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1-Aryltetralin privileged structure-based libraries: parallel synthesis of *N*-aryl and *N*-biaryl γ-lactam lignans

Matthieu Dorbec,[a] Jean-Claude Florent,[a,*] Claude Monneret,[a] Marie-Noëlle Rager[b] and Emmanuel Bertounesque[a,*]

[a]*UMR 176 CNRS-Institut Curie, Centre de Recherche, 26 rue d'Ulm, 75248 Paris Cedex 05, France*
[b]*Département de RMN, Ecole Nationale Supérieure de Chimie de Paris, 11 rue P. et M. Curie, 75231 Paris Cedex 05, France*

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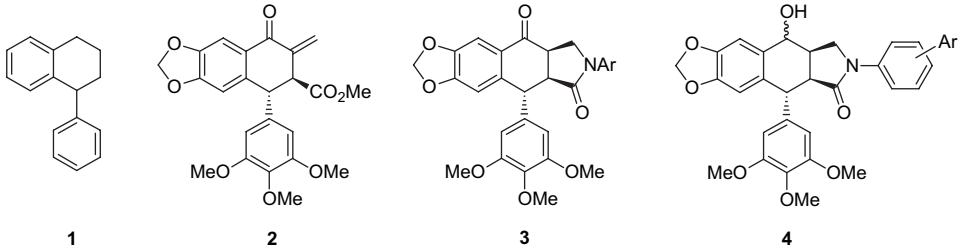
Abstract—The parallel solution-phase synthesis of two libraries of product-like compounds derived from a 1-aryltetralin privileged structure is described. The *N*-aryl picropodophyllone γ-lactams were synthesized from methyl ester thuriferic acid via $InCl_3$-tandem aza-Michael addition–cyclization reaction of anilines. Bromo-aryl compounds from this library were subjected to a ligandless palladium Suzuki cross-coupling to give the expected *N*-biaryl picropodophyllin γ-lactams.

1. Introduction

There is growing current interest in using specific structures, generally found within a class of natural products, as starting points for library design.[1] The core scaffold of a natural product can provide a biologically validated framework with diverse functional groups. The resulting libraries can then be used to address a variety of biological targets.[2] Within this context, we initiated the synthesis of γ-lactam lignans based on the 1-aryltetralin skeleton **1** as a privileged structure[3–9] (Fig. 1). Lignans of 1-aryltetralin type possess a diverse range of biological activities[10–13] including inhibition of the tubulin polymerization, inhibition of DNA topoisomerase II, and immunosuppressive, anti-HIV, and antidepressant activities. Recently, cyclolignans as inhibitors of the phosphorylation of the insuline-like growth factor receptor (IGF-1R) have been reported.[14–20] γ-Lactam motif as well as the biaryl subunit[21] are also valuable pharmacophoric groups found in a variety of molecules presenting biological properties. The combination of such fragments may qualitatively enrich the compounds collection. In the field of podophyllotoxin chemistry, it is worth noting that only two syntheses exemplifying the combination of **1** with γ-lactam rings have been reported so far, i.e., the semi-synthesis of etoposide-lactam derivatives[22] and the total synthesis of (±)-demethoxy epiisopicropodophyllin *N*-benzyl lactam.[23]

Our first approach involved a synthesis of *N*-aryl picropodophyllone γ-lactams[24] via aza-Michael addition from thuriferic acid methyl ester **2** under basic conditions. In this paper, we describe the extension of our work with the parallel solution-phase synthesis of *N*-aryl γ-lactam lignans **3** via a tandem aza-Michael addition–cyclization from **2**[25–31] using a catalytic amount of $InCl_3$, and then the parallel



1 2 3 4

Figure 1.

Keywords: Biaryls; Lactam lignans; Privileged structure; Tandem reaction; $InCl_3$; Ligandless Suzuki reaction; Parallel solution-phase synthesis.
* Corresponding authors. Tel.: +33142346659; fax: +33142346631 (E.B.); e-mail: emmanuel.bertounesque@curie.fr

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solution-phase synthesis of *N*-biaryl γ-lactam lignans **4** from the corresponding bromo adducts via a ligandless palladium Suzuki cross-coupling (Fig. 1).

2. Results and discussion

2.1. Parallel solution-phase synthesis of *N*-aryl γ-lactam lignans

Michael addition of amines to α,β-unsaturated ketones usually require basic conditions or acid catalysis. In the past few years, a number of alternative procedures have been developed and in particular, various Lewis acid-induced and transition metal salts catalyzed reactions have been reported.[32–42] Recently, indium salts have emerged as powerful catalysts in many chemical processes both in aqueous and organic media.[43–50] Loh and co-workers have reported indium trichloride as an excellent catalyst in the Mukaiyama aldol reactions,[51–53] Diels–Alder reactions,[54] aldol-type Mannich reactions,[55] and Michael reaction[56,57] under mild conditions. As indium trichloride has these unique properties compared to other Lewis acids—which include stability and recoverability from water[56]—and since indium salts allowed tandem reactions[49,50] and one-pot multistep transformation,[47] we decided to exploit this catalyst to construct our small γ-lactam lignans libraries from methyl ester thuriferic acid **2** with the aim to develop a one-pot protocol, which would be an improvement over our previous synthesis.[24]

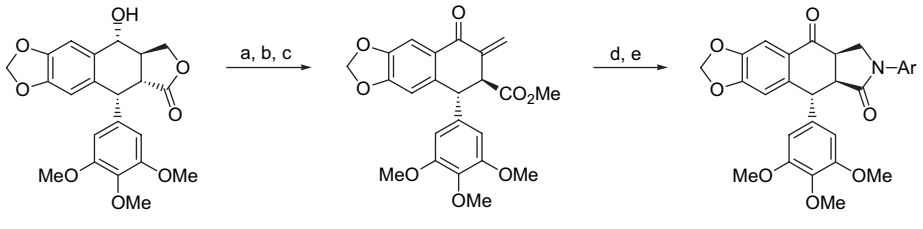
Methyl ester thuriferic acid **2** was obtained in a three-step sequence[24] from podophyllotoxin **5**, as outlined in Scheme 1. To our delight, the *N*-aryl picropodophyllone γ-lactams **3** were synthesized from **2** via $InCl_3$-catalyzed tandem aza-Michael addition–cyclization reaction of substituted anilines. γ-Lactams **3** were obtained as a single isomer and their stereochemistry were determined to be cis by NOESY experiment.[24] The parallel solution-phase synthesis of *N*-aryl picropodophyllone lactams was conducted on the Quest 210® (Argonaut Technologies) using 10 mL Teflon reaction vessels (Table 1). We used sulfonyl chloride resin as a polymer-supported scavenger[58] for anilines in order to facilitate the purification of products.

For monohalogenated anilines (Table 1, entries 1–6) and activated anilines (Table 1, entries 7–13), the tandem reaction with **2** catalyzed by $InCl_3$ (0.5 equiv) afforded exclusively *cis*-γ-lactams **3a–f** and **3g–m** after 48 h at 80 °C in DCE in 61–94% yields. Surprisingly, one activated aniline (entry 14) required addition of a base for the synthesis of **3n** under these catalytic conditions. Indeed, for 2-aminofluorene, a mixture of the *cis*-γ-lactam **3n** as a major product together with the *cis*- and *trans*-β-amino ketones **6n** was obtained under $InCl_3$ catalysis[59] (^{1}H NMR analysis). Addition of DBU to the reaction mixture favored the cyclization step providing the *cis*-γ-lactam **3n** in 66% yield. The scope of this tandem reaction found to be limited. Deactivated anilines 4-nitroaniline and 4-trifluoroaniline behave differently during the necessary one-pot process since no cyclization products were obtained by using only $InCl_3$: following addition of DBU, while the formation of the desired *cis*-γ-lactam **3o** was observed (50%), demonstrating the reactivity of the aza-Michael adduct **6o** obtained from 4-nitro-aniline (Fig. 2), no cyclization occurred from the *cis*- and *trans*-β-amino ketones **6p**.[59] Furthermore, reaction of deactivated 5-aminoanthraquinone resulted only in recovered starting material **2**. Reaction of *ortho*-substituted anilines such as 2-bromoaniline, 2,4-dibromoaniline, 5-chloro-2-methylaniline, 1-amino-5,6,7,8-tetrahydronaphthalene, and 2,3-dimethylaniline furnished the corresponding aza-Michael adduct **6** in the presence of the starting material **2** (^{1}H NMR analysis of the crude product). For example, for 1-amino-5,6,7,8-tetrahydronaphthalene and 2,3-dimethylaniline we obtained a mixture of starting material **2** and aza-Michael adduct **6** in 33 and 66% yields, respectively. Finally, in the case of 4-iodoaniline, the expected products (**6** and/or **3**) could not be observed in the NMR spectra, only an unidentified mixture of products being obtained.

2.2. Parallel solution-phase synthesis of *N*-biaryl γ-lactam lignans

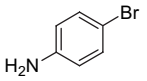
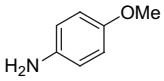
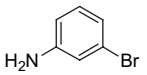
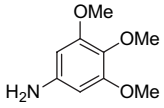
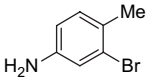
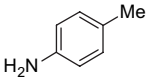
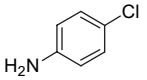
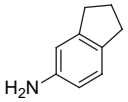
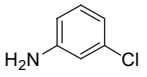
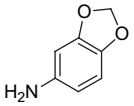
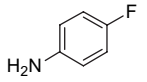
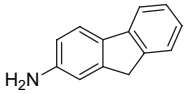
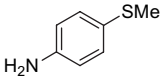
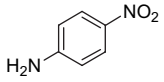
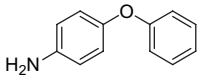
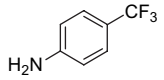
The synthesis of libraries of biaryl small molecules is vitally important to the pharmaceutical industry in the search for biologically active compounds. Consequently, we turned out our attention to the parallel solution-phase synthesis of *N*-biaryl γ-lactam lignans **4** from the bromo adducts **3a** and **3b**. We used 'ligandless' palladium catalytic conditions, which have demonstrated many advantages over classical coupling methodologies.[60–68]

We therefore decided to apply this methodology from compounds **3a** and **3b** for the parallel solution-phase synthesis of *N*-biaryl γ-lactam lignans on the Quest 210®. The Suzuki–Miyaura coupling of **3a** with substituted phenylboronic acids (i.e., phenylboronic acid, 4-chlorophenylboronic acid, and 4-methoxyphenylboronic acid) was examined under a variety of conditions. Unfortunately, the reaction afforded partial conversion of **3a** into the desired biaryl derivative and/or degradation products. In the latter case, ^{1}H NMR analysis of the crude product revealed the disappearance of the signals of the H_1, H_2, and H_3 protons and appearance of other aromatic protons. Given the acidity of the H_3 proton, this result is likely due to aromatization reaction

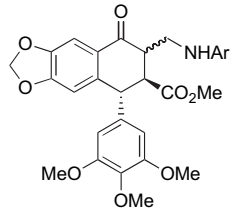


Scheme 1. (a) PCC, DCM, rt; (b) *t*-BuOK, *t*-BuOH, reflux; (c) MeI, $NaHCO_3$, DMF, rt; (d) $ArNH_2$, $InCl_3$, DCE, 80 °C; (e)  $ArSO_2Cl$, Et_3N.

Table 1

Entry	Aniline	Product[a] (%)	Yield[b] (%)	Purity[c] (%)	Entry	Aniline	Product[a] (%)	Yield[b] (%)	Purity[c] (%)
1[d]		**3a**	94	87	9[d]		**3i**	90	91
2[d]		**3b**	91	89	10[d]		**3j**	90	77
3[d]		**3c**	85	92	11[d]		**3k**	92	79
4[d]		**3d**	91	94	12[d]		**3l**	81	81
5[d]		**3e**	76	79	13[d]		**3m**	61	87
6[d]		**3f**	85	92	14[e]		**3n**	66[59]	86
7[d]		**3g**	82	88	15[e]		**3o**	50[59]	80
8[d]		**3h**	71	79	16[f]		**3p**	0[59]	

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopy.
[b] Isolated yields.
[c] ^{1}H NMR estimation after scavenging with sulfonyl chloride resin and filtration on silica pad.
[d] $InCl_3$ (0.5 equiv), 48 h.
[e] $InCl_3$ (0.5 equiv), 48 h, then DBU (5 equiv), 24 h.
[f] Obtention of β-aminoketone **6p** and recovered starting material **2**.

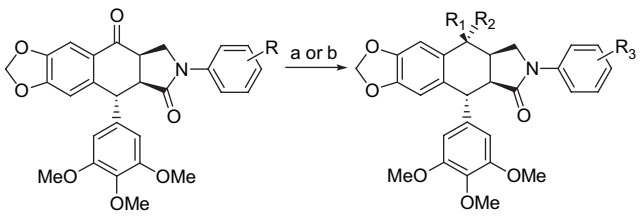


6n (aniline = 2-aminofluorene)
6o (aniline = 4-nitroaniline)
6p (aniline = 4-trifluoroaniline)

Figure 2.

occurring during cross-coupling. To circumvent this problem, we opted for a reduction of the carbonyl function at C-4 on the picropodophyllone derivatives **3a** and **3b**.

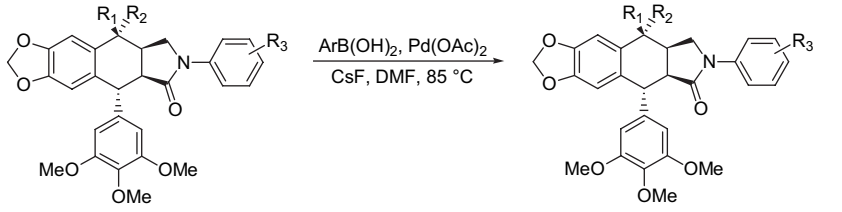
Accordingly, we examined the reduction of the carbonyl function at C-4 of the picropodophyllone *N*-4-bromophenyl γ-lactam **3a** and the picropodophyllone *N*-3-bromophenyl γ-lactam **3b** under different reducing conditions (i.e., $NaBH_4$, $NaBH_4/CeCl_3$, $NaHB(OAc)_3$, L-Selectride, catecholboranehydride). It was found that $NaBH_4$ at −78 °C gave the best results to obtain the 4-OH group in the α-configuration, thereby leading to **7a** (75%, dr=87%) and **8a** (67%, dr=87%) from **3a** and **3b**, respectively (Scheme 2). In contrast, the use of L-Selectride at −78 °C allowed the opposite selectivity, **7b** (86%) and **8b** (80%) were thus prepared with an excellent diastereoisomeric excess (dr>95%). The relative stereochemistry of these compounds was deduced from the $J_{3,4}$ coupling constants (8.2 Hz for **7a**, 5.0 Hz for



3a: R = 4-Br
3b: R = 3-Br

7a: R_1 = H, R_2 = OH, R_3 = 4-Br
7b: R_1 = OH, R_2 = H, R_3 = 4-Br
8a: R_1 = H, R_2 = OH, R_3 = 3-Br
8b: R_1 = OH, R_2 = H, R_3 = 3-Br

Scheme 2. (a) $NaBH_4$, THF, MeOH, −78 °C; (b) L-Selectride, THF, −78 °C.



7a: R_1 = H, R_2 = OH, R_3 = 4-Br
7b: R_1 = OH, R_2 = H, R_3 = 4-Br
8a: R_1 = H, R_2 = OH, R_3 = 3-Br
8b: R_1 = OH, R_2 = H, R_3 = 3-Br

4aa-ai: R_1 = H, R_2 = OH, R_3 = 4-aryl
4ba-bd: R_1 = OH, R_2 = H, R_3 = 4-aryl
4ca,cb: R_1 = H, R_2 = OH, R_3 = 3-aryl
4da,db: R_1 = OH, R_2 = H, R_3 = 3-aryl

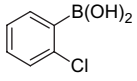
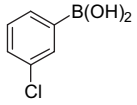
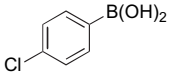
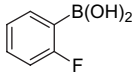
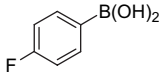
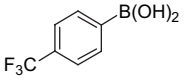
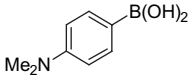
Scheme 3. Suzuki–Miyaura cross-coupling reaction.

7b, 7.5 Hz for **8a**, and 4.5 Hz for **8b**) and was confirmed from NOESY correlations (H_3/H_2, H_1/H_4, $H_{2'}$–$H_{6'}/H_2$ for **7a**).

Since the Suzuki–Miyaura reaction is tolerant of a broad range of functional groups including hydroxyl group,[68–71] the biphenyl synthesis from **7** or **8** was realized without the protection of the benzyl alcohol.

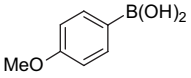
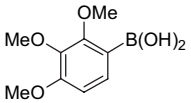
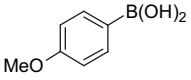
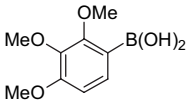
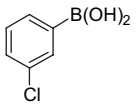
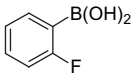
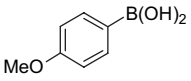
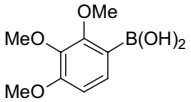
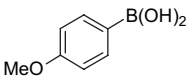
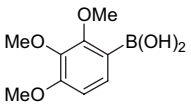
The optimized reaction conditions have been determined by coupling **7a** with 2-chlorophenylboronic acid, 4-fluorophenylboronic acid, and the sterically hindered 2,3,4-trimethoxyphenylboronic acid. The best results were obtained with 2.5 equiv of boronic acid in the presence of CsF (7.5 equiv) and $Pd(OAc)_2$ (10%) in DMF at 85 °C for 20 h (Scheme 3). DMF was chosen since the substrates **7** and **8** exhibit poor solubility in other solvent systems. The results of the parallel Suzuki–Miyaura coupling (Quest 210®) from **7a** with a variety of phenylboronic acids are summarized in Table 2.

Table 2

Entry[a]	Substrate	$ArB(OH)_2$	Time (h)	Product	Yield[b] (%)
1	**7a**		20	**4aa**	59[c]
2	**7a**		20	**4ab**	67[d]
3	**7a**		20	**4ac**	67[e]
4	**7a**		20	**4ad**	82
5	**7a**		20	**4ae**	81
6	**7a**		20	**4af**	85
7	**7a**		20	**4ag**	18

(*continued*)

Table 2. (*continued*)

Entry[a]	Substrate	$ArB(OH)_2$	Time (h)	Product	Yield[b] (%)
8	**7a**		20	**4ah**	95
9	**7a**		20	**4ai**	66
10	**8a**		20	**4ca**	72
11	**8a**		20	**4cb**	63
12	**7b**		5	**4ba**	70[f]
13	**7b**		5	**4bb**	79
14	**7b**		5	**4bc**	81
15	**7b**		5	**4bd**	67
16	**8b**		5	**4da**	75
17	**8b**		5	**4db**	59

[a] $ArB(OH)_2$ (2.5 equiv), $Pd(OAc)_2$ (10%), CsF (10 equiv), DMF, 85 °C.
[b] Isolated yields with purity>95% after workup (i.e., extraction and silica pad filtration).
[c] Triphenyl (11%), starting material (15%) (HPLC/LC–MS analysis).
[d] Triphenyl (15%), tetraphenyl (2%), starting material (11%) (HPLC/LC–MS analysis).
[e] Triphenyl (25%), tetraphenyl (4%) (HPLC/LC–MS analysis).
[f] Polyphenyls (e), starting material (10%).

Cross-coupling of **7a** with halogenated phenylboronic acids provided biaryls **4aa–ae** in 59–82% yields (entries 1–5). In addition, triphenyl and tetraphenyl derivatives resulting from successive Suzuki coupling of **4aa** and **4ab** with the corresponding chlorophenylboronic acid were formed in low yields. The electron-deficient 4-(trifluoromethyl)phenylboronic acid afforded biaryl **4af** in 85% yield (entry 6). Surprisingly, the reaction of the electron-rich 4-(dimethylamino)phenylboronic acid gave low conversion of **7a** (entry 7). In contrast, 4-methoxyphenylboronic acid furnished the biaryl **4ah** in 95% yield (entry 8). Sterically hindered 2,3,4-trimethoxyphenylboronic acid was also reactive and the desired product **4ai** was isolated in 66% (entry 9). An attempt to couple this boronic acid with **7a** failed using K_2CO_3 as base and a shorter reaction time, this is likely due to the formation of the deprotoboranation product under these conditions.[72] Suzuki reaction of **8a** with 4-methoxyphenylboronic and 2,3,4-trimethoxyphenylboronic acids gave the corresponding biaryls **4ca** (72%) and **4cb** (63%). The Suzuki coupling proceeds faster from the substrates **7b** and **8b** with some representative boronic acids. Indeed, the biaryls **4ba–bd** (67–81%) and **4da** and **4db** (59 and 75%) were obtained in good yields after 5 h. This observation suggests that the stereochemistry of the alcohol at C-4 may exert an influence on the kinetic of the coupling reaction.

3. Conclusion

We have synthesized two small libraries of *N*-aryl γ-lactam lignans and *N*-biaryl γ-lactam lignans based on the 1-aryltetralin privileged structure with parallel solution-phase methodologies. In particular, the above-descripted procedure catalyzed by indium(III) chloride represents an efficient synthesis of *N*-aryl picropodophyllone γ-lactams from the methyl ester of thuriferic acid via tandem aza-Michael addition–cyclization reaction of anilines. We are currently examining the biological activity of these compounds as well as the preparation of larger and more diverse 1-aryltetralin-based libraries.

4. Experimental

4.1. General

Reactions were carried out in dried glassware under an argon atmosphere and parallel synthesis with the Quest 210® (Argonaut Technologies) in dried Teflon reactors. All commercial reagents were used without purification, and all solvents were reaction grade and dried over molecular sieves. THF was freshly distilled from sodium/benzophenone under argon and dichloromethane from phosphorus pentoxide. All reaction mixtures were stirred magnetically and monitored by thin-layer chromatography using Merck silica gel 60 F_{256}, visualized with UV light, and then developed by using Merck silica gel 60 (230–400 mesh). ^{1}H NMR and ^{13}C NMR spectra (1D and 2D) were recorded on a Bruker AM 300 spectrometer. Deuteriated chloroform was used as the solvent, and chemical shift values (δ) are reported in parts per million relative to the residual signals of this solvent (δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Melting points were determined with Electrothermal (Digital Melting Point Apparatus). Infrared spectra were recorded on a Perkin–Elmer 1710 spectrometer. Optical rotations were measured with Perkin–Elmer 241 polarimeter. Mass spectra were recorded on a Nermag R10-10C.

4.2. Preparation of the methyl ester of thuriferic acid 3

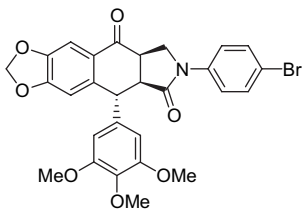
4.2.1. Podophyllotoxone. To a solution of podophyllotoxin (**5**, 8.05 g, 19.4 mmol) in anhydrous dichloromethane was added pyridinium chlorochromate (6.55 g, 30.4 mmol). The mixture was stirred at room temperature for 2 h, then filtered on Celite and washed with distilled water. The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column (cyclohexane/ethyl acetate 3/2) to give podophyllotoxone (80%) as a white solid. Spectral and physical properties were identical to those described in Ref. 29.

4.2.2. Methyl ester of thuriferic acid 2. To a solution of podophyllotoxone (7.74 g, 18.8 mmol) in *t*-BuOH (280 mL) was added *t*-BuOK (19 mmol). The mixture was stirred at reflux for 2.5 h under nitrogen atmosphere. The solvent was then removed in vacuo and the residue was dissolved in DMF. Iodomethane (6.60 mL, 0.1 mol) and $NaHCO_3$ were added to the mixture, which was stirred at room temperature for 24 h. The reaction mixture was quenched with water (250 mL). The aqueous layer was extracted with ethyl acetate (3×300 mL) and the combined organic layers were washed with water and brine (300 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column (cyclohexane/ethyl acetate 1/1) to yield **2** (95%) as a off-white solid. Spectral and physical properties of **2** were identical to those described in Refs. 25 and 73.

4.3. Representative experimental procedure for tandem addition–cyclization catalyzed by $InCl_3$

To a 10 mL Quest 210 Teflon reaction vessel was added a solution of the methyl ester of thuriferic acid **2** (50 mg, 0.117 mmol) in DCE (3 mL) followed by $InCl_3$ (13 mg, 0.058 mmol) and 4-bromoaniline (101 mg, 0.585 mmol, 5 equiv). The solution was stirred for 48 h at 80 °C. Chlorosulfonyl resin (560 mg, 12 equiv) and Et_3N (0.25 mL, 15 equiv) were added and the reaction mixture was stirred for 24 h at 60 °C in order to scavenge excess of aniline. Filtration and evaporation of the solvent under reduced pressure afforded a residue, which was purified by filtration on silica pad (H 3.5 cm, Ø 1.7 cm) with cyclohexane then cyclohexane/EtOAc gradient [9/1 to 2/8] to give 62 mg (94%) of **3a**.

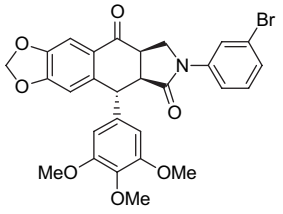
4.3.1. (1*R*,2*S*,3*R*)-*N*-(4-Bromophenyl)-picropodophyllone-*cis*-γ-lactam 3a.



White solid; 62 mg; yield: 94%; mp: 143–145 °C; $[\alpha]_D^{20}$ −252 (*c* 0.25, $CHCl_3$); IR 3014, 2980–2900, 1702, 1668,

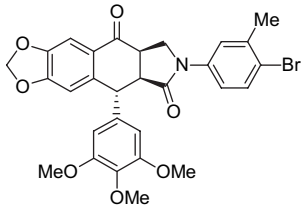
1591, 1505, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43 (m, 5H, H_5, $H_{2''}$, $H_{3''}$, $H_{5''}$, $H_{6''}$), 6.72 (s, 1H, H_8), 6.27 (s, 2H, $H_{2'}$, $H_{6'}$), 6.03 (m, 2H, OCH_2O), 4.79 (d, J=1.6 Hz, 1H, H_1), 4.24 (d, J=9.7 Hz, 1H, H_{11a}), 3.95 (dd, J=9.7, 6.3 Hz, 1H, H_{11b}), 3.81 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.34 (dd, J=7.5, 1.6 Hz, 1H, H_2), 3.23 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.7 (C_4), 171.7 (C_{13}), 153.7 ($C_{3'}$, $C_{5'}$), 153.6 (C_7), 148.2 (C_6), 139.9 (C_9), 138.6 ($C_{1'}$), 137.9 ($C_{1''}$), 137.1 ($C_{4'}$), 131.8 ($C_{3''}$, $C_{5''}$), 127.2 (C_{10}), 121.0 ($C_{2''}$, $C_{6''}$), 117.8 ($C_{4''}$), 109.5 (C_8), 105.9 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 102.1 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 50.9 (C_{11}), 50.5 (C_2), 43.1 (C_1), 39.9 (C_3); HRMS (DCI/NH_3): calcd for $C_{28}H_{25}BrNO_7$ 566.0814 and 568.0799, found 566.0809 and 568.0798.

4.3.2. (1*R*,2*S*,3*R*)-*N*-(3-Bromophenyl)-picropodophyllone-*cis*-γ-lactam 3b.



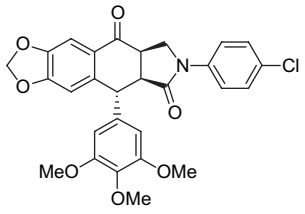
White solid; 60 mg; yield: 91%; mp: 128–130 °C; $[\alpha]_D^{20}$ −187 (c 0.17, $CHCl_3$); IR ($CHCl_3$) 3028, 3012, 2970–2900, 1704, 1669, 1592, 1506, 1480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J=1.7 Hz, 1H, $H_{2''}$), 7.46 (dd, J=8.0, 1.7 Hz, 1H, $H_{6''}$), 7.45 (s, 1H, H_5), 7.24 (m, 1H, $H_{4''}$), 7.16 (t, J=8 Hz, 1H, $H_{5''}$), 6.70 (s, 1H, H_8), 6.26 (s, 2H, $H_{2'}$, $H_{6'}$), 6.01 (m, 2H, OCH_2O), 4.79 (d, J=1.6 Hz, 1H, H_1), 4.26 (d, J=9.7 Hz, 1H, H_{11a}), 3.96 (dd, J=9.7, 6.3 Hz, 1H, H_{11b}), 3.81 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.35 (dd, J=7.5, 1.6 Hz, 1H, H_2), 3.23 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.6 (C_4), 171.8 (C_{13}), 153.7 (C_7), 153.6 ($C_{3'}$, $C_{5'}$), 148.2 (C_6), 140.1 ($C_{1''}$), 139.9 (C_9), 138.5 ($C_{1'}$), 137.1 ($C_{4'}$), 130.1 ($C_{5''}$), 127.8 ($C_{4''}$), 127.2 (C_{10}), 122.6 ($C_{3''}$), 122.5 ($C_{2''}$), 117.8 ($C_{6''}$), 109.5 (C_8), 105.9 (C_5), 104.8 ($C_{2'}$, $C_{5'}$), 102.1 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 50.9 (C_{11}), 50.5 (C_2), 43.1 (C_1), 39.9 (C_3); HRMS (DCI/NH_3): calcd for $C_{28}H_{25}BrNO_7$ 566.0814 and 568.0799, found 566.0803 and 568.0794.

4.3.3. (1*R*,2*S*,3*R*)-*N*-(3-Bromo-4-methyl-phenyl)-picropodophyllone-*cis*-γ-lactam 3c.



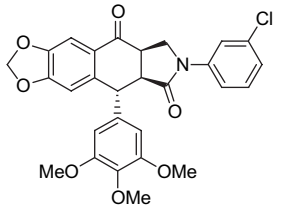
White solid; 58 mg; yield: 85%; mp: 121–123 °C; $[\alpha]_D^{20}$ −230 (c 0.18, $CHCl_3$); IR ($CHCl_3$) 2940, 1699, 1669, 1592, 1506, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46 (m, 1H, H_5), 7.44 (m, 2H, $H_{2''}$, $H_{5''}$), 7.24 (dd, J=8.3, 2.5 Hz, 1H, $H_{6''}$), 6.72 (s, 1H, H_8), 6.27 (s, 2H, $H_{2'}$, $H_{6'}$), 6.03 (m, 2H, OCH_2O), 4.79 (d, J=1.7 Hz, 1H, H_1), 4.24 (d, J=9.7 Hz, 1H, H_{11a}), 3.96 (m, J=9.8, 6.3 Hz, 1H, H_{11b}), 3.81 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.33 (dd, J=7.5, 1.7 Hz, 1H, H_2), 3.21 (m, 1H, H_3), 2.36 (s, 3H, Ph-*Me*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.8 (C_4), 171.7 (C_{13}), 153.7 (C_7), 153.6 ($C_{3'}$, $C_{5'}$), 148.2 (C_6), 139.9 (C_9), 138.6 ($C_{1'}$), 138.5 ($C_{1''}$), 138.0 ($C_{3''}$), 137.0 ($C_{4'}$), 132.5 ($C_{5''}$), 127.2 (C_{10}), 121.8 ($C_{2''}$), 120.4 ($C_{4''}$), 118.4 ($C_{6''}$), 109.5 (C_8), 105.9 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 102.1 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 51.0 (C_{11}), 50.5 (C_2), 43.1 (C_1), 40.0 (C_3), 23.1 (Ph-*Me*); HRMS (DCI/NH_3): calcd for $C_{29}H_{27}NO_7Br$ 580.0971 and 582.0956, found 580.0970 and 582.0954.

4.3.4. (1*R*,2*S*,3*R*)-*N*-(4-Chlorophenyl)-picropodophyllone-*cis*-γ-lactam 3d.



White solid; 56 mg; yield: 91%; mp: 138–140 °C; $[\alpha]_D^{20}$ −211 (c 0.22, $CHCl_3$); IR 3012, 2960–2900, 1702, 1671, 1592, 1495, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, J=9 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.45 (s, 1H, H_5), 7.27 (d, J=9 Hz, 2H, $H_{3''}$, $H_{5''}$), 6.70 (s, 1H, H_8), 6.26 (s, 2H, $H_{2'}$, $H_{6'}$), 6.00 (m, 2H, OCH_2O), 4.79 (d, J=1.7 Hz, 1H, H_1), 4.23 (d, J=9.7 Hz, 1H, H_{11a}), 3.95 (dd, J=9.7, 6.3 Hz, 1H, H_{11b}), 3.79 (s, 3H, $OMe_{(4')}$), 3.74 (s, 6H, $OMe_{(3',5')}$), 3.34 (dd, J=7.5, 1.7 Hz, 1H, H_2), 3.21 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.8 (C_4), 171.7 (C_{13}), 153.7 (C_7), 153.6 ($C_{3'}$, $C_{5'}$), 148.2 (C_6), 139.9 (C_9), 138.6 ($C_{1'}$), 137.4 ($C_{1''}$), 137.0 ($C_{4'}$), 130.0 ($C_{4''}$), 128.9 ($C_{3''}$, $C_{5''}$), 127.2 (C_{10}), 120.7 ($C_{2''}$, $C_{6''}$), 109.5 (C_8), 105.9 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 102.1 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 50.9 (C_{11}), 50.5 (C_2), 43.1 (C_1), 39.9 (C_3); HRMS (DCI/NH_3): calcd for $C_{28}H_{25}ClNO_7$ 522.1320 and 524.1305, found 522.1318 and 524.1311.

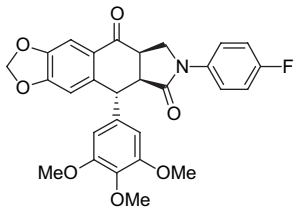
4.3.5. (1*R*,2*S*,3*R*)-*N*-(3-Chlorophenyl)-picropodophyllone-*cis*-γ-lactam 3e.



White solid; 46 mg; yield: 76%; mp: 124–126 °C; $[\alpha]_D^{20}$ −124 (c 0.32, $CHCl_3$); IR ($CHCl_3$) 3036, 2978–2900, 1706, 1671, 1594, 1505, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (t, J=1.8 Hz, 1H, $H_{2''}$), 7.47 (s, 1H, H_5), 7.43 (dd, J=8.2, 1.0 Hz, 1H, $H_{6''}$), 7.25 (t, J=8.2 Hz, 1H, $H_{5''}$), 7.11 (dd, J=8.2, 1.0 Hz, 1H, $H_{4''}$), 6.72 (s, 1H, H_8), 6.30 (s, 2H, $H_{2'}$, $H_{6'}$), 6.02 (m, 2H, OCH_2O), 4.80 (d, J=1.7 Hz, 1H, H_1), 4.27 (d, J=9.7 Hz, 1H, H_{11a}), 3.97 (dd, J=9.7, 6.4 Hz, 1H, H_{11b}), 3.81 (s, 3H, $OMe_{(4')}$), 3.76

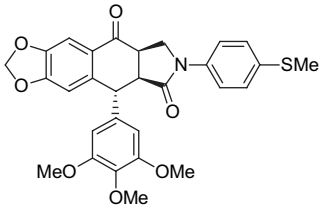
(s, 6H, $OMe_{(3',5')}$), 3.35 (dd, J=7.5, 1.7 Hz, 1H, H_2), 3.23 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.7 (C_4), 171.9 (C_{13}), 153.7 (C_7), 153.6 ($C_{3'}$, $C_{5'}$), 148.2 (C_6), 139.9 (C_9), 139.8 ($C_{1''}$), 138.5 ($C_{1'}$), 137.0 ($C_{4'}$), 134.6 ($C_{3''}$), 129.8 ($C_{5''}$), 127.2 (C_{10}), 124.9 ($C_{4''}$), 119.7 ($C_{2''}$), 117.3 ($C_{6''}$), 109.5 (C_8), 105.9 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 102.1 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 50.9 (C_{11}), 50.5 (C_2), 43.1 (C_1), 39.9 (C_3); HRMS (DCI/NH_3): calcd for $C_{28}H_{25}ClNO_7$ 522.1320 and 524.1305, found 522.1312 and 524.1312.

4.3.6. (1*R*,2*S*,3*R*)-*N*-(4-Fluorophenyl)-picropodophyllone-*cis*-γ-lactam 3f.



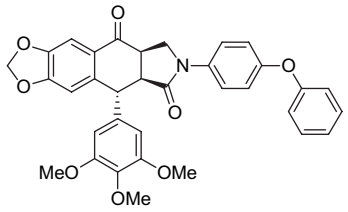
White solid; 50 mg; yield: 85%; mp: 127–129 °C; $[\alpha]_D^{20}$ −202 (*c* 0.23, $CHCl_3$); IR 3022, 3011, 2970–2900, 1699, 1668, 1592, 1510, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.49 (m, 2H, $H_{2''}$, $H_{6''}$), 7.46 (s, 1H, H_5), 7.00 (t, J=8.6 Hz, 2H, $H_{3''}$, $H_{5''}$), 6.71 (s, 1H, H_8), 6.27 (s, 2H, $H_{2'}$, $H_{6'}$), 6.01 (m, 2H, OCH_2O), 4.79 (d, 1.6 Hz, 1H, H_1), 4.23 (d, J=9.7 Hz, 1H, H_{11a}), 3.96 (dd, J=9.7, 6.3 Hz, 1H, H_{11b}), 3.80 (s, 3H, $OMe_{(4')}$), 3.75 (s, 6H, $OMe_{(3',5')}$), 3.34 (dd, J=7.5, 1.6 Hz, 1H, H_2), 3.21 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.9 (C_4), 171.6 (C_{13}), 161.4 (d, J=249 Hz, $C_{4''}$), 153.7 (C_7), 153.6 ($C_{3'}$, $C_{5'}$), 148.2 (C_6), 139.9 (C_9), 138.7 ($C_{1'}$), 137.0 ($C_{4'}$), 135.0 ($C_{1''}$), 127.3 (C_{10}), 121.5 (d, J=7.5 Hz, $C_{2''}$, $C_{6''}$), 115.6 (d, J=22.5 Hz, $C_{3''}$, $C_{5''}$), 109.6 (C_8), 105.9 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 102.1 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 51.3 (C_{11}), 50.4 (C_2), 43.2 (C_1), 40.1 (C_3); MS (DCI/NH_3): 506 $[M+H]^+$, 523 $[M+NH_4]^+$.

4.3.7. (1*R*,2*S*,3*R*)-*N*-(4-Thiomethylphenyl)-picropodophyllone-*cis*-γ-lactam 3g.



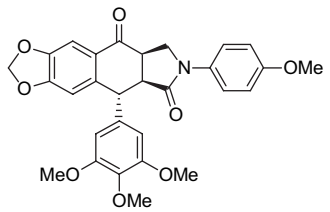
Off-white solid; 51 mg; yield: 82%; mp: 120–122 °C; $[\alpha]_D^{20}$ −306 (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) 3021, 3012, 2971–2900, 1697, 1669, 1592, 1498, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, J=8.8 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.46 (s, 1H, H_5), 7.21 (d, J=8.8 Hz, 2H, $H_{2''}$, $H_{6''}$), 6.71 (s, 1H, H_8), 6.28 (s, 2H, $H_{2'}$, $H_{6'}$), 6.01 (m, 2H, OCH_2O), 4.79 (d, J=1.6 Hz, 1H, H_1), 4.23 (d, J=9.8 Hz, 1H, H_{11a}), 3.96 (dd, J=9.8, 6.4 Hz, 1H, H_{11b}), 3.80 (s, 3H, $OMe_{(4')}$), 3.75 (s, 6H, $OMe_{(3',5')}$), 3.34 (dd, J=7.5, 1.6 Hz, 1H, H_2), 3.20 (m, 1H, H_3), 2.43 (s, 3H, *S*-Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.0 (C_4), 171.6 (C_{13}), 153.6 ($C_{3'}$, $C_{5'}$, C_7), 148.2 (C_6), 139.9 (C_9), 138.7 ($C_{1'}$), 137.1 ($C_{4'}$), 136.4 ($C_{1''}$), 134.6 ($C_{4''}$), 127.5 ($C_{3''}$, $C_{5''}$), 127.3 (C_{10}), 120.1 ($C_{2''}$, $C_{6''}$), 109.6 (C_8), 105.9 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 102.1 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.2($OMe_{(3',5')}$), 51.0 (C_{11}), 50.5 (C_2), 43.2 (C_1), 40.1 (C_3), 16.4 (*S*-Me); HRMS (DCI/NH_3): calcd for $C_{29}H_{28}NO_7S$ 534.1586, found 534.1591.

4.3.8. (1*R*,2*S*,3*R*)-*N*-(4-Phenoxyphenyl)-picropodophyllone-*cis*-γ-lactam 3h.



Off-white solid; 48 mg; yield: 71%; mp: 218–220 °C; $[\alpha]_D^{20}$ −113 (*c* 0.22, $CHCl_3$); IR ($CHCl_3$) 3025, 2970–2900, 1696, 1670, 1591, 1507, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, J=9 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.48 (s, 1H, H_5), 7.29 (m, 2H, $H_{3''}$, $H_{5''}$), 7.07 (t, J=7.5 Hz, 1H, $H_{4''}$), 6.97 (m, 4H, $H_{3''}$, $H_{5''}$, $H_{2'''}$, $H_{6'''}$), 6.72 (s, 1H, H_8), 6.28 (s, 2H, $H_{2'}$, $H_{6'}$), 6.01 (m, 2H, OCH_2O), 4.81 (d, J =1.6 Hz, 1H, H_1), 4.25 (d, J=9.7 Hz, 1H, H_{11a}), 3.97 (dd, J=9.7, 6.3 Hz, 1H, H_{11b}), 3.81 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.35 (dd, J=7.4, 1.6 Hz, 1H, H_2), 3.23 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.0 (C_4), 171.5 (C_{13}), 157.3 ($C_{1'''}$), 154.0 ($C_{4''}$), 153.6 ($C_{3'}$, $C_{5'}$, C_7), 148.2 (C_6), 139.9 (C_9), 138.7 ($C_{1'}$), 136.9 ($C_{4'}$), 134.3 ($C_{1''}$), 129.7 ($C_{3'''}$, $C_{5'''}$), 127.3 (C_{10}), 123.2 ($C_{4'''}$), 121.3 ($C_{2''}$, $C_{6''}$), 119.3 ($C_{2'''}$, $C_{6'''}$), 118.5 ($C_{3''}$, $C_{5''}$), 109.5 (C_8), 105.9 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 102.0 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 51.3 (C_{11}), 50.4 (C_2), 43.2 (C_1), 40.1 (C_3); HRMS (DCI/NH_3): calcd for $C_{34}H_{30}NO_8$ 580.1971, found 580.1968.

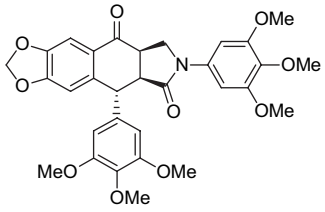
4.3.9. (1*R*,2*S*,3*R*)-*N*-(4-Methoxyphenyl)-picropodophyllone-*cis*-γ-lactam 3i.



Off-white solid; 54 mg; yield: 90%; mp: 124–126 °C; $[\alpha]_D^{20}$ −246 (*c* 0.18, $CHCl_3$); IR ($CHCl_3$) 3022, 3016, 2965–2900, 1694, 1670, 1592, 1512, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46 (s, 1H, H_5), 7.42 (d, J=9 Hz, 2H, $H_{2''}$, $H_{6''}$), 6.84 (d, J=9 Hz, 2H, $H_{3''}$, $H_{5''}$), 6.71 (s, 1H, H_8), 6.27 (s, 2H, $H_{2'}$, $H_{6'}$), 6.01 (m, 2H, OCH_2O), 4.80 (d, J=1.7 Hz, 1H, H_1), 4.21 (d, J=9.8 Hz, 1H, H_{11a}), 3.96 (dd, J=9.8, 6.4 Hz, 1H, H_{11b}), 3.80 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.75 (s, 3H, $OMe_{(4'')}$), 3.33 (dd, J=7.4, 1.7 Hz, 1H, H_2), 3.20 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2 (C_4), 171.3 (C_{13}), 156.8 ($C_{4''}$), 153.6 ($C_{3'}$, $C_{5'}$, C_7), 148.1 (C_6), 139.9 (C_9), 138.8 ($C_{1'}$), 136.9 ($C_{4'}$), 132.1 ($C_{1''}$), 127.3 (C_{10}), 121.4 ($C_{2''}$, $C_{6''}$), 114.0 ($C_{3''}$, $C_{5''}$), 109.5 (C_8), 105.8 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 102.0

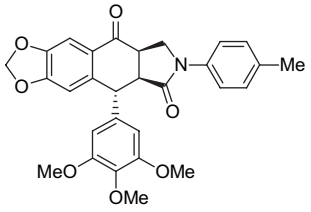
(OCH_2O), 60.8 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 55.4 ($OMe_{(4'')}$), 51.5 (C_{11}), 50.3 (C_2), 43.2 (C_1), 40.2 (C_3); HRMS (DCI/NH_3): calcd for $C_{29}H_{28}NO_8$ 518.1815, found 518.1807.

4.3.10. (1*R*,2*S*,3*R*)-*N*-(3,4,5-Trimethoxyphenyl)-picropodophyllone-*cis*-γ-lactam 3j.



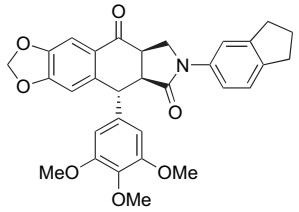
Pale yellow solid; 61 mg; yield: 90%; mp: 125–127 °C; $[\alpha]_D^{20}$ −244 (*c* 0.16, $CHCl_3$); IR 3023, 3010, 2970–2900, 1698, 1668, 1593, 1508, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (s, 1H, H_5), 6.87 (s, 2H, $H_{2''}$, $H_{6''}$), 6.71 (s, 1H, H_8), 6.26 (s, 2H, $H_{2'}$, $H_{6'}$), 6.01 (m, 2H, OCH_2O), 4.78 (d, *J*=1.3 Hz, 1H, H_1), 4.28 (d, *J*=9.7 Hz, 1H, H_{11a}), 3.95 (dd, *J*=9.7, 6.4 Hz, 1H, H_{11b}), 3.84 (s, 6H, $OMe_{(3'',5'')}$), 3.81 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(4'')}$), 3.74 (s, 6H, $OMe_{(3',5')}$), 3.35 (dd, *J*=7.4, 1.3 Hz, 1H, H_2), 3.20 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.8 (C_4), 171.7 (C_{13}), 153.7 ($C_{3'}$, $C_{5'}$, C_7), 153.2 ($C_{3''}$, $C_{5''}$), 148.2 (C_6), 139.9 (C_9), 138.7 ($C_{1'}$), 137.1 ($C_{4'}$), 135.6 ($C_{4''}$), 135.0 ($C_{1''}$), 127.2 (C_{10}), 109.6 (C_8), 105.9 (C_5), 104.9 ($C_{2'}$, $C_{6'}$), 102.1 (OCH_2O), 97.6 ($C_{2''}$, $C_{6''}$), 60.9 (OMe), 60.8 (OMe), 56.2 ($OMe_{(3',5',3'',5'')}$), 51.3 (C_{11}), 50.7 (C_2), 43.2 (C_1), 39.8 (C_3); HRMS (DCI/NH_3): calcd for $C_{31}H_{32}NO_{10}$ 578.2026, found 578.2021.

4.3.11. (1*R*,2*S*,3*R*)-*N*-(4-Methylphenyl)-picropodophyllone-*cis*-γ-lactam 3k.



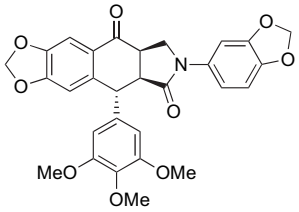
White solid; 54 mg; yield: 92%; mp: 129–130 °C; $[\alpha]_D^{20}$ −259 (*c* 0.60, $CHCl_3$); IR ($CHCl_3$) 3012, 2975–2900, 1693, 1669, 1592, 1506, 1482 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (s, 1H, H_5), 7.41 (d, *J*=8.4 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.13 (d, *J*=8.4 Hz, 2H, $H_{3''}$, $H_{5''}$), 6.72 (s, 1H, H_8), 6.28 (s, 2H, $H_{2'}$, $H_{6'}$), 6.02 (m, 2H, OCH_2O), 4.81 (d, *J*=1.8 Hz, 1H, H_1), 4.24 (d, *J*=9.9 Hz, 1H, H_{11a}), 3.95 (dd, *J*=9.9, 6.2 Hz, 1H, H_{11b}), 3.81 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.34 (dd, *J*=7.5, 1.8 Hz, 1H, H_2), 3.21 (m, 1H, H_3), 2.30 (s, 3H, Ph-*Me*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2 (C_4), 171.5 (C_{13}), 153.7 (C_7, $C_{3'}$, $C_{5'}$), 148.1 (C_6), 139.9 (C_9), 138.8 ($C_{1'}$), 136.9 ($C_{4'}$), 136.4 ($C_{1''}$), 134.6 ($C_{4''}$), 129.4 ($C_{3''}$, $C_{5''}$), 127.3 (C_{10}), 119.7 ($C_{2''}$, $C_{6''}$), 109.5 (C_8), 105.9 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 102.0 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 51.2 (C_{11}), 50.4 (C_2), 43.2 (C_1), 40.1 (C_3), 20.8 (Ph-*Me*); HRMS (DCI/NH_3): calcd for $C_{29}H_{28}NO_7$ 502.1866, found 502.1865.

4.3.12. (1*R*,2*S*,3*R*)-*N*-Indan-5-yl-picropodophyllone-*cis*-γ-lactam 3l.



Off-white solid; 50 mg; yield: 81%; mp: 114–116 °C; $[\alpha]_D^{20}$ −258 (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 3029, 3012, 2973–2900, 1695, 1669, 1592, 1505, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46 (s, 1H, H_5), 7.40 (d, *J*=1.5 Hz, 1H, $H_{4''}$), 7.21 (dd, *J*=8.2, 1.5 Hz, 1H, $H_{6''}$), 7.15 (d, *J*=8.2 Hz, 1H, $H_{7''}$), 6.72 (s, 1H, H_8), 6.28 (s, 2H, $H_{2'}$, $H_{6'}$), 6.01 (m, 2H, OCH_2O), 4.81 (d, *J*=1.6 Hz, 1H, H_1), 4.22 (d, *J*=9.8 Hz, 1H, H_{11a}), 3.97 (dd, *J*=9.8, 6.4 Hz, 1H, H_{11b}), 3.80 (s, 3H, $OMe_{(4')}$), 3.75 (s, 6H, $OMe_{(3',5')}$), 3.33 (dd, *J*=7.4, 1.6 Hz, 1H, H_2), 3.19 (m, 1H, H_3), 2.84 (m, 4H, $H_{1''}$, $H_{3''}$), 2.04 (m, 2H, $H_{2''}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2 (C_4), 171.4 (C_{13}), 153.6 ($C_{3'}$, $C_{5'}$, C_7), 148.1 (C_6), 145.1 ($C_{3a''}$), 141.1 ($C_{7a''}$), 140.0 (C_9), 138.8 ($C_{1'}$), 137.1 ($C_{5''}$), 137.0 ($C_{4'}$), 127.4 (C_{10}), 124.4 ($C_{7''}$), 118.0 ($C_{6''}$), 116.5 ($C_{4''}$), 109.5 (C_8), 105.8 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 102.0 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 51.7 (C_{11}), 50.4 (C_2), 43.2 (C_1), 40.2 (C_3), 33.0 ($C_{3''}$), 32.3 ($C_{1''}$), 25.6 ($C_{2''}$); HRMS (DCI/NH_3): calcd for $C_{31}H_{30}NO_7$ 528.2022, found 528.2028.

4.3.13. (1*R*,2*S*,3*R*)-*N*-(3,4-Methylenedioxyphenyl)-picropodophyllone-*cis*-γ-lactam 3m.

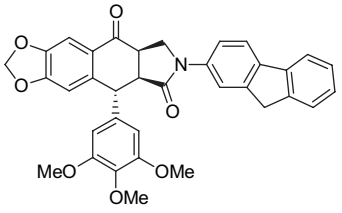


Off-white solid; 38 mg; yield: 61%; yellow powder; mp 187–190 °C; $[\alpha]_D^{20}$ −91 (*c* 0.15, $CHCl_3$); IR 3023, 2970–2900, 1714, 1672, 1597, 1505, 1480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47 (s, 1H, H_5), 7.22 (d, *J*=1.8 Hz, 1H, $H_{2''}$), 6.78 (dd, *J*=10.4, 1.8 Hz, 1H, $H_{6''}$), 6.73 (d, *J*=10.4 Hz, 1H, $H_{5''}$), 6.71 (s, 1H, H_8), 6.27 (s, 2H, $H_{2'}$, $H_{6'}$), 6.02 (m, 2H, $OCH_2O_{(6,7)}$), 5.92 (d, *J*=1.0 Hz, 2H, $OCH_2O_{(3'',4'')}$), 4.79 (d, *J*=1.7 Hz, 1H, H_1), 4.18 (d, *J*=9.7 Hz, 1H, H_{11a}), 3.93 (dd, *J*=9.7, 6.3 Hz, 1H, H_{11b}), 3.80 (s, 3H, $OMe_{(4')}$), 3.75 (s, 6H, $OMe_{(3',5')}$), 3.32 (dd, *J*=7.4, 1.7 Hz, 1H, H_2), 3.19 (dd, *J*=7.4, 6.3 Hz, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.1 (C_4), 171.4 (C_{13}), 153.6 (C_7), 153.5 ($C_{3'}$, $C_{5'}$), 148.2 (C_6), 147.8 ($C_{3''}$), 144.8 ($C_{4''}$), 139.2 ($C_{1'}$), 138.8 ($C_{1''}$), 136.9 ($C_{4'}$), 133.2 (C_9), 127.3 (C_{10}), 112.9 ($C_{6''}$), 109.5 (C_8), 107.9 ($C_{5''}$), 105.8 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 102.6 ($C_{2''}$), 102.1 ($OCH_2O_{(6,7)}$), 101.3 ($OCH_2O_{(3'',4'')}$), 60.8 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 51.8 (C_{11}), 50.3 (C_2), 43.2 (C_1), 40.1 (C_3); MS (ES+): 532 $[M+H]^+$, 554 $[M+Na]^+$.

4.4. Representative experimental procedure for sequential one-pot addition–cyclization catalyzed by $InCl_3$

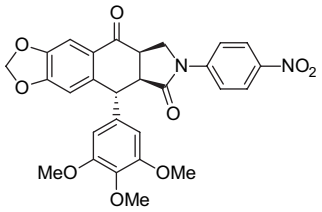
To a 10 mL Quest 210 Teflon reaction vessel was added a solution of the methyl ester of thuriferic acid **2** (50 mg, 0.117 mmol) in DCE (3 mL) followed by $InCl_3$ (13 mg, 0.058 mmol) and 2-aminofluorene (106 mg, 0.585 mmol, 5 equiv). The solution was stirred for 48 h at 80 °C and then DBU (88 μL, 0.585 mmol) was added and the solution was stirred for 24 h at 80 °C. Chlorosulfonyl resin (560 mg, 12 equiv) and Et_3N (0.25 mL, 15 equiv) were added and the reaction mixture was stirred for 24 h at 60 °C in order to scavenge excess of aniline. Filtration and evaporation of the solvent under reduced pressure gave a residue, which was purified by filtration on silica pad with cyclohexane then cyclohexane/EtOAc gradient [9/1 to 2/8] to furnish 44 mg (66%) of **3n**.

4.4.1. (1*R*,2*S*,3*R*)-*N*-Fluoren-2-yl-picropodophyllone-*cis*-γ-lactam 3n.



Yellow solid; 44 mg; yield: 66%; mp: 139–141 °C; $[\alpha]_D^{20}$ −227 (*c* 0.19, $CHCl_3$); IR ($CHCl_3$) 3026, 3014, 2974–2900, 1696, 1668, 1592, 1505, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, *J*=2.0 Hz, 1H, $H_{1''}$), 7.72 (m, 2H, $H_{4''}$, $H_{5''}$), 7.51 (m, 1H, $H_{8''}$), 7.49 (s, 1H, H_5), 7.48 (m, 1H, $H_{3''}$), 7.35 (t, *J*=7.2 Hz, 1H, $H_{6''}$), 7.27 (dt, *J*=7.2, 1.2 Hz, 1H, $H_{7''}$), 6.74 (s, 1H, H_8), 6.30 (s, 2H, $H_{2'}$, $H_{6'}$), 6.03 (m, 2H, OCH_2O), 4.84 (d, *J*=1.8 Hz, 1H, H_1), 4.34 (d, *J*=9.8 Hz, 1H, H_{11a}), 4.06 (dd, *J*=9.8, 6.3 Hz, 1H, H_{11b}), 3.87 (s, 2H, $H_{9''}$), 3.82 (s, 3H, $OMe_{(4')}$), 3.77 (s, 6H, $OMe_{(3',5')}$), 3.39 (dd, *J*=7.5, 1.8 Hz, 1H, H_2), 3.25 (dd, *J*=7.5, 6.3 Hz, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.1 (C_4), 171.7 (C_{13}), 153.6 (C_7, $C_{3'}$, $C_{5'}$), 148.2 (C_6), 144.0 ($C_{9a'}$), 143.2 ($C_{8a'}$), 141.2 ($C_{4b''}$), 139.9 ($C_{1'}$), 138.8 (C_9), 138.6 ($C_{2''}$), 137.7 ($C_{4a''}$), 136.9 ($C_{4'}$), 127.3 (C_{10}), 126.8 ($C_{7''}$), 126.6 ($C_{6''}$), 125.0 ($C_{8''}$), 120.0 ($C_{4''}$), 119.7 ($C_{5''}$), 118.4 ($C_{3''}$), 116.9 ($C_{1''}$), 109.6 (C_8), 105.9 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 102.1 (OCH_2O), 60.8 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 51.5 (C_{11}), 50.6 (C_2), 43.2 (C_1), 40.2 (C_3), 37.0 ($C_{9''}$); HRMS (DCI/NH_3): calcd for $C_{35}H_{29}NO_7S$ 576.2056, found 576.2013.

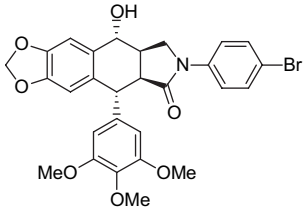
4.4.2. (1*R*,2*S*,3*R*)-*N*-(4-Nitrophenyl)-picropodophyllone-*cis*-γ-lactam 3o.



Yellow solid; 31 mg; yield: 50%; yellow powder; mp 235–240 °C; $[\alpha]_D^{20}$ −110 (*c* 0.34, $CHCl_3$); IR 3020, 2970–2900, 1713, 1670, 1596, 1504, 1481 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J*=9.3 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.79 (d, *J*=9.3 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.48 (s, 1H, H_5), 6.73 (s, 1H, H_8), 6.27 (s, 2H, $H_{2'}$, $H_{6'}$), 6.04 (m, 2H, OCH_2O), 4.81 (d, *J*=1.7 Hz, 1H, H_1), 4.38 (d, *J*=9.7 Hz, 1H, H_{11a}), 4.01 (m, 1H, H_{11b}), 3.81 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.40 (dd, *J*=7.6, 1.7 Hz, 1H, H_2), 3.29 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.9 (C_4), 172.3 (C_{13}), 153.7 (C_7), 153.5 ($C_{3'}$, $C_{5'}$), 148.2 (C_6), 144.1 ($C_{1''}$), 143.6 ($C_{4''}$), 139.6 (C_9), 138.1 ($C_{1'}$), 137.0 ($C_{4'}$), 126.9 (C_{10}), 124.5 ($C_{2''}$, $C_{6''}$), 118.6 ($C_{3''}$, $C_{5''}$), 109.3 (C_8), 105.8 (C_5), 104.6 ($C_{2'}$, $C_{6'}$), 102.0 (OCH_2O), 60.6 ($OMe_{(4')}$), 56.0 ($OMe_{(3',5')}$), 50.5 (C_2), 43.3 (C_{11}), 42.9 (C_1), 39.5 (C_3); MS (DCI/NH_3): 533 $[M+H]^+$, 550 $[M+NH_4]^+$.

4.5. Reduction procedures of bromo *N*-aryl lactam lignans

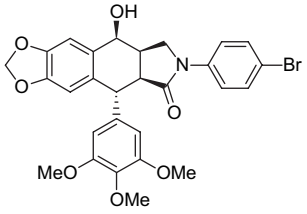
4.5.1. (1*R*,2*S*,3*R*,4*R*)-*N*-(4-Bromophenyl)-picropodophyllin-*cis*-γ-lactam 7a.



To a mixture of **3a** (247 mg, 0.436 mmol) in THF (4 mL) was added MeOH (4 mL). The solution was cooled to −78 °C and $NaBH_4$ (25 mg, 0.654 mmol) was added. The reaction mixture was removed from the cold bath and was stirred for 3 h, water was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/EtOAc 3/2) and recrystallized from cyclohexane and EtOAc to yield 186 mg (75%) of **7a** as a white solid.

Compound **7a**: 186 mg; yield: 75%; mp: 228–230 °C; $[\alpha]_D^{20}$ −69 (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3008, 2960–2900, 1695, 1592, 1504, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, *J*=8.6 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.45 (d, *J*=8.6 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.03 (s, 1H, H_5), 6.47 (s, 2H, $H_{2'}$, $H_{6'}$), 6.37 (s, 1H, H_8), 5.92 (m, 2H, OCH_2O), 4.51 (t, *J*=8.0 Hz, 1H, H_4), 4.20 (d, *J*=4.9 Hz, 1H, H_1), 3.95 (m, 2H, H_{11}), 3.85 (s, 3H, $OMe_{(4')}$), 3.82 (s, 6H, $OMe_{(3',5')}$), 3.35 (dd, *J*=9.2, 4.9 Hz, 1H, H_2), 2.69 (m, 1H, H_3), 2.15 (d, *J*=8.0 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0 (C_{13}), 153.5 ($C_{3'}$, $C_{5'}$), 147.2 (C_7), 146.8 (C_6), 140.1 ($C_{1'}$), 138.2 ($C_{1''}$), 136.7 ($C_{4'}$), 132.2 (C_9), 131.8 ($C_{2''}$, $C_{6''}$), 131.1 (C_{10}), 121.0 ($C_{3''}$, $C_{5''}$), 117.5 ($C_{4''}$), 109.3 (C_8), 105.5 ($C_{2'}$, $C_{6'}$), 105.3 (C_5), 101.1 (OCH_2O), 70.2 (C_4), 60.9 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 50.2 (C_{11}), 48.9 (C_2), 44.2 (C_1), 38.7 (C_3); HRMS (FAB+): calcd for $C_{28}H_{26}NO_7Br$ 567.0893 and 569.0877, found 567.0886 and 569.0887; HRMS (DIC/NH_3): calcd for $C_{28}H_{27}NO_7Br$ 568.0971 and 570.0955, found 568.0956 and 570.0966.

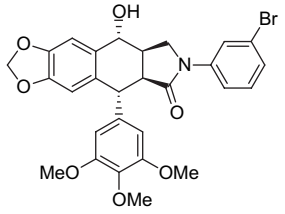
4.5.2. (1*R*,2*S*,3*R*,4*S*)-*N*-(4-Bromophenyl)-epipicropodophyllin-*cis*-γ-lactam 7b.



To a mixture of **3a** (199 mg, 0.351 mmol) in anhydrous THF (5 mL) at −78 °C was added 1 M L-Selectride solution in THF (422 μL, 0.422 mmol) dropwise. The reaction mixture was removed from the cold bath and was stirred for 2 h. A saturated solution of NH_4Cl was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/EtOAc 3/2) to yield 172 mg (86%) of **7b** as a white solid.

Compound **7b**: 172 mg; yield: 86%; mp: 149–152 °C; $[\alpha]_D^{20}$ +51 (*c* 0.23, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3020, 3013, 2970–2900, 1692, 1591, 1505, 1491 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, *J*=10.4 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.41 (d, *J*=10.4 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.07 (s, 1H, H_5), 6.66 (s, 1H, H_8), 6.34 (s, 2H, $H_{2'}$, $H_{6'}$), 5.95 (m, 2H, OCH_2O), 4.89 (t, *J*=4.7 Hz, 1H, H_4), 4.55 (d, *J*=2.2 Hz, 1H, H_1), 3.82 (s, 3H, $OMe_{(4')}$), 3.80 (m, 1H, H_{11a}), 3.77 (s, 6H, $OMe_{(3',5')}$), 3.67 (m, 1H, H_{11b}), 3.61 (dd, *J*=10.6, 2.2 Hz, 1H, H_2), 3.20 (m, 1H, H_3), 2.08 (d, *J*=4.7 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (C_{13}), 153.2 ($C_{3'}$, $C_{5'}$), 147.1 (C_6, C_7), 138.2 ($C_{1'}$ or $C_{1''}$), 138.0 ($C_{1''}$ or $C_{1'}$), 136.6 ($C_{4'}$), 131.7 ($C_{3''}$, $C_{5''}$), 131.6 (C_9), 129.7 (C_{10}), 121.4 ($C_{2''}$, $C_{6''}$), 117.5 ($C_{4''}$), 109.9 (C_8), 105.7 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 101.1 (OCH_2O), 67.6 (C_4), 60.9 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 48.7 (C_2), 48.2 (C_{11}), 45.7 (C_1), 35.4 (C_3); HRMS (FAB+): calcd for $C_{28}H_{27}NO_7Br$ 568.0971 and 570.0955, found 568.0980 and 570.0940.

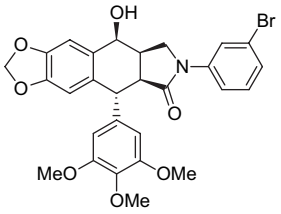
4.5.3. (1*R*,2*S*,3*R*,4*R*)-*N*-(3-Bromophenyl)-picropodophyllin-*cis*-γ-lactam 8a.



To a mixture of **3b** (218 mg, 0.385 mmol) in THF (4 mL) was added MeOH (4 mL). The solution was cooled to −78 °C and $NaBH_4$ (29 mg, 0.770 mmol) was added. The reaction mixture was removed from the cold bath and was stirred for 3 h, water was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/EtOAc 3/2) and then recrystallized from hexane and benzene to yield 147 mg (67%) of **8a** as a white solid.

Compound **8a**: 147 mg; yield: 67%; mp: 216–218 °C; $[\alpha]_D^{20}$ −59 (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3020, 3012, 2970–2900, 1702, 1592, 1504, 1480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, *J*=1.8 Hz, 1H, $H_{2''}$), 7.59 (m, 1H, $H_{6''}$), 7.27 (m, 1H, $H_{4''}$), 7.22 (m, 1H, $H_{5''}$), 7.04 (s, 1H, H_5), 6.48 (s, 2H, $H_{2'}$, $H_{6'}$), 6.35 (s, 1H, H_8), 5.92 (m, 2H, OCH_2O), 4.48 (t, *J*=7.5 Hz, 1H, H_4), 4.19 (d, *J*=5.1 Hz, 1H, H_1), 3.97 (m, 2H, H_{11}), 3.85 (s, 3H, $OMe_{(4')}$), 3.82 (s, 6H, $OMe_{(3',5')}$), 3.36 (dd, *J*=9.3, 5.1 Hz, 1H, H_2), 2.69 (m, 1H, H_3), 2.31 (d, *J*=7.5 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2 (C_{13}), 153.4 ($C_{3'}$, $C_{5'}$), 147.2 (C_7), 146.8 (C_6), 140.4 ($C_{1''}$), 140.1 ($C_{1'}$), 136.7 ($C_{4'}$), 132.2 (C_9), 131.1 (C_{10}), 130.1 ($C_{5''}$), 127.6 ($C_{4''}$), 122.6 ($C_{3''}$), 122.5 ($C_{2''}$), 117.9 ($C_{6''}$), 109.3 (C_8), 105.5 ($C_{2'}$, $C_{6'}$), 105.3 (C_5), 101.1 (OCH_2O), 70.1 (C_4), 60.9 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 50.2 (C_{11}), 48.9 (C_2), 44.2 (C_1), 38.8 (C_3); MS (ES+): *m*/*z*=568, 570 $[M+H]^+$, 590, 592 $[M+Na]^+$.

4.5.4. (1*R*,2*S*,3*R*,4*S*)-*N*-(3-Bromophenyl)-epipicropodophyllin-*cis*-γ-lactam 8b.



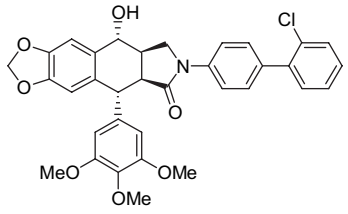
To a mixture of **3b** (196 mg, 0.346 mmol) in anhydrous THF (5 mL) at −78 °C was added 1 M L-Selectride solution in THF (415 μL, 0.415 mmol) dropwise. The reaction mixture was removed from the cold bath and was stirred for 2 h. A saturated solution of NH_4Cl was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (cyclohexane/EtOAc 3/2) to yield 157 mg (80%) of **8b** as a white solid.

Compound **8b**: 157 mg; yield: 80%; mp: 149–153 °C; $[\alpha]_D^{20}$ +46 (*c* 2.30, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3011, 2980–2900, 1694, 1591, 1505, 1482 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, *J*=1.7 Hz, 1H, $H_{2''}$), 7.53 (m, 1H, $H_{6''}$), 7.23 (m, 1H, $H_{4''}$), 7.13 (m, 1H, $H_{5''}$), 7.08 (s, 1H, H_5), 6.65 (s, 1H, H_8), 6.34 (s, 2H, $H_{2'}$, $H_{6'}$), 5.95 (m, 2H, OCH_2O), 4.89 (t, *J*=4.5 Hz, 1H, H_4), 4.55 (d, *J*=2.0 Hz, 1H, H_1), 3.82 (s, 3H, $OMe_{(4')}$), 3.80 (m, 1H, H_{11a}), 3.77 (s, 6H, $OMe_{(3',5')}$), 3.67 (m, 1H, H_{11b}), 3.61 (dd, *J*=10.7, 2.0 Hz, 1H, H_2), 3.20 (m, 1H, H_3), 2.16 (d, *J*=4.5 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (C_{13}), 153.3 ($C_{3'}$, $C_{5'}$), 147.2 (C_6, C_7), 140.3 ($C_{1'}$), 138.1 ($C_{1''}$), 136.7 ($C_{4'}$), 131.4 (C_9), 130.0 ($C_{5''}$), 129.8 (C_{10}), 127.5 ($C_{4''}$), 122.6 ($C_{2''}$), 122.5 ($C_{3''}$), 118.1 ($C_{6''}$), 109.9 (C_8), 105.7 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 101.1 (OCH_2O), 67.7 (C_4), 60.9 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 48.7 (C_2), 48.1 (C_{11}), 45.7 (C_1), 35.4 (C_3); MS (ES+): *m*/*z*=568, 570 $[M+H]^+$, 590, 592 $[M+Na]^+$.

4.6. Representative experimental procedure for Suzuki cross-coupling

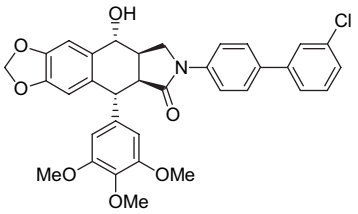
To a 10 mL Quest 210 Teflon reaction vessel was added a solution of *N*-4-bromophenyl γ-lactam lignan **7b** (30 mg, 0.053 mM) and $Pd(OAc)_2$ (1.2 mg, 10 mol %) in DMF (3 mL) followed by substituted phenylboronic acid (0.132 mM, 2.5 equiv) and CsF (Table 2). The reaction mixture was stirred at 85 °C, filtered, and poured into water. After extraction with EtOAc (3×7 mL), the combined organic phases were washed with brine and evaporated under reduced pressure. The residue was purified on silica pad with cyclohexane then cyclohexane/EtOAc gradient [9/1 to 2/8] to give the desired biaryl product.

4.6.1. (1*R*,2*S*,3*R*,4*R*)-*N*-(2′-Chlorobiphenyl)-picropodophyllin-*cis*-γ-lactam 4aa.



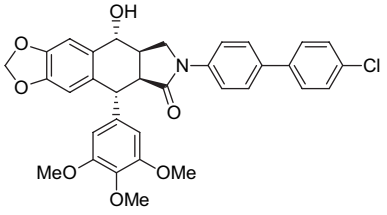
White solid; 18.8 mg; yield: 59%; mp: 151–155 °C; $[\alpha]_D^{20}$ −72 (*c* 0.29, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3019, 2960–2900, 1696, 1593, 1505, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, *J*=8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.45 (m, 3H, $H_{3''}$, $H_{5''}$, $H_{6'''}$), 7.24 (m, 3H, $H_{3'''}$, $H_{4'''}$, $H_{5'''}$), 7.04 (s, 1H, H_5), 6.50 (s, 2H, $H_{2'}$, $H_{6'}$), 6.40 (s, 1H, H_8), 5.93 (m, 2H, OCH_2O), 4.51 (dd, *J*=8.0, 7.1 Hz, 1H, H_4), 4.25 (d, *J*=4.7 Hz, 1H, H_1), 4.02 (m, 2H, H_{11}), 3.85 (s, 3H, $OMe_{(4')}$), 3.83 (s, 6H, $OMe_{(3',5')}$), 3.38 (dd, *J*=9.2, 4.7 Hz, 1H, H_2), 2.73 (m, 1H, H_3), 2.08 (d, *J*=7.1 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0 (C_{13}), 153.5 ($C_{3'}$, $C_{5'}$), 147.4 (C_7), 146.8 (C_6), 139.7 ($C_{1'}$), 138.5 ($C_{4''}$), 137.6 ($C_{1'''}$), 136.6 ($C_{4'}$), 135.8 ($C_{1''}$), 132.5 ($C_{2'''}$), 132.1 (C_9), 131.3 (C_{10}, $C_{3'''}$), 130.0 ($C_{3''}$, $C_{5''}$, $C_{6'''}$), 128.6 ($C_{4'''}$), 126.9 ($C_{5'''}$), 119.1 ($C_{2''}$, $C_{6''}$), 109.5 (C_8), 105.5 (C_5, $C_{2'}$, $C_{6'}$), 101.1 (OCH_2O), 70.5 (C_4), 60.9 (OMe), 56.1 ($OMe_{(3',5')}$), 50.4 (C_{11}), 49.0 (C_2), 44.3 (C_1), 38.8 (C_3); HRMS (DCI/NH_3): calcd for $C_{34}H_{31}NO_7Cl$ 600.1789 and 602.1779, found 600.1774 and 602.1768.

4.6.2. (1*R*,2*S*,3*R*,4*R*)-*N*-(3′-Chlorobiphenyl)-picropodophyllin-*cis*-γ-lactam 4ab.



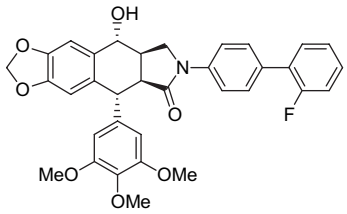
White solid; 21.3 mg; yield: 67%; $[\alpha]_D^{20}$ −90 (*c* 0.83, $CHCl_3$); IR ($CHCl_3$) 3600–3300, 3020, 2970–2900, 1697, 1593, 1505, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, *J*=8.6 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.53 (m, 3H, $H_{3''}$, $H_{5''}$, $H_{2'''}$), 7.36 (m, 3H, $H_{4'''}$, $H_{5'''}$, $H_{6'''}$), 7.05 (s, 1H, H_5), 6.49 (s, 2H, $H_{2'}$, $H_{6'}$), 6.37 (s, 1H, H_8), 5.92 (m, 2H, OCH_2O), 4.49 (t, *J*=7.0 Hz, 1H, H_4), 4.22 (d, *J*=4.8 Hz, 1H, H_1), 4.01 (m, 2H, H_{11}), 3.85 (s, 3H, $OMe_{(4')}$), 3.82 (s, 6H, $OMe_{(3',5')}$), 3.37 (dd, *J*=9.2, 4.8 Hz, 1H, H_2), 2.69 (m, 1H, H_3), 2.42 (d, *J*=7.0 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1 (C_{13}), 153.5 ($C_{3'}$, $C_{5'}$), 147.2 (C_7), 146.8 (C_6), 142.1 ($C_{3'''}$), 140.3 ($C_{1'}$), 138.9 ($C_{1''}$), 136.7 ($C_{4'}$), 135.9 ($C_{1'''}$), 134.7 ($C_{4''}$), 132.3 (C_9), 131.1 (C_{10}), 130.0 ($C_{5'''}$), 127.4 ($C_{3''}$, $C_{5''}$), 127.2 ($C_{4'''}$), 126.9 ($C_{2'''}$), 125.0 ($C_{6'''}$), 119.9 ($C_{2''}$, $C_{6''}$), 109.3 (C_8), 105.6 ($C_{2'}$, $C_{6'}$), 105.3 (C_5), 101.1 (OCH_2O), 70.1 (C_4), 60.9 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 50.3 (C_{11}), 49.0 (C_2), 44.2 (C_1), 38.8 (C_3); HRMS (DCI/NH_3): calcd for $C_{34}H_{31}NO_7Cl$ 600.1789 and 602.1779, found 600.1787 and 602.1752.

4.6.3. (1*R*,2*S*,3*R*,4*R*)-*N*-(4′-Chlorobiphenyl)-picropodophyllin-*cis*-γ-lactam 4ac.



White solid; 21.3 mg; yield: 67%; mp: 125–130 °C; $[\alpha]_D^{20}$ −29 (*c* 0.11, $CHCl_3$); IR ($CHCl_3$) 3500–3200, 3022, 3014, 2975–2900, 1702, 1592, 1505, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J*=8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.55 (d, *J*=8.7 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.49 (d, *J*=8.6 Hz, 2H, $H_{3'''}$, $H_{5'''}$), 7.39 (d, 2H, *J*=8.6 Hz, $H_{2'''}$, $H_{6'''}$), 7.04 (s, 1H, H_5), 6.49 (s, 2H, $H_{2'}$, $H_{6'}$), 6.40 (s, 1H, H_8), 5.94 (m, 2H, OCH_2O), 4.56 (t, *J*=7.4 Hz, 1H, H_4), 4.26 (d, *J*=4.6 Hz, 1H, H_1), 4.03 (m, 2H, H_{11}), 3.86 (s, 3H, $OMe_{(4')}$), 3.83 (s, 6H, $OMe_{(3',5')}$), 3.40 (dd, *J*=9.4, 4.6 Hz, 1H, H_2), 2.74 (m, 1H, H_3), 2.06 (d, *J*=7.4 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4 (C_{13}), 153.7 ($C_{3'}$, $C_{5'}$), 147.1 (C_7), 146.7 (C_6), 140.2 ($C_{1'}$), 138.9 ($C_{1'''}$), 138.7 ($C_{4''}$), 136.8 ($C_{4'}$, $C_{1''}$), 134.6 ($C_{4'''}$), 132.3 (C_9), 131.2 (C_{10}), 128.8 ($C_{3'''}$, $C_{5'''}$), 127.7 ($C_{3''}$, $C_{5''}$, $C_{2'''}$, $C_{6'''}$), 120.0 ($C_{2''}$, $C_{6''}$), 109.5 (C_8), 105.5 (C_5, $C_{2'}$, $C_{6'}$), 101.1 (OCH_2O), 70.4 (C_4), 60.9 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 50.4 (C_{11}), 49.0 (C_2), 44.3 (C_1), 38.9 (C_3); HRMS (DCI/NH_3): calcd for $C_{34}H_{31}NO_7Cl$ 600.1789 and 602.1779, found 600.1774 and 602.1768.

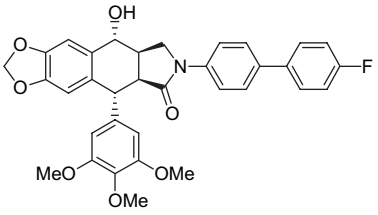
4.6.4. (1*R*,2*S*,3*R*,4*R*)-*N*-(2′-Fluorobiphenyl)-picropodophyllin-*cis*-γ-lactam 4ad.



White solid; 25.4 mg; yield: 82%; mp: 82 °C; $[\alpha]_D^{20}$ −44 (*c* 0.13, $CHCl_3$); IR ($CHCl_3$) 3550–3300, 3031, 3011, 2974–2900, 1693, 1591, 1504, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, *J*=8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.53 (d, *J*=8.7 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.40 (dt, *J*=7.8, 1.6 Hz, 1H, $H_{6'''}$), 7.29 (m, 1H, $H_{4'''}$), 7.20 (m, 1H, $H_{5'''}$), 7.13 (m, 1H, $H_{3'''}$),

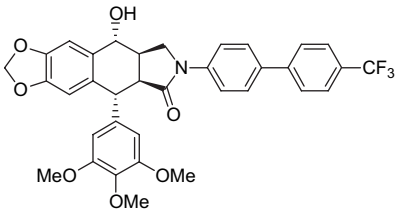
7.05 (s, 1H, H_5), 6.49 (s, 2H, $H_{2'}$, $H_{6'}$), 6.38 (s, 1H, H_8), 5.92 (m, 2H, OCH_2O), 4.50 (dd, J=7.0, 4.1 Hz, 1H, H_4), 4.24 (d, J=4.8 Hz, 1H, H_1), 4.01 (m, 2H, H_{11}), 3.85 (s, 3H, $OMe_{(4')}$), 3.82 (s, 6H, $OMe_{(3',5')}$), 3.37 (dd, J=9.2, 4.8 Hz, 1H, H_2), 2.71 (m, 1H, H_3), 2.35 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8 (C_{13}), 158.3 (d, J=247.4 Hz, $C_{2''}$), 153.2 ($C_{3'}$, $C_{5'}$), 147.1 (C_6, C_7), 140.3 ($C_{1'}$), 138.5 ($C_{1''}$), 136.6 ($C_{4'}$), 132.3 (C_9), 131.0 (C_{10}), 130.5 ($C_{4''}$, $C_{6'''}$), 129.3 ($C_{3''}$, $C_{5''}$), 129.1 (d, J=8.1 Hz, $C_{4'''}$), 128.5 (d, J=13.3 Hz, $C_{1'''}$), 124.4 ($C_{5'''}$), 119.7 ($C_{2''}$, $C_{6''}$), 116.3 (d, J=22.6 Hz, $C_{3'''}$), 109.3 (C_8), 105.6 ($C_{2'}$, $C_{6'}$, C_5), 101.1 (OCH_2O), 70.1 (C_4), 60.9 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 50.3 (C_{11}), 49.0 (C_2), 44.2 (C_1), 38.8 (C_3); MS (ES+): m/z=584 $[M+H]^+$.

4.6.5. (1*R*,2*S*,3*R*,4*R*)-*N*-(4′-Fluorobiphenyl)-picropodophyllin-*cis*-γ-lactam 4ae.



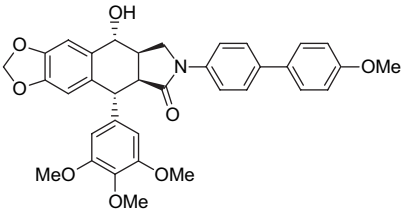
White solid; 28.4 mg; yield: 92%; mp: 209–212 °C; $[\alpha]_D^{20}$ −77 (c 0.35, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3005, 2960–2900, 1695, 1593, 1500, 1482 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J=8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.52 (d, J=8.7 Hz, 2H, $H_{2'''}$, $H_{6'''}$), 7.50 (d, J=8.7 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.11 (t, 2H, J=8.7 Hz, $H_{3'''}$, $H_{5'''}$), 7.05 (s, 1H, H_5), 6.49 (s, 2H, $H_{2'}$, $H_{6'}$), 6.40 (s, 1H, H_8), 5.93 (m, 2H, OCH_2O), 4.53 (t, J=7.7 Hz, 1H, H_4), 4.25 (d, J=4.8 Hz, 1H, H_1), 4.04 (m, 2H, H_{11}), 3.85 (s, 3H, $OMe_{(4')}$), 3.83 (s, 6H, $OMe_{(3',5')}$), 3.38 (dd, J=9.2, 4.8 Hz, 1H, H_2), 2.72 (m, 1H, H_3), 2.17 (d, J=7.7 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0 (C_{13}), 162.5 (d, J=226.4 Hz, $C_{4'''}$), 153.5 ($C_{3'}$, $C_{5'}$), 147.2 (C_7), 146.8 (C_6), 140.3 ($C_{1'}$), 138.4 ($C_{1''}$), 136.7 ($C_{4'}$), 136.5 ($C_{4''}$, $C_{1'''}$), 132.2 (C_9), 131.2 (C_{10}), 128.4 (d, J=7.9 Hz, $C_{2'''}$, $C_{6'''}$), 127.3 ($C_{3''}$, $C_{5''}$), 120.0 ($C_{2''}$, $C_{6''}$), 115.6 (d, J=21.3 Hz, $C_{3'''}$, $C_{5'''}$), 109.4 (C_8), 105.5 ($C_{2'}$, $C_{6'}$), 105.4 (C_5), 101.1 (OCH_2O), 70.4 (C_4), 60.9 (OMe), 56.1 ($OMe_{(3',5')}$), 50.4 (C_{11}), 49.0 (C_2), 44.2 (C_1), 38.8 (C_3); HRMS (DCI/NH_3): calcd for $C_{34}H_{31}FNO_7$ 584.2085, found 584.2075.

4.6.6. (1*R*,2*S*,3*R*,4*R*)-*N*-(4′-Trifluoromethylbiphenyl)-picropodophyllin-*cis*-γ-lactam 4af.



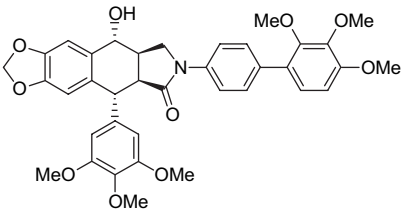
White gum; 28.5 mg; yield: 85%; $[\alpha]_D^{20}$ −26 (c 0.13, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3029, 3012, 2975–2900, 1697, 1592, 1504, 1482 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, J=8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.67 (m, 4H, $H_{2'''}$, $H_{3'''}$, $H_{5'''}$, $H_{6'''}$), 7.60 (d, J=8.7 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.05 (s, 1H, H_5), 6.50 (s, 2H, $H_{2'}$, $H_{6'}$), 6.40 (s, 1H, H_8), 5.93 (m, 2H, OCH_2O), 4.55 (d, J=8.0 Hz, 1H, H_4), 4.27 (d, J=4.8 Hz, 1H, H_1), 4.05 (m, 2H, H_{11}), 3.86 (s, 3H, $OMe_{(4')}$), 3.83 (s, 6H, $OMe_{(3',5')}$), 3.41 (dd, J=9.2, 4.8 Hz, 1H, H_2), 2.75 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1 (C_{13}), 153.5 ($C_{3'}$, $C_{5'}$), 147.3 (C_7), 146.8 (C_6), 143.5 ($C_{1'''}$), 140.2 ($C_{1'}$), 139.4 ($C_{1''}$), 136.6 ($C_{4'}$), 135.9 ($C_{4''}$), 132.1 (C_9), 131.1 (C_{10}), 130.1 (m, $C_{4'''}$), 127.7 ($C_{3''}$, $C_{5''}$), 127.1 ($C_{2'''}$, $C_{6'''}$), 125.7 (m, $C_{3'''}$, $C_{5'''}$), 122.4 (q, J=251 Hz, CF_3), 120.0 ($C_{2''}$, $C_{6''}$), 109.4 (C_8), 105.5 ($C_{2'}$, $C_{6'}$, C_5), 101.1 (OCH_2O), 70.4 (C_4), 60.9 ($OMe_{(4')}$), 56.1 ($OMe_{(3',5')}$), 50.3 (C_{11}), 49.0 (C_2), 44.3 (C_1), 38.9 (C_3); MS (ES+): m/z=558 $[M+H]^+$.

4.6.7. (1*R*,2*S*,3*R*,4*R*)-*N*-(4′-Methoxybiphenyl)-picropodophyllin-*cis*-γ-lactam 4ah.



White solid; 30.0 mg, yield: 95%; mp: 227 °C; $[\alpha]_D^{20}$ −91 (c 0.42, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3021, 3008, 2960, 1697, 1592, 1502, 1482 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J=8.6 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.51 (d, J=8.6 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.49 (d, J=8.6 Hz, 2H, $H_{2'''}$, $H_{6'''}$), 7.06 (s, 1H, H_5), 6.95 (d, J=8.6 Hz, 2H, $H_{3'''}$, $H_{5'''}$), 6.49 (s, 2H, $H_{2'}$, $H_{6'}$), 6.36 (s, 1H, H_8), 5.92 (m, 2H, OCH_2O), 4.48 (t, J=7.1 Hz, 1H, H_4), 4.21 (d, J=4.9 Hz, 1H, H_1), 4.00 (m, 2H, H_{11}), 3.85 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.82 (s, 6H, $OMe_{(3',5')}$), 3.36 (dd, J=9.0, 4.9 Hz, 1H, H_2), 2.68 (m, 1H, H_3), 2.54 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0 (C_{13}), 159.1 ($C_{4'''}$), 153.5 ($C_{3'}$, $C_{5'}$), 147.2 (C_7), 146.8 (C_6), 140.4 ($C_{1'}$), 137.8 ($C_{1''}$), 137.2 ($C_{4''}$), 136.7 ($C_{4'}$), 132.8 ($C_{1'''}$), 132.3 (C_9), 131.2 (C_{10}), 129.9 ($C_{2'''}$, $C_{6'''}$), 127.0 ($C_{3''}$, $C_{5''}$), 120.0 ($C_{2''}$, $C_{6''}$), 114.2 ($C_{3'''}$, $C_{5'''}$), 109.4 (C_8), 105.6 ($C_{2'}$, $C_{6'}$), 105.4 (C_5), 101.1 (OCH_2O), 70.2 (C_4), 60.9 (OMe), 56.1 ($OMe_{(3',5')}$), 55.3 (OMe), 50.4 (C_{11}), 49.0 (C_2), 44.2 (C_1), 38.8 (C_3); HRMS (DCI/NH_3): calcd for $C_{35}H_{34}NO_8$ 596.2284, found 596.2272.

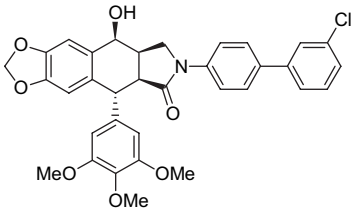
4.6.8. (1*R*,2*S*,3*R*,4*R*)-*N*-(2′,3′,4′-Trimethoxybiphenyl)-picropodophyllin-*cis*-γ-lactam 4ai.



Off-white solid; 22.9 mg; yield: 66%; mp: 148–153 °C; $[\alpha]_D^{20}$ −56 (c 0.17, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 2970–2900, 1693, 1594, 1504, 1488 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J=8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.51 (d, J=8.7 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.04 (s, 1H, H_5), 7.00 (d, J=8.6 Hz, 1H, $H_{6'''}$), 6.72 (d, J=8.6 Hz, 1H, $H_{5'''}$), 6.50 (s, 2H, $H_{2'}$, $H_{6'}$), 6.41 (s, 1H, H_8), 5.93 (m, 2H, OCH2O), 4.54 (t,

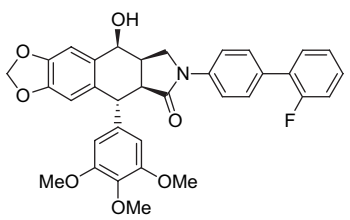
J=8.5 Hz, 1H, H_4), 4.27 (d, J=4.7 Hz, 1H, H_1), 4.03 (m, 2H, H_{11}), 3.92 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.83 (s, 6H, OMe), 3.65 (s, 3H, OMe), 3.38 (dd, J=9.2, 4.7 Hz, 1H, H_2), 2.73 (m, 1H, H_3), 2.17 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9 (C_{13}), 153.5 ($C_{3'}$, $C_{5'}$), 153.2 ($C_{4''}$), 151.5 ($C_{2''}$), 147.2 (C_7), 146.8 (C_6), 142.1 ($C_{3''}$), 140.4 ($C_{1'}$), 137.8 ($C_{1''}$), 136.8 ($C_{4'}$), 134.8 ($C_{4''}$), 132.2 (C_9), 131.2 (C_{10}), 129.5 ($C_{3''}$, $C_{5''}$), 128.0 ($C_{1''}$), 124.6 ($C_{6''}$), 119.4 ($C_{2''}$, $C_{6''}$), 109.5 (C_8), 107.5 ($C_{5''}$), 105.5 (C_5, $C_{2'}$, $C_{6'}$), 101.1 (O–CH_2–O), 70.4 (C_4), 60.9 (OMe), 56.2 (OMe), 50.4 (C_{11}), 49.0 (C_2), 44.2 (C_1), 38.8 (C_3); HRMS (DCI/NH_3): calcd for $C_{37}H_{38}NO_{10}$ 656.2496, found 656.2493.

4.6.9. (1*R*,2*S*,3*R*,4*S*)-*N*-(3′-Chlorobiphenyl)-epipicropodophyllin-*cis*-γ-lactam 4ba.



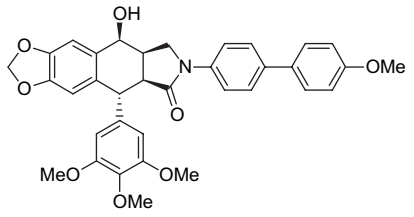
White solid; 22.3 mg; yield: 70%; mp: 168–173 °C; $[\alpha]_D^{20}$ +35 (c 0.48, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3010, 2970–2900, 1690, 1591, 1505, 1483 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, J=8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.49 (m, 3H, $H_{3''}$, $H_{5''}$, $H_{2'''}$), 7.33 (m, 3H, $H_{4'''}$, $H_{5'''}$, $H_{6'''}$), 7.10 (s, 1H, H_5), 6.67 (s, 1H, H_8), 6.35 (s, 2H, $H_{2'}$, $H_{6'}$), 5.94 (m, 2H, OCH_2O), 4.91 (t, J=4.1 Hz, 1H, H_4), 4.59 (d, 1H, J=2.4 Hz, H_1), 3.84 (m, 1H, H_{11a}), 3.82 (s, 3H, $OMe_{(4')}$), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.72 (m, 1H, H_{11b}), 3.63 (dd, J=10.7, 2.4 Hz, 1H, H_2), 3.22 (m, 1H, H_3), 2.44 (d, J=4.1 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (C_{13}), 153.2 ($C_{3'}$, $C_{5'}$), 147.1 (C_7, C_6), 142.2 ($C_{3'''}$), 138.8 ($C_{1''}$), 138.2 ($C_{1'}$), 136.6 ($C_{4'}$), 135.9 ($C_{1'''}$), 134.7 ($C_{4''}$), 131.7 (C_9), 130.0 ($C_{5'''}$), 129.8 (C_{10}), 127.4 ($C_{3''}$, $C_{5''}$), 127.3 ($C_{4'''}$), 127.2 ($C_{2'''}$), 125.4 ($C_{6'''}$), 121.4 ($C_{2''}$, $C_{6''}$), 109.9 (C_8), 105.7 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 101.1 (OCH_2O), 67.6 (C_4), 60.9 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 48.8 (C_2), 48.2 (C_{11}), 45.8 (C_1), 35.5 (C_3); MS (ES+): m/z=600, 602 $[M+H]^+$, 622, 624 $[M+Na]^+$.

4.6.10. (1*R*,2*S*,3*R*,4*S*)-*N*-(2′-Fluorobiphenyl)-epipicropodophyllin-*cis*-γ-lactam 4bb.



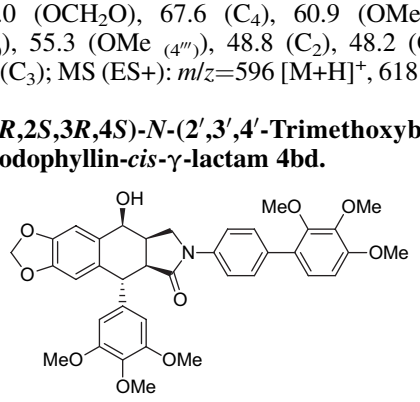
White solid; 24.2 mg; yield: 79%; mp: 146–148 °C; $[\alpha]_D^{20}$ +49 (c 0.61, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3025, 3018, 2960–2900, 1686, 1590, 1506, 1485 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J=8.8 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.49 (dd, J=8.8, 1.3 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.37 (dt, J=7.7, 1.8 Hz, 1H, $H_{6'''}$), 7.28 (m, 1H, $H_{4'''}$), 7.17 (dt, J=7.7, 1.2 Hz, 1H, $H_{5'''}$), 7.10 (m, 2H, H_5, $H_{3'''}$), 6.68 (s, 1H, H_8), 6.36 (s, 2H, $H_{2'}$, $H_{6'}$), 5.94 (m, 2H, OCH_2O), 4.91 (t, J=4.5 Hz, 1H, H_4), 4.59 (d, J=2.3 Hz, 1H, H_1), 3.84 (m, 1H, H_{11a}), 3.82 (s, 3H, $OMe_{(4')}$), 3.77 (s, 6H, $OMe_{(3',5')}$), 3.72 (m, 1H, H_{11b}), 3.64 (dd, J=10.7, 2.3 Hz, 1H, H_2), 3.22 (m, 1H, H_3), 2.36 (d, J=4.5 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5 (C_{13}), 159.7 (d, J=246.1 Hz, $C_{2'''}$), 153.2 ($C_{3'}$, $C_{5'}$), 147.2 (C_6, C_7), 138.5 ($C_{1''}$), 138.2 ($C_{1'}$), 136.6 ($C_{4'}$), 131.9 (C_9), 131.6 ($C_{6'''}$), 130.5 ($C_{4''}$), 129.7 (C_{10}), 129.3 ($C_{3''}$, $C_{5''}$), 128.9 (d, J=8.2 Hz, $C_{4'''}$), 128.3 (d, J=13.3 Hz, $C_{1'''}$), 124.4 (d, J=3.5 Hz, $C_{5'''}$), 119.7 ($C_{2''}$, $C_{6''}$), 116.1 (d, J=22.6 Hz, $C_{3''}$), 109.9 (C_8), 105.7 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 101.1 (OCH_2O), 67.7 (C_4), 60.9 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 48.8 (C_2), 48.2 (C_{11}), 45.8 (C_1), 35.5 (C_3); MS (ES+): m/z=584 $[M+H]^+$, 606 $[M+Na]^+$.

4.6.11. (1*R*,2*S*,3*R*,4*S*)-*N*-(4′-Methoxybiphenyl)-epipicropodophyllin-*cis*-γ-lactam 4bc.



White solid; 25.6 mg; yield: 81%; mp: 148–150 °C; $[\alpha]_D^{20}$ +43 (c 0.48, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3020, 3008, 2960–2900, 1688, 1590, 1502, 1484 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, J=8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.48 (d, J=8.7 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.43 (d, J=8.8 Hz, 2H, $H_{2'''}$, $H_{6'''}$), 7.10 (s, 1H, H_5), 6.94 (d, J=8.8 Hz, 2H, $H_{3'''}$, $H_{5'''}$), 6.69 (s, 1H, H_8), 6.36 (s, 2H, $H_{2'}$, $H_{6'}$), 5.94 (m, 2H, OCH_2O), 4.91 (t, J=4.3 Hz, 1H, H_4), 4.59 (d, J=2.2 Hz, 1H, H_1), 3.84 (m, 1H, H_{11a}), 3.83 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.77 (s, 6H, $OMe_{(3',5')}$), 3.72 (m, 1H, H_{11b}), 3.63 (dd, J=10.7, 2.2 Hz, 1H, H_2), 3.22 (m, 1H, H_3), 2.29 (d, J=4.3 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3 (C_{13}), 159.1 ($C_{4'''}$), 153.2 ($C_{3'}$, $C_{5'}$), 147.1 (C_6, C_7), 138.2 ($C_{1'}$), 137.7 ($C_{1''}$), 137.1 ($C_{4''}$), 136.7 ($C_{4'}$), 132.9 ($C_{1'''}$), 131.6 (C_9), 129.8 (C_{10}), 127.9 ($C_{2'''}$, $C_{6'''}$), 126.9 ($C_{3''}$, $C_{5''}$), 120.2 ($C_{2''}$, $C_{6''}$), 114.2 ($C_{3'''}$, $C_{5'''}$), 110.0 (C_8), 105.6 (C_5), 104.7 ($C_{2'}$, $C_{6'}$), 101.0 (OCH_2O), 67.6 (C_4), 60.9 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 55.3 ($OMe_{(4''')}$), 48.8 (C_2), 48.2 (C_{11}), 45.8 (C_1), 35.5 (C_3); MS (ES+): m/z=596 $[M+H]^+$, 618 $[M+Na]^+$.

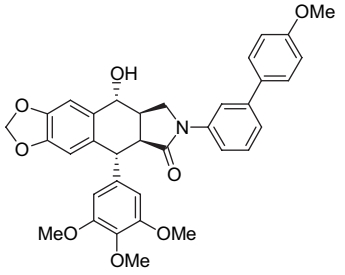
4.6.12. (1*R*,2*S*,3*R*,4*S*)-*N*-(2′,3′,4′-Trimethoxybiphenyl)-epipicropodophyllin-*cis*-γ-lactam 4bd.



Off-white solid; 23.3 mg; yield: 67%; mp: 136–139 °C; $[\alpha]_D^{20}$ +42 (c 0.59, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3018, 2980–2900, 1690, 1591, 1504, 1485 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, J=8.8 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.43 (d, J=8.8 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.12 (s, 1H, H_5), 6.97 (d, J=8.6 Hz, 2H, $H_{6'''}$), 6.70 (d, J=8.6 Hz, 2H, $H_{5'''}$), 6.69 (s, 1H, H_8), 6.35 (s, 2H, $H_{2'}$, $H_{6'}$), 5.94 (m, 2H, OCH_2O), 4.91

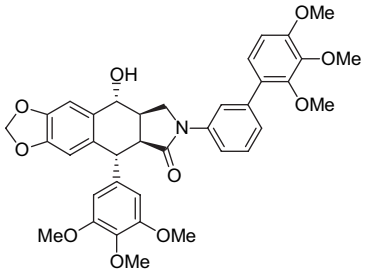
(t, J=4.5 Hz, 1H, H_4), 4.59 (d, J=2.1 Hz, 1H, H_1), 3.90 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.86 (m, 1H, H_{11a}), 3.81 (s, 3H, OMe), 3.76 (s, 6H, $OMe_{(3',5')}$), 3.75 (m, 1H, H_{11b}), 3.65 (s, 3H, OMe), 3.62 (m, 1H, H_2), 3.22 (m, 1H, H_3), 2.55 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4 (C_{13}), 153.2 ($C_{3'}$, $C_{5'}$), 153.1 ($C_{4'''}$), 151.3 ($C_{2'''}$), 147.2 (C_7), 147.0 (C_6), 142.5 ($C_{3'''}$), 138.3 ($C_{1'}$), 137.7 ($C_{1''}$), 136.6 ($C_{4'}$), 134.5 ($C_{4''}$), 131.8 (C_9), 129.7 (C_{10}), 129.4 ($C_{3''}$, $C_{5''}$), 127.8 ($C_{1'''}$), 124.6 ($C_{6'''}$), 119.6 ($C_{2''}$, $C_{6''}$), 109.9 (C_8), 107.5 ($C_{5'''}$), 105.7 (C_5), 104.8 ($C_{2'}$, $C_{6'}$), 101.0 (OCH_2O), 67.5 (C_4), 61.0 (OMe), 60.9 (OMe), 56.2 (OMe), 56.0 (OMe), 48.9 (C_2), 48.2 (C_{11}), 45.9 (C_1), 35.5 (C_3); MS (ES+): m/z=656 $[M+H]^+$, 678 $[M+Na]^+$.

4.6.13. (1*R*,2*S*,3*R*,4*R*)-*N*-(4′-Methoxybiphen-2-yl)-picropodophyllin-*cis*-γ-lactam 4ca.



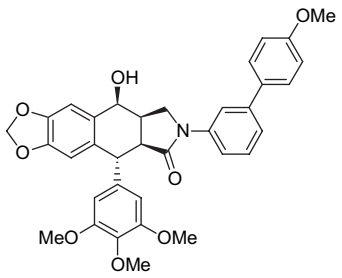
White solid; 22.7 mg; yield: 72%; mp: 220–223 °C; $[\alpha]_D^{20}$ −73 (c 0.34, $CHCl_3$); IR ($CHCl_3$) 3500–3200, 2980–2900, 1697, 1591, 1482 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (s, 1H, $H_{2''}$), 7.49 (m, 3H, $H_{6''}$, $H_{2'''}$, $H_{6'''}$),7.35 (m, 2H, $H_{4''}$, $H_{5''}$), 7.04 (s, 1H, H_5), 6.94 (d, J=8.4 Hz, 2H, $H_{3'''}$, $H_{5'''}$), 6.49 (s, 2H, $H_{2'}$, $H_{6'}$), 6.37 (s, 1H, H_8), 5.91 (m, 2H, OCH_2O), 4.50 (t, J=7.7 Hz, 1H, H_4), 4.23 (d, J=5.0 Hz, 1H, H_1), 4.03 (m, 2H, H_{11}), 3.85 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.82 (s, 6H, $OMe_{(3',5')}$), 3.35 (dd, J=9.2, 5.0 Hz, 1H, H_2), 2.68 (m, 1H, H_3), 2.26 (d, J=7.7 Hz, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0 (C_{13}), 159.3 ($C_{4'''}$), 153.5 ($C_{3'}$, $C_{5'}$), 147.2 (C_7), 146.7 (C_6), 141.7 ($C_{3''}$), 140.5 ($C_{1'}$), 139.6 ($C_{1''}$), 136.7 ($C_{4'}$), 133.2 ($C_{1'''}$), 132.3 (C_9), 131.1 (C_{10}), 129.2 ($C_{5''}$), 128.3 ($C_{2'''}$, $C_{6'''}$), 123.1 ($C_{4''}$), 118.3 ($C_{2''}$), 118.0 ($C_{6''}$), 114.2 ($C_{3'''}$, $C_{5'''}$), 109.4 (C_8), 105.6 ($C_{2'}$, $C_{6'}$), 105.4 (C_5), 101.1 (OCH_2O), 70.2 (C_4), 60.8 (OMe), 56.2 ($OMe_{(3',5')}$), 55.3 (OMe), 50.5 (C_{11}), 49.1 (C_2), 44.2 (C_1), 38.8 (C_3); MS (ES+): m/z=618 $[M+Na]^+$.

4.6.14. (1*R*,2*S*,3*R*,4*R*)-*N*-(2′,3′,4′-Trimethoxybiphen-2-yl)-picropodophyllin-*cis*-γ-lactam 4cb.



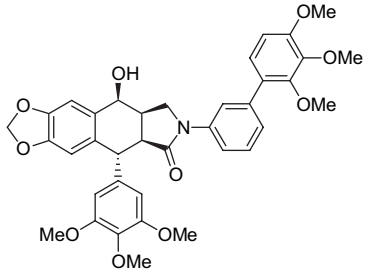
White solid; 10 mg; yield: 29%; mp: 203–208 °C; $[\alpha]_D^{20}$ −69 (c 0.33, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3009, 2980–2900, 1695, 1592, 1504, 1483 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (s, 1H, $H_{2''}$), 7.66 (d, J=7.8 Hz, 1H, $H_{6''}$), 7.37 (t, J=7.8 Hz, 1H, $H_{5''}$), 7.28 (m, 1H, $H_{4''}$), 7.03 (s, 1H, H_5), 7.02 (d, J=9.4 Hz, 1H, $H_{6'''}$), 6.71 (d, J=9.4 Hz, 1H, $H_{5'''}$), 6.49 (s, 2H, $H_{2'}$, $H_{6'}$), 6.39 (s, 1H, H_8), 5.92 (m, 2H, OCH_2O), 4.52 (d, J=8.0 Hz, 1H, H_4), 4.26 (d, J=4.8 Hz, 1H, H_1), 4.01 (m, 2H, H_{11}), 3.92 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.84 (s, 3H, $OMe_{(4')}$), 3.82 (s, 6H, $OMe_{(3',5')}$), 3.67 (s, 3H, OMe), 3.36 (dd, J=9.0, 4.8 Hz, 1H, H_2), 2.71 (m, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9 (C_{13}), 153.4 ($C_{3'}$, $C_{5'}$), 153.3 ($C_{4'''}$), 151.3 ($C_{2'''}$), 147.2 (C_7), 146.8 (C_6), 142.5 ($C_{3''}$), 140.5 ($C_{1'}$), 139.0 ($C_{1''}$, $C_{3''}$), 136.7 ($C_{4'}$), 132.2 (C_9), 131.2 (C_{10}), 128.5 ($C_{5''}$), 128.1 ($C_{1'''}$), 125.6 ($C_{4''}$), 124.9 ($C_{6'''}$), 120.5 ($C_{2''}$), 118.4 ($C_{6''}$), 109.4 (C_8), 107.5 ($C_{5'''}$), 105.7 (C_5, $C_{2'}$, $C_{6'}$), 101.1 (OCH_2O), 70.3 (C_4), 61.1 (OMe), 61.0 (OMe), 60.9 (OMe), 56.2 ($OMe_{(3',5')}$), 56.1 (OMe), 50.6 (C_{11}), 49.0 (C_2), 44.2 (C_1), 38.8 (C_3); MS (ES+): m/z=656 $[M+H]^+$, 678 $[M+Na]^+$.

4.6.15. (1*R*,2*S*,3*R*,4*S*)-*N*-(4′-Methoxybiphen-2-yl)-epipicropodophyllin-*cis*-γ-lactam 4da.



White solid; 23.7 mg; yield: 75%; mp: 147–152 °C; $[\alpha]_D^{20}$ +28 (c 0.49, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3020, 3010, 2960–2900, 1689, 1590, 1504, 1484 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (s, 1H, $H_{2''}$), 7.46 (m, 3H, $H_{6''}$, $H_{2'''}$, $H_{6'''}$),7.31 (m, 2H, $H_{4''}$, $H_{5''}$), 7.11 (s, 1H, H_5), 6.93 (d, 2H, J=8.4 Hz, $H_{3'''}$, $H_{5'''}$), 6.68 (s, 1H, H_8), 6.34 (s, 2H, $H_{2'}$, $H_{6'}$), 5.93 (m, 2H, OCH_2O), 4.90 (m, 1H, H_4), 4.59 (d, J=2.1 Hz, 1H, H_1), 3.85 (m, 1H, H_{11a}), 3.83 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.75 (s, 6H, $OMe_{(3',5')}$), 3.74 (m, 1H, H_{11b}), 3.62 (dd, 1H, J=10.7, 2.1 Hz, H_2), 3.21 (m, 1H, H_3), 2.54 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (C_{13}), 159.3 ($C_{4'''}$), 153.2 ($C_{3'}$, $C_{5'}$), 147.2 (C_7), 147.0 (C_6), 141.5 ($C_{3'''}$), 139.4 ($C_{1'}$), 138.3 ($C_{1''}$), 136.5 ($C_{4'}$), 133.2 ($C_{1'''}$), 131.7 (C_9), 129.7 (C_{10}), 129.1 ($C_{5''}$), 128.3 ($C_{2'''}$, $C_{6'''}$), 123.1 ($C_{4''}$), 118.5 ($C_{2''}$), 118.2 ($C_{6''}$), 114.1 ($C_{3'''}$, $C_{5'''}$), 109.9 (C_8), 105.7 (C_5), 104.6 ($C_{2'}$, $C_{6'}$), 101.0 (OCH_2O), 67.5 (C_4), 60.9 ($OMe_{(4')}$), 56.2 ($OMe_{(3',5')}$), 55.3 ($OMe_{(4''')}$), 49.0 (C_2), 48.4 (C_{11}), 45.9 (C_1), 35.5 (C_3); MS (ES+): m/z=596 $[M+H]^+$, 618 $[M+Na]^+$.

4.6.16. (1*R*,2*S*,3*R*,4*S*)-*N*-(2′,3′,4′-Trimethoxybiphen-2-yl)-epipicropodophyllin-*cis*-γ-lactam 4db.



Off-white solid; 20.5 mg; yield: 59%; mp: 147–150 °C; $[\alpha]_D^{20}$ +24 (*c* 0.57, $CHCl_3$); IR ($CHCl_3$) 3500–3300, 3023, 3007, 2974–2900, 1689, 1590, 1504, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (s, 1H, $H_{2''}$), 7.54 (d, J=8.0 Hz, 1H, $H_{6''}$), 7.32 (t, J=8.0 Hz, 1H, $H_{5''}$), 7.24 (m, 1H, $H_{4''}$), 7.01 (s, 1H, H_5), 6.99 (d, J=8.6 Hz, 1H, $H_{6'''}$), 6.70 (d, J=8.6 Hz, 1H, $H_{5'''}$), 6.67 (s, 1H, H_8), 6.34 (s, 2H, $H_{2'}$, $H_{6'}$), 5.93 (m, 2H, OCH_2O), 4.90 (t, J=4.1 Hz, 1H, H_4), 4.58 (d, J=2.0 Hz, 1H, H_1), 3.90 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.84 (m, 1H, H_{11a}), 3.81 (s, 3H, $OMe_{(4')}$), 3.75 (s, 6H, $OMe_{(3',5')}$), 3.72 (m, 1H, H_{11b}), 3.67 (s, 3H, OMe), 3.62 (dd, J=10.5, 2.0 Hz, 1H, H_2), 3.22 (m, 1H, H_3), 2.57 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4 (C_{13}), 153.2 ($C_{3'}$, $C_{5'}$, $C_{4'''}$), 151.3 ($C_{2'''}$), 147.2 (C_7), 147.0 (C_6), 142.4 ($C_{3'''}$), 138.9 ($C_{1'}$), 138.8 ($C_{1''}$), 138.3 ($C_{3''}$), 136.6 ($C_{4'}$), 131.8 (C_9), 129.7 (C_{10}), 128.4 ($C_{5''}$), 128.1 ($C_{1'''}$), 125.6 ($C_{4''}$), 124.9 ($C_{6'''}$), 120.8 ($C_{2''}$), 118.6 ($C_{6''}$), 110.0 (C_8), 107.4 ($C_{5'''}$), 105.6 (C_5), 104.6 ($C_{2'}$, $C_{6'}$), 101.0 (OCH_2O), 67.5 (C_4), 61.1 (OMe), 61.0 (OMe), 60.9 (OMe), 56.2 ($OMe_{(3',5')}$), 56.0 (OMe), 48.9 (C_2), 48.4 (C_{11}), 45.8 (C_1), 35.5 (C_3); MS (ES+): m/z=656 $[M+H]^+$, 678 $[M+Na]^+$.

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