JOC Article

New Picropodophyllin Analogs via Palladium-Catalyzed Allylic Alkylation−Hiyama Cross-Coupling Sequences

Maxime Vitale,[†] Guillaume Prestat,*[,†] David Lopes,[†] David Madec,[†] Claire Kammerer,[†] Giovanni Poli,*[,†] and Leonard Girnita[‡]

UPMC Univ Paris 06, UMR CNRS 7611 Laboratoire de Chimie Organique, FR2769 Institut de Chimie Moléculaire, case 183, F-75005 Paris, France, Department of Oncology-Pathology, Cellular and Molecular Tumor Pathology, Cancer Center Karolinska R8:04, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden

giovanni.poli@upmc.fr; guillaume.prestat@upmc.fr

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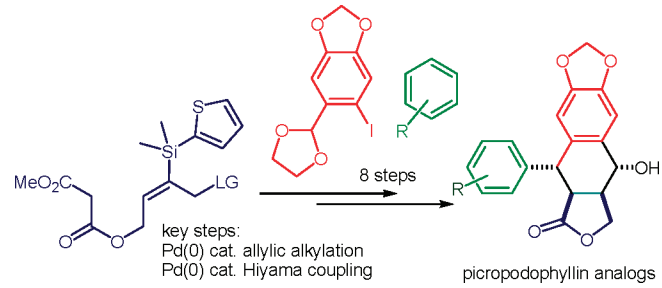
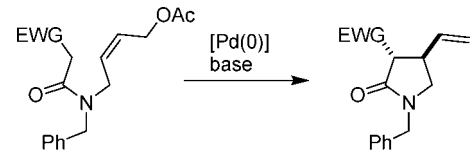


Unsaturated malonyl esters underwent Pd-catalyzed intramolecular allylic alkylation to give 4-vinyl-substituted γ-lactones. In contrast to the formerly studied cyclization of malonamides, this reaction could be achieved only with a substrate incorporating a suitably positioned silicon moiety, which directs the ionization toward the desired η^3-allylpalladium complex. The resulting 4-[dimethyl-(2-thienyl)silylvinyl]lactone could be subsequently engaged into Hiyama couplings with various iodoarenes, to give the corresponding 4-(α-styryl)-γ-lactones. The use of a specifically substituted iodoarene generated an advanced tetracyclic lactone intermediate incorporating rings A−D of lignans belonging to the podophyllotoxin family. Subsequent electrophilic aromatic substitution with a variety of electron-rich arenes afforded the target picropodophyllin analogs.

Introduction

In 1998 we reported a stereoselective approach toward 3,4-disubstituted γ-lactams based on the intramolecular palladium-catalyzed allylic alkylation of unsaturated amides (eq 1).[1] Interestingly, such cyclizations took place exclusively via a 5-*exo* process. This result is in contrast with what was observed by Tsuji[2] and Pfalz[3] with analogous β-ketoesters precursors, which led competitively to 5-*exo* and 7-*endo* products. Such a method was revealed to be very effective for the synthesis of a variety of substituted γ-lactams and totally stereoselective in favor of the *trans* diastereomer.

A few years later, the concatenation of such cyclization with a suitably conceived intramolecular Mizoroki−Heck coupling set the stage for the synthesis of a lactam analog of the podophyllotoxin family.[4]



(1)

EWG = CO_2Me, CN, SO_2Ph, $PO(OEt)_2$, COMe, SPh

Podophyllotoxin (Figure 1, left) is a well-known natural product showing high affinity for tubulin.[5] Its action halts cellular division during mitosis, which in turn triggers cellular death.[6] However, the use of this molecule as a anticancer agent

[†] UPMC Univ Paris 6.
[‡] Karolinski Institutet.

(1) Giambastiani, G.; Pacini, B.; Porcelloni, M.; Poli, G. *J. Org. Chem.* **1998**, *63*, 804–807.
(2) Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 1475–1478.
(3) Koch, G.; Pfaltz, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2213–2216.
(4) Poli, G.; Giambastiani, G. *J. Org. Chem.* **2002**, *67*, 9456–9459.

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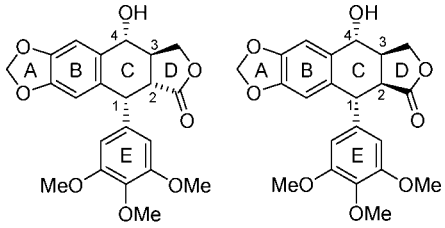


FIGURE 1. Structure of podophyllotoxin and picropodophyllin.

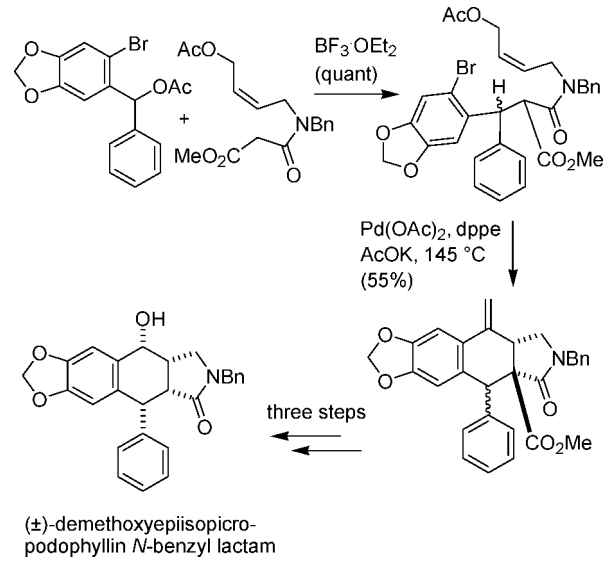
is hampered as a result of its high toxicity and secondary effects such as nausea, diarrhea, vomiting, and injury of healthy tissues.[7] As a consequence, several modifications of podophyllotoxin structure have been accomplished with the aim of reducing its toxicity. Structure−activity relationship (SAR) studies[8] established that the 2,3-*trans* junction of the lactone is necessary, whereas the presence of methoxy groups on the E aromatic cycle appears not to be compulsory for antimitotic activity.[9]

A few years ago we disclosed the synthesis of an original aza-analog of podophyllotoxin exploiting the above cited method as the key step.[4] The synthesis started with the benzhydrylation[10] of a suitable unsaturated amide, according to a protocol previously developed in our laboratory. Subsequent pseudo-domino[4,11] Pd-catalyzed intramolecular allylic alkylation/Mizoroki−Heck sequence gave the desired pentacyclic structure. Finally, Krapcho decarboxylation followed by double bond oxidative cleavage and reduction of the resulting keto function afforded the final aza-analog (Scheme 1).

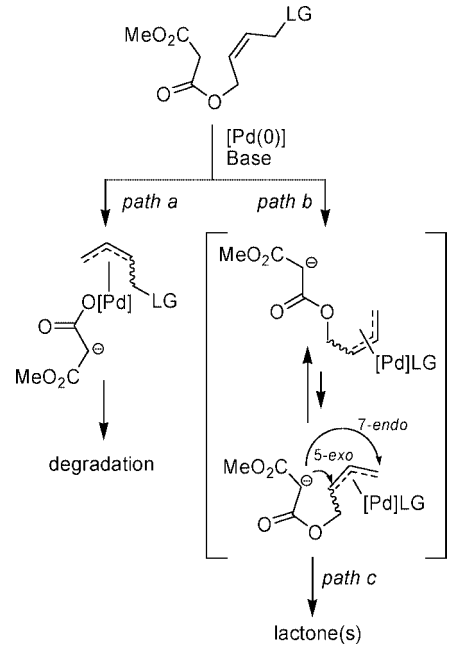
As a logical continuation of this project, we next envisaged to replace the amide function with an ester, so as to target γ-lactones instead of γ-lactams.[12] In particular, we were interested in the synthesis of 4-(α-styryl)-γ-lactones[13] as potential precursors of new podophyllotoxin analogs as well as biologically interesting lignan derivatives.[14]

Although such a modification is seemingly trivial, a number of challenges become apparent: (a) The new substrate incorporates two allylically disposed leaving groups. As a consequence, oxidative addition of the substrate to Pd(0) may take an alternative path that cleaves the precursor (Scheme 2, path a). (b) A switch from a tertiary amide to an ester precursor may

SCHEME 1. Synthesis of (±)-Demethoxyepiisopicropodophyllin



SCHEME 2. Possible Paths for the Ester Precursor under Pd(0) Catalysis



dramatically lower the proportion of the conformer(s) having a suitable geometry for cyclization (Scheme 2, path b).[15] (c) Although with the lactam precursor the caprolactam corresponding to a 7-*endo* mode of cyclization was not observed, a corresponding lactone precursor may not be as regioselective, giving a mixture of the desired 5-*exo* and undesired 7-*endo* product (Scheme 2, path c).[16] As a consequence, the success of such a deceptively simple variant could not be taken for granted at the outset.

(5) Reviews: (a) Damayanthi, Y.; Lown, J. W. *Curr. Med. Chem.* **1998**, *5*, 205–252. (b) Zhang, Y.; Lee, K.-H. *Chin. Pharm. J.* **1994**, *46*, 319–369. (c) Ramos, A. C.; Pelaéz-Lamamié de Clairac, R.; Medarde, M. *Heterocycles* **1999**, *51*, 1443–1470. (d) Ward, R. S. *Chem. Soc. Rev.* **1982**, 75–125. (e) Ward, R. S. *Synthesis* **1992**, 719–730. (f) Sellars, J. D.; Steel, P. G. *Eur. J. Org. Chem.* **2007**, 3815–3828. (g) Gordaliza, M.; García, P. A.; Miguel del Corral, J. M.; Castro, M. A.; Gómez-Zurita, M. A. *Toxicon* **2004**, *44*, 441–459.

(6) (a) Cortese, F.; Bhattacharyya, B.; Wolff, J. *J. Biol. Chem.* **1977**, *252*, 1134–1140. (b) Andreu, J. M.; Timasheff, S. N. *Biochemistry* **1982**, *21*, 6465–6476. (c) Sackett, D. L. *Pharm. Ther.* **1993**, *59*, 163–228.

(7) Kelly, M. G.; Hartwell, J. L. *J. Nat. Cancer Inst.* **1954**, *14*, 967–1010.

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(9) Berkowitz, D. B.; Maeng, J.-H.; Dantzig, A. H.; Shepard, R. L.; Norman, B. H. *J. Am. Chem. Soc.* **1996**, *118*, 9426–9427.

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(11) (a) Lemaire, S.; Prestat, G.; Giambastiani, G.; Madec, D.; Pacini, B.; Poli, G. *J. Organomet. Chem.* **2003**, *687*, 291–300. (b) Prestat, G.; Poli, G. *Chemtracts: Org. Chem.* **2004**, *17*, 97–103. (c) Kammerer, C.; Prestat, G.; Gaillard, T.; Madec, D.; Poli, G. *Org. Lett.* **2008**, *10*, 405–408.

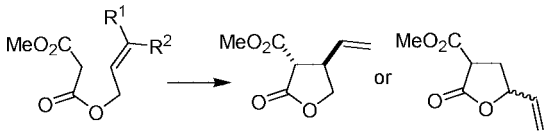
(12) Mingoia, F.; Vitale, V.; Madec, D.; Prestat, G.; Poli, G. *Tetrahedron Lett.* **2008**, *49*, 760–763.

(13) See, for example: Sibi, M. P.; Liu, P.; Ji, J.; Hajra, S.; Chen, J.-X. *J. Org. Chem.* **2002**, *67*, 1738–1745.

(14) For a preliminary account on this work, see:(a) Vitale, M.; Prestat, G.; Lopes, D.; Madec, D.; Poli, G. *Synlett* **2006**, 2231–2234.

(15) Esters are known to prefer the *s-trans* conformation, which does not possess the correct geometry for cyclization. (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1984. (b) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224–232. For a radical cyclization concerning an ester precursor see, for example: (c) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041–1047.

TABLE 1. Preliminary Essays of Cyclization[a]



1a-d **2** **3**

entry	**1**	R^1	R^2	prod (%)	method[b]
1	**1a**	H	CH_2OAc		A
2	**1b**	H	CH_2OCO_2Me		B
3	**1b**	H	CH_2OCO_2Me	**3**[c] (25)	C
4	**1c**	H	Y		B
5	**1d**	Y	H	**2** (25)	A

[a] Y = $CH_2OCOCH_2CO_2Me$. [b] Method A: NaH (1.0 equiv), $Pd(OAc)_2$ (5 mol %), dppe (10 mol %), 1.5 h, DMF, 80 °C. Method B: as method A, at 60 °C. Method C: $Pd(OAc)_2$ (5 mol %), dppe (10 mol %), 1.5 h, DMF, 60 °C. [c] 1:1 diastereomeric mixture.

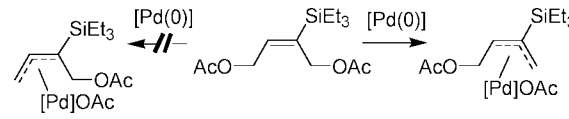
From a synthetic point of view, we were particularly interested in the development of new analogs possessing the picropodophyllin *cis* configuration (Figure 1, right).[17] Indeed, this podophyllotoxin epimer, although having no activity against tubuline,[18] showed inhibitory activity against insulin-like growth factor 1 receptor (IGF-1R),[19] which plays a crucial role in the transformation, growth, and survival of malignant cells. As a consequence, the development of more potent IGF-1R inhibitors appears a new challenge in the fight against cancer.

Results and Discussion

Unsaturated esters **1a**−**d** were first prepared according to known procedures. Treatment of the acetate precursor **1a** or the carbonate **1b** under reaction conditions analogous to those used to cyclize the lactam precursors gave only degradation products (Table 1, entries 1 and 2). On the other hand, in the absence of base, **1b** gave the undesired rearranged lactone **3** as the only isolated product (Table 1, entry 3).[20]

To circumvent the above-mentioned regioselectivity problem, we first tested the corresponding dimalonyl derivatives as the precursors. In the event, the *Z*-configured **1c** precursor gave a complicated mixture devoid of **2** (Table 1, entry 4), whereas the *E*-configured isomer **1d** afforded the desired lactone **2** in a rather low yield (Table 1, entry 5). This result suggested that the released malonate moiety may participate in other undesired intramolecular processes.

SCHEME 3. Control of Regioselectivity in the Ionization



We speculated that the failure of **1a** and **1b** to cyclize could be mainly due to the regioselective generation of the undesired η^3-allylic complex. Accordingly, we decided to bias such substrates toward the desired pathway. Malacria and Thorimbert have reported that the ionization of 1,4-diallyl systems carrying a triethylsilyl group on one of the vinylic carbon atoms takes place with complete chemoselectivity, so as to expel the acetoxy group vicinal to the silicon atom (Scheme 3).[21]

We thus decided to test the above silicon effect in the hope to direct ionization of our precursor toward the desired site.[22] Accordingly, starting from the commercially available butyn-1,4-diol, the silicon-substituted precursors **8a**−**c** were synthesized for subsequent cyclization tests. Platinum-catalyzed *syn*-hydrosilylation[23] of butyn-1,4-diol followed by regioselective silylation and acetylation gave the fully protected intermediate **6**. Desilylation followed by standard malonylation afforded the first precursor **8a**. A three-step sequence entailing generation of the monomethylcarbonate **9**, regioselective hydrosilylation to give the allylic alcohol **10**, and malonylation gave carbonate **8b**. Finally, **8c** was prepared via dimalonylation of the starting diol, followed by *syn*-hydrosilylation of the corresponding tetraester **11** (Scheme 4).

To our delight, our first cyclization attempt using substrate **8a** gave diastereoselectively the *trans* diastereomer of lactone **12** in a satisfactory yield (Table 2, entry 1).

The desired lactone **12** was also obtained using carbonate **8b** in the presence (Table 2, entry 2) as well as in the absence (Table 2, entry 3) of base. The readily available dimalonyl derivative **8c** was also easily cyclized. This result confirms the good leaving group ability of the malonyl moiety and suggests that the silicon moiety not only assists the η^3-allylpalladium complex formation but also inhibits the side reactions mentioned above (compare Table 1, entry 4 with Table 2, entry 4). Finally, a test with substrate **8c** indicated that the amount of catalyst could be decreased without any loss of efficiency (Table 2, entry 5).[24]

(16) (a) Norrby, P.-O.; Mader, M. M.; Vitale, M.; Prestat, G.; Poli, G. *Organometallics* **2003**, *22*, 1849–1855. Erratum: **2006**, *25*, 4234. (b) Madec, D.; Prestat, G.; Martini, E.; Fristrup, P.; Poli, G.; Norrby, P.-O. *Org. Lett.* **2005**, *7*, 995–998.

(17) For recent synthetic approaches, see: (a) Berkowitz, D. B.; Choi, S.; Maeng, J.-H. *J. Org. Chem.* **2000**, *65*, 847–860. (b) Meresse, P.; Monneret, C.; Bertounesque, E. *Tetrahedron* **2004**, *60*, 2657–2671. (c) Dorbec, M.; Florent, J. C.; Monneret, C.; Rager, M.-N.; Bertounesque, E. *Tetrahedron* **2006**, *62*, 11766–11781. See also: (d) Pullin, R. D. C.; Sellars, J. D.; Steel, P. G. *Org. Biomol. Chem.* **2007**, *5*, 3201–3206.

(18) Seidlova-Masinova, V.; Malinsky, J.; Santavy, F. *J. Natl. Cancer Inst.* **1957**, *18*, 359–371.

(19) See, for example: (a) Girnita, A.; Girnita, L.; del Prete, F.; Bartolazzi, A.; Larsson, O.; Axelson, M. *Cancer Res.* **2004**, *64*, 236–242. (b) Girnita, A.; All-Ericsson, C.; Economou, M. A.; Åström, K.; Axelson, M.; Seregard, S.; Larsson, O.; Girnita, L. *Clin. Cancer Res.* **2006**, *12*, 1383–1391. (c) Colón, E.; Zaman, F.; Axelson, M.; Larsson, O.; Carlsson-Skwirut, C.; Svechnikov, K. V.; Söder, O. *Endocrinology* **2007**, *148*, 128–139. (d) Karolinska Innovations AB; Larsson, O.; Axelson, M. PCT Int. Appl. WO 02/102804, 2002. (e) Echeverria, C. G. In *Topics in Medicinal Chemistry*; Bradbury, R. H., Ed.; Springer-Verlag: Berlin, Heidelberg Germany, 2007; pp 169−206.

(20) Formation of the lactone **3** may derive from addition of the malonyl carbon acid to the distal terminus of the η^3-allylpalladium complex, followed by lactonization via carboxylate addition to a newly generated η^3-allyl complex. In this case, the Pd-catalyzed cleavage of the malonyl moiety from the substrate might take place either before or after the C−C bond formation. See also: (a) Silvestri, M. A.; He, C.; Khoram, A.; Lepore, S. D. *Tetrahedron Lett.* **2006**, *47*, 1625–1626.

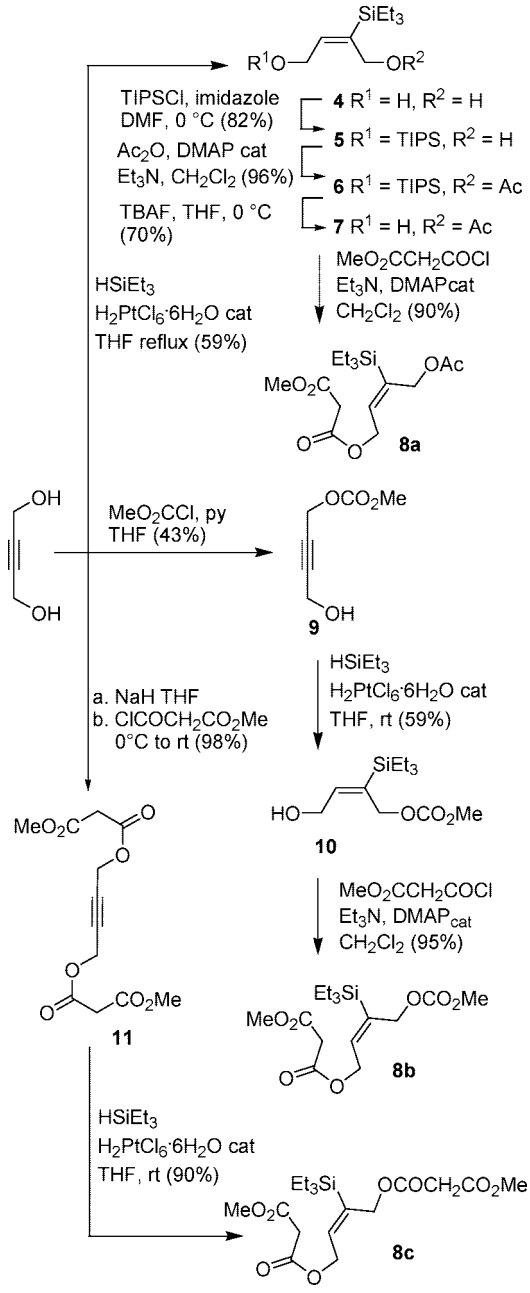
(21) (a) Thorimbert, S.; Malacria, M. *Tetrahedron Lett.* **1996**, *37*, 8483–8486. (b) Commandeur, C.; Thorimbert, S.; Malacria, M. *J. Org. Chem.* **2003**, *68*, 5588–5592. (c) Branchadell, V.; Moreno-Mañas, M.; Pleixats, R.; Thorimbert, S.; Commandeur, C.; Boglio, C.; Malacria, M. *J. Organomet. Chem.* **2003**, *687*, 337–345. (d) Thorimbert, S.; Tailler, C.; Bareyt, S.; Humilière, D.; Malacria, M. *Tetrahedron Lett.* **2004**, *45*, 9123–9126. (e) Boglio, C.; Stahike, S.; Thorimbert, S.; Malacria, M. *Org. Lett.* **2005**, *7*, 4851–4854.

(22) Inspection of molecular models of the silylated substrate **8** suggests that the allylic C−O bond vicinal to silicon is likely to be forced by the bulky Et_3Si group to be almost orthogonal to the C=C, whereas the distal allylic C−O bond is not expected to suffer such a restriction. Since the oxidative addition of allylic acetates to Pd(0) is known to be operative only if the substrate can adopt an orthogonal C=C/C−O disposition, (Fiaud, J. C.; Aribi-Aouioueche, L. *J. Chem. Soc., Chem. Commun.* **1986**, 390–391) it appears that the silylated substrates **8** might be intrinsically biased to expel the vicinal rather than the distal allylic leaving group.

(23) Speier, J. L.; Webster, J. A.; Barnes, G. H. *J. Am. Chem. Soc.* **1957**, *79*, 974–979.

(24) Although the yields are only moderate, ^1H NMR of the crude products as well as TLC analysis indicate complete disappearance of the starting material and the absence of other possible regio- or stereoisomers of **8**. Partial decomposition of the starting material as polymeric material is thus likely.

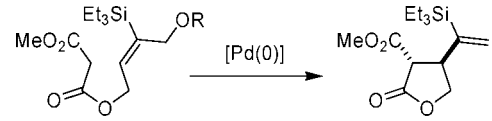
SCHEME 4. Synthesis of Silylated Cyclization Precursors 8a−c



Having succeeded in transposing the catalytic cyclization strategy from γ-lactams to γ-lactones, we planned to take advantage of the newly generated vinylsilane moiety to incorporate the desired aryl moieties.

Hiyama coupling[25] is a powerful transformation attracting ever-increasing interest. However, in contrast to the related Stille[26] coupling, vinyl trialkyl derivatives are not suitable substrates for such transformations. Indeed, in the case of fluoride-activated Hiyama couplings, the silicon atom requires specific nontransferable groups. For our purpose, such groups should also be compatible with the allylic alkylation step. With this constraint, the dimethyl-2-thienylsilyl moiety emerged as a suitable candidate, due to its recognized stability.[27]

TABLE 2. Intramolecular Allylic Alkylation of the Triethylsilyl Precursors 8a−c

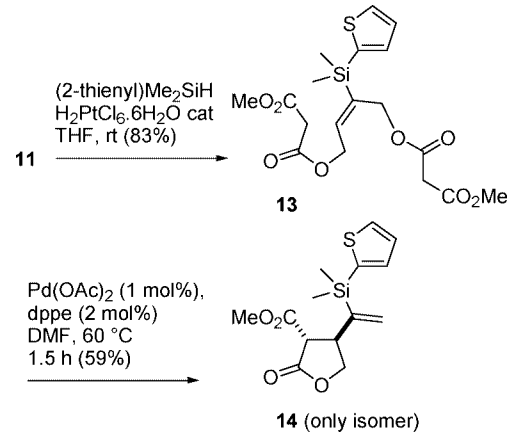


8a-c 12

entry	8	OR	method[a]	yield[b] (%)
1	**8a**	OAc	A	53
2	**8b**	OCO_2Me	A	48
3	**8b**	OCO_2Me	B	61
4	**8c**	$OCOCH_2CO_2Me$	A	57
5	**8c**	$OCOCH_2CO_2Me$	C	59

[a] Method A: NaH (1.1 equiv), $Pd(OAc)_2$ (5 mol %), dppe (10 mol %), 1.5 h, DMF, 60 °C. Method B: $Pd(OAc)_2$ (5 mol %), dppe (10 mol %), 1.5 h, DMF, 60 °C. Method C: NaH (1.1 equiv), $Pd(OAc)_2$ (1 mol %), dppe (2 mol %), 1.5 h, DMF, 60 °C. [b] Only one diastereoisomer was detected in each experiment (^{1}H NMR of the crude product) whose *trans* configuration was assigned via NOE experiments.

SCHEME 5. Intramolecular Allylic Alkylation To Give Silylated Lactone 14



Silane **13** was easily obtained via standard dimalonylation of butyn-1,4-diol followed by platinum-catalyzed *syn*-hydrosilylation of the resulting tetraester with (2-thienyl)Me_2SiH. Cyclization of **13** under the conditions previously described gave the corresponding lactone **14** (59% yield) as the only isomer (Scheme 5).[28]

Hiyama coupling of some representative aryl halides with lactone **14** was then undertaken (Table 3). Following a brief optimization study, the reactions were conducted in the presence of *n*-Bu_4NF and catalytic $Pd_2(dba)_3$, in THF at room temperature.

The efficiency of the coupling was found to be strongly dependent on the nature of the aryl halide. Indeed and not unexpectedly, iodobenzene cross-coupled with **14** in a more satisfactory yield (Table 3, entry 2, 70% yield) than bromobenzene (Table 3, entry 1, 25% yield). The nature of the substituents on the aryl iodides was also found to be crucial. In particular, electron-donating methoxy groups in the *para* or *ortho* position

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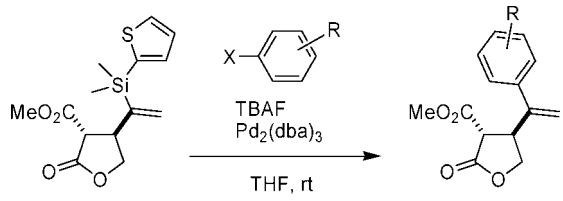
(26) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524. (b) Mitchell, T. N. In *Metal-Catalysed Cross-Coupling Reactions*; Dietrich, F., ; Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 4.

(27) Hosoi, K.; Nozaki, K.; Hiyama, T. *Chem. Lett.* **2002**, *2*, 138–139.

(28) The *trans* configuration of **14** was assigned on the basis of the well known stereochemical outcome of this type of cyclizations as well as the relative stereochemistry of the intermediates deriving from it (see later).

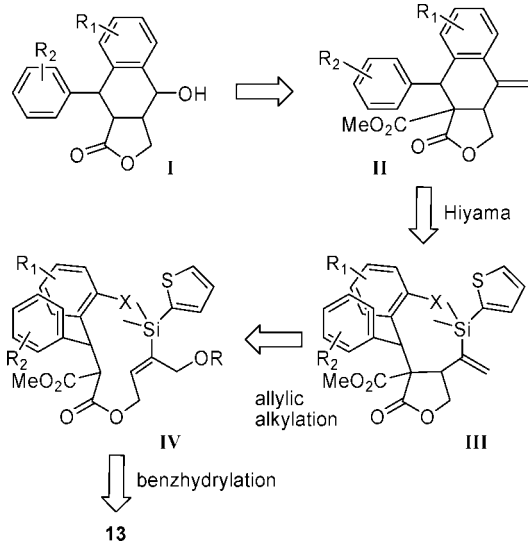
TABLE 3. Cross-Coupling of Lactone 14 with Aryl Halides[a]



entry	X	R	product	yield (%)
1	Br	H	**15a**	25
2	I	H	**15a**	70
3	I	4-MeO	**15b**	95
4	I	3-MeO	**15c**	38
5	I	2-MeO	**15d**	79
6	I	4-MeCO	**15e**	45
7	I	4-NO_2	**15f**	20
8	I	4-CF_3	**15g**	26

[a] Conditions: TBAF (2.4 equiv, 1.0 M solution in THF), $Pd_2(dba)_3$ (2.5 mol %), THF, rt, 16 h.

SCHEME 6. First Retrosynthetic Plan of Podophyllotoxin and/or Picropodopyllin Analogs



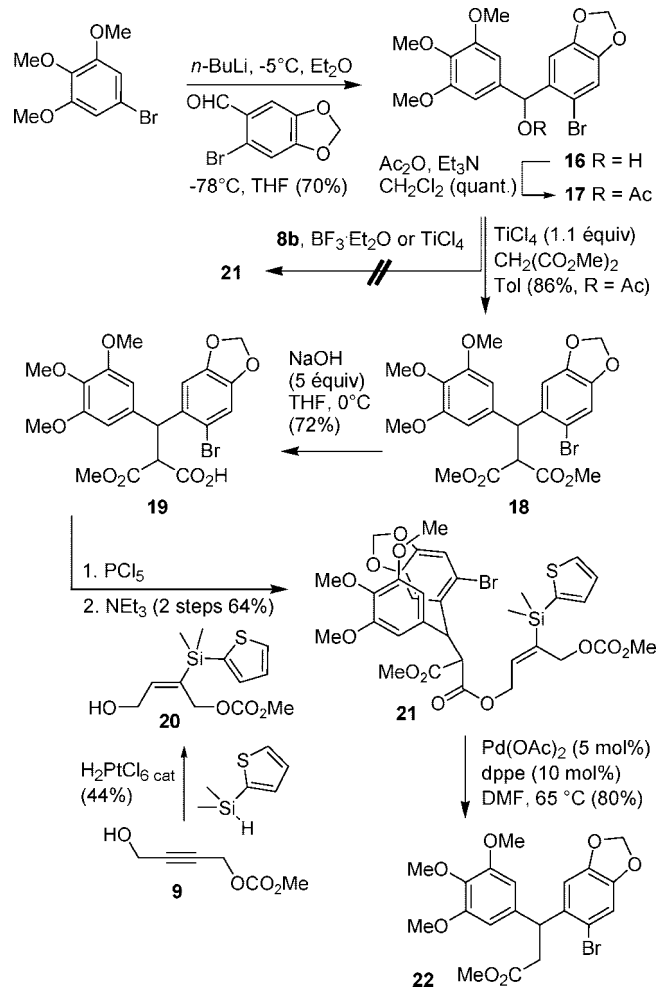
gave good coupling yields (Table 3, entries 3 and 5). On the other hand, a methoxy substituent in the *meta* position or an acetyl group in the *para* position was less satisfactory (Table 3, entries 4 and 6). Such behavior suggests that, in the case of the aryl iodides tested, transmetalation rather than oxidative addition is likely to be the rate determining step.[29]

After validation of the "allylic alkylation/Hiyama" sequence, we next tackled the synthesis of podophyllotoxin analogs. The retrosynthetic plan first conceived is depicted in Scheme 6. Its first part, involving the terminal alkene **II** as the precursor, strictly follows the same logic as the previously mentioned lactam synthesis (Scheme 1).[4] The C ring is generated by an intramolecular Hiyama coupling of vinylsilane **III**, whereas the D ring comes from the intramolecular allylic alkylation of precursor **IV**. The latter intermediate may be in turn derived from benzhydrylation of the known silyl precursor **13**.

Bromine−lithium exchange on 3,4,5-trimethoxybromobenzene[30] and subsequent treatment with 2-bromo-piperonaldehyde,

(29) Hiyama couplings involving 1,2-disubstituted vinylsilanes do not show the same trend.

SCHEME 7. First Attempts toward Podophyllotoxin and/or Picropodophyllin Analogs



according to the protocol described by Jung et al.,[31] gave benzhydrol **16** (70% yield), which was quantitatively converted into the corresponding acetate **17** (Scheme 7).

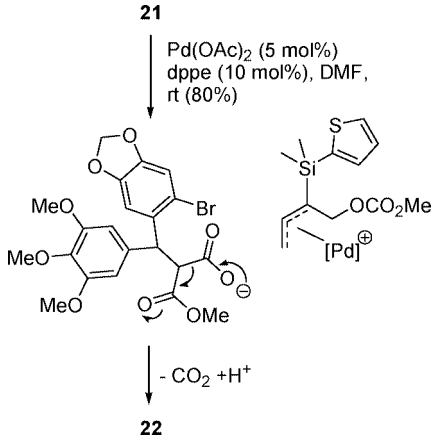
Lewis acid promoted benzhydrylation of the model ester **8b** with **17** was then attempted. However, neither $BF_3 \cdot OEt_2$ nor $TiCl_4$ were successful in promoting the desired alkylation, the starting ester being recovered in both cases. Therefore, an alternative route to access precursor **21** was envisioned. After a brief survey of reaction conditions, we found that treatment of benzhydryl acetate **17** with dimethyl malonate in the presence of $TiCl_4$ in toluene at room temperature gave the coupling product **18** in 86% yield. Exposure of the latter diester to NaOH in H_2O/THF triggered a clean monosaponification[32] affording the corresponding monoacid **19** as an equimolar mixture of the two possible diastereoisomers in 72% yield. Esterification of the corresponding acid chloride with silylalcohol **20**, previously obtained in 44% yield via regioselective hydrosilylation of butyn-1,4-diol monomethylcarbonate, gave uneventfully the desired ester **21**. Much to our disappointment, treatment of either diastereomer of **21** with $Pd(OAc)_2$ (5 mol%) and dppe (10 mol%) in DMF did not afford the expected cyclized lactone,

(30) Kozád, I.; Konrád, L.; Procházka, M. *J. Labelled Compd. Radiopharm.* **1978**, *XV*, 401–405.

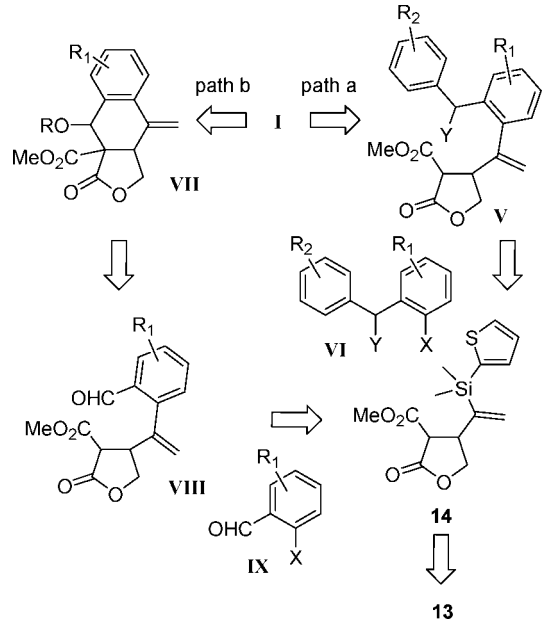
(31) Jung, M. E.; Lam, P. Y. S.; Mansuri, M. M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087–1105.

(32) Niwayama, S. *J. Org. Chem.* **2000**, *65*, 5834–5836.

SCHEME 8. Mechanistic Hypothesis for the Generation of Ester 22



SCHEME 9. Variations of the Retrosynthetic Plan



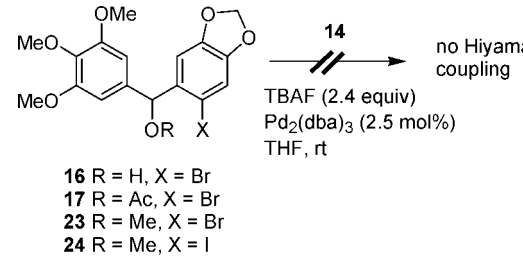
the bromoester **22** being the only isolated product. This undesired cleavage product is very likely generated via the departure of the malonate moiety during η^3-allyl formation, followed by decarboxylation and final reprotonation (Scheme 8).

In view of the above failure, two alternative retrosynthetic plans were next considered (Scheme 9). The first one (path a) entails the same key steps as the original plan but with different chronological order and molecularity. Thus, the advanced intermediate **I** was thought to derive from an intramolecular benzhydrylation of **V**, this latter in turn stemming from an intermolecular Hiyama coupling of the already known vinyl silane **14**.

Unfortunately, attempted Hiyama coupling between vinylsilane **14** and bromobenzhydrol **16** using the reaction conditions previously optimized degraded the lactone moiety without producing the desired coupling product (Scheme 10). The same negative result was obtained using the bromoacetate **17**, the bromomethyl ether **23**, and the iodomethyl ether **24** as the benzhydryl counterpart.

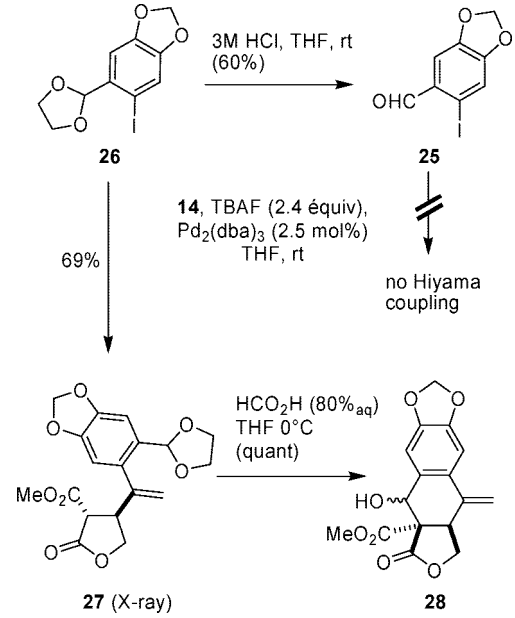
Judging that the failure of the coupling was likely due to the excessive bulk of the aryl halide, we turned our attention to the

SCHEME 10. Attempted Hiyama Couplings between 14 and Benzhydrol Derivatives



16 R = H, X = Br
17 R = Ac, X = Br
23 R = Me, X = Br
24 R = Me, X = I

SCHEME 11. Successful Hiyama Coupling and Generation of the C Ring

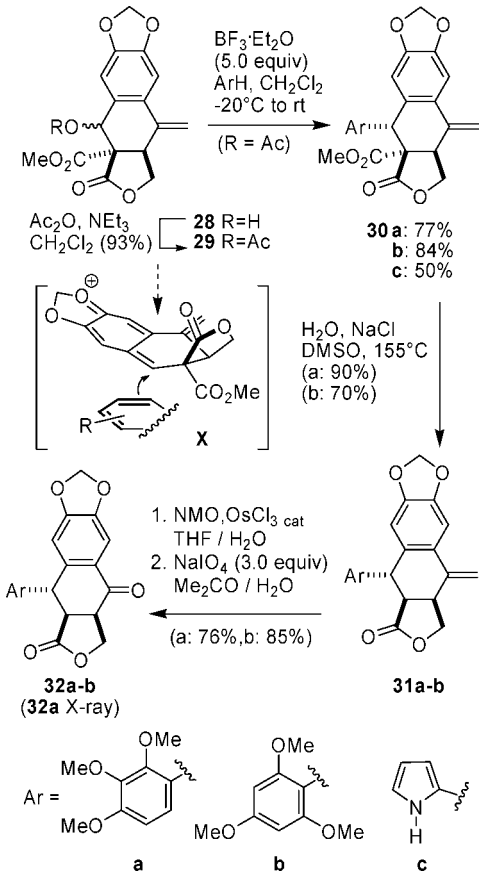


second variant of the synthetic plan (Scheme 9, path b), which involves a less advanced (and less bulky) aryl halide building block for the Hiyama coupling. Such a strategy derives **I** from an aromatic electrophilic substitution of an appropriate electron-rich derivative[33] on the tricyclic intermediate **VII**. This latter is expected to derive from an intermolecular Hiyama coupling involving lactone **14** and an aromatic haloaldehyde **IX**, followed by an intramolecular aldol condensation. This new strategy is more modular than the former one and is well suited for the synthesis of a family of podophyllotoxin analogs having different E rings. Indeed, such diversification may be obtained just by varying the aromatic partner in a late stage of the synthetic sequence.

The known aldehyde **25**[34] was first submitted to Hiyama coupling with lactone **14**. Although this coupling was again unsuccessful, submission to the same coupling with **14** of the dioxolane derivative **26**, immediate precursor of **25**, finally gave the desired adduct **27** (Scheme 11). A single crystal X-ray diffraction structure of **27** revealed the *trans* stereochemistry of the substituted lactone and, assuming that the coupling took place under nonepimerizing conditions, that of its silane precursor also. Treatment of the dioxolane **27** with formic acid in THF at 0 °C with the aim of demasking the aldehyde function took place with concomitant intramolecular aldolization, af-

(33) Stadler, D.; Bach, T. *Chem. Asian J.* **2008**, *3*, 272–284.
(34) Bogucki, D. E.; Charlton, J. L. *J. Org. Chem.* **1995**, *60*, 588–593.

SCHEME 12. Introduction of the E Ring and Double Bond Oxidative Cleavage for Three Analogs



fording the tetracyclic lactone **28** as an equimolar mixture of two diastereomers in quantitative yield. Inspection of molecular models indicated that a *cis* C/D ring junction was reasonably the only possible issue. This in turn revealed, as will be later confirmed, that the mixture was due to the presence of the two possible epimers at the carbinol center.

With the desired carbinol **28** in our hands, our next plan was to introduce various electron-rich aromatic rings via aromatic substitution. Our first choice went to 1,2,3-trimethoxybenzene. Because of the well-known selectivity rules of the aromatic electrophilic substitution, we were aware that use of such a nucleophile could not generate an adduct bearing an E ring trimethoxylated at the same positions as picropodophyllin. Although this may be viewed as a limitation, this strategy appeared attractive in that it could open the way to the synthesis of picropodophyllin analogs bearing diverse E rings substitution patterns with a late stage diversification.

After some experimentations, the desired aromatic substitution could be satisfactorily accomplished (77% yield) by reacting excess 1,2,3-trimethoxybenzene in the presence of $BF_3 \cdot OEt_2$ and the acetate **29**, in turn obtained via standard acetylation of carbinol **28** (Scheme 12). Worthy of note, the epimeric mixture of **29** converged into the single diastereoisomer **30a**. 1,3,5-Trimethoxybenzene and pyrrole behaved analogously, giving the corresponding arylated products in 84% and 50% yield, respectively, as single diastereomers. The stereoconvergence of these electrophilic couplings can be easily accounted for according to approach mode **X** deriving from exclusive addition of the aromatic partner on the more accessible convex face of the transient cationic intermediate.

SCHEME 13. Oxidative Cleavage for a Fourth Analog

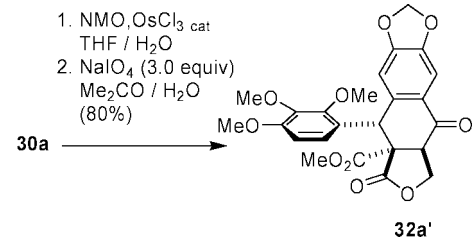
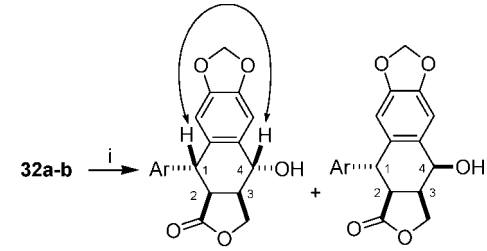


TABLE 4. Reduction of Ketones 32a,b[a]



entry	method	ketone	**33**:**34**	yield (%)
1	A	**32a**	89:11	86
2	B	**32a**	92:8	89
3	B	**32b**	95: 5	82

[a] (i) Method A: $NaBH_4$, MeOH, rt. Method B: $NaBH_4$, $CeCl_3$, MeOH, −78°C, rt.

Two of the three advanced intermediates were then submitted to the protocol previously reported for the synthesis of the aza-analog.[4] Decarboxylation of **30a** and **30b** under classical Krapcho[35] conditions gave lactones **31a** and **31b** in 90% and 70% yield, respectively. Subsequent *cis*-dihydroxylation[36] followed by periodate cleavage of the crude diols[37] gave ketones **32a** and **32b** in 76% and 85% yield. Single crystal X-ray analysis of **32a** disclosed the relative configuration between the benzhydrylic center and the carbon α to the lactone. This analysis confirmed unambiguously our previous assignment of *cis* C/D ring junction for this structure as well as for the precursors **30a**[38] and **31a**. The relative configuration of **30b**,[38] **30c**,[38] **31b**, and **32b** are deduced by analogy with that of **32a**.

In order to make a further analog, nonepimerizable at the α position relative to the lactone function, the nondecarboxylated tetracycle **30a** was also submitted to the above-described oxidative cleavage to give ketone **32a′** (Scheme 13).

Having in hand the three ketones **32a,b** and **32a′**, we tackled the final reduction step. Treatment of ketone **32a** with $NaBH_4$ in MeOH at room temperature gave the expected alcohols **33a** and **34a** as an 89/11 diastereomeric mixture in 86% yield (Table 4, entry 1). A NOESY experiment showing a spatial proximity between the hydrogen atoms in positions 1 and 4 unequivocally indicated the picropodophyllin relative configuration of the major isomer. In a second experiment, reduction of the same

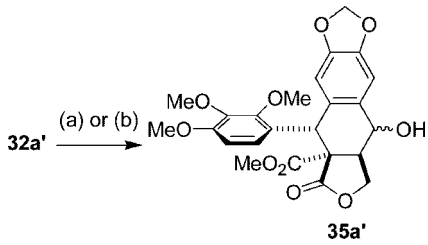
(35) For reviews, see: (a) Krapcho, A. P. *Synthesis* **1982**, 805–822. (b) Krapcho, A. P. *Synthesis* **1982**, 893–914. (c) Krapcho, A. P. *Arkivoc* **2007**, 54–120.

(36) Poli, G., Scolastico, C. In *Houben Weyl Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds; Georg Thieme Verlag: Stuttgart, New York, 1995; Chapter 4.4, Vol. E21, pp 4547−4598.

(37) (a) Manzoni, L.; Pilati, T.; Poli, G.; Scolastico, C. *J. Chem. Soc., Chem. Commun.* **1992**, 1027–1029. (b) Fatiadi, A. J. *Synthesis* **1976**, 133–167.

(38) Assuming that the Krapcho decarboxylation took place with retention of configuration.

SCHEME 14. Reduction of Ketone 32a′[a]



[a] $NaBH_4$, MeOH, rt, d.r. 72:28 (60%). [b] $NaBH_4$, $CeCl_3$, MeOH, 78 °C--> rt, d.r. 18:82 (quant).

ketone under Luche conditions[39] ($NaBH_4$, $CeCl_3$, MeOH, −78 °C) (Table 4, entry 2) gave the same alcohols as a 92/8 diastereomeric ratio and 89% yield. Reduction of ketone **32b** under Luche conditions gave the alcohol **33b** as the sole observable diastereoisomer (Table 4, entry 3). In this case too, a NOE experiment (12%) showed the spatial proximity between the hydrogen atoms at positions 1 and 4, confirming again a picropodophyllin stereochemistry.

It is worthy to note that the hydride attacks on the carbonyl functionality of compounds **32a,b** takes place with a strong or total preference for the face opposite to the E ring, independently of the reaction conditions used. Such a behavior can be accounted for by the strong steric bulk of the axial[40] E ring that disfavors attack from that side.

Ketone **32a′** was also reduced with $NaBH_4$ alone or in the presence of $CeCl_3$. In this case, the former method provided the expected diastereomeric alcohols **35a′** in a 72/28 ratio and 60% yield, whereas the Luche conditions gave quantitatively a reversed ratio of 18/82. The relative configuration of the two diastereomeric alcohols has not been assigned (Scheme 14).[41]

Conclusion

In summary, we have been able to transpose the Pd-catalyzed cyclization of unsaturated malonyl amides previously reported by us, to the corresponding malonyl esters, so as to obtain γ-lactones instead of γ-lactams. Such cyclization is less straightforward than the previously studied nitrogen-based one and can only be achieved in the presence of a juxtaposed silicon atom in the substrate, which directs the palladium-catalyzed ionization to the desired transient η^3-allylpalladium complex. The resulting silylvinyl-lactone **14** could be subsequently engaged into Hiyama cross-couplings to give the corresponding 4-styryl-lactones **15a**−**g**. Exploitation of this methodology allowed the successful synthesis of the podophyllotoxin analogs **33a/34a**, **33b**, and **35a′** featuring picropodophyllin configuration and a modified E ring substitution pattern. Key steps to achieve these analogs, after the palladium-catalyzed cyclization and the Hiyama coupling, are an intramolecular aldol condensation and a stereoconvergent electrophilic aromatic substitution.

The present work has established an original method to build up vinyl-lactones and aryltetralin lignan derivatives belonging to picropodophyllin configuration.[42]

(39) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

(40) It is supposed that the same conformation as observable in the X-ray crystal structure of **32a** is maintained in solution.

(41) Although a serious stereochemical analysis is not possible at this stage, we suspect that in the absence of Ce(III) addition of the hydride takes place preferentially from the same side as cycle E under assistance of the neighboring methyl ester oxygen atom. On the other hand, Ce ions may forbid such assistance via competitive coordination, thereby favoring attack from the side opposite to E ring.

Experimental Section

(±)-Methyl (3*S*,4*S*)-4-{1-[6-(1,3-Dioxolan-2-yl)-1,3-benzodioxol-5-yl]vinyl}-2-oxotetrahydrofuran-3-carboxylate (27). At room temperature, a freshly prepared 1.0 M solution of tetra-*n*-butylammonium fluoride (7.85 mL, 7.85 mmol, 2.4 equiv) in THF was added to a solution of vinylsilyl-lactone **14** (1.22 g, 3.92 mmol, 1.2 equiv). The reaction mixture was then stirred for 10 min and 5-[1,3]dioxolan-2-yl-6-iodo-benzo[1,3]dioxole **26** (1.05 g, 3.27 mmol, 1 equiv) and $Pd_2(dba)_3$ (75 mg, 0.082 mmol, 0.025 equiv) were added successively. After being stirred overnight, the resulting mixture was quenched with a saturated solution of ammonium chloride. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was washed with brine. Solvents were removed under reduced pressure, and the crude material was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate 70/30). Precipitation in Et_2O and filtration afforded **27** (818 mg, 69% yield) as a white solid. Recrystallization from cyclohexane/ethyle acetate gave a suitable single crystal for X-ray analysis (data available in Supporting Information); mp 132−133 °C; IR (neat) 2906, 1787, 1743, 1500, 1478 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.65 (d, J = 10.4 Hz, 1H), 3.78 (s, 3H), 3.92−3.98 (m, 2H), 3.98−4.08 (m, 2H), 4.08−4.15 (m, 2H), 4.42 (m, 1H), 5.18 (s,1H), 5.33 (s, 1H), 5.66 (s, 1H), 5.96 (s, 2H), 6.51 (s, 1H), 7.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.9, 50.7, 53.2, 65.5, 70.4, 100.9, 101.6, 107.1, 108.3, 118.0, 128.9, 133.4, 142.8, 147.7, 148.3, 167.7, 171.4; MS (CI, NH_3) m/z 363 $(M + H)^+$, 380 $(M + NH_4)^+$, Anal. Calcd for $C_{18}H_{18}O_8$: C, 59.67; H, 5.01, found: C, 59.89; H, 5.29.

(±)-Methyl (5a*R*,8a*R*)-5-Hydroxy-9-methylene-6-oxo-5,8,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxole-5a(6*H*)-carboxylate (28). To a solution of dioxolane **27** (1.00 g, 2.76 mmol, 1 equiv) in THF (30 mL) was added at 0 °C a solution of formic acid in water (80%, 10 mL). After 2.5 h of stirring at 0 °C, a saturated solution of sodium bicarbonate was added until a basic pH was reached. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layer was dried over Na_2SO_4. Solvents were removed under reduced pressure to afford **28** (880 mg, quantitative yield) as a 1/1 mixture of 2 diastereomers and as a white foam. This crude material was pure enough to be used in the next step without further purification. First distereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.94 (dd, J = 8.4, 4.3 Hz, 1H), 4.20 (dd, J = 8.4, 4.3 Hz, 1H), 4.71 (t, J = 8.4 Hz, 1H), 5.04 (s, 1H), 5.17 (s, 1H), 5.39 (s, 1H), 5.97 (m, 2H), 6.90 (s, 1H), 7.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.1, 53.7, 59.2, 70.3, 74.4, 101.6, 105.7, 106.3, 113.0, 127.6, 130.7, 141.0, 148.4, 148.8, 169.0, 174.5. Second diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.07−4.16 (m, 2H), 4.76 (dd, J = 8.5, 7.4 Hz, 1H), 5.14 (s, 1H), 5.26 (s, 1H), 5.41 (s, 1H), 5.97 (m, 2H), 6.85 (s, 1H), 6.93 (s, 1H); ^{13}C NMR (100 MHz; $CDCl_3$,) δ 43.1, 53.9, 60.1, 70.9, 74.9, 101.6, 106.4, 108.8, 113.0, 128.9, 129.0, 142.9, 148.5, 149.2, 169.0, 171.6.

(±)-Methyl (5a*R*,8a*R*)-5-(Acetyloxy)-9-methylene-6-oxo-5,8,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxole-5a(6*H*)-carboxylate (29). To a solution of diastereomeric alcohols **28** (880 mg, 2.76 mmol, 1 equiv) in CH_2Cl_2 (30 mL) were added successively at 0 °C triethylamine (580 μL, 4.14 mmol, 1.5 equiv), acetic anhydride (390 μL, 4.14 mmol, 1.5 equiv), and DMAP (17 mg, 0.14 mmol, 0.05 equiv). The mixture was then allowed to reach room temperature and was stirred for 2 h. A saturated solution of ammonium chloride (10 mL) was added, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layer was washed with a saturated sodium bicarbonate (10 mL) and brine (10 mL). The resulting organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude material was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate 70/30) to afford a 1/1 diastereoisomeric mixture of

(42) The results of the biological tests of the synthesized picropodophyllotoxin analogs will be reported elsewhere.

acetates **29** (930 mg, 93% yield from **27**) as a white foam. IR (neat) 2921, 1779, 1740, 1608, 1505, 1483 cm^{-1}. First diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 1.91 (s, 3H), 3.67 (s, 3H), 4.25−4.40 (m, 2H), 4.85 (dd, J = 8.4, 6.6 Hz, 1H), 4.98 (d, J = 1.8 Hz, 1H), 5.53 (d, J = 1.8 Hz, 1H), 5.93 (d, J = 1.3 Hz, 1H), 5.95 (d, J = 1.3 Hz, 1H), 6.46 (s, 1H), 6.95 (s, 1H), 7.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 41.4, 53.7, 58.1, 71.4, 72.7, 101.7, 105.0, 110.5, 111.3, 125.4, 129.0, 139.2, 148.0, 149.4, 167.6, 168.9, 172.0. Second diastereomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.89 (s, 3H), 3.82 (s, 3H), 4.14 (dd, J = 8.8, 1.5 Hz, 1H), 4.19 (bd, J = 7.4 Hz, 1H), 4.75 (dd, J = 8.8, 7.4 Hz, 1H), 5.16 (s, 1H), 5.37 (s, 1H), 5.91 (d, J = 1.3 Hz, 1H), 5.92 (d, J = 1.3 Hz, 1H), 6.41 (s, 1H), 6.87 (s, 1H), 6.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 42.4, 53.8, 59.4, 71.7, 75.9, 101.6, 105.8, 110.8, 113.2, 125.3, 130.1, 143.2, 148.0, 149.4, 166.6, 169.5, 170.4; HRMS (CI) *m/z* calcd for $C_{18}H_{16}O_8Na$ (M + Na^+) 383.0737, found 383.0738.

(±)-Methyl (5*S*,5a*S*,8a*R*)-9-Methylene-6-oxo-5-(2,3,4-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxole-5a(6*H*)-carboxylate (30a). To a solution of acetates **29** (50 mg, 0.139 mmol, 1 equiv) in CH_2Cl_2 (1.5 mL) were added, at −20 °C under argon atmosphere, 1,2,3-trimethoxybenzene (70 mg, 0.416 mmol, 3 equiv) and, dropwise, $BF_3 \cdot Et_2O$ (90 μL, 0.694 mmol, 5 equiv). The mixture was then allowed to warm up slowly to room temperature over 1 h before a saturated solution of sodium bicarbonate (1 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL), the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude material was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate 70/30) to afford **30a** (50 mg, 77% yield) as a white solid. Mp 181−183 °C; IR (neat) 2909, 1770, 1736, 1598, 1476 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 3.77 (s, 3H), 3.83 (s, 3H), 4.00 (s, 3H), 4.27 (dd, J = 8.8, 1.0 Hz, 1H), 4.35 (m, 1H), 4.64 (dd, J = 8.8, 6.6 Hz, 1H), 5.22 (d, J = 1.0 Hz, 1H), 5.30 (s, 1H), 5.49 (s, 1H), 5.87 (d, J = 1.4 Hz, 1H), 5.92 (d, J = 1.4 Hz, 1H), 6.47 (d, J = 8.8 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 6.83 (s, 1H), 6.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.1, 43.8, 53.27, 55.7, 59.3, 60.6, 61.0, 75.4, 101.2, 105.1, 107.0, 109.1, 112.0, 122.3, 126.3, 127.6, 131.5, 142.1, 144.6, 147.7, 148.5, 151.5, 152.7, 167.6, 173.1; HRMS (CI) *m/z* calcd for $C_{25}H_{24}O_9Na$ (M + Na^+) 491.1313, found 491.1310.

(±)-Methyl (5*S*,5a*S*,8a*R*)-9-Methylene-6-oxo-5-(2,4,6-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxole-5a(6*H*)-carboxylate (30b). To a solution of acetates **29** (500 mg, 1.39 mmol, 1 equiv) in CH_2Cl_2 (15 mL) at −20 °C were added 1,3,5-trimethoxybenzene (700 mg, 4.16 mmol, 3 equiv) and, dropwise, $BF_3 \cdot Et_2O$ (900 μL, 6.94 mmol, 5 equiv). The mixture was then allowed to warm up slowly to room temperature over 1 h before a saturated solution of sodium bicarbonate (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude material was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate 70/30) to afford **30b** (550 mg, 84% yield) as a white foam. IR (neat) 2951, 1779, 1735, 1605, 1482 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.10−4.10 (bs, 6H), 3.44 (s, 3H), 3.75 (s, 3H), 4.28 (bd = 5.6 Hz, 1H), 4.34 (d, J = 8.7 Hz, 1H), 4.54 (dd, J = 8.7, 5.6 Hz, 1H), 5.09 (d, J = 1.5 Hz, 1H), 5.56 (d, J = 1.5 Hz, 1H), 5.74 (s, 1H), 5.82 (d, J = 1.4 Hz, 1H), 5.87 (d, J = 1.4 Hz, 1H), 6.05 (bs, 2H), 6.65 (s, 1H), 7.00 (s, 1H); ^1H NMR (400 MHz, DMSO-d_6, 80 °C) δ 3.41 (s, 3H), 3.71(s, 6H), 3.76 (s, 3H), 4.20 (m, 1H), 4.29 (d, J = 9.0 Hz, 1H), 4.50 (dd, J = 9.0, 5.8 Hz, 1H), 5.23 (d, J = 1.5 Hz, 1H), 5.57 (s, 1H), 5.65 (d, J = 1.5 Hz, 1H), 5.88 (s, 1H), 5.93 (s, 1H), 6.18 (s, 2H), 6.52 (s, 1H), 7.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.2, 44.0, 52.8, 55.3, 58.0, 75.8, 90.6, 101.1, 103.3, 108.6, 109.1, 109.6, 127.6, 130.3, 144.9, 147.1, 148.0, 159.2, 160.5, 167.9, 174.0; HRMS (CI) *m/z* calcd for $C_{25}H_{24}O_9Na$ (M + Na^+) 491.1313, found 491.1311.

(±)-Methyl (5*R*,5a*S*,8a*R*)-9-Methylene-6-oxo-5-(1*H*-pyrrol-2-yl)-5,8,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxole-5a(6*H*)-carboxylate (30c). To a solution of acetates **29** (50 mg, 0.139 mmol, 1 equiv) in CH_2Cl_2 (1 mL) at −30 °C were added freshly distilled pyrrole (50 μL, 0.694 mmol, 5 equiv) and, dropwise, $BF_3 \cdot Et_2O$ (53 μL, 0.416 mmol, 3 equiv). The mixture was then allowed to warm up slowly to room temperature over 1 h before a saturated solution of sodium bicarbonate (1 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL), the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude material was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate 85/15) to afford **30c** (25 mg, 50% yield) as a yellow foam. ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.17 (bd, J = 6.6 Hz, 1H), 4.22 (dd, J = 8.8, 1.0 Hz, 1H), 4.68 (dd, J = 8.8, 6.6 Hz, 1H), 4.95 (s, 1H), 5.23 (s, 1H), 5.50 (s, 1H), 5.87 (m, 1H), 5.92 (d, J = 1.4 Hz, 1H), 5.95 (d, J = 1.4 Hz, 1H), 6.01 (m, 1H), 6.71 (s, 1H), 6.95 (s, 1H), 8.02 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.4, 43.6, 53.7, 60.5, 75.8, 101.5, 108.5, 105.8, 107.7, 109.1, 113.2, 118.1, 128.1, 128.7, 130.0, 144.9, 148.3, 148.9, 167.4, 172.4; HRMS (CI) *m/z* calcd for $C_{20}H_{17}O_6NNa$ (M + Na^+) 390.0948, found 390.0949.

(±)-(5*S*,5a*S*,8a*S*)-9-Methylene-5-(2,3,4-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one (31a). To a solution of **30a** (120 mg, 0.256 mmol, 1 equiv) in DMSO (2 mL) were added NaCl (30 mg, 0.512 mmol, 2 equiv) and H_2O (11 μL, 0.611 mmol, 2.4 equiv). The resulting mixture was stirred at 155 °C and completion of the reaction was monitored by TLC. After cooling down to room temperature, H_2O (30 mL) and AcOEt (10 mL) were added. The aqueous layer was extracted with AcOEt (3 × 10 mL), the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude material was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate 65/35) to afford **31a** (95 mg, 90% yield) as a white foam. IR (neat) 2904, 2254, 1766, 1600, 1480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.38 (dd, J = 9.0, 2.7 Hz, 1H), 3.47 (m, 1H), 3.79, (s, 3H), 3.88 (s, 3H), 4.01 (s, 3H), 4.18 (dd, J = 9.0, 2.3 Hz, 1H), 4.50 (dd, J = 9.0, 6.9 Hz, 1H), 4.72 (d, J = 2.7 Hz, 1H), 5.01 (s, 1H), 5.44 (s, 1H), 5.93 (d, J = 1.3 Hz, 1H), 5.94 (d, J = 1.3 Hz, 1H), 6.27 (d, J = 8.7 Hz, 1H), 6.44 (d, J = 8.7 Hz, 1H), 6.62 (s, 1H), 7.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.5, 39.6, 44.7, 56.0, 60.9, 61.2, 74.8, 101.3, 105.3, 106.7, 109.5, 111.8, 123.3, 127.7, 129.6, 130.9, 142.2, 143.9, 147.8, 148.5, 151.5, 152.9, 177.5; HRMS (CI) *m/z* calcd for $C_{23}H_{22}O_7Na$ (M + Na^+) 433.1258, found 433.1256.

(±)-(5*S*,5a*S*,8a*S*)-9-Methylene-5-(2,4,6-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one (31b). To a solution of **30b** (200 mg, 0.427 mmol, 1 equiv) in DMSO (3.5 mL) were added NaCl (50 mg, 0.854 mmol, 2 equiv) and H_2O (18 μL, 1.025 mmol, 2.4 equiv). After cooling down to room temperature, H_2O (30 mL) and AcOEt (10 mL) were added. The aqueous layer was extracted with AcOEt (3 × 10 mL), the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude material was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate 7/3) to afford **31b** (123 mg, 70% yield) as a white foam. IR (neat) 2902, 2253, 1769, 1591, 1478 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.31 (t, J = 8.6 Hz, 1H), 3.65−3.75 (m, 1H), 3.69 (s, 6H), 3.81 (s, 3H), 4.28 (t, J = 8.6 Hz, 1H), 4.53 (t, J = 8.6 Hz, 1H), 4.76 (d, J = 8.6 Hz, 1H), 5.00 (s, 1H), 5.49 (s, 1H), 5.84 (s, 1H), 5.87 (s, 1H), 6.17 (s, 2H), 6.33 (s, 1H), 7.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 41.1, 42.5, 55.3, 55.8, 71.2, 91.2, 100.9, 104.1, 107.1, 109.7, 109.7, 127.6, 132.8, 140.6, 146.3, 148.0, 159.2, 160.5, 178.0; HRMS (CI) *m/z* calcd for $C_{23}H_{22}O_7Na$ (M + Na^+) 433.1258, found 433.1259.

(±)-(5a*R*,8a*S*,9*S*)-9-(2,3,4-Trimethoxyphenyl)-5a,6,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxole-5,8-dione (32a). To a solution of alkene **31a** (220 mg, 0.536 mmol, 1 equiv) in a mixture of THF/H_2O (11 mL/1.4 mL) were added successively 4-methylmorpholine-*N*-oxide (126 mg, 1.07 mmol, 2 equiv) and $OsCl_3 \cdot xH_2O$ (8 mg). The resulting dark suspension was stirred at room temperature until no starting alkene was detected by TLC. A 50%

sodium bisulfite solution (10 mL) was then added and the resulting solution was stirred for 15 min. The aqueous layer was extracted with AcOEt (3 × 10 mL), the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude material was filtered on a pad of silica gel (cyclohexane/ethyl acetate 6/4). The filtrate was concentrated under reduced pressure, the residue was dissolved in a mixture of acetone/H_2O (30 mL/20 mL) and $NaIO_4$ (345 mg, 1.61 mmol, 3 equiv) was added in one portion. The reaction mixture was stirred at room temperature until no diol was detected by TLC. Acetone was removed under reduced pressure, brine was added (25 mL), and the resulting aqueous layer was extracted with AcOEt (3 × 25 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, and the crude material was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate 7/3) to afford **32a** (169 mg, 76% yield) as a white foam. IR (neat) 2910, 2254, 1772, 1667, 1614, 1478 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.25 (dd, J = 8.0, 6.0 Hz, 1H), 3.33 (dd, J = 8.0, 1.5 Hz, 1H), 3.79 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.30 (dd, J = 9.1, 6.0 Hz, 1H), 4.72 (d, J = 9.1 Hz, 1H), 4.91 (bd, J = 1.5 Hz, 1H), 6.00 (s, 2H), 6.32 (d, J = 8.6 Hz, 1H), 6.48 (d, J = 8.6 Hz, 1H), 6.63 (s, 1H), 7.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.7, 43.7, 45.0, 55.9, 60.7, 61.0, 70.3, 102.1, 105.9, 106.9, 109.3, 123.1, 127.7, 128.1, 140.2, 142.4, 148.1, 151.1, 153.3, 153.5, 175.9, 194.0; HRMS (CI) m/z calcd for $C_{22}H_{20}O_8Na$ (M + Na^+) 435.1050, found 435.1049.

(±)-(5a*R*,8a*S*,9*S*)-9-(2,4,6-Trimethoxyphenyl)-5a,6,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxole-5,8-dione (32b). To a solution of alkene **31b** (139 mg, 0.339 mmol, 1 equiv) in a mixture of THF/H_2O (7 mL/0.9 mL) were added successively 4-methylmorpholine-*N*-oxide (80 mg, 0.677 mmol, 2 equiv) and $OsCl_3 \cdot xH_2O$ (5 mg). The resulting dark suspension was stirred at room temperature until no starting alkene was detected by TLC. A 50% sodium bisulfite solution (10 mL) was then added and the resulting solution was stirred for 15 min. The aqueous layer was extracted with AcOEt (3 × 10 mL), the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude material was filtered on a pad of silica gel (cyclohexane/ethyl acetate 6/4). The filtrate was concentrated under reduced pressure, the residue was dissolved in a mixture of acetone/H_2O (15 mL/10 mL) and $NaIO_4$ (217 mg, 1.02 mmol, 3 equiv) was added in one portion. The reaction mixture was stirred at room temperature until no diol was detected by TLC. Acetone was removed under reduced pressure, brine was added (25 mL) and the resulting aqueous layer extracted with AcOEt (3 × 25 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, and the crude material was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate 7/3) to afford **32b** (119 mg, 85% yield) as a white foam. IR (neat) 2911, 2841, 1769, 1665, 1606, 1477 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.14 (dd, J = 8.7, 1.9 Hz, 1H), 3.56 (ddd, J = 8.7, 6.9, 1.4 Hz, 1H), 3.66 (bs, 6H), 3.76 (s, 3H), 4.35 (dd, J = 9.1, 6.9 Hz, 1H), 4.68 (dd, J = 9.1, 1.4 Hz, 1H), 5.42 (d, J = 1.9 Hz, 1H), 5.89 (s, 1H), 5.91 (s, 1H), 6.09 (s, 2H), 6.55 (s, 1H), 7.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$,) δ 31.3, 43.9, 45.2, 55.3, 55.5, 69.8, 91.1, 101.7, 105.2, 108.5, 111.8, 127.2, 141.5, 147.1, 152.7, 158.7, 160.6, 177.2, 194.6; HRMS (CI) m/z calcd for $C_{22}H_{20}O_8Na$ (M + Na^+) 435.1050, found 435.1049.

(±)-Methyl (5*S*,5a*S*,8a*R*)-6,9-Dioxo-5-(2,3,4-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxole-5a(6*H*)-carboxylate (32a′). To a solution of alkene **30a** (186 mg, 0.397 mmol, 1 equiv) in a mixture of THF/H_2O (8 mL/1 mL) were added successively 4-methylmorpholine-*N*-oxide (93 mg, 0.794 mmol, 2 equiv) and $OsCl_3 \cdot xH_2O$ (6 mg). The resulting dark suspension was stirred at 50 °C until no starting alkene was detected by TLC. A 50% sodium bisulfite solution (10 mL) was then added and the resulting solution was stirred for 15 min. The aqueous layer was extracted with AcOEt (3 × 20 mL), the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude material was filtered on a pad of silica gel (cyclohexane /ethyl acetate 6/4). The filtrate was concentrated under reduced pressure, the residue was dissolved in a mixture of acetone/H_2O (18 mL/12 mL), and $NaIO_4$ (255 mg, 1.19 mmol, 3 equiv) was added in one portion. The reaction mixture was stirred at room temperature until no diol was detected by TLC. Acetone was removed under reduced pressure, brine was added (25 mL), and the resulting aqueous layer was extracted with AcOEt (3 × 25 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, and the crude material was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate 7/3) to afford **32a′** (149 mg, 80% yield) as a white foam. IR (neat) 2943, 2255, 1785, 1737, 1668, 1478 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.46 (s, 3H), 3.50 (s, 3H), 3.73 (s, 3H), 3.77 (s, 3H), 4.08 (d, J = 5.8 Hz, 1H), 4.38 (dd, J = 9.1, 5.8 Hz, 1H), 4.68 (d, J = 9.1 Hz, 1H), 5.07 (bs, 1H), 5.91 (m, 1H), 5.94 (m, 1H), 6.53 (d, J = 8.5 Hz, 1H), 6.66 (s, 1H), 6.79 (bd, J = 8.5 Hz, 1H), 7.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.8, 47.8, 53.2, 55.9, 58.7, 60.1, 60.6, 70.9, 102.1, 105.7, 106.9, 108.9, 124.0, 124.9, 126.3, 139.3, 142.3, 147.9, 152.0, 153.3, 153.8, 166.1, 172.3, 193.6; HRMS (CI) m/z calcd for $C_{24}H_{22}O_{10}Na$ (M + Na^+) 493.1105, found 493.1103.

(±)-(5*S*,5a*S*,8a*R*)-9-Hydroxy-5-(2,3,4-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one (33a (9*R*) and 34a (9*S*)). Procedure A. To a solution of ketone **32a** (42 mg, 0.102 mmol, 1 equiv) in dry MeOH (10 mL) was added $NaBH_4$ (11.5 mg, 0.305 mmol, 3 equiv) in one portion at room temperature. After 1.5 h of stirring, a saturated solution of ammonium chloride (20 mL) and Et_2O (10 mL) was added. The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organic layer was concentrated under reduced pressure. The residue was treated with CH_2Cl_2 (20 mL) and filtered to remove residual boron salts. The filtrate was concentrated under reduced pressure, and the crude material was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate 6/4) to afford the mixture of epimers **33a** and **34a** (36 mg, 86% yield) in a 89/11 ratio and as a white foam. **Procedure B.** To a solution of ketone **32a** (19 mg, 0.046 mmol, 1 equiv) and $CeCl_3 \cdot 7H_2O$ (26 mg, 0.069 mmol, 1.5 equiv) in a 1/1 mixture of dry MeOH and CH_2Cl_2 (2 mL) was added $NaBH_4$ (2.6 mg, 0.069 mmol, 1.5 equiv) in one portion at −78 °C. The solution was allowed to warm up slowly to room temperature before a saturated solution of ammonium chloride (10 mL) and CH_2Cl_2 (5 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude material was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate 6/4) to afford the mixture of epimers **33a** and **34a** (17 mg, 89% yield) in a 92/8 ratio and as a white foam. Major diastereomer (**33a**): IR (neat) 3442, 2941, 1769, 1664, 1661, 1479 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.59−2.68 (m, 1H), 3.23 (dd, J = 9.1, 6.0 Hz, 1H), 3.67 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.18 (d, J = 6.0 Hz, 1H), 4.38 (dd, J = 9.6, 6.0 Hz, 1H), 4.43 (d, J = 9.5 Hz, 1H), 4.58 (dd, J = 9.6, 1.5 Hz, 1H), 5.84 (d, J = 1.4 Hz, 1H), 5.87 (d, J = 1.4 Hz, 1H), 6.18 (s, 1H), 6.66 (d, J = 8.6 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 7.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.8, 43.1, 44.5, 56.1, 60.7, 60.8, 68.7, 69.7, 101.1, 104.8, 107.3, 108.0, 124.5, 129.2, 131.5, 132.4, 142.7, 146.5, 146.9, 151.9, 153.3, 178.8; HRMS (CI) m/z calcd for $C_{22}H_{22}O_8Na$ (M + Na^+) 437.1207, found 437.1206.

(±)-(5*S*,5a*S*,8a*R*,9*R*)-9-Hydroxy-5-(2,4,6-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one (33b). To a solution of ketone **32b** (28 mg, 0.068 mmol, 1 equiv) and $CeCl_3 \cdot 7H_2O$ (38 mg, 0.102 mmol, 1.5 equiv) in dry MeOH (2 mL) was added $NaBH_4$ (3.8 mg, 0.102 mmol, 1.5 equiv) in one portion at −78 °C. The solution was allowed to warm up slowly to room temperature before a saturated solution of ammonium chloride (10 mL) and CH_2Cl_2 (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude material was purified by silica gel

flash column chromatography (cyclohexane/ethyl acetate 6/4) to afford **33b** (23 mg, 82% yield) as a white foam. IR (neat) 3442, 2940, 1754, 1591, 1476 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.50−2.60 (m, 1H), 3.42 (dd, J = 9.4, 7.6 Hz, 1H), 3.72 (s, 6H), 3.84 (s, 3H), 4.39 (dd, J = 9.6, 6.3 Hz, 1H), 4.46 (bdd, J = 10.0, 6.7 Hz, 1H), 4.59 (d, J = 7.6 Hz, 1H), 4.63 (dd, J = 9.6, 1.9 Hz, 1H), 5.83 (d, J = 1.4 Hz, 1H), 5.88 (d, J = 1.4 Hz, 1H), 6.19 (d, J = 1.0 Hz, 1H), 6.21 (s, 2H), 7.07 (s, 1H); ^1H NMR (400 MHz, C_6D_6) δ 2.20 (dddd, J = 10.6, 9.5, 6.2, 1.4 Hz, 1H), 1.68 (d, J = 6.2 Hz, 1H), 3.23−3.28 (m, 1H), 3.26 (bs, 6H), 3.42 (s, 3H), 3.68 (dd, J = 9.4, 6.2 Hz, 1H), 3.90 (bdd, J = 10.6, 6.2 Hz, 1H), 4.18 (dd, J = 9.4, 1.4 Hz, 1H), 5.00 (d, J = 7.3 Hz, 1H), 5.26 (d, J = 1.4 Hz, 1H), 5.28 (d, J = 1.4 Hz, 1H), 6.15 (s, 2H), 6.63 (d, J = 1.0 Hz, 1H), 7.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.4, 42.1, 44.0, 55.5, 56.1, 68.9, 69.1, 91.6, 100.9, 104.0, 106.8, 110.5, 131.7, 132.4, 146.0, 146.9, 159.2, 160.7, 179.1; HRMS (CI) *m*/*z* calcd for $C_{22}H_{22}O_8Na$ ($M + Na^+$) 437.1207, found 437.1205.

(±)-Methyl (5*S*,5a*S*,8a*R*)-9-Hydroxy-6-oxo-5-(2,3,4-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxole-5a(6*H*)-carboxylate (35a′). Procedure A. To a solution of ketone **32a′** (30 mg, 0.064 mmol, 1 equiv) in dry MeOH (5 mL), $NaBH_4$ (5 mg, 0.127 mmol, 2 equiv) was added in one portion at room temperature. The resulting reaction mixture was stirred 2 h at room temperature before a saturated solution of ammonium chloride (10 mL) and Et_2O (10 mL) were added. The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organic layer was concentrated under reduced pressure. The residue was treated with CH_2Cl_2 (20 mL) and filtered to remove residual boron salts. The filtrate was concentrated under reduced pressure, and the crude material was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate 7/3 to 1/1) to afford **35a′** as a 72/28 mixture of epimers and as a white foam (18 mg, 60% yield). (Starting material **32a′** was also recovered (10 mg, 33%). **Procedure B.** To a solution of ketone **32a′** (20 mg, 0.042 mmol, 1 equiv) and $CeCl_3 \cdot 7H_2O$ (24 mg, 0.064 mmol, 1.5 equiv) in dry MeOH (1 mL) was added $NaBH_4$ (2.4 mg, 0.064 mmol, 1.5 equiv) in one portion at −78 °C. The solution was allowed to warm up slowly to room temperature before a saturated solution of ammonium chloride (10 mL) and CH_2Cl_2 (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude material was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate 6/4) to afford **35a′** as a 18/82 mixture of epimers and as a white foam (20 mg, quantitative yield). First diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 3.45 (s, 3H), 3.54 (td, J = 5.2, 0.8 Hz, 1H), 3.71(s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 4.41 (dd, J = 9.1, 0.8 Hz, 1H), 4.47 (dd, J = 9.1, 5.2 Hz, 1H), 4.66 (bd, J = 5.2 Hz, 1H), 5.07 (s, 1H), 5.87 (d, J = 1.3 Hz, 1H), 5.89 (d, J = 1.3 Hz, 1H), 6.57 (d, J = 8.8 Hz, 1H), 6.66 (s, 1H), 6.89 (s, 1H), 7.01 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$,) δ 41.8, 45.5, 53.1, 56.0, 59.1, 60.6, 60.8, 71.6, 72.3, 101.3, 106.9, 107.1, 109.5, 124.7, 126.4, 129.4, 130.5, 142.3, 147.2, 147.8, 152.3, 153.3, 167.7, 173.4. Second diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 3.59 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 3.88 (s, 3H), 4.10 (m, 1H), 4.36 (dd, J = 9.1, 8.5 Hz, 1H), 4.52 (dd, J = 9.1, 2.5 Hz, 1H), 5.17 (s, 1H), 5.20 (m, 1H), 5.90 (m, 2H), 6.50 (d, J = 8.7 Hz, 1H), 6.71 (d, J = 8.7 Hz, 1H), 6.96 (s, 1H), 6.99 (s, 1H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 43.9, 45.2, 53.6, 56.0, 59.6, 60.5, 60.8, 65.7, 66.6, 101.1, 104.7, 106.1, 111.0, 121.3, 125.3, 129.2, 130.8, 142.7, 147.0, 147.3, 152.5, 153.0, 168.8, 173.9; IR (neat) 3412, 2919, 2850, 1775, 1735, 1599, 1482 cm^{-1}; HRMS (CI) *m*/*z* calcd for $C_{24}H_{24}O_{10}Na$ ($M + Na^+$) 495.1262, found 495.1260.

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Supporting Information Available: Experimental details concerning the preparations and cyclizations of precursors **1a**−**d**, **8a**−**c**, and **13**; general procedure for the Hiyama cross-coupling of **14** to give **15a**−**g**; preparation and cyclization attempt of precursor **21**; preparation of compounds **23**−**26**; copies of ^1H and ^{13}C NMR spectra; and X-ray diffraction analysis data of compounds **27** and **32a** and their checkCIF validated cif files. This material is available free of charge via the Internet at http://pubs.acs.org.

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