropoisomer B), 6.40 (s, 0.5H, atropoisomer A), 6.45, 6.48 (2s, 0.5H, atropoisomer B), 8.15 (m, 1H).

[3a*R*-(3aα,11*β*,12α,12aα)]-12-(Acetyloxy)-3a,11,12,12a-tetrahydro-6-methoxy-2,2-dimethyl-11-(*O*-methylhydroxylamino)-5*H*-[1,3]benzodioxolo[5,6-*c*]-1,3-dioxolo[4,5-*h*]-[1]benzopyran-5-one (27) and [3a*R*-(3aα,11α,12α,12aα)]-12-(Acetyloxy)-3a,11,12,12a-tetrahydro-6-methoxy-2,2-dimethyl-11-(*O*-methylhydroxylamino)-5*H*-[1,3]benzodioxolo[5,6-*c*]-1,3-dioxolo[4,5-*h*][1]benzopyran-5-one (28). To a solution of enone **10** (105 mg, 0.22 mmol) in THF (5 mL) was added *O*-methylhydroxylamine hydrochloride (22 mg, 1.2 mmol). The reaction was stirred for 24 h at room temperature. NMR monitoring of the reaction indicated an incomplete reaction. The same amount of *O*-methylhydroxylamine was added and the mixture heated at reflux for further 15 h. After cooling, water (10 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over sodium sulfate and concentrated in vacuo. Hydroxylamines were separated by column chromatography (hexane/EtOAc, 2:3) giving **27** (15 mg, 15%) and **28** (20 mg, 20%). Compound **27**: R_f 0.43 (hexane/EtOAc, 2:3); ^{1}H NMR δ 1.46 (s, 3H), 1.55 (s, 3H), 2.25 (s, 3H), 3.70 (s, 3H), 4.08 (m, 1H), 4.13 (s,3H), 4.70 (dd, 1H, J = 8.5, 6.5 Hz), 5.09 (d, 1H, J = 6.5 Hz), 5.99 (d, 1H, J = 6 Hz), 6.12 (d, 2H, J = 2 Hz), 7.05 (s, 1H), 7.65 (s, 1H). Compound **28**: R_f 0.73 (hexane/EtOAc, 3:2); ^{1}H NMR δ 1.38 (s, 3H), 1.41 (s, 3H), 2.05 (s, 3H), 3.70 (s, 3H), 4.01 (s, 3H), 4.37 (dd, 1H, J = 11, 2 Hz), 4.84 (ddd, 1H, J = 3, 5.5, 1.5 Hz), 4.93 (d, 1H, J = 5.5 Hz,), 6.03 (dd, 1H, J = 2, 3 Hz), 6.13 (d, 2H, J = 1.5 Hz), 6.16 (dd, 1H, J = 1.5, 11 Hz), 7.20 (s, 1H), 7.65 (s, 1H).

[3a*R*-(3aα,12α,12aα)]-3a,11,12,12a-Tetrahydro-12-acetyloxy-6-methoxy-2,2-dimethyl-5*H*-[1,3]benzodioxolo[5,6-*c*]-1,3-dioxolo[4,5-*h*][1]benzopyran-5-one (29). To a solution of enone **10** (238 mg, 0.5 mmol) in dry THF (5 mL) at −30 °C was added L-Selectride (0.9 mL, 1.5 mmol). The mixture was stirred for 15 min at this temperature. A few drops of 3 N HCl were added and the products extracted with diethyl ether (3 × 15 mL). The organic phase was washed with water until neutral, dried, and concentrated in vacuo. Compound **29** was purified by column chromatography (36 mg, 18%): R_f 0.78 (EtOAc); $[\alpha]_D$ +1.87 (*c* 1.7, $CHCl_3$); ^{1}H NMR δ 1.20 (s, 3H), 1.24 (s, 3H), 2.10 (s, 3H), 2.58 (dd, 1H, J = 16.5, 6 Hz), 2.98 (dd, 1H, J = 4.5, 16.5 Hz), 4.14 (s, 3H), 4.41 (dd, 1H, J = 6.5, 6 Hz), 4.94 (d, 1H, J = 6 Hz), 5.33 (ddd, 1H, J = 6.5, 6, 4.5 Hz), 6.10 (s, 2H), 6.60 (s, 1H).

[3a*R*-(3aα,11*β*,12α,12aα)]-12-(Acetyloxy)-3a,11,12,12a-tetrahydro-6-methoxy-2,2-dimethyl-11-(phenylthio)-5*H*-[1,3]benzodioxolo[5,6-*c*]-1,3-dioxolo[4,5-*h*][1]benzopyran-5-one (30) and [3a*R*-(3aα,11α,12α,12aα)]-12-(Acetyloxy)-3a,11,12,12a-tetrahydro-6-methoxy-2,2-dimethyl-11-(phenylthio)-5*H*-[1,3]benzodioxolo[5,6-*c*]-1,3-dioxolo[4,5-*h*][1]benzopyran-5-one (31). To a solution of enone **10** (1.1 g, 2.3 mmol) in anhydrous THF (40 mL) were added thiophenol (2.7 mL, 26 mmol) and triethylamine (1 mL, 11 mmol). The mixture was then refluxed for 15 h. Removal of the solvents in vacuo followed by three codistillations with toluene (15 mL) gave the final residue purified over a silica gel column (hexane/EtOAc, 2:3). Compounds **30** (825 mg, 70%) and **31** (188 mg, 16%) were isolated. Compound **30**: R_f 0.68 (hexane/EtOAc, 2:3); mp 205−208 °C; $[\alpha]_D$ +118.1 (*c* 0.5, $CHCl_3$); IR ν_{max} 1730, 1720, 1483 cm^{-1}; ^{1}H NMR δ 1.40 (s, 3H), 1.50 (s, 3H), 1.65 (s, 3H), 4.15 (s, 3H), 4.75 (d, 1H, J = 4 Hz), 4.90 (m, 2H), 5.14 (dd, 1H, J = 8.5, 4 Hz), 6.11 (d, 2H, J = 10 Hz), 6.85 (s, 1H), 7.30 (m, 3H), 7.50 (m, 2H); ^{13}C NMR δ 20.3, 25.5, 27.6, 44.5, 60.9, 61.9, 73.6, 73.8, 97.5, 102.5, 108.7, 109.9, 111.3, 145.4, 147.3, 154.8, 156.8, 170.9. Anal. Calcd for $C_{26}H_{24}O_9S$: C, 60.93; H, 4.72; S, 6.25. Found: C, 60.77; H, 4.98; S, 6.17. Compound **31**: R_f 0.58 (hexane/EtOAc, 2:3); $[\alpha]_D$ −138.3 (*c* 0.9, $CHCl_3$); IR ν_{max} 1725, 1600, 1610, 1480, 1390 cm^{-1}; ^{1}H NMR δ 1.41 (s, 3H), 1.51 (s, 3H), 2.00 (s, 3H), 4.05 (s, 3H), 4.25 (d, 1H, J = 2.5 Hz), 4.59 (dd, 1H, J = 3, 6.5 Hz), 4.98 (d, 1H, J = 6.5 Hz), 5.83 (dd, 1H, J = 2.5, 3 Hz), 6.01 (AB, 2H, J = 9 Hz), 6.34 (s, 1H), 7.30 (m, 3H), 7.50 (d, 2H, J = 8 Hz); ^{13}C NMR δ 20.9, 25.3, 27.3, 45.2, 60.9, 70.9, 71.6, 74.5, 76.5, 98.1, 102.3, 108.9,

109.1, 111.5, 127.7, 129.4, 131.3, 134.3, 136.5, 137.7, 145.2, 147.2, 154.5, 157.5, 169.8. Anal. Calcd for $C_{26}H_{24}O_9S$: C, 60.93; H, 4.72; S, 6.25. Found: C, 60.81; H, 4.81; S, 6.22.

(3′a*R*,7′*S*,7′a*R*)-3′a,4′,7′,7′a-Tetrahydro-7′-hydroxy-7-methoxy-2′,2′-dimethyl-4′-oxo[5,5′-bi-1,3-benzodioxole]-6-carboxamide (32). A solution of lactone **30** (496 mg, 1 mmol) in methanol (20 mL) was cooled at 0 °C. A stream of gaseous ammonia was bubbled through the solution until saturated. The mixture was then allowed to warm to room temperature for 4 h while a gentle stream of ammonia was maintained. Excess of ammonia was cautiously removed under vacuum, and the solvent was then removed. The rather instable amide **32** (301 mg) was not fully characterized but used as such in the next step: R_f 0.3 (EtOAc); IR ν_{max} 3847, 1650 cm^{-1}; ^{1}H NMR δ 1.40 (s, 3H), 1.60 (s, 3H), 4.05 (s, 3H), 4.29−4.31 (m, 2H), 4.84 (dd, 1H, J = 2, 5 Hz), 6.05 (s, 2H), 6.4 (s, 1H), 6.50 (d, 1H, J = 2 Hz), 6.88 (s, 1H), 7.30 (s, 1H), 7.50 (s, 1H).

[3a*S*-(3aα,3bα,12α,12aα)]-12-Hydroxy-3b,4,12,12a-tetrahydro-6-methoxy-2,2-dimethylbis[1,3]dioxolo[4,5-*c*:4′,5′-*j*]phenanthridin-5(3a*H*)-one (34), [3a*S*-(3aα,12α,12aα)]-4,11,12,12a-Tetrahydro-12-hydroxy-6-methoxy-2,2-dimethylbis[1,3]dioxolo[4,5-*c*:4′,5′-*j*]phenanthridin-5(3a*H*)-one (36), [1a*S*-(1aα,1b*β*,4a*β*,11cα)]-1b,4a,5,11c-Tetrahydro-7-methoxy-3,3-dimethylbis[1,3]dioxolo[4,5-*c*:4′,5′-*j*]-oxireno[*a*]phenanthridin-6(1a*H*)-one (38), and [3a*R*-(3aα,12α,12aα)]-3a,11,12,12a-Tetrahydro-12-hydroxy-6-methoxy-2,2-dimethyl-5*H*-[1,3]benzodioxolo[5,6-*c*]-1,3-dioxolo[4,5-*h*][1]benzopyran-5-one (37). To a solution of **32** (301 mg, 0.8 mmol) in dry acetonitrile (8 mL) were added formic acid (3 mL) and sodium cyanoborohydride (100 mg, 1.6 mmol). The mixture was heated at reflux for 24 h. After cooling 3 N hydrochloric acid (4 mL) and CH_2Cl_2 (50 mL) were added. The organic phase was washed with saturated sodium bicarbonate solution and water and dried. After concentration, the residue was chromatographed on a silica gel column to give **34** (74 mg, 20% further charactrized as its acetate **35**), **36** (92 mg, 25%), **38** (15 mg, 5%), and **37** (28 mg, 10%). Compound **36**: IR ν_{max} 3849, 3741, 3212, 2922, 2359, 2339, 1644, 1480, 1434, 1383 cm^{-1}; ^{1}H NMR δ 1.40 (s, 3H), 1.50 (s, 3H), 2.60 (dd, 1H, J = 15.5, 7.5 Hz), 2.96 (dd, 1H, J = 4.5, 15.5 Hz), 3.98 (s, 3H), 4.17 (m, 1H), 4.33 (dd, 1H, J = 7, 6 Hz), 4.95 (d, 1H, J = 6 Hz), 6.02 (m, 2H), 6.75 (s, 1H); CIMS (methane) negative mode (m/z) 346 (60) [M − CH$_3$]$^-$, 360 (100) [M − H]$^-$, 361 (54) [M + 1 − H]$^-$. Compound **37**: IR ν_{max} 3404, 2922, 1650, 1481 cm^{-1}; ^{1}H NMR δ 1.35 (s, 3H), 1.45 (s, 3H), 2.68 (dd, 1H, J = 11, 6 Hz), 3.00 (dd, 1H, J = 4.5, 11 Hz), 4.1 (s, 3H), 4.45 (dd, 1H, J = 6, 6 Hz), 4.96 (d, 1H, J = 6 Hz), 5.39 (m, 1H), 6.10 (m, 2H), 6.75 (s, 1H). Compound **38**: mp 258−260 °C, [α]$_D$ +22.8 (c 0.6, MeOH); IR ν_{max} 3404, 1650, 1479 cm^{-1}; ^{1}H NMR (CD$_3$OD)δ 1.45 (s, 3H), 1.50 (s, 3H), 3.85 (dd, 1H, J = 4,5, 10 Hz), 4.05 (s, 3H), 4.30 (dd, 1H, J = 6.5 Hz), 5.05 (d, 1H, J = 6.5 Hz), 5.37 (d, 1H, J = 4.5 Hz), 6.00 (s, 1H), 6.03 (d, 2H, J = 4.5 Hz), 6.92 (s, 1H), ^{13}C NMR δ 24.06, 24.38, 44.38, 59.30, 69.88, 71.20, 74.90, 96.16, 101.51, 109.28, 109.77, 131.22, 134.66, 136.68, 142.73, 153.10, 160, 171.47. Anal. Calcd for $C_{18}H_{17}NO_7$: C, 60.17; H, 4.77; N, 3.90. Found: C, 59.98; H, 4.62; N, 3.85.

[3a*S*-(3aα,3bα,12α,12aα)]-12-(Acetyloxy)-3b,4,12,12a-tetrahydro-6-methoxy-2,2-dimethylbis[1,3]dioxolo[4,5-*c*:4′,5′-*j*]phenanthridin-5(3a*H*)-one (35). Compound **34** was acetylated under standard conditions (AC_2O, pyridine) to give **35**: R_f 0.30 (MeOH/EtOAc, 1:9), [α]$_D$ +44.6 (c 1.37, CHCl$_3$); IR ν_{max} 1722, 1651, 1485; ^{1}H NMR δ 1.38 (s, 3H), 1.45 (s, 3H), 2.05 (s, 3H), 3.96 (s, 3H), 4.62 (dd, 1H, J = 1, 6.5 Hz), 5.03 (dd, 1H, J = 4.5, 1 Hz), 5.17, (d, 1H, J = 6.5 Hz), 5.56 (dd, 1H, J = 9, 4.5 Hz), 6.00 (s, 1H), 6.05 (s, 1H), 6.62 (d, 1H, J = 9 Hz), 6.65 (s, 1H); ^{13}C NMR δ 22.9, 25.6, 27.7, 44.3, 61.3, 71.8, 72.3, 72.9, 79.5, 102.3, 109.8, 111.4, 113.8, 131.7, 135.1, 137.7, 143.0, 153.7, 170.8, 171.0. Anal. Calcd for $C_{20}H_{21}NO_8$: C, 59.55; H, 5.25; N, 3.47. Found: C, 59.40; H, 5.18; N, 3.52.

[1*R*-(1*β*,2α,3*β*,4*β*)]-6-Methoxy-2,3,4-tri(methoxymethyl)-1,2,3,4-tetrahydro-1-(phenylthio)-2*H*-[1,3]benzodioxolo-[5,6-*c*]-[1]benzopyran-6-one (40). Compound **30** (540 mg, 1.05 mmol) was suspended in a water/THF mixture (44 mL, 3:1 v/v), and then TFA (2.4 mL) was added. The reaction mixture was refluxed for 2 h and then concentrated to dryness and coevaporated three times with toluene. The crude residue was dissolved in dichloromethane (30 mL), diisopropylamine (2 mL) and MOMCl (2 mL) were added, and the resulting mixture was refluxed for 2 h. After the mixture was cooled to room temperature, dichloromethane (50 mL) was added, and the solution was washed twice with water. The organic phase was dried and concentrated. The crude residue was chromatographed on a silica gel column to give pure **40** (413 mg, 70%): R_f 0.13 (hexanes/EtOAc, 3:2); [α]$_D$ +115.1 (c 0.4, CHCl$_3$); IR ν_{max} 3848, 1600, 1614 cm^{-1}; ^{1}H NMR δ 3.46 (s, 6H), 3.47 (s, 3H), 4.12 (s, 3H), 4.57 (m, 1H), 4.65−4.95 (m, 8H), 5.51 (dd, 1H, J = 4, 10 Hz), 6.08 (s, 2H), 6.82 (s, 1H), 7.24−7.54 (m, 5H). Anal. Calcd for $C_{27}H_{30}O_{11}S$: C, 57.64; H, 5.37; S, 5.70. Found: C, 57.92; H, 5.42; S, 5.55.

4-Methoxy-6-[(3*R*,4*S*,5*R*)(3,4,5-tris-methoxomethoxy-6-oxocyclohex-1-enyl)]benzo[1,3]dioxole-5-carboxamide (41). A solution of lactone **40** (160 mg, 0.28 mmol) in methanol (12 mL) was cooled to 0 °C. A stream of gaseous ammonia was bubbled through the solution until saturation occurred. The mixture was then allowed to warm to room temperature for 4 h while a gentle stream of ammonia was maintained. Excess ammonia was cautiously removed under vacuum, and the solvent was then removed. The crude residue was chromatographed on a silica gel column to give pure **41** (98 mg, 73%): R_f 0.21 (EtOAc); [α]$_D$ −112 (c 0.6, CHCl$_3$); IR ν_{max} 3323, 1731, 1668, 1609 cm^{-1}; ^{1}H NMR δ 3.37 (s, 3H), 3.38 (s, 3H), 3.55 (s, 3H), 4.04 (s, 3H), 4.12 (d, 1H, J = 2 Hz), 4.23 (m, 1H), 4.34 (dd,1H, J = 5, 4 Hz), 4.71−4.90 (m, 6H), 5.97 (s, 1H), 5.99 (s, 1H),6.08 (s, 2H), 6.10 (d, 1H, J = 5 Hz), 6.76 (s, 1H). Anal. Calcd for $C_{21}H_{27}O_{11}N$: C, 53.70; H, 5.75; N, 2.98. Found: C, 53.4; H, 5.82; N, 2.68.

[2*S*-(2α,3*β*,4*β*)]-7-Methoxy-2,3,4-tri(methoxymethoxy)-1,3,4,5-tetrahydro-2*H*-[1,3]dioxolo[4,5-*j*]phenanthridin-6-one (42) and [2*R*-(2α,3*β*,4*β*)]-6-methoxy-2,3,4-tri(methoxymethyl)-1,2,3,4-tetrahydro-2*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-6-one (43). To a solution of **41** (90 mg, 0.2 mmol) in dry acetonitrile (9 mL) were added formic acid (1 mL) and sodium cyanoborohydride (25 mg, 0.4 mmol). The mixture was heated at reflux for 12 h. After cooling, 3 N hydrochloric acid (1 mL) and CH_2Cl_2 (25 mL) were added. The organic phase was washed with saturated sodium bicarbonate solution and water and dried. After concentration, the residue was chromatographed on a silica gel column to give **42** (54 mg, 62%) and **43** (12 mg, 13%). Compound **42**: R_f 0.48 (CH_2Cl_2/MeOH 18/1); [α]$_D$ +52.7 (c 0.15, CHCl$_3$); IR ν_{max} 2924, 1649 cm^{-1}; ^{1}H NMR δ 2.66 (dd, 1H, J = 11, 8 Hz), 3.04 (dd, 1H, J = 5, 11 Hz), 3.38 (s, 3H), 3.41 (s, 3H), 3.50 (s, 3H), 4.09 (s, 3H), 4.12 (dd, 1H, J = 3.5, 5 Hz), 4.29 (m, 1H), 4.96 (d, 1H, J = 3.5 Hz), 4.73−4.99 (m, 6H), 6.05 (s, 2H), 6.70 (s, 1H), 8.88 (s, 1H). Anal. Calcd for $C_{21}H_{27}O_{10}N$: C, 55.63; H, 6.00; N, 3.09; Found: C, 55.30; H, 6.16; N, 2.88. Compound **43**: R_f 0.43 (CH_2Cl_2/MeOH 18/1); IR ν_{max} 3344, 1643 cm^{-1}; ^{1}H NMR δ 2.55 (dd, 1H, J = 10, 5 Hz), 3.12 (dd, 1H, J = 7, 10 Hz), 3.43 (s, 3H), 3.45 (s, 3H), 3.48 (s, 3H), 3.88 (dd, J = 6.5, 3.5 Hz), 4.07 (s, 3H), 4.32 (m, 1H), 4.52 (d, 1H, J = 3.5 Hz), 4.72−4.94 (m, 6H), 6.05 (s, 2H), 6.70 (s, 1H).

[6a*S*-(6aα,7*β*,8*β*,9α)]-6a,7,8,9-Tetrahydro-4methoxy-7,8,9-trihydroxy-5*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-5-one (44) and [6a*R*-(6aα,7*β*,8*β*,9α)]-6a,7,8,9-Tetrahydro-4-methoxy-7,8,9-trihydroxy-5*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-5-one (45). To a solution of **23** or **20** (477 mg, 1 mmol) in 95% acetic acid (20 mL) was added trifluoroacetic acid (1 mL). The mixture was heated under reflux for 8 h and then concentrated. The residue was coevaporated three times with methanol (15 mL). Pure compounds **44** (158 mg, 49%) or **45** (174 mg, 54%) were obtained after silica gel column

chromatography using MeOH/EtOAc, 1:9 as eluent. Compound **44**: R_f 0.3 (MeOH/EtOAc 1:9); mp 136−138 °C; $[\alpha]_D$ +15 (*c* 0.2, MeOH); IR ν_{max} 3379, 2920, 1702, 1606, 1480, 1368, 1254, 1090 cm^{-1}; ^{1}H NMR (CD_3OD) δ 3.51 (dd, 1H, J = 1.5, 8.5 Hz) 3.95 (s, 3H), 4.23 (dd, 1H, J = 3.5, 1.5 Hz), 4.45 (ddd, 1H, J = 2, 1, 8.5 Hz), 5.05 (m, 1H), 6.00 (d, 2H, J = 10 Hz), 6.22 (dd, 1H, J = 1.5, 2 Hz), 6.85 (s, 1H); ^{13}C NMR (CD_3OD) δ 60.9, 69.3, 70.7, 73.4, 76.9, 102.1, 102.2, 116.9; 125.4, 126.8, 132.5, 139.3, 148.5, 153.1, 164.6. Anal. Calcd for $C_{15}H_{14}O_8$: C, 55.90; H, 4.38. Found: C, 56.12; H, 4.34. Compound **45**: R_f 0.3 (MeOH/EtOAc 1:9); mp 116−118 °C; $[\alpha]_D$ +102.1 (*c* 0.5, MeOH); IR ν_{max} 3379, 2920, 1702, 1606, 1480, 1368, 1254, 1090 cm^{-1}; ^{1}H NMR (CD_3OD) δ 3.85 (ddd, 1H, J = 1, 2, 3.5 Hz) 3.98 (s, 3H), 4.12 (dd, 1H, J = 7.5, 2 Hz), 4.24 (dd, 1H, J = 4.5, 3.5 Hz), 4.86 (dd, 1H, J = 1.5, 7.5 Hz), 6.03 (d, 2H, J = 12 Hz), 6.29 (dt, 1H, J = 1, 1.5, 4.5 Hz), 6.86 (s, 1H); ^{13}C NMR (CD_3OD) δ 60.4, 70.0, 70.5, 74.4, 79.2, 99.7, 103.8, 110.9, 126.2, 131.4, 136.1, 139.1, 146.8, 155.5, 165.0. Anal. Calcd for $C_{15}H_{14}O_8$: C, 55.90; H, 4.38. Found: C, 55.98; H, 4.68.

[6a*S*-(6aα,7*β*,8*β*,9α)]-6a,7,8,9-Tetrahydro-7,8,9-trihydroxy-5*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-5-one (47): R_f 0.35 (MeOH/EtOAc 1:10); $[\alpha]_D$ −54.9 (*c* 0.7, MeOH); IR ν_{max} 3368, 2921, 1704, 1613, 1121, 1038 cm^{-1}; ^{1}H NMR (CD_3OD) δ 3.63 (dd, 1H, J = 2, 8 Hz), 4.34 (dd, 1H, J = 2, 3 Hz), 4.54 (ddd, 1H, J = 2.5, 3, 8 Hz), 5.25 (ddd, 1H, J = 2, 2, 3 Hz), 6.09 (d, 2H, J = 1.5 Hz), 6.30 (dd, 1H, J = 2.5, 2 Hz), 7.16 (s, 1H), 7.38 (s, 1H); ^{13}C NMR (CD_3OD) δ 60.3, 70.7, 73.4, 76.9, 102.1, 102.2, 108.1, 116.9, 125.4, 126.8, 132.5, 139.3, 148.5, 153.1, 164.6. Anal. Calcd for $C_{14}H_{12}O_7$: C, 57.54; H, 4.14; Found: C, 57.69; H, 4.08.

[6a*R*-(6aα,7*β*,8*β*,9α)]-6a,7,8,9-Tetrahydro-7,8,9-trihydroxy-5*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-5-one (48): R_f 0.44 (MeOH/EtOAc 1:10); mp 148−150 °C; $[\alpha]_D$ +77.3 (*c* 0.5, MeOH); IR ν_{max} 3370, 2360, 1694, 1483, 1270, 1033 cm^{-1}; ^{1}H NMR (CD_3OD) δ 3.96 (ddd, 1H, J = 1, 3, 2.6 Hz), 4.22 (dd, 1H, J = 7.5, 2.6 Hz), 4.31 (dd, 1H, J = 4.5, 3 Hz), 5.08 (dd, 1H, J = 2, 7.5 Hz), 6.10 (d, 2H, J = 2.5 Hz), 6.33 (dt, 1H, J = 1, 2, 4.59 Hz), 7.16 (s, 1H), 7.40 (s, 1H); ^{13}C NMR (CD_3OD) δ 69.5, 69.8, 73.9, 69.6, 103.2, 103.6, 109.1, 118.1; 125.2, 130.2, 134.1, 149.7, 154.1, 164.0. Anal. Calcd for $C_{14}H_{12}O_7$: C, 57.54; H, 4.14. Found: C, 57.68; H, 4.10.

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Supporting Information Available: General experimental methods. Copies of NMR spectra of compound **6**−**14**, **18**, **20**−**22**, **25**, **26**, **29**−**31**, **35**, **38**, **41**, **42**, **44**, **45**, **47**, and **48**. This material is available free of charge via the Internet at http://pubs.acs.org.

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