JOC Article

Naphthalene Analogues of Lignans†

Blanca Madrigal, Pilar Puebla, Rafael Peláez, Esther Caballero, and Manuel Medarde*

Laboratorio de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad de Salamanca, Campus Miguel de Unamuno, E-37007 Salamanca, Spain

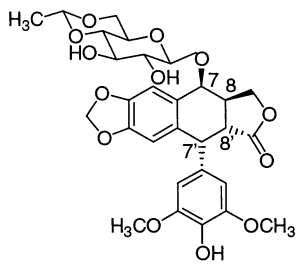
medarde@usal.es

Received August 19, 2002

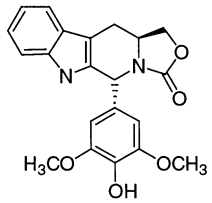
The methodology for the synthesis of podophyllotoxin and thuriferic acid-type lignans has been applied to derivatives carrying a naphthalene moiety. Starting from the 1,3-dithiane of 2-naphthaldehyde afforded the expected analogues in the 2,1-naphthalene series. The preferred conformations of these compounds are influenced by the bulky naphthalene system. By contrast, 1,8-bridged products were obtained from the 1,3-dithiane of 1-naphthaldehyde. In this series, polycyclic naphthalene lignan analogues were isolated after deprotection and/or desulfurization reactions. The cyclizations produced in this process are due to the proximity between the 3,4,5-trimethoxyphenyl moiety and the reacting C-2 of the 1,3-dithiane ring.

Introduction

Lignans are a very interesting class of natural products[1] due to their pharmacological properties,[2] their great number of structural possibilities,[3] and the chemical approaches[4] to their synthesis. Among the lignan family, the cytotoxic podophyllotoxin[5] has been the most studied and its derivative etoposide is currently used in cancer chemotherapy.[6] The synthesis of podophyllotoxin and other arylnaphthalene lignans has been accomplished by several methods, whose most demanding challenge is to complete the stereochemical arrangement in the C ring: the so-called cis−trans (7′−8′ cis; 8−8′ trans) stereochemistry. During our previous work, we prepared and assayed several families of heterolignans[7] carrying heterocyclic moieties in their structure.[8] Azatoxin[9] is the most representative heterolignan with well-known biological activities, the most interesting of which is its anticancer potential as a DNA Topoisomerase II[10] inhibitor.



Etoposide



Azatoxin

As part of our research on lignans, a new approach to the synthesis of podophyllotoxin based on key epimerization reactions, from the (7′,8′−8,8′)-trans−trans stereochemistry of the major cyclization product to the required (7′,8′−8,8′)-cis−trans stereochemistry of podophyllotoxin (Scheme 1), has been described.[11]

With this procedure we have been able to synthesize several new families of compounds carrying heterocyclic ring systems instead of the A,B-ring system of podophyllotoxins (Figure 1).[12] Finally, the naphthyl and heterocyclic (furan, thiophene, carbazole) analogues of thuriferic acid and podophyllotoxin have been evaluated for their cytotoxicity.[13] On the basis of this research, the existence of a different mechanism of action for thuriferic acid and

* To whom correspondence should be addressed.

† This paper is dedicated in memory of our colleague Dr. Benedicto del Rey.

(1) (a) Rao, C. B. S. *Chemistry of Lignans*; Andhra University Press: Waltair, 1978. (b) Ayres, D. C.; Loike, J. D. *Lignans: Chemical, Biological and Clinical Properties*; Cambridge University Press: Cambridge, 1990.

(2) (a) Gordaliza, M.; Castro M. A.; Miguel del Corral, J. M.; San Feliciano, A. *Curr. Pharm. Des.* **2000**, *6*, 1811. (b) Damayanthi, Y.; Lown, J. W. *Curr. Med. Chem.* **1998**, *5*, 205.

(3) (a) Whiting, D. A. *Nat. Prod. Rep.* **1985**, *2*, 191. (b) Moss, G. P. *Pure Appl. Chem.* **2000**, *72*, 1493.

(4) (a) Ward, R. S. *Chem. Soc. Rev.* **1982**, *11*, 75. (b) Ward, R. S. *Synthesis* **1992**, 719.

(5) Jardine, I. Podofilotoxins. In *Anticancer Agents Based on Natural Products Models;* Cassady, J. M., Douras, J. D., Eds.; Academic Press: New York, 1980; Chapter 9.

(6) (a) Hande, K. R. *Eur. J. Can.* **1998**, *34*, 1514. (b) Stähelin, H.; von Wartburg, A. From Podophyllotoxin Glucoside to Etoposide. In *Progress in Drug Research*; 1989; Vol. 33, pp 169−266.

(7) Ramos, A. C.; Peláez- Lamamié de Clairac, R.; Medarde, M. *Heterocycles* **1999**, *51*, 1443.

(8) Medarde, M.; Peláez-Lamamié de Clairac, R.; Tomé, F.; López, J. L.; San Feliciano, A. *Arch. Pharm. (Weinheim)* **1995**, *328*, 403.

(9) Leteurtre, F.; Madalengoitia, J. S.; Orr, A.; Guzi, T. J.; Lehnert, E. K.; Macdonald, T. L.; Pommier, Y. *Cancer Res.* **1992**, *52*, 4478.

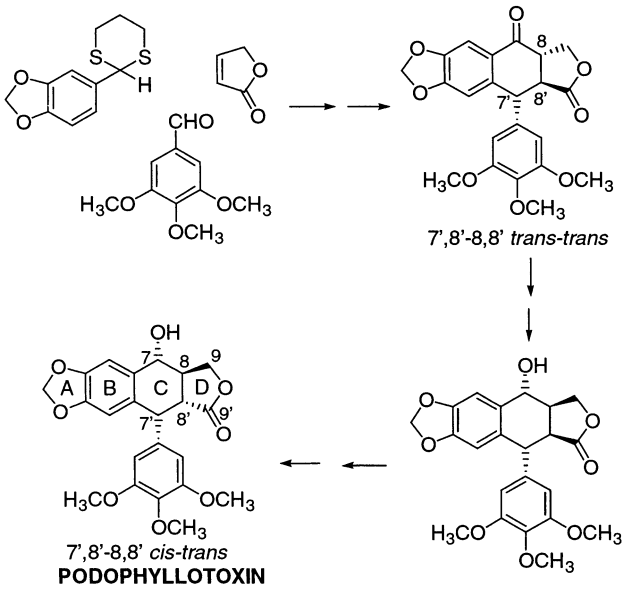
(10) (a) Eymin, B.; Solary, E.; Chevillard, S.; Dubrez, L.; Goldwasser, F.; Duchamp, O.; Genne, P.; Leteurtre, F.; Pommier, Y. *Int. J. Cancer* **1995**, *63*, 268. (b) Leteurtre, F.; Sackett, D. L.; Madalengoitia, J.; Kohlhagen, G.; Macdonald, T.; Hamel, E.; Paull, K. D.; Pommier, Y. *Biochem. Pharmacol.* **1995**, *49*, 1283.

(11) Medarde, M.; Ramos, A. C.; Caballero, E.; López, J. L.; Peláez-Lamamié, R.; San Feliciano, A. *Tetrahedron Lett.* **1996**, *37*, 2663.

(12) Ramos, A.C.; Peláez, R.; López, J. L.; Caballero, E.; Medarde, M.; San Feliciano, A. *Tetrahedron* **2001**, *57*, 3963.

10.1021/jo0263364 CCC: $25.00
Published on Web 12/19/2002

SCHEME 1. Synthetic Approach to Podophyllotoxin



its analogues with respect to the podophyllotoxin and its analogues has been proposed due to the very dissimilar structure−activity relationships observed for both families of compounds.

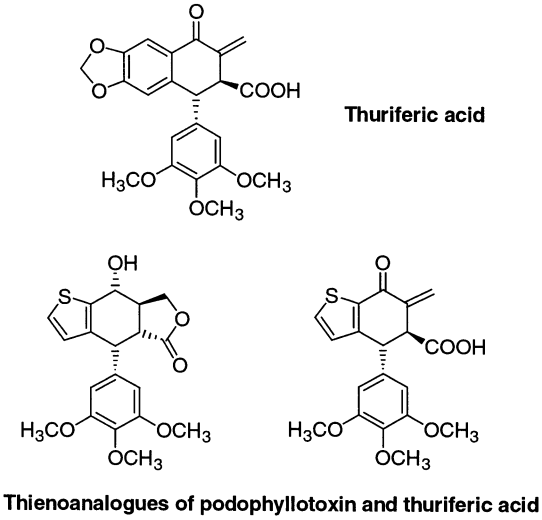


FIGURE 1.

To prepare further derivatives for the activity assays and to demonstrate the usefulness of our approach in the synthesis of new lignan analogues, we decided to study the preparation of naphtho analogues of podophyllotoxins and thuriferic acid starting from 1- and 2-naphthaldehydes. Here, we report the results obtained during this research.

Methods and Results

The synthesis of the three types of naphthalene analogues of podophyllotoxin was planned as depicted in Scheme 2.

2,1-Naphtho-podophyllotoxin could be synthesized starting from the dithioketal of 2-naphthaldehyde, an approach that would lead to the final product without the competition of other cyclization regiochemistries. The higher reactivity at position 1 of the naphthalene system must direct the cyclization step of the 2-naphthyl podorhizol-like intermediate to form the 2,1-fused naphthalene analogue (Scheme 2A). According to our previous methodology, the 2,1-naphtho analogue of podophyllotoxin would be obtained in a stereocontrolled way from the cyclized synthetic intermediate (Scheme 1). Thuriferic acid analogues would be obtained through lactone opening by treatment with base.

The electrophilic cyclization procedure is not suited for the preparation of the 2,3-naphtho-podophyllotoxin regioisomeric products. Taking into account that yatein is a known intermediate in the biosynthetic pathway to podophyllotoxin,[14] the naphthyl analogue depicted in Scheme 2B can be used in cell culture feeding experiments to assay such a cyclization. Preliminary attempts[15] in this direction have so far been unsuccessful, and future work must be done to check the feasibility of this approach.

For the synthesis of 1,2-naphtho-podophyllotoxin regioisomers, a competition between cyclization at the required 2-position and cyclization at the 8-position could be foreseen (Scheme 2C). Position 2 is less reactive, but cyclization at the preferred 8-position would form a highly strained seven-membered ring, with a planar 1,8a,8 moiety and a trans-fused lactone. Under these circumstances, 1,2-naphthopodophyllotoxin analogues could be produced in the cyclization.

With this plan, we decided to study the synthesis of 2,1-naphthalene (starting from 2-(2-naphthyl)-1,3-dithiane) and 1,2-naphthalene (starting from 2-(1-naphthyl)-1,3-dithiane) analogues of podophyllotoxins using the proposed methodology.

Synthesis from 2-(2-Naphthyl)-1,3-dithiane (1). Starting from 2-(2-naphthyl)-1,3-dithiane (**1**), lithiation at position 2 with butyllithium followed by conjugate addition to 5*H*-furan-2-one and alkylation with 3,4,5-trimethoxybenzaldehyde, at low temperature in the presence of 2 equiv of TMEDA, yielded a 2:1 mixture of the erythro (**2**) and threo (**3**) alcohols. Minor amounts of nonalkylated lactone **4** were observed in some reactions (Scheme 3).

These results are consistent with those usually observed when 2-aryl-1,3-dithianes are used as starting materials.[16] The cyclization of isolated compounds or mixtures of **2** and **3** under different acidic conditions[17] always yielded the same cyclization products at the 1-position of the naphthalene. The stereochemical outcome of the cyclization is the formation of compounds **5**

(13) Madrigal, B.; Puebla, P.; Ramos, A.; Peláez, R.; Grávalos, D.; Caballero, E.; Medarde, M. *Bioorg. Med. Chem.* **2002**, *10*, 303.

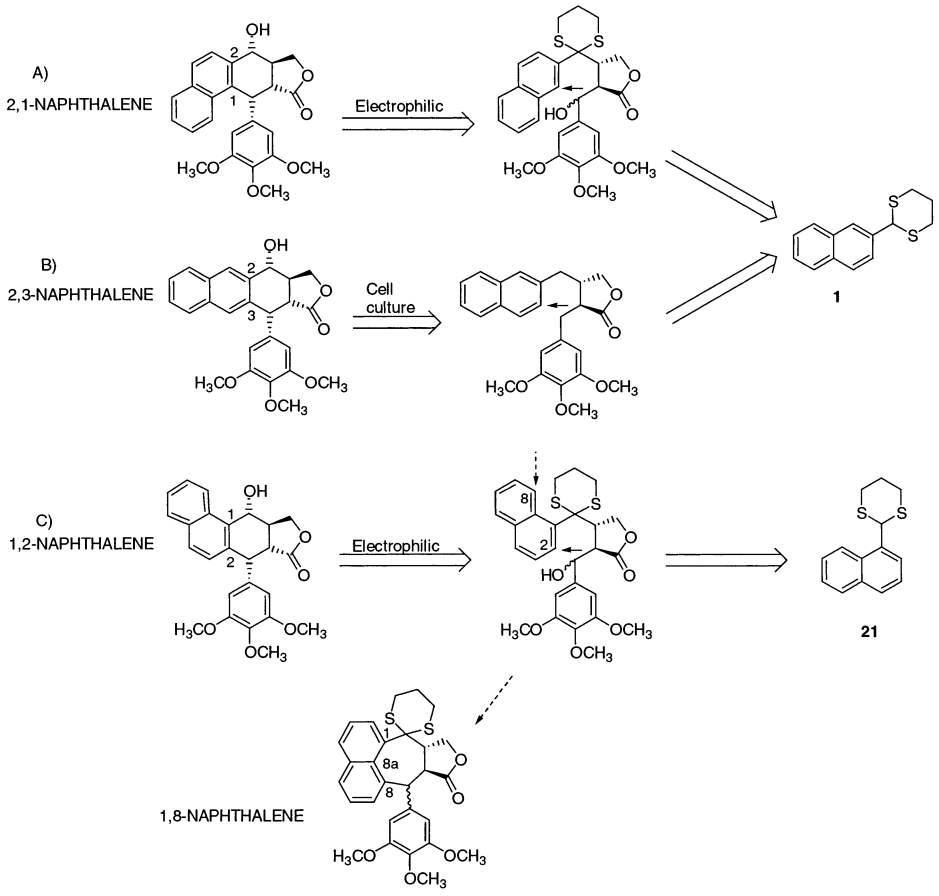
(14) Lewis, N. G.; Davin, L. B. Lignans: Biosynthesis and Function. In *Comprehensive Natural Products Chemistry*. Pinto, B. M., Ed.; Pergamon Press: Oxford, 1999. Vol. 3, pp 639−712.

(15) Pras, N.; Koulhman, A. Farmaceutische Biology. Rijks Universiteit, Groningen, The Netherlands. Personal communication, 2001.

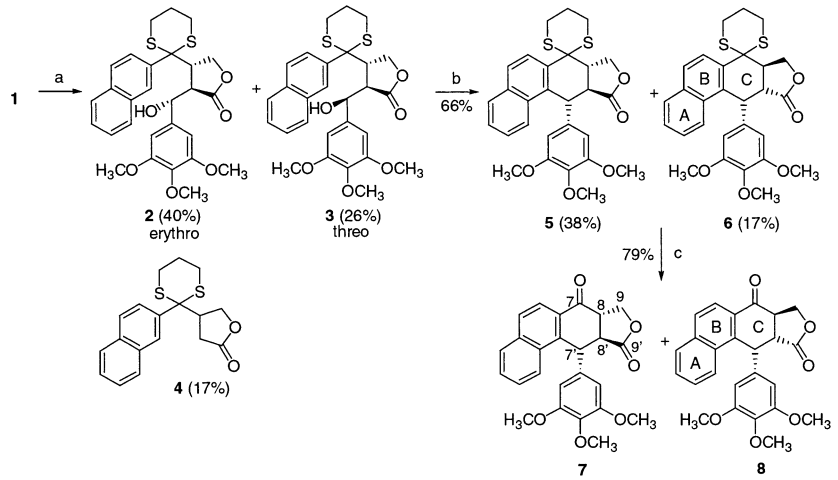
(16) (a) Eich, E.; Pertz, H.; Schulz, J.; Fesen, M. R.; Mazumder, A.; Pommier, Y. *J. Med. Chem.* **1996**, *39*, 86. (b) Medarde, M.; Peláez-Lamamié de Clairac, R.; Tomé, F.; López, J. L.; San Feliciano, A. *Arch. Pharm.* (*Weinheim*) **1994**, *327*, 91. (c) Hanessian, S.; Murray, P. J. *J. Can. Chem.* **1986**, *64*, 2231. (d) Michael, Y. L.; Paddon-Row, N.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3648. (e) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1975**, *79*, 1920.

(17) (a) Ogiku, T.; Yoshida, S. I.; Ohmizu, H. E.; Iwasaki, T. *J. Org. Chem.* **1995**, *60*, 4585. (b) González, A. G.; de la Rosa, R.; Trujillo, J. M. *Tetrahedron* **1986**, *42*, 3899. (c) Pelter, A.; Ward, R. S.; Prichard, M. C.; Kay, I. T. *Tetrahedron Lett.* **1985**, *26*, 6377.

SCHEME 2



SCHEME 3[a,b]



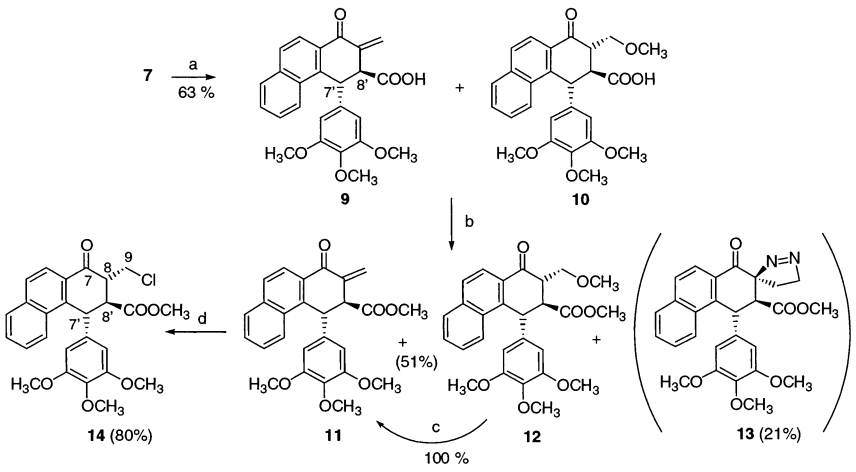
[a] Each structure depicted represents the relative stereochemistry of a racemic mixture. Yields under structures: isolated compounds. Yields under arrows: purified crude of reaction. [b]Reagents and conditions: (a) 1.6 M BuLi, THF, −78 °C, 45 min, then 5*H*-furan-2-one, THF, −78 °C, 3 h, then 3,4,5-trimethoxybenzaldehyde, THF, TMEDA, −50 °C, 12 h; (b) TFA, CH_2Cl_2, rt, 24 h; (c) THF/H_2O, HgO, 0 °C, then $BF_3{\cdot}OEt_2$, 24 h, rt.

(trans−trans, isopodophyllotoxin-type; major product) and **6** (cis−trans, podophyllotoxin-type; minor product), as usually described for such a cyclization reaction.[18] Deprotection of **5** and **6** gave ketoderivatives **7** and **8**, with no change in the relative stereochemistry at positions 8 or 8′. The H-7′ NMR signal clearly differentiates both stereoisomers, showing a large coupling constant (trans) for the isopodophyllotoxin analogue **7** and a strong deshielding for the podophyllotoxin analogue **8**, which has H-7′ near the plane containing A−B−C rings, deshielded by the naphthalene.

Compound **7** is the key intermediate for the synthesis of podophyllotoxin and thuriferic acid analogues[19] (which can also be obtained from **8**). The opening of the lactone

(18) Brown, E.; Daugan, A. *Tetrahedron* **1989**, *45*, 141.

SCHEME 4[a]



[a] Reagents and conditions: (a) KOH/MeOH (1%), 1.5 h, rt; (b) CH_2N_2/ether, 5 min; (c) *p*-TsOH, benzene, Δ, 7 h; (d) HCl, CH_2Cl_2, 2 h, rt.

TABLE 1. Comparison of ^{1}H NMR Data of Thuriferates and Their Naphtho Analogues

	H-7′	H-8′	H-8
methyl thuriferate	4.64 *d* 3.7	3.91 *d* 3.7	
methyl 9-chlorodihydrothuriferate	4.33 *d* 11.7	3.58 *dd* 11.7; 10.8	3.26 *ddd* 10.8; 3.1; 2.9
11	5.41 *s*	4.04 *s*	
12	5.38 *d* 1.8	3.75 *dd* 1.8; 4.7	3.18 *ddd* 8.3; 5.4; 4.7
14	5.46 *s*	3.91 *d* 4.2	3.17 *ddd* 10.4; 5.4; 4.2

ring by treatment with base yields a mixture of the expected acidic derivative **9** and the product from methanol conjugate addition **10** (Scheme 4). Both compounds were converted into methyl esters **11** and **12** with diazomethane, which also yielded **13** as a byproduct. Conjugate addition products of type **12** are easily obtained from unsaturated ketones, as it was confirmed by the isolation of **14** after treatment of **11** with hydrochloric acid. The methoxy derivative **12** was converted into a thuriferic acid analogue **11** by acidic treatment.

The relative stereochemistry at H-7′−H-8′ for thuriferic acid and derivatives was unequivocally established as trans in the literature, on the basis of coupling constants, NOE studies, and theoretical calculations,[20] but the data for the naphtho analogues are different from those described. As shown in Table 1, there are significant variations in the chemical shifts and coupling constants.

These differences can be explained by the effect of the naphthalene ring oriented toward the 3,4,5-trimethoxyphenyl residue, thus triggering a change in the conformational preference for the substituents on C-7′ and C-8′ in the naphtho analogues. The most striking variation lies in the small coupling constants between H-7′−H-8′−H-8 for the 9-chloro (**14**) and 9-methoxy (**12**) derivatives, in agreement with a trans−trans equatorial arrangement for these hydrogens, whereas in the 9-chloro (9-methoxy) derivatives from methyl thuriferate, these couplings are >10 Hz, in agreement with a trans−trans axial arrangement. The proposed stereochemistry is confirmed by the NOEs between the H-atoms Ar-2′-6′ and 9ab of

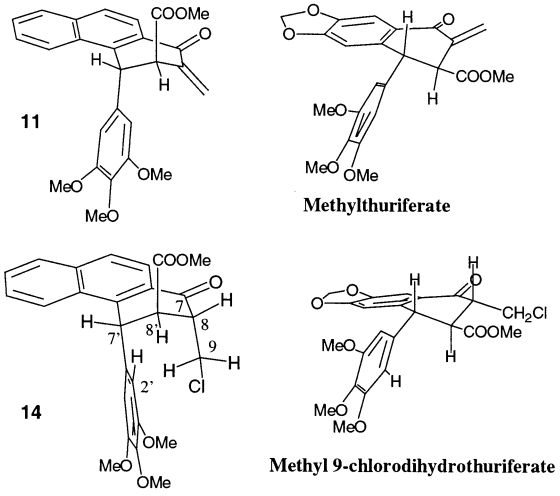


FIGURE 2. Conformations of thuriferates and their analogues **11** and **14**.

compounds **12** and **14**. The strong deshielding produced on H7′ in compounds **11**−**14** is a consequence of its proximity to the plane of the naphthalene system. The results of molecular modeling, in agreement with the more stable conformations deduced from NMR, are shown in Figure 2.

Following our strategy for the preparation of podophyllotoxin, the synthesis of 2,1-naphtho-podophyllotoxin is straightforward from intermediate **7** (Scheme 5).

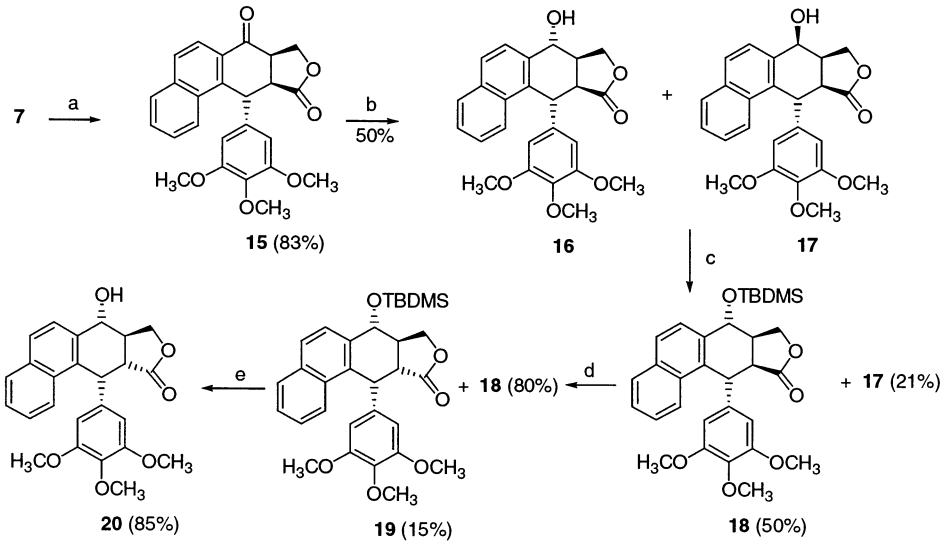
In agreement with the results described for isopodophyllotoxone,[21] the acidic epimerization at C8 yielded the

(19) San Feliciano, A.; López, J. L.; Medarde, M.; Miguel del Corral, J. M.; Pascual-Teresa, B.; Puebla, P. *Tetrahedron* **1988**, *44*, 7255.

(20) (a) López, J. L.; Olmo, E.; Pascual-Teresa, B.; Merino, M.; Martín, S.; San Feliciano, A. *Tetrahedron* **1995**, *51*, 6343. (b) López, J. L.; Olmo, E.; Pascual-Teresa, B.; Merino, M.; San Feliciano, A. *Tetrahedron* **1996**, *52*, 4903.

(21) (a) Medarde, M.; Ramos, A. C.; Caballero, E.; López, J. L.; Peláez-Lamamié, R.; San Feliciano, A. *Tetrahedron Lett.* **1996**, *37*, 2663. (b) Miguel del Corral, J. M.; Gordaliza, M.; López, J. L.; Olmo, E.; Castro, M. A.; López, M. L. *Helv. Chim. Acta* **1995**, *78*, 1793. (c) Jackson, D. E.; Dewick, P. M. *Phytochemistry* **1985**, *24*, 2407.

SCHEME 5[a]



[a] Reagents and conditions: (a) AcOH, EtOH, 72 h, Δ; (b) $LiAlH(^tBuO)_3$/THF, 24 h, rt; (c) TBDMSTf, CH_2Cl_2, $^iPr_2NEt$, 4 h, 0 °C; (d) LDA, THF, 15 min, −78 °C, then, AcOH; (e) $Et_3N{\cdot}3HF$, CH_3CN, 72 h, rt.

picropodophyllone stereochemistry for compound **15**. Upon reduction with the bulky tri-*tert*-butoxy lithium aluminum hydride, a 2:1 mixture of epimeric alcohols **16** and **17** was obtained. Although these alcohols could not be separated, the required *tert*-butyldimethylsilylation was stereoselective toward **16**, thus allowing the isolation of the protected α-siloxy derivative **18** from its mixture with the unprotected *β*-hydroxyderivative **17**. Following Kende's methodology,[22] deprotonation of **18** with lithium hexamethyldisilazide followed by kinetic reprotonation only produced the starting material, but a similar procedure using lithium diisopropylamide yielded a mixture of both stereoisomers at C-8′ (**18** + **19**). In this case a 4:1 ratio between the nontransformed "picro" isomer **18** and the epimerized "podo" isomer **19** was observed (ratios from 1.2:1 to 2:1 are usually described in the literature for podophyllotoxins). The large coupling between H-8 and H-8′ (14.4 Hz) and NOEs on H-8′ upon irradiation of H-7(*β*) are in agreement with the "podo" configuration of **19**.

Standard deprotection of compound **19** with TBAF regenerated **16**, with the more stable "picro" configuration. The base character of fluoride ion in aprotic media favors the epimerization at C-8′. To obtain the deprotected "podo" isomer, triethylamine trihydro fluoride was used, yielding deprotected **20** with no detectable epimerization to **16**.

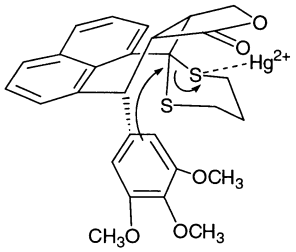
The synthesis of 2,1-naphthopodophyllotoxin, **20**, confirmed the interest of this methodology. The most demanding step is the epimerization via deprotonation−kinetic reprotonation, which in some instances was useless for the heterocyclic analogues of podophyllotoxin.[12]

Synthesis from 2-(1-Naphthyl)-1,3-dithiane (21). Once synthesis of the 2,1-naphtho analogues had been completed, the preparation of the 1,2-naphtho derivatives was attempted by the same procedure, using dithiane **21** as starting material. As depicted in Scheme 6, the conjugate addition alkylation process yielded a mixture of alcohols **22** and **23** and lactone **24**.

The mixture of **22** and **23** could not be separated, and its NMR spectra (^1H and ^{13}C) showed an unusual line broadening in all the solvents assayed ($CDCl_3$, DMSO-d_6, pyr-d_5) in the temperature range from −7 to 60 °C. The structures of **22** and **23** were confirmed by Raney Ni reduction to hydroxy derivatives **25** and **26**, analogues of the natural products podorhizol and *epi*-podorhizol.[23]

The mixture of **22** + **23** was treated with trifluoroacetic acid, yielding a mixture of two isomeric cyclization products **27** and **28**, which were isolated but could not be identified directly because of spectral broadening. The structural confirmation was completed by means of chemical transformation in other derivatives, as discussed below. One possible explanation for the line broadening seen in the NMR spectra is the presence of several interconverting conformations of similar thermodynamic stability, exchanging at intermediate rates on the NMR time scale. Molecular modeling for these compounds revealed the existence of two main conformational clusters, arising from conformational changes of the dithiane chair and the cycloheptane fused to the naphthalene. Conformations of similar stabilities also exist, due to rotation of the trimethoxyphenyl ring.

Accordingly, we decided to remove the no longer required dithiane group, expecting a beneficial effect on the NMR spectra. However, treatment of a **27** + **28** mixture following a standard procedure yielded compound **29**, instead of the deprotected ketones (Scheme 7).

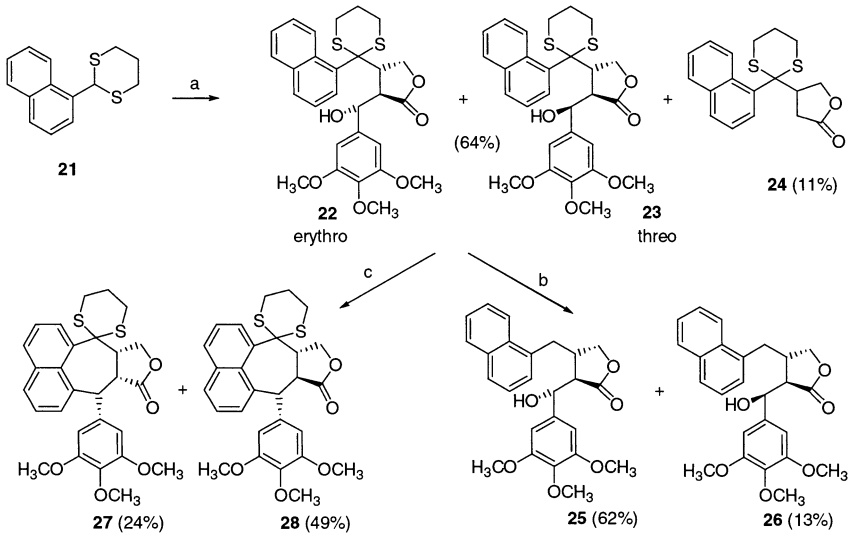


Molecular modeling of compound **27** showed the close proximity between position 2′ of the 3′,4′,5′-trimethox-

(22) Kende, A. S.; King, M. L.; Curran, D. P. *J. Org. Chem.* **1981**, *46*, 2826.

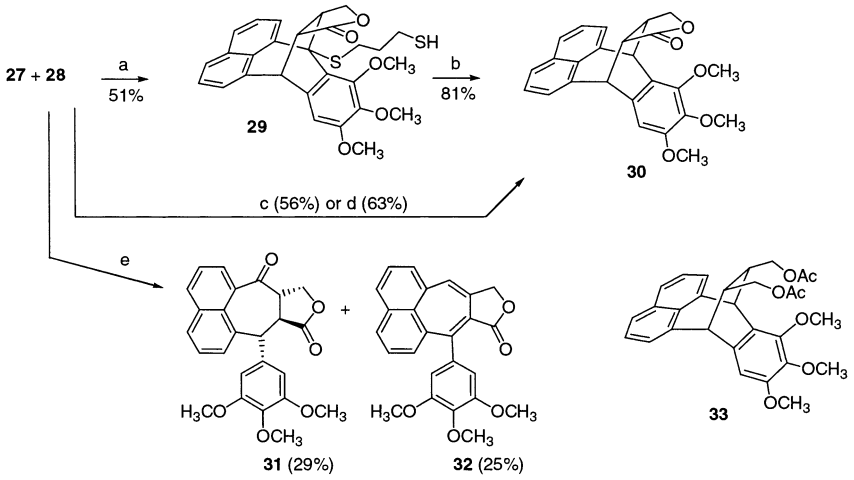
(23) Khun, M.; von Wartburg, A. *Helv. Chim. Acta* **1967**, 1546.

SCHEME 6[a]



[a] Reagents and conditions: (a) 1.6 M BuLi, THF, −78 °C, 45 min, then 5*H*-furan-2-one, THF, −78 °C, 3 h, then 3,4,5-trimethoxybenzaldehyde, THF, TMEDA, −50 °C, 12 h; (b) Raney Ni, EtOH, 1 h, Δ; (c) TFA, CH_2Cl_2, 2 h, rt.

SCHEME 7[a]



[a] Reagents and conditions: (a) THF/H_2O, HgO, 0 °C, then BF_3·OEt_2, 24 h, rt; (b) Raney Ni, EtOH, 2 h, Δ; (c) Raney Ni, EtOH, 15 min, Δ; (d) Bu_3SnH, AIBN, toluene, 72 h, 90 °C; (e) $Me_3O^+BF_4^-$, CH_2Cl_2, 10 h, rt.

yphenyl ring and the dithioketal position. The association of the Hg^{2+} with the dithiane sulfur favors the cleavage of the C−S bond[24] and facilitates the attack of the aromatic ring on the other side, explaining the unexpected ring closure.

Raney Ni reduction of **29** produced **30**, whose structure was unequivocally established by full spectroscopic characterization. In the absence of key NOEs between the lactone protons and those of the aromatic rings, the disposition of the lactone toward the trimethoxyphenyl ring was deduced from the strong deshielding effect on both moieties upon addition of the europium shift reagent $Eu(fod)_3$.[25] A similar deshielding effect was not observed on the naphthalene resonances.

Transformation of **27** + **28** into the cyclized product **30** was also achieved with Raney Ni or tributyltin hydride[26] (TBTH, used to generate radicals from carbon−heteroatom bonds).

Treatment of the mixture **27** + **28** with the alkylating agent trimethyloxonium tetrafluoroborate (TFBTO),[27] which is able to methylate the sulfur atoms, producing the opening of the 1,3-dithiane moiety, generated ketone **31** and product **32**. Compound **31** is formed by hydration of the intermediate from the dithiane methylation and opening. Compound **32** would result from elimination of the methylated 1,3-dithiane. Compound **31** is the key intermediate for the synthesis of thuriferic acid and podophyllotoxin analogues, although its synthesis was

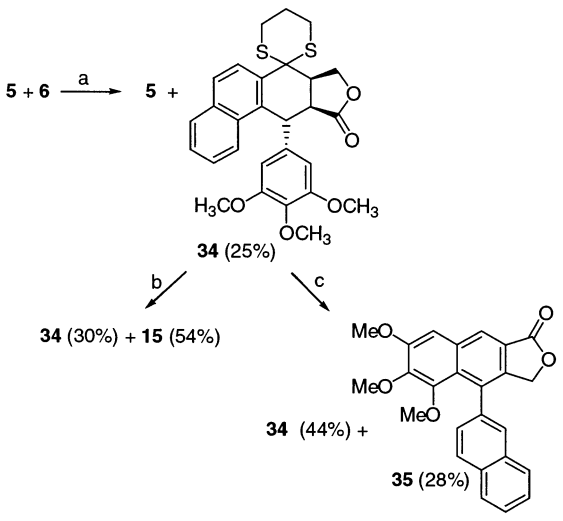
(24) Saigo, K.; Hashimoto, Y.; Kihara, N.; Hara, K.; Hasgawy, M. *Chem. Lett.* **1990**, 1097.

(25) (a) Jiang J−L.; Li, A.-H.; Jang, S.-Y.; Chang, L.; Melman, N.; Moro, S.; Ji, X.-D.; Lobkovsky, E. B.; Clardy, J. C.; Jacobson, K. A. *J. Med. Chem.* **1999**, *42*, 3055. (b) Günther, H. *NMR Spectroscopy*; Wiley & Sons: Chichester, UK, 2001; pp 431−435.

(26) (a) Anaya, J.; Barton, D. H. R.; Gero, S. D.; Grande, M.; Martín, N.; Tachdijian, C. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 867. (b) Yadav, V. K.; Fallis, A. G. *Tetrahedron Lett.* **1988**, *29*, 897.

(27) (a) Stahl, I. *Synthesis* **1981**, 135. (b) Oishi, T.; Kamemoto, K.; Ban, Y. *Tetrahedron Lett.* **1972**, *13*, 1085.

SCHEME 8[a]



[a] Reagents and conditions: (a) KOH/MeOH (10%), 12 h, rt; (b) Bu_3SnH, AIBN, toluene, 72 h, 90 °C; (c) $Me_3O^+BF_4^-$, CH_2Cl_2, 24 h, rt.

preferably accomplished from **22** and **23**, as will be detailed below.

Reduction and acetylation of the mixture **27** + **28** prior to the HgO and Raney Ni treatment had no effect on the cyclization because the bridged diacetate **33** was produced. This compound is also directly obtained from **30**. An easy epimerization at the α-position of the strained trans-fused lactone, from **28** to **27**, explains the stereochemistry of compounds **29**, **30**, and **33**; obtained as single diastereomers.

To check whether the formation of bridged compounds is produced from any compound with the structural moieties of **27** and **28** or whether a specific conformation is needed for such a cyclization to take place, we prepared compound **34**. This derivative of the 2,1-naphtho series was obtained by epimerization of compound **6** (Scheme 8).

If a specific conformation is not strictly required, compounds with the same groupings but with lower proximity between the 3′,4′,5′-trimethoxyphenyl ring and the 1,3-dithiane would lead to similar bridged derivatives. Compound **34** was subjected to radical (TBTH) and cationic (TFBTO) conditions. In both cases, unreacted material was recovered, along with deprotected ketone **15** in the first case and the rearranged product **35** in the second. Compound **35** shows a new bond between former positions 2′ of the 3′,4′,5′-trimethoxyphenyl ring and 2 of the 1,3-dithiane moiety, but we have no mechanistic explanation for this transformation. These results demonstrate that the easy cyclizations of the 1,8-naphthalene series are strongly induced by their particular conformation.

Ketone **31**, required for the synthesis of thuriferic acid analogues, was alternatively prepared by cyclization of keto-lactones **36** and **37** (Scheme 9). TFA treatment of **36** + **37** gave **38** as the major reaction product and ketone **31** as the minor one. Due to the deactivation of the naphthalene ring by the conjugated keto group, dehydration is a competitive reaction and anhydropodorhizol[28] analogue **38** can be obtained.

Treatment of **31** with base produced a mixture of **39** and **40**, which were transformed into the methyl thuriferate analogue **41** by reaction with diazomethane followed by acidic conditions. Comparing its ^{1}H NMR spectrum with that of compound **11** showed the 1,8-naphtho derivative **41** to have deshielding of olefinic methylene protons and higher coupling constants between 7′ and 8′ protons. The different conformation of the cycloheptane ring explains these variations. The general methodology for the preparation of podophyllotoxin analogues was also tried in this series. Accordingly, trans ketone **31** was treated under acidic conditions, but lactone ring opening was produced instead of epimerization. The formation of compound **42** prevents the epimerization at C-8, thus avoiding the synthesis of the podophyllotoxin analogue in the 1,8-naphtho series.

As a final attempt to synthesize 1,2-naphtho analogues of the podophyllotoxins from 1-naphthyl derivatives, ketone **38** was used as the starting material. Considering the possibility of a pericyclic reaction to circumvent the lower reactivity of the naphthalene position 2 toward electrophilic reagents, enol derivatives from **38** might present the π-system for such a pericyclic reaction to take place. The use of acetic anhydride as a solvent and a reagent, for the formation of the enol acetate and the pericyclic reaction, is very appealing. Treatment of **38** in refluxing acetic anhydride led to the phenanthrene derivative **43**, whose formation can be explained in terms of the expected electrocyclic ring closure[29] of the enolate **44**, followed by dehydrogenation of the rearranged intermediate.

In conclusion, we have demonstrated the validity of our methodology for the preparation of podophyllotoxin and thuriferic acid analogues by the synthesis of 2,1-naphtho analogues of lignans starting from naphthalene-2-carbaldehyde. The same methodology, when used from naphthalene-1-carbaldehyde, resulted in unexpected cyclizations to 1,8-naphtho-fused and -bridged products. A representative compound of the 1,2-naphthalene series was obtained by electrocyclic ring closure of a ketone derived from 1-naphthyl starting materials.

Experimental Section

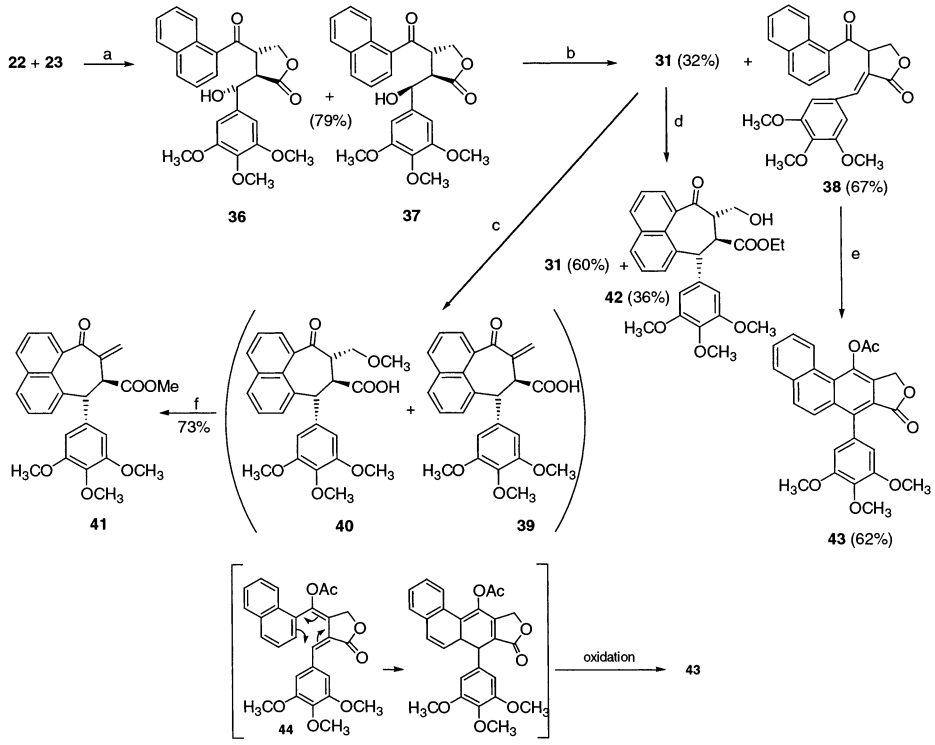
General Methods. All chemicals were reagent grade and used as purchased. All moisture-sensitive reactions were performed under an inert atmosphere of argon using distilled dry solvents. Reactions were monitored by TLC analysis using silica gel 60 F_{254} thin layer plates. Flash chromatography was carried out on silica gel 60 (230−400 mesh). Melting points were determined in capillary tubes and are uncorrected. IR spectra were recorded in a range of 4000−600 cm^{-1}. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were acquired in $CDCl_3$ or DMSO-d_6 as a solvent; all chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane, and all coupling constants (J) are in hertz. Mass spectra were recorded by electronic impact or chemical ionization. For FABMS analyses, a VG-TS 250 apparatus (70 eV) was used. Elemental analyses were recorded in a 2400 CHN apparatus. Systematic conformational searches using Monte Carlo and MM2 as molecular force field and clustering of the resulting conformations were performed under Macromodel and Xcluster v.5.1 on Silicon Graphics workstations.

2-Naphthalene Series: Conjugate Addition−Alkylation Reaction. *n*-BuLi (1.6 M in hexane) (9.6 mL, 15.4 mmol)

(28) Turabelidze, D. G.; Kikaya, G. A.; Kemertelidze, E. P.; Wulfson, N. S. *Bioorg. Chim.* **1982**, *8*, 695.

(29) Anjaneyulu, A. S. R.; Rao, V. K.; Rao, A. M.; Row, L. R. *Curr. Sci.* **1974**, *43*, 542.

SCHEME 9[a]



[a] Reagents and conditions: (a) THF/H_2O, HgO, 0 °C, then BF_3·OEt_2, 24 h, rt; (b) TFA, CH_2Cl_2, 24 h, rt; (c) KOH/MeOH (1%), 15 h, rt; (d) AcOH, EtOH, 48 h, Δ; (e) Ac_2O exc, 7 h, Δ; (f) excess CH_2N_2/ether, then *p*-TsOH, 8 h, Δ.

was added to a solution of 2-(2-naphthyl)-1,3-dithiane (**1**, 3.4 g, 14 mmol) in dry THF (140 mL) at −78 °C under argon. After 45 min, a solution of 5*H*-furan-2-one (0.9 mL, 14 mmol) in dry THF (14 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 3 h and then allowed to warm to −50 °C. A solution of 3,4,5-trimethoxybenzaldehyde (4.1 g, 21 mmol) in dry THF and TMEDA (4.2 mL, 28 mmol) were successively added. The mixture was stirred for 12 h at −50 °C, and then the reaction was quenched by addition of NH_4Cl (concentrated solution). After the usual workup and flash chromatography (7:3 hexane/ethyl acetate) afforded **4** (0.8 g, 17%), **2** (2.9 g, 40%) and **3** (1.9 g, 26%) were isolated.

Cyclization Reaction. TFA (13 mL) was added dropwise to a solution of **2** and **3** (1.4 g, 2.7 mmol) in CH_2Cl_2 (27 mL). The reaction mixture was stirred for 24 h at room temperature, and then the reaction was quenched with $NaHCO_3$ (concentrated solution). After the usual workup and crystallization (hexane/ethyl acetate) of the crude product, a 2:1 mixture (0.9 g, 66%) of **5** and **6** was obtained. This mixture was separated by flash chromatography (4:3 Hex/AcOEt) yielding **5** (0.52 g, 38%) and **6** (0.23 g, 17%).

Deprotection Reaction. A solution of **5** and **6** (1.5 g, 2.9 mmol) in 60 mL of 85:15 THF/H_2O was added to a suspension of HgO (1.25 g, 5.8 mmol) in 85:15 THF/H_2O at 0 °C under argon followed by BF_3·OEt_2 (0.7 mL, 5.8 mmol). The reaction mixture was stirred for 24 h at room temperature, and then CH_2Cl_2 (20 mL) was added and the precipitate filtered. Crystallization (from hexane/ethyl acetate) of the organic phase afforded a 2:1 mixture of **7** and **8** (1 g, 79%), which were isolated by chromatography (8:2 hexane/ethyl acetate).

(±)-(7a*S*,10a*S*,11*R*)-11-(3,4,5-Trimethoxyphenyl)-7,7a,8,-10,10a,11-hexahydronaphtho[1,2-*f*]isobenzofuran-7,10-dione (7). IR ($CHCl_3$): 1775; 1690; 1596. ^{1}H NMR ($CDCl_3$): 3.07 (dd, 1H, J_1 = 9.8, J_2 = 10.2); 3.50 (dd, 1H, J_1 = 6.4, J_2 = 10.2); 3.65 (br s, 6H); 3.76 (s, 3H); 4.44−4.66 (m, 2H); 5.14 (d, 1H, J = 10.2); 6.40 (br s, 2H); 7.33 (t, 1H, J = 6.9); 7.50 (t, 1H, J = 6.9); 7.81−7.94 (m, 2H); 7.83 (d, 1H, J = 8.4); 8.30 (d, 1H, J = 8.4). ^{13}C NMR ($CDCl_3$): 46.8; 47.6; 48.6; 56.2 (2C); 60.8; 65.9; 106.0 (2C); 121.7; 126.9; 127.7; 128.5; 128.9; 129.1; 131.6; 132.2; 136.6 (2C); 139.4; 142.7; 153.2 (2C); 173.3; 194.6. MS (FAB) (*m*/*z*): 418 (M^+, 100). Anal. Calcd for $C_{25}H_{22}O_6$: C, 71.76; H, 5.30. Found: C, 71.41; H, 5.00.

(±)-(7a*R*,10a*R*,11*R*)-11-(3,4,5-Trimethoxyphenyl)-7,7a,8,-10,10a,11-hexahydronaphtho[1,2-*f*]isobenzofuran-7,10-dione (8). Mp: 224 °C (from MeOH). IR (KBr): 1779; 1695; 1590; 1450. ^{1}H NMR ($CDCl_3$): 3.37 (dd, 1H, J_1 = 4.2, J_2 = 15.7); 3.65 (br s, 6H); 3.67 (m, 1H); 3.80 (s, 3H); 4.47 (dd, 1H, J_1 = 9.4, J_2 = 10.3); 4.60 (dd, 1H, J_1 = 7.6, J_2 = 9.4); 5.58 (d, 1H, J = 4.2); 6.40 (br s, 2H); 7.51 (t, 1H, J = 8.4); 7.61 (t, 1H, J = 8.4); 7.91 (d, 2H J = 8.4); 7.94 (d, 1H, J = 8.7); 8.22 (d, 1H, J = 8.7). ^{13}C NMR ($CDCl_3$): 41.6; 43.8; 46.9; 56.2 (2C); 60,7; 67.0; 107.3 (2C); 122.2; 126.0; 127.7; 128.8; 129.0; 129.1; 130.9 (2C); 131.6; 136.4, 137.6; 143.0; 153.2 (2C); 173.1; 194.3. MS (FAB) (*m*/*z*): 418 (M^+, 20). Anal. Calcd for $C_{25}H_{22}O_6$: C, 71.76; H, 5.30. Found: C, 71.73; H, 5.24.

Lactone-Opening Reaction. Compound **7** (380 mg, 0.9 mmol) was treated with a solution of KOH in MeOH (1%) for 1.5 h at room temperature. Then, HCl (2 N) was added and the reaction worked-up, affording 250 mg of a mixture of **10** and **9**.

Esterification Reaction. A mixture of **10** and **9** (1.7 g) was treated with an excess of a saturated solution of CH_2N_2 in ether for 5 min. The crude product was purified by chromatography (1:1 hexane/ethyl acetate) affording a 3:1 mixture of **12** and **11** (890 mg, 51%) and **13** (400 mg, 21%). Methyl esters **11** and **12** were isolated by further chromatography.

(±)-Methyl (3*S*,4*R*)-2-Methylen-1-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydrophenanthrene-3-carboxylate (11). Mp: 218 °C (from MeOH). IR (KBr): 1732; 1678; 1589. ^{1}H NMR ($CDCl_3$): 3.51 (s, 3H); 3.68 (s, 6H); 3.75 (s, 3H); 4.04 (s, 1H); 5.41 (s, 1H); 5.58 (s, 1H); 6.27 (s, 2H); 6.43 (s, 1H); 7.50 (t, 1H, J = 8.4); 7.87 (t, 1H, J = 8.4); 7.89 (d, 1H, J = 8.4); 8.02 (d, 1H, J = 8.4); 8.28 (d, 1H, J = 8.4). ^{13}C NMR ($CDCl_3$): 44.8; 52.6; 55.9; 56.0 (2C); 60.7; 105.1 (2C); 122.9; 125.4; 126.7; 126.8; 127.2; 128.5; 128.7; 130.5; 131.0; 136.3;

136.7; 136.9; 137.6; 140.0; 153.3 (2C); 172.1; 186.1. MS (FAB) (*m*/*z*): 433 (M^+, 100). Anal. Calcd for $C_{26}H_{24}O_6$: C, 72.21; H, 5.59. Found: C, 71.97; H, 5.48.

(±)-Methyl (2*S*,3*S*,4*R*)-2-Methoxymethyl-1-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydrophenanthrene-3-carboxylate (12). IR ($CHCl_3$): 1733; 1676. ^{1}H NMR ($CDCl_3$): 3.18 (ddd, 1H, $J_1 = 4.7$, $J_2 = 5.4$, $J_3 = 8.3$); 3.29 (s, 3H); 3.57 (s, 3H); 3.67 (s, 6H); 3.73 (dd, 1H, $J_1 = 8.3$, $J_2 = 9.9$); 3.75 (dd, 1H, $J_1 = 1.8$, $J_2 = 4.7$); 3.80 (s, 3H); 4.12 (dd, 1H, $J_1 = 5.4$, $J_2 = 9.9$); 5.38 (d, 1H, $J = 1.8$); 6.28 (s, 2H); 7.47 (t, 1H, $J = 8.6$); 7.54 (t, 1H, $J = 8.6$); 7.80 (d, 1H, $J = 8.6$); 7.83 (d, 1H, $J = 8.6$); 7.90 (d, 1H, $J = 8.6$); 8.24 (d, 1H, $J = 8.6$). ^{13}C NMR ($CDCl_3$): 42.6; 44.0; 49.3; 51.5; 55.4 (2C); 58.1; 60.0; 69.1; 104.8 (2C); 121.4; 124.8; 126.4; 127.5; 127.9; 128.1; 129.8; 130.3; 135.5; 136.0; 136.4; 137.3; 152.8 (2C); 172.0; 195.1. MS (FAB) (*m*/*z*): 465 ($M^+ + 1$, 30). Anal. Calcd for $C_{27}H_{28}O_7$: C, 63.85; H, 5.74. Found: C, 63.59; H, 5.48.

By treatment of **12** (86 mg, 0.2 mmol) with *p*-TsOH (38 mg, 0.2 mmol) in benzene at reflux for 7 h, compound **11** (86 mg, 100%) was obtained as a pure product.

Chlorination Reaction. By treatment of **11** (70 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) with a dry stream of HCl for 2 h followed by argon to eliminate the excess of reagent, the chloro derivative **14** (60 mg, 80%) was obtained in pure form.

Acidic Epimerization. To a solution of **7** (1.8 g, 4.3 mmol) in ethanol (70 mL) was added glacial acetic acid (140 mL). The reaction mixture was refluxed for 72 h and then allowed to cool to room temperature, and the reaction was quenched with a concentrated solution of $NaHCO_3$. After the usual workup and flash chromatography (2:3 hexane/ethyl acetate), 1.5 g of **15** (83%) was isolated.

(±)-(7a*R*,10a*S*,11*R*)-11-(3,4,5-Trimethoxyphenyl)-7,7a,8,-10,10a,11-hexahydronaphtho[1,2-*f*]isobenzofuran-7,10-dione (15). IR ($CHCl_3$): 1774; 1673; 1591. ^{1}H NMR ($CDCl_3$): 3.40 (dd, 1H, $J_1 = 5.9$, $J_2 = 8.0$); 3.53 (dd, 1H, $J_1 = 1.8$, $J_2 = 8.0$); 3.69 (s, 6H); 3.76 (s, 3H); 4.42 (dd, 1H, $J_1 = 5.9$, $J_2 = 9.2$); 4.86 (d, 1H, $J = 9.2$); 5.53 (s, 1H); 6.29 (s, 2H); 7.53 (t, 1H, $J = 8.6$); 7.60 (t, 1H, $J = 8.6$); 7.85 (d, 1H, $J = 8.6$); 7.89 (d, 1H, $J = 8.6$); 8.10 (d, 1H, $J = 8.6$); 8.13 (d, 1H, $J = 8.6$). ^{13}C NMR ($CDCl_3$): 39.4; 43.2; 47.1; 56.1 (2C); 60.7; 70.6; 104.4 (2C); 122.2; 125.4; 127.8; 128.5, 129.0; 129.2; 130.1; 130.9; 136.6; 137.2; 137.6; 140.7; 153.8 (2C); 175.5, 195.9. MS (FAB) (*m*/*z*): 418 (M^+, 100). Anal. Calcd for $C_{25}H_{22}O_6$: C, 71.76; H, 5.30. Found: C, 71.68; H, 5.21.

Reduction Reaction. Ketone **15** (250 mg, 0.6 mmol) in THF (60 mL) was slowly added to $LiAlH(^tBuO)_3$ (0.6 g, 2.4 mmol) in THF (3 mL) and allowed to react at room temperature for 24 h. The reaction was quenched with a saturated NH_4Cl solution and acidified with aqueous oxalic acid (saturated solution). Flash chromatography (3:2 hexane/ethyl acetate) of the crude product afforded a 2:1 mixture of compounds **16** and **17** (125 mg, 50%).

(±)-(7*R*,7a*R*,10a*S*,11*R*)-7-Hydroxy-11-(3,4,5-trimethoxyphenyl)-7,7a,8,10,10a,11-hexahydronaphtho[1,2-*f*]-isobenzofuran-10-one (16). Data were taken from the product isolated in the TBAF deprotection reaction. IR ($CHCl_3$): 3480; 1770; 1590. ^{1}H NMR ($CDCl_3$): 3.10 (m, 1H); 3.53 (dd, 1H, $J_1 = 1.8$, $J_2 = 8.4$); 3.68 (s, 6H); 3.78 (s, 3H); 4.42 (dd, 1H, $J_1 = 5.8$, $J_2 = 9.2$); 4.86 (d, 1H, $J = 9.2$); 4.90 (d, 1H, $J = 4.4$); 5.53 (s, 1H); 6.29 (s, 2H); 7.41−7.56 (m, 2H); 7.55 (d, 1H, $J = 8.0$); 7.74−7.95 (m, 2H); 7.85 (d, 1H, $J = 8.0$). ^{13}C NMR ($CDCl_3$): 38.1; 45.2; 55.2; 56.1; 60.7; 61.1; 69.9; 105.4 (2C); 122.3; 125.4; 127.8; 128.5; 128.7; 128.9; 130.7; 130.9; 136.7; 137.2; 137.6; 140.0; 153.5 (2C); 172.4. MS (FAB) (*m*/*z*): 420 (M^+, 10). Anal. Calcd for $C_{25}H_{24}O_6$: C, 71.41; H, 5.75. Found: C, 71.18; H, 5.58.

(±)-(7*S*,7a*R*,10a*S*,11*R*)-7-Hydroxy-11-(3,4,5-trimethoxyphenyl)-7,7a,8,10,10a,11-hexahydronaphtho[1,2-*f*]isobenzofuran-10-one (17). Data were taken from the product isolated in the protection reaction. IR ($CHCl_3$): 3469; 1760; 1591. ^{1}H NMR ($CDCl_3$): 3.50 (m, 1H); 3.64 (s, 6H); 3.70 (m, 1H); 3.79 (s, 3H); 4.25 (t, 1H, $J = 5.0$); 4.33 (t, 1H, $J = 8.4$); 5.03 (d, 1H, $J = 6.6$); 5.50 (s, 1H); 6.25 (s, 2H); 7.30−7.90 (m, 4H); 7.44 (d, 1H, $J = 8.4$); 7.83 (d, 1H, $J = 8.4$). ^{13}C NMR ($CDCl_3$): 40.0; 40.4; 47.1; 56.1 (2C); 60.8; 71.7; 72.0; 104.8 (2C); 124.5; 125.7; 126.3; 127.0; 128.5; 128.6; 129.0; 131.0; 133.6; 134.2; 136.8; 139.9; 153.6 (2C); 177.2. Anal. Calcd for $C_{25}H_{24}O_6$: C, 71.41; H, 5.75. Found: C, 71.40; H, 5.62.

Protection Reaction. To a solution of **16** and **17** (125 mg, 0.3 mmol) in CH_2Cl_2 (5.9 mL) and $^iPr_2NEt$ (0.3 mL, 1.7 mmol), at 0 °C under argon, TBDMSTf (0.3 mL, 1.2 mmol) was added dropwise. After 4 h, a solution of oxalic acid was added until acidic pH was reached. Workup and flash chromatography (2:1 hexane/ethyl acetate) of the crude product afforded **18** (80 mg, 50%) and **17** (26 mg, 21%).

Basic Epimerization. A solution of **18** (75 mg, 0.14 mmol) in THF (2.8 mL) under argon was cooled to −78 °C, and LDA (0.28 mmol) was added. The solution was maintained at this temperature for 15 min, and then glacial acetic acid (40 μL, 0.7 mmol) in THF (4.3 M) was added. Extraction with ethyl acetate and flash chromatography (2:1 hexane/ethyl acetate) of the crude product afforded **19** (11 mg, 15%) and **18** (60 mg, 80%).

Deprotection Reactions. To a solution of **19** (20 mg, 0.04 mmol) in CH_3CN (1.8 mL) under argon was added TBAF (69 mg, 0.22 mmol) and the reaction maintained for 48 h at room temperature. After the usual work up, alcohol **16** (10 mg, 60%) was obtained as a pure product.

To a solution of **19** (28 mg, 0.05 mmol) in CH_3CN (2.6 mL) under argon was added a solution of $Et_3N{\cdot}3HF$ (2.0 M) in CH_3CN added. The reaction mixture was maintained at room temperature for 72 h and then evaporated in a vacuum affording **20** (18 mg, 85%).

(±)-(7*R*,7a*R*,10a*R*,11*R*)-7-Hydroxy-11-(3,4,5-trimethoxyphenyl)-7,7a,8,10,10a,11-hexahydronaphtho[1,2-*f*]isobenzofuran-10-one (20). Mp: 240 °C (from ether). IR (KBr): 3476; 1773. ^{1}H NMR ($CDCl_3$): 2.91(dd, 1H, $J_1 = 4.4$, $J_2 = 14.4$); 2.97 (m, 1H); 3.67 (s, 6H); 3.80 (s, 3H); 4.15 (t, 1H, $J = 8.4$); 4.68 (dd, 1H, $J_1 = 6.8$, $J_2 = 8.4$); 5.04 (d, 1H, $J = 8.4$); 5.30 (d, 1H, $J = 4.4$); 6.45 (br s, 2H); 7.41 (t, 1H, $J = 8.4$); 7.46 (t, 1H, $J = 8.4$); 7.76 (br d, 1H, $J = 8.4$); 7.83 (d, 1H, $J = 8.4$); 7.85 (br d, 1H, $J = 8.4$); 7.89 (d, 1H, $J = 8.4$). ^{13}C NMR ($CDCl_3$): 40.7; 41.2; 45.5; 56.2 (2C); 60.7; 71.5; 73.4; 108.8 (2C); 124.1; 124.7; 126.2; 127.1; 128.9; 129.0; 131.5, 133.0; 133.3 (2C); 134.7; 136.9; 152.8 (2C); 174.5. MS (FAB) (*m*/*z*): 420 (M^+, 10). Anal. Calcd for $C_{25}H_{24}O_6$: C, 71.41; H, 5.75. Found: C, 71.04; H, 5.68.

1-Naphthalene Series: Conjugate Addition−Alkylation Reaction. By the same procedure used for the 2-naphthalene series, from 2-(1-naphthyl)-1,3-dithiane (**21**, 3.6 g, 15 mmol; in 150 mL of dry THF), *n*-BuLi (1.6 M in hexane; 10.3 mL, 16.5 mmol), 5*H*-furan-2-one (0.9 mL, 15 mmol; in 15 mL of dry THF), and 3,4,5-trimethoxybenzaldehyde (4.4 g, 23 mmol; in dry THF and 4.5 mL, 30 mmol of TMEDA) were isolated **22** and **23** (5.0 g, 64%) and **24** (0.6 g, 11%) after chromatography (7:3 hexane/ethyl acetate).

Cyclization Reaction. By the same procedure used for the 2-naphthalene series, from a mixture of **22** and **23** (1.0 g, 1.9 mmol) in CH_2Cl_2 (9.5 mL) with TFA (9.5 mL) were isolated **28** (485 mg, 49%) and **27** (425 mg, 24%) after chromatography (99:1 CH_2Cl_2/MeOH).

Treatment with Raney Ni. A mixture of **22** and **23** (20 mg, 0.038 mmol) in EtOH (5 mL) was treated with an excess of Raney Ni and stirred at reflux for 1 h. The crude product was purified by chromatography (99:1 CH_2Cl_2/MeOH) affording **25** (10 mg, 62%) and **26** (2 mg, 13%).

A mixture of **28** and **27** (40 mg, 0.08 mmol) in EtOH (8 mL) was treated with an excess of Raney Ni and stirred at reflux for 15 min. The filtrate was extracted with ethyl acetate and purified by chromatography (8:2 hexane/ethyl acetate) affording **30** (18 mg, 56%).

Compound **29** (see synthesis below, 50 mg, 0.1 mmol) in EtOH (10 mL) was treated with an excess of Raney Ni and

stirred at reflux for 2 h. By the same procedure described above, **30** (32 mg, 81%) was isolated

(±)-(7*S*,7a*R*,10a*S*,11*R*)-7,11-(3,4,5-Trimethoxy-1,2-phenylene)-7,7a,10a,11-tetrahydro-8*H*-10*H*-naphtho[1′,8a′,8′:4,5,6]cyclohepta[*c*]furan-8-one (30). IR ($CHCl_3$): 1765; 1478; 1125. ^1H NMR ($CDCl_3$): 3.35 (m, 1H); 3.40−3.87 (dd, 1H, $J_1 = 6.1$, $J_2 = 11.9$); 3.82 (s, 6H); 3.85 (s, 3H); 3.93 (dd, 1H, $J_1 = 4.7$, $J_2 = 9.5$); 4.44 (t, 1H, $J = 4.7$); 4.56 (d, 1H, $J = 6.1$); 4.70 (d, 1H, $J = 5.9$); 6.71 (s, 1H); 7.33 (t, 1H, $J = 8.1$); 7.34 (t, 1H, $J = 8.1$); 7.38 (d, 1H, $J = 8.1$); 7.43 (d, 1H, $J = 8.1$); 7.67 (d, 1H, $J = 8.1$); 7.68(d, 1H, $J = 8.1$). ^{13}C NMR ($CDCl_3$): 40.7; 43.5; 47.0; 50.1; 56.1; 60.9; 61.4; 69.5; 106.0; 125.4; 125.5; 125.9; 127.1 (2C); 128.6; 128.7; 129.2; 135.3; 135.6; 135.8; 136.0; 141.1; 149.8; 152.4; 176.4. MS (FAB) (*m*/*z*): 403 ($M^+ + 1$, 100). Anal. Calcd for $C_{25}H_{22}O_5$: C, 74.61; H, 5.51. Found: C, 74.49; H, 5.50.

Deprotection Reaction. By the same procedure used for the 2-naphthalene series, from **27** and **28** (3 g, 5.8 mmol; in 100 mL of 85:15 THF/H_2O), HgO (2.5 g, 11.6 mmol; in 18 mL of 85:15 THF/H_2O), and $BF_3{\cdot}OEt_2$ (1.3 mL, 10.7 mmol) was obtained **29** (1.5 g, 51%).

(±)-(7*R*,7a*R*,10a*S*,11*R*)-7,11-(3,4,5-Trimethoxy-1,2-phenylene)-11-(3-mercaptopropylthio)-7,7a,10a,11-tetrahydro-8*H*-10*H*-naphtho[1′,8a′,8′:4,5,6]cyclohepta[*c*]furan-8-one (29). IR ($CHCl_3$): 1768; 1596. ^1H NMR ($CDCl_3$): 2.18 (m, 2H); 2.65 (m, 2H); 2.77 (m, 2H); 3.52 (s, 3H); 3.78 (s, 3H); 3.79 (s, 3H); 3.80 (m, 1H); 3.40−3.87 (m, 2H); 4.50 (m, 1H); 4.51 (d, 1H, $J = 6.0$); 6.72 (s, 1H); 7.26−7.44 (m, 4H); 7.69 (d, 1H, $J = 8.0$); 8.00 (d, 1H, $J = 7.3$). ^{13}C NMR ($CDCl_3$): 29.0; 33.5; 34.5; 45.5; 46.2; 51.2; 56.0; 59.4; 61.3; 62.0; 70.6; 107.2; 123.7; 125.1; 125.9 (2C); 127.6; 128.5; 129.4; 129.8; 135.6 (2C); 135.9; 136.2; 142.4; 151.8; 152.7; 176.6. MS (FAB) (*m*/*z*): 508 (M^+, 10). Anal. Calcd for $C_{28}H_{28}O_5S_2$: C, 66.12; H, 5.56. Found: C, 65.94; H, 5.36.

Treatment with $Me_3O^+BF_4^-$. A mixture of **27** and **28** (100 mg, 0.2 mmol) in 20 mL of CH_2Cl_2 was treated with $Me_3O^+BF_4^-$ (89 mg, 0.6 mmol). The reaction was stirred for 10 h at room temperature. The crude product was purified by chromatography (8:2 hexane/ethyl acetate) affording **31** (24 mg, 29%) and **32** (20 mg, 25%).

(±)-(7*R*,7a*S*,10a*S*)-7-(3,4,5-Trimethoxyphenyl)-7,8,10a,11-tetrahydro-7*H*,10*H*-naphtho[1′,8a′,8′:4,5,6]cyclohepta[*c*]furan-8,11-dione (31). IR ($CHCl_3$): 1770; 1682; 1590. ^1H NMR ($CDCl_3$): 3.30 (dd, 1H, $J_1 = 6.2$, $J_2 = 14.6$); 3.54 (s, 6H); 3.68 (s, 3H); 4.15 (m, 1H); 4.40 (dd, 1H, $J_1 = 7.3$, $J_2 = 9.5$); 4.89 (t, 1H, $J = 9.5$); 5.07 (d, 1H, $J = 6.2$); 6.08 (s, 2H); 7.46−7.66 (m, 3H); 7.90 (d, 1H, $J = 8.0$); 8.10 (d, 1H, $J = 8.4$); 8.39 (d, 1H, $J = 7.3$). ^{13}C NMR ($CDCl_3$): 51.4; 51.9; 52.5; 55.7 (2C); 60.6; 65.3; 103.8 (2C); 124.8; 130.7 (2C); 133.5, 135.0; 135.5; 135.6; 135.7; 136.4 (2C); 137.5; 141.7; 153.1 (2C); 175.7; 194.7. MS (*m*/*z*): 419 ($M^+ + 1$, 5). Anal. Calcd for $C_{25}H_{22}O_6$: C, 71.76; H, 5.30. Found: C, 71.80; H, 5.32.

7-(3,4,5-Trimethoxyphenyl)-8*H*,10*H*-naphtho[1′,8a′,8′:4,5,6]cyclohepta[*c*]furan-8-one (32). IR ($CHCl_3$): 1761; 1584. ^1H NMR ($CDCl_3$): 3.48−3.95 (m, 2H); 3.88 (s, 6H); 3.99 (s, 3H); 5.54 (s, 2H); 6.62 (s, 2H); 7.45−7.50 (m, 2H); 7.67−7−78 (m, 2H); 7.90 (m, 2H); 8.80 (s, 1H). ^{13}C NMR ($CDCl_3$): 56.2 (2C); 61.1; 68.5; 107.6 (2C); 115.3; 123.6; 124.8; 126.9; 128.0; 128.9; 129.6; 129.7; 130.2; 130.4; 132.8; 134.7; 138.0; 139.0; 141.5; 142.2; 153.0 (2C); 170.0. MS (FAB) (*m*/*z*): 401 ($M^+ + 1$, 5). Anal. Calcd for $C_{25}H_{20}O_5$: C, 74.99; H, 5.03. Found: C, 74.66; H, 4.89.

Diacetate 33. A solution of **28** (70 mg, 0.14 mmol) in 20 mL of dry THF was added to a suspension of $LiAlH_4$ (100 mg, 2.8 mmol) in dry THF. After 1 h at room temperature, the reaction mixture was filtered affording 70 mg (98%) of the diol, which was treated with an excess of acetic anhydride in pyridine. The resulting diacetate (60 mg, 0.1 mmol) in 2 mL of 85:15 THF/H_2O was deprotected with HgO (32 mg, 0.15 mmol; in 2 mL of 85:15 THF/H_2O) followed by $BF_3{\cdot}OEt_2$ (19 μL, 0.15 mmol) yielding, after chromatography (7:3 hexane/ethyl acetate), 45 mg (78%) of the cyclized diacetate. This compound (20 mmol, 0.03 mmol) in EtOH (4 mL) was treated with an excess of Raney Ni, yielding **33** (15 mg, 90%).

To a solution of **30** (29 mg, 0.05 mmol) in 5 mL of dry THF was added 29 mg of $LiAlH_4$ (0.08 mmol) in dry THF. After 1 h, the reaction mixture was filtered affording 15 mg (73%) of the corresponding diol. This reaction product was treated with an excess of acetic anhydride in pyridine for 7 h. After the usual workup, **33** (18 mg, 73%) was obtained.

Treatment with KOH/MeOH. To a 2:1 mixture of **5** and **6** (630 mg, 1.2 mmol) was added 12 mL of KOH/MeOH (10%). After 12 h, 2 N HCl was added and the white precipitate filtered and crystallized in MeOH, affording a 2:1 mixture of **5** and **34**, which were then separated by chromatography (7:3 hexane/ethyl acetate), yielding **34** (150 mg, 25%).

Treatment with Bu_3SnH. A solution of Bu_3SnH (166 μL) and AIBN (10 mg) in 30 mL of toluene was added to a solution of **34** (100 mg, 0.2 mmol) in dry toluene (70 mL) at 80−90 °C. The reaction was maintained at reflux for 72 h. The crude product (90 mg) was chromatographed (6:4 hexane/ethyl acetate), yielding **15** (45 mg, 54%) and **34** (30 mg, 30%).

Treatment with $Me_3O^+BF_4^-$. $Me_3O^+BF_4^-$ (29 mg, 0.2 mmol) was added to a solution of **34** (90 mg, 0.18 mmol) in 25 mL of anhydrous CH_2Cl_2. The reaction mixture was stirred for 24 h at room temperature, and the reaction was quenched with water; the mixture was then extracted with CH_2Cl_2, affording a mixture of **34** (40 mg, 44%) and **35** (20 mg, 28%).

5,6,7-Trimethoxy-4-(2-naphthyl)-3*H*-naphtho[2,3-*c*]-furan-1-one (35). IR ($CHCl_3$): 3417; 1766; 1589. ^1H NMR ($CDCl_3$): 3.18 (s, 3H); 3.91 (s, 3H); 4.05 (s, 3H); 4.94 (d, 1H, $J = 14.8$); 5.15 (d, 1H, $J = 14.8$); 7.20 (s, 1H); 7.43 (dd, 1H, $J_1 = 1.6$, $J_2 = 8.2$); 7.54 (m, 1H); 7.55 (m, 1H); 7.75 (s, 1H); 7.85 (m, 1H); 7.94 (m, 2H); 8.37 (s, 1H). ^{13}C NMR ($CDCl_3$): 56.1; 60.7; 61.1; 70.0; 104.5; 122.4; 125.1; 125.6; 126.1 (2C); 126.4; 127.1; 127.3; 127.9 (2C); 131.9; 132.0; 132.3; 132.9; 137.2; 139.0; 144.9; 149.6; 153.5; 171.3. MS (FAB) (*m*/*z*): 401 ($M^+ + 1$, 30). Anal. Calcd for $C_{25}H_{20}O_5$: C, 74.99; H, 5.03. Found: C, 74.83; H, 4.94.

Deprotection Reaction. By the usual procedure, **22** and **23** (3 g, 5.8 mmol; in 100 mL of 85:15 THF/H_2O) were treated with HgO (2.25 g, 10.4 mmol; in 18 mL of THF/H_2O 85:15) and $BF_3{\cdot}OEt_2$ (1.3 mL, 10.7 mmol) affording, after chromatography (7:3 hexane/ethyl acetate), a mixture of **36** and **37** (2.02 g, 79%) that was used in the next reaction without further purification.

Cyclization Reaction. By the usual procedure, a mixture of **36** and **37** (390 mg, 0.89 mmol; in 2 mL of CH_2Cl_2) was treated with TFA (2 mL), followed by chromatography (7:3 hexane/ethyl acetate), yielding **31** (120 mg, 32%) and **38** (250 mg, 67%).

Lactone-Opening Reaction. By the usual procedure, from **31** (50 mg, 0,12 mmol), 40 mg of a mixture of **39** and **40** was obtained and used in the next reaction without further purification.

Esterification Reaction. A mixture of **39** and **40** (40 mg) was treated with an excess of a saturated solution of CH_2N_2 in ether for 5 min. The solvent was evaporated, and the crude product was refluxed in benzene with *p*-TsOH for 8 h, affording **41** (30 mg, 73%).

(±)-Methyl (7*R*,8*S*)-9-Methylene-10-oxo-7-(3,4,5-trimethoxyphenyl)-7,8,9,10-tetrahydro-cyclohepta[*d*,*e*]naphthalene-8-carboxylate (41). IR ($CHCl_3$): 1738; 1591. ^1H NMR ($CDCl_3$): 3.30 (s, 3H); 3.63 (s, 6H); 3.87 (s, 3H); 4.40 (d, 1H, $J = 7.8$); 5.22 (d, 1H, $J = 7.8$); 6.03 (s, 1H); 6.24 (s, 2H); 6.66 (s, 1H); 7.41−7.60 (m, 4H); 7.87 (m, 1H); 8.07 (m, 1H). ^{13}C NMR ($CDCl_3$): 52.1; 52.5; 54.2; 56.1 (2C); 60.9; 105.9 (2C); 125.5; 125.9; 126.4; 126.8; 128.8; 129.3; 131.2; 131.4; 134.2; 134.4; 135.4; 137.0; 137.5; 144.0; 153.3 (2C); 171.9; 185.0. Anal. Calcd for $C_{26}H_{24}O_6$: C, 72.21; H, 5.59. Found: C, 72.13; H, 5.41.

Acidic Treatment for Epimerization. By the usual treatment with glacial acetic acid (5 mL), a solution of **31** (100 mg, 0.24 mmol; in 24 mL of EtOH) was refluxed for 48 h,

yielding **31** (60 mg, 60%) and **42** (40 mg, 36%) after flash chromatography (2:3 hexane/ethyl acetate).

(±)-Ethyl (7*R*,8*S*,9*S*)-9-Hydroxymethyl-10-oxo-7-(3,4,5-trimethoxyphenyl)-7,8,9,10-tetrahydrocyclohepta[*d*,*e*]-naphthalene-8-carboxylate (42). IR ($CHCl_3$): 3417; 1778; 1688. ^{1}H NMR ($CDCl_3$): 1.31 (t, 3H, $J_1 = 6.4$); 3.50 (s, 6H); 3.40 (dd, 1H, $J_1 = 3.0$, $J_2 = 7.8$); 3.75 (s, 3H); 3.85 (m, 1H); 4.03 (d, 1H, $J = 7.6$); 4.24 (dd, 1H, $J_1 = 3.2$, $J_2 = 7.6$); 4.26 (q, 2H, $J_1 = 6.4$); 5.04 (d, 1H, $J = 3.0$); 6.08 (s, 2H); 7.45 (dd, 1H, $J_1 = 1.8$, $J_2 = 7.0$); 7.46 (t, 1H, $J = 7.0$); 7.53 (t, 1H, $J = 7.0$); 7.61 (dd, 1H, $J_1 = 1.4$, $J_2 = 7.0$); 7.90 (dd, 1H, $J_1 = 1.8$, $J_2 = 7.6$); 8.00 (dd, 1H, $J_1 = 1.4$, $J_2 = 7.6$). ^{13}C NMR ($CDCl_3$): 14.4; 48.6; 52.1; 52.5; 55.8 (2C); 60.9; 61.7; 62.0; 105.3 (2C); 125.3; 126.5; 127.2; 128.6; 129.2; 129.8; 131.2; 133.0; 134.5; 135.1; 136.3; 138.7; 153.3 (2C); 173.1; 204.8. MS (FAB) (*m*/*z*): 465 ($M^+ + 1$, 5). Anal. Calcd for $C_{28}H_{27}O_7$: C, 69.81; H, 6.08. Found: C, 69.44; H, 6.01.

Treatment with Ac_2O. Compound **38** (100 mg, 0.24 mmol) was treated with an excess of acetic anhydride under argon. The reaction mixture was stirred at reflux for 7 h; the reaction was quenched with water, and the mixture was then worked-up. Flash chromatography (8:2 hexane/ethyl acetate) of the crude product afforded **43** (70 mg, 62%).

8-oxo-7-(3,4,5-Trimethoxy-phenyl)-8,10-dihydro-furo-[3,4-*b*]phenanthren-11-yl Acetate (43). IR ($CHCl_3$): 1770; 1583. ^{1}H NMR ($CDCl_3$): 2.61 (s, 3H); 3.85 (s, 6H); 3.99 (s, 3H); 5.36 (s, 2H); 6.61 (s, 2H); 7.70 (m, 2H); 7.92 (m, 2H); 9.24 (m, 2H). ^{13}C NMR ($CDCl_3$): 21.5; 56.2, 61.1; 66.7; 107.7 (2C); 125.1; 126.9; 127.3; 127.7; 128.0; 128.4 (2C); 128.5, 129.0; 130.0; 133.7; 134.8; 135.4; 138.0; 139.4; 141.7; 153.0 (2C); 167.9; 169.0. MS (FAB) (*m*/*z*): 459 ($M^+ + 1$, 5). Anal. Calcd for $C_{27}H_{22}O_7$: C, 70.73; H, 4.84. Found: C, 7.69; H, 4.70.

Acknowledgment. We thank Mr. Nicholas Skinner (Languages Service; Universidad de Salamanca) for the revision of the English of the manuscript. Financial support came from Junta de Castilla y León (SA073/02), Spanish DGESIC-MCyT (PPQ2001-1977), and E.C. (Feder Funds and COST contract BIO4CT98-0451). B.M. thanks the MCyT for her predoctoral grant position.

Supporting Information Available: Fully detailed experimental procedures for the synthesis, as well as characterization of the compounds described and several minor products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0263364