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ARTICLE

Formal Synthesis of (-)-Podophyllotoxin through the Photocyclization of an Axially Chiral 3,4-Bisbenzylidene Succinate Amide Ester - a Flow Photochemistry Approach

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We have developed a strategy for the stereoselective synthesis of cyclolignans related to podophyllotoxin and its derivatives. The crucial step of the synthesis is the photocyclization of a chiral atropoisomeric 1,2-bisbenzylidenesuccinate amide ester, which can be prepared from the suitable aromatic aldehydes, diethyl succinate and L-prolinol. The photocyclization was found to be more efficient when the irradiation was performed in a home-built continuous flow photochemical reactor. The in-flow irradiation also allowed us to perform the reaction on a multigram scale. The chiral auxiliary was removed by reductive cleavage with the Schwartz's reagent to give the cytotoxic 1*R*,2*R*-*cis*-podophyllic aldehyde, which in turn could be easily reduced to the corresponding alcohol, completing the formal synthesis of (-)-podophyllotoxin.

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Introduction

Lignans, a large family of secondary metabolites consisting of dimerized phenylpropanoid units, are widely distributed in the plant kingdom.[1-5] Among them, the aryltetralin lignans are one of the most extensively studied groups of natural products due to their antiviral, antibacterial and antineoplastic properties.[6] Particularly valuable in the chemotherapy of cancer is podophyllotoxin **1** (Fig. 1) which served as a lead structure for the development of its semisynthetic derivatives etoposide **2** and teniposide **3**, both of which are currently in clinical use.[7] Interestingly, the diverse biological activity of podophyllotoxin derivatives is a result of not one, but at least two different, unrelated molecular mechanisms.[8-11] The fact that similar compounds exhibit such potent, yet fundamentally distinct activities prompted extensive screening for new leads. Such are desirable, since the therapeutic potential of podophyllotoxin and its derivatives is often hindered by problems of drug resistance,[12] hydrophobicity and low selectivity.[13] Although many bioactive compounds were derived from natural lignans, podophyllotoxin finds limited use as a direct synthetic precursor to more valuable analogues because of its sensitivity to extensive chemical modification. Therefore, there has been intense interest in the development of general synthetic schemes for related compounds over the last decades.[14,15] Very recently, three interesting contributions to the enantioselective synthesis of podophyllotoxin have been disclosed. Ishikawa[16] completed the formal synthesis of (-)-**1** from (2*S*,3*R*)-3-arylaziridine-2-carboxylate 3,3-diarylpropanoate as common intermediate. On the other hand, Maimone and Ting[17] presented a short total synthesis of podophyllotoxin using a Pd-catalyzed C(sp^3)-H arylation reaction. Finally, Nishi and co-workers[18] reported on organocatalyzed enantioselective cyclopropanation and Lewis acid-mediated ring expansion leading to chiral podophyllic aldehydes, highly valuable intermediates which can easily be modified enabling diverse analogue preparation.

In this paper, we explore the relatively less studied strategy to synthesize cyclolignans through the photocyclization of 3,4-bisbenzylidenesuccinic acid amide esters. Although this kind of photocyclization was excessively studied for photochromic compounds belonging to the fulgide family (fulgides, fulgimides,

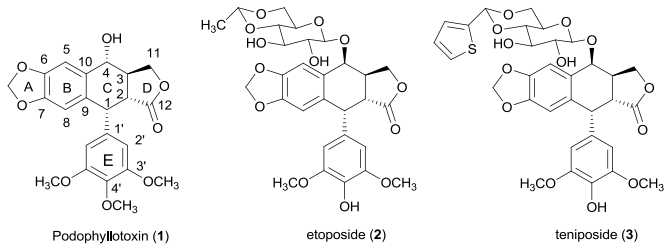

Figure 1. Structure of podophyllotoxin (with numbering and ring lettering systems), etoposide and teniposide

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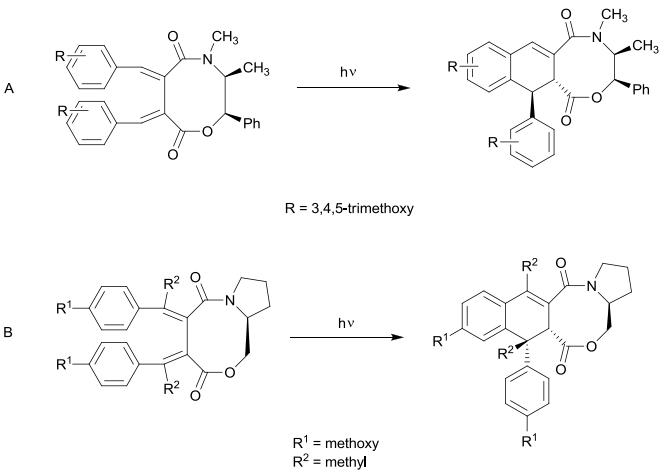
†Electronic Supplementary Information (ESI) available: NMR, UV spectra, photo of the system for "in-flow" photoreactions and crystallographic data. For ESI and crystallographic data in CIF see DOI: 10.1039/x0xx00000x



Scheme 1. The use of chiral auxiliaries in cyclolignans synthesis - A (-)-ephedrine[23] , B L-prolinol[24]

fulgenates),[19,20] there are only few examples where it was employed in the synthesis of cyclolignans.[21-23] In 2004 Charlton et al. used (-)-ephedrine as a chiral auxiliary to obtain a cyclic 3,4-bisbenzylidenesuccinic amide ester, which upon photocyclization resulted in enantiomerically pure (1*S*,2*R*)-*trans*-dihydronaphthalene (Scheme 1A).[23] Although 1,2-*cis*-dihydronaphthalene would have been the more desired product, it was shown that a bidentate chiral auxiliary could impose a single configuration of the pseudoenantiomeric 2,3-bisbenzylidenesuccinate by asymmetrically "pinning" the carboxylate moieties.

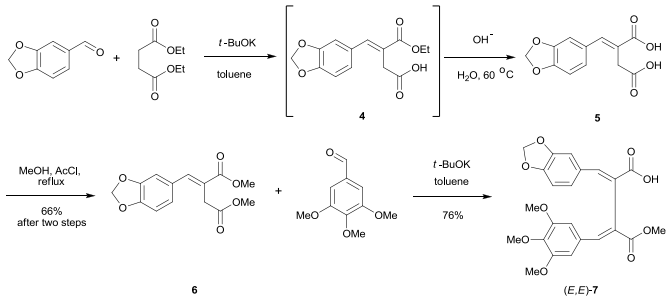
In a previous report,[24] we demonstrated that when L-prolinol is used instead of (-)-ephedrine, a (1*R*,2*R*)-*cis*-dihydronaphthalene is obtained as the major photocyclization product, which has the same stereochemical features at C-1 and C-2 as podophyllotoxin (Scheme 1B). Those results encouraged us to adapt this strategy for the synthesis of podophyllotoxin and its close analogues.

In order to study further transformations of 1,2-*cis*-dihydronaphtalenes, the key photoreaction in our synthetic scheme should be performed on a multigram scale. To meet this practical requirement we have decided to employ flow chemistry, which is known to be readily scalable.[25] Perhaps especially in the case of photochemical preparations, flow chemistry is an attractive alternative to batch synthesis, as it allows to overcome difficulties arising from the logarithmic decrease of light transmission through the reactive medium.[26] Precise tuning of only one parameter, i.e. the flow rate, enables residence time to be adjusted to avoid over-irradiation, which could lead to the formation of side products and photopolymers[27].

Results and discussion

Synthesis of 3,4-bisbenzylidenesuccinate cyclic amide ester 10

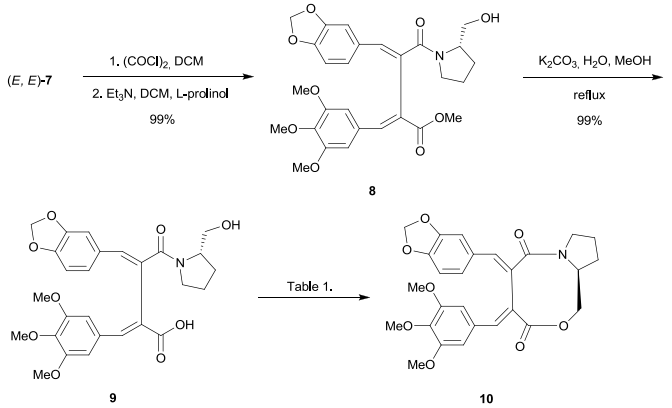
The methylenedioxy substituent forming ring A of podophyllotoxin and the 3,4,5-trimethoxyphenyl ring E are regarded as the "optimal" substituents responsible for the potent activity of podophyllotoxin derivatives. Our synthesis



Scheme 2. Double Stobbe condensation leading to bisbenzylidenesuccinic acid methyl monoester **7**

starts thus from the construction of a non-symmetric bisbenzylidenesuccinic acid derivative by means of a double Stobbe condensation. We have previously[24] found that the cyclization of 3,4-bisbenzylidenesuccinates occurred exclusively on the aryl ring adjacent to the amide moiety (Scheme 1B), which allowed us to rationally design our synthetic scheme. We take advantage of the excellent regioselectivity of the Stobbe condensation,[28] during which only one ester moiety (opposite to the introduced benzylidene group) is hydrolyzed. Diethyl succinate was thus first reacted with piperonal in the presence of *t*-BuOK in toluene, leading to the α,β-unsaturated ester **4** which was hydrolyzed to diacid **5** in a one-pot procedure. Fischer esterification of the crude product with MeOH gave the corresponding diester **6** in 66% yield after two steps. The dimethyl ester can be purified on a short column or by distillation under reduced pressure, which is beneficial in case of large scale preparations. The second condensation with 3,4,5-trimethoxybenzaldehyde proceeded in 76% yield to give the *E,E*-bisbenzylidenesuccinic acid monomethyl ester **7** (Scheme 2).

The chiral auxiliary was introduced using a one-pot protocol leading to the amide-ester **8**, which was subsequently hydrolyzed using K_2CO_3 in methanol/water to give the corresponding acid **9**. The whole reaction sequence gives the succinamic acid **9** in nearly quantitative overall yield (Scheme 3). The closing of the 8-membered ring *via* macrolactonization of **9** was optimized in a series of experiments, summarized in Table 1.



Scheme 3. The synthesis of cyclic amide-ester **10**

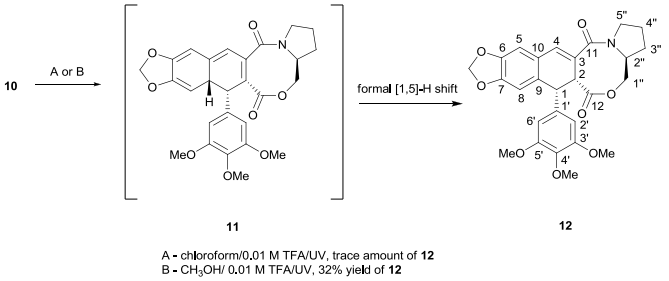
Table 1. Optimization of the macrolactonization reaction

Entry	Conditions	Isolated yield
1	BOP, DCM, 5 °C, 25 mM of **9**	60%
2	BOP, DCM, 25 °C, 25 mM of **9**	64%
3	BOP, THF, 25 to 60 °C, 25 mM of **9**	54%
4	BOP, toluene, 25 to 80 °C, 25 mM of **9**	25%
5	DCC, HOBT, DCM, 25 °C, 100 mM of **9**	23%
6	DCC, DMAP, DCM, -40 °C, 100 mM of **9**	64%
7	DCC, DMAP, DCM, 25 °C, 100 mM of **9**	46%
8	DCC, DMAP, DCM, 25 °C, addition with syringe pump	74%

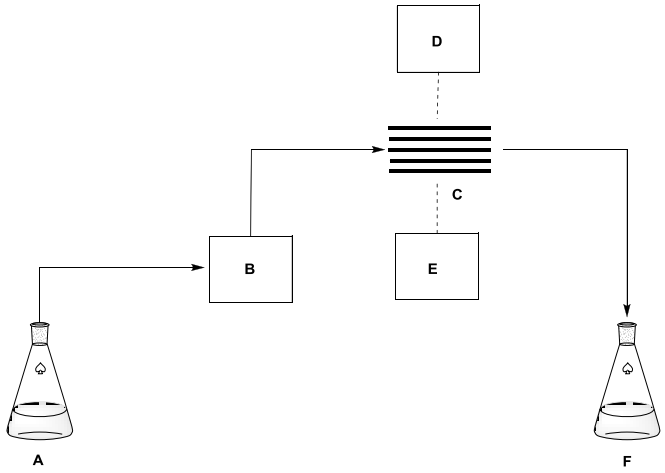
We found that both the coupling with (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and Steglich esterification[29] are possible alternatives for the macrolactonization of **9**. While the reaction with BOP was preferred for small scale preparations due to the simpler workup, the DCC/DMAP protocol is a more cost efficient alternative for large scale preparations, and also gave a slightly higher yield. As expected, high dilution conditions, achieved by slow addition of the substrate were beneficial since the undesired intermolecular reaction was suppressed.

Photocyclization of 10

Having product **10** in hand, we could start optimizing the conditions for photocyclization. The batch experiments were carried out in a quartz cuvette, which was irradiated for 1 h using a medium pressure mercury lamp (λ_{max}≈365 nm, Fig. S3 in the SI). At first, we tried the same conditions for irradiation as previously reported (1 mM solution irradiated in chloroform).[24] Under those conditions, however, only trace amounts of the desired product **12** were obtained, even after prolonged irradiation. Interestingly, upon irradiation, the reaction mixture quickly turned deep orange, indicating the formation of the intermediate **11** (Scheme 4A). The low yield of the reaction suggests that the sigmatropic hydrogen shift transforming intermediate **11** into product **12** is not likely to occur in the applied reaction conditions. In order to achieve the formal [1-5]-H shift we decided to use a protic solvent. Solvent protonation at C-2 was previously described as an alternative mechanism to a concerted [1,5]-sigmatropic hydrogen shift.[19] Indeed, we succeeded to obtain the desired product **12** when the irradiation was performed in methanol. Further experiments confirmed, that the use of an acidic additive (0.01 mM TFA) further accelerated the reaction, and helped avoid excessive photolytic degradation, as proposed previously by Charlton.[22] We also found that the relatively strong absorption of dihydronaphthalene lignans in the UV region (Fig. S1 in the SI), may result in an inner filter effect leading to photodegradation upon prolonged irradiation. Indeed, the batch synthesis could be completed significantly faster when the substrate was irradiated at high dilution, which also led to an increased yield of **12**, probably by minimizing photodegradation. Although we managed to obtain product 12 with 32% yield (Scheme 4B),



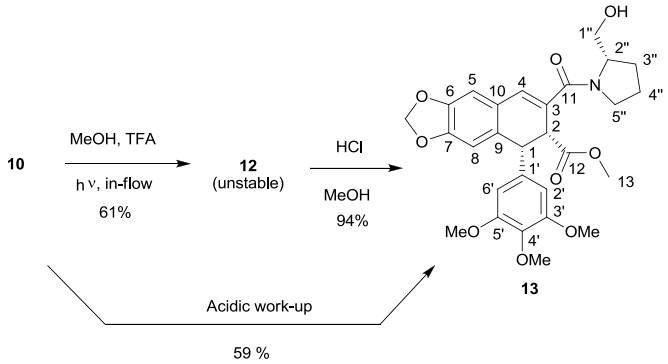
Scheme 4. Irradation of **10** leading to cyclolignan structure



Scheme 5. Block diagram showing components of the system for photoreactions "in flow". A - substrate tank; B - HPLC pump; C - quartz reactor; D - UV source; E - cooler, F - product tank

the high dilution conditions make the batch synthesis inefficient, due to the time consuming work up.

We therefore decided to use a simple home-made apparatus for continuous flow irradiation (Scheme 5; Figure S2). The apparatus consists of a quartz tube, which is multiply folded to form a rectangular reactor. The reactor was placed in front of the window of the mercury lamp. The diagonal of the lamp window was ca. 18 cm and the total length of the quartz tube within the reactor was ca. 3 m. A solution of **10** in MeOH containing 0.01 mM of TFA was pumped through the reactor, which was placed ca. 3 cm away from the UV light source. To precisely regulate the flow, we used a HPLC pump, but a simple peristaltic pump is a possible alternative. To avoid overheating of the irradiated solution of the sample, we cooled the tube with a stream of air during the irradiation (the temperature at the surface of the reactor was ca. 30 °C). The use of a quartz tube allowed us to use relatively high flow velocities: a 0.4 mM solution of **10** in methanol containing 0.01 mM TFA could be irradiated at a flow rate of 0.7 mL/min. These conditions allowed us to obtain compound **12** with an isolated yield of 61%. The continuous flow process is easily scalable and the excessive solvent can be quantitatively recycled.



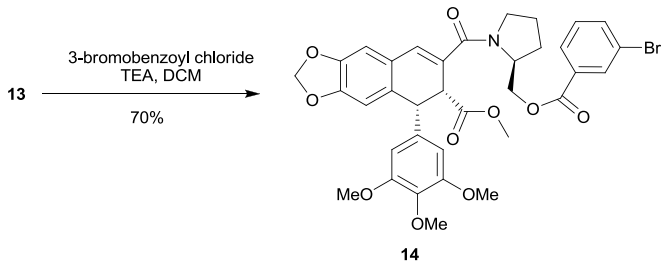
Scheme 6. Synthesis of stable derivative **13** from compound **10** through unstable intermediate and in direct acidic work-up procedure

The resulting product **12** proved to be unstable - upon prolonged exposure to air, aromatization of the C ring occurs.

We found that the strained 8-membered ring can easily be opened by methanolysis, which proceeds with very good yield (94%) to give the stable product **13**. Since the conditions for the methanolysis are essentially the same as for the irradiation, we found that photocyclization and transesterification can be carried out during direct acidic work-up, which was more practical (Scheme 6).

We were not able to grow a crystal of neither **12** nor **13**. To determine the configuration of **12** at C-1 and C-2, we therefore performed 2D NMR experiments (HSQC, HMBC, and ROESY).

From the HSQC and HMBC spectra it can be concluded that the proton at C-1 appeared as a doublet of doublets at 4.42 ppm, whereas the proton at C-2 as a doublet at 3.88 ppm. In the ROESY spectrum an interaction between those protons was observed, indicating that the relative configuration at C-1 and C-2 must be *cis*. In order to obtain crystals suitable for X-ray analysis to unequivocally determine the regio- and stereoselectivity of the photocyclization, we decided to derivatize the stable ester **13** (Scheme 7). A monocrystal suitable for X-ray diffraction analysis could be grown by slow evaporation of a methanol solution of **14**. As expected, the absolute configuration at C-1 and C-2 turned out to be the same as in **1** (1*R*, 2*R*) (Fig. 2.).



Scheme 7. Synthesis of **14**

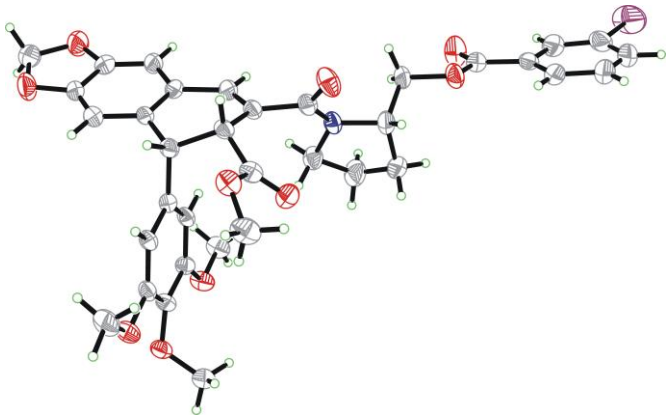


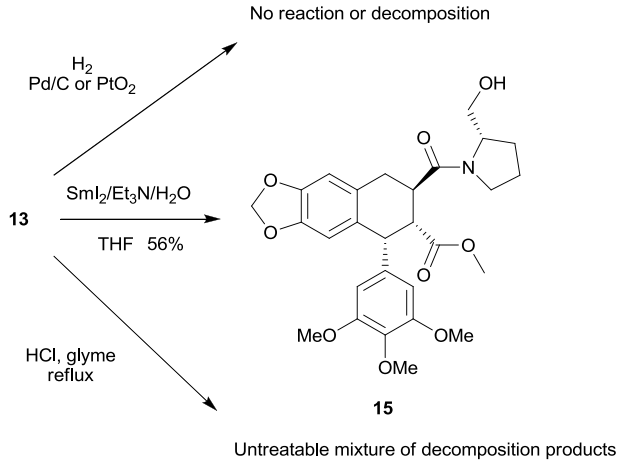
Figure 2. ORTEP diagram of compound **14**. The non-H atoms are shown as 30% probability ellipsoids

Removal of the chiral auxiliary

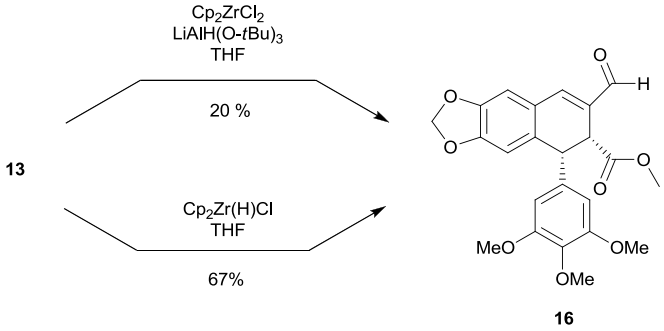
Our initial attempt was to remove the chiral auxiliary by acid catalyzed hydrolysis, since basic hydrolysis is known to result in epimerization at C-2. Although similar amides could be hydrolyzed at 85 °C in 5 M HCl/glyme,[30] amide ester **13** was converted into an untreatable mixture of decomposition products.

Procter et al. have recently reported a mild method for the reduction of tertiary amides to alcohols using the SmI_2/amine/H_2O reducing system.[31] It was expected that SmI_2 would in the first place lead to the reduction of the double bond and we hoped that the excess of reducing complex would be capable of amide cleavage. Although the latter proved not true, we were able to successfully reduce the double bond, yielding product **15** with 56% yield. Interestingly, only one diastereomer of **15** was obtained. The coupling constant of ^3J = 16.8 Hz indicates the *trans* configuration of the substituents at C-3 and C-2 atoms. The SmI_2/amine/H_2O system could thus be a competitive method for the reduction of aryldihydronaphthalenes to aryltetralines (Scheme 8). Interestingly, our attempts to hydrogenate **13** over Pd or Pt proved unsuccessful (a complex mixture of products was obtained).

As both acid hydrolysis and the reduction of the amide to the alcohol have failed, we decided to use the Schwartz's reagent ($Cp_2Zr(H)Cl$), which is known to reduce tertiary amides to the corresponding aldehydes.[32,33] The advantage of this reaction is its compatibility with many functional groups, including esters and double bonds. Very recently Snieckus[34] reported that *in situ* generation of the Schwartz's reagent overcomes the disadvantage of this reagent related to the contamination with unreacted reducing agent (which may react with the substrate and the intermediates) and over-reduced Cp_2ZrH_2. Considering this, we decided to compare the reaction of **13** with commercially available Schwartz's reagent with *in situ* generated complex (Scheme 9).

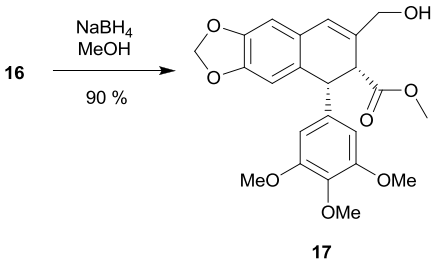


Scheme 8. Reactions of **13** with hydrogen, HCl and $SmI_2/Et_3N/H_2O$ reducing system



Scheme 9. Reduction of **13** to aldehyde using commercially available Schwartz's reagent and *in situ* generated reagent

We discovered that the reduction of amide **13** to aldehyde **16** is more efficient with commercially available Schwartz's reagent (67% yield). The low yield of the reaction with *in situ* generated complex may be caused by the formation of a coordinated $Al(O\text{-}tBu)_3$-Schwartz's reagent species, which provides additional steric hindrance in the reduction process.[34]
It is noteworthy that aldehyde **16** shows potent cytotoxicity and its benzimidazole derivatives, obtained by condensation with o-phenyldiamines, were proven to be inhibitors of tubulin polymerization.[35] To complete the formal synthesis of **1**, the aldehyde **16** must be reduced to alcohol (+)-**17** which is a chiral intermediate in the Thompson synthesis of rac-**1**.[36,37] Simple reduction with $NaBH_4$ proved successful, leaving the methyl ester moiety intact. As expected, no epimerization at C-2 was observed[35] (Scheme 10) and the desired product was obtained with 90% yield.
By synthesizing compound (+)-**17** we have also completed the formal synthesis[37] of (1*R*, 2*R*)-podophyllic aldehyde, a cytotoxic C-2 epimer of **16**, which exhibits high selectivity towards human colon carcinoma and is a starting material in the synthesis of cytotoxic, C-9 oxidized podophyllotoxin derivatives.[38]



Scheme 10. Reduction of the aldehyde **16** using $NaBH_4$

Conclusions

We have completed the formal synthesis of (-)-**1** by preparing compound **17** from piperonal in 9 steps with 13% overall yield, using L-prolinol as the source of chirality. The crucial step of the synthesis, a photocyclization, was optimized to be performed in continuous flow, which showed clear advantages over batch photochemical synthesis. In comparison to previous total syntheses of podophyllotoxin our approach employs exclusively cheap and easily available substrates, and avoids the use of sophisticated organocatalysts or heavy metal catalysts. It can be assumed that our synthetic strategy allows various substitution patterns on rings B, C and E (*e.g.* the introduction of an additional substituent at C-1)[24], thus granting access to cyclolignan analogs which are inaccessible from natural plant sources.

Experimental section

General Experimental Methods

All chemicals were purchased from Sigma-Aldrich and used as received. Piperonal, 3,4,5-trimethoxybenzaldehyde and *t*-BuOK were flushed with dry argon and kept under inert atmosphere after every use. Toluene was dried by boiling for ca. 2 h with pieces of Na metal and subsequent distillation, and was stored over activated molecular sieves, 3Å. Methanol was dried with KOH powder for 24 h, distilled and was stored over activated molecular sieves, 3Å. Dichloromethane (DCM) was dried by storing it over activated molecular sieves, 3Å, for at least 3 days. TLC analysis was performed on Merck TLC plates (silica gel 60 F_{254} on glass plates). ^{1}H-NMR and ^{13}C-NMR spectra were recorded with Bruker AVANCE 500/300 spectrometer. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in $CDCl_3$ solution. High-resolution mass (ESI-TOF MS) spectra were run on the Micromass LCT spectrometer.

E-(3,4-methylenedioxybenzylidene)butanedioic acid (5)

To an oven dried 500 mL three-neck round-bottom flask, equipped with a large stirring bar and flushed with argon, 30.0 g (6.67 eq, 0.26 mol) of *t*-BuOK were inserted and suspended in 150 mL of dry toluene. To the vigorously stirring suspension a solution of 18.0 g (1.33 eq, 0.12 mol) of piperonal and 15.7 g (1 eq, 0.09 mol) of diethyl succinate in 200 mL of dry toluene were added dropwise. The color of the suspension changed

immediately from white to yellow, and later to brown. After complete addition, the suspension was stirred for another 1.5 h. The reaction mixture was then transferred into a 1 L round-bottom flask and the solvent was removed on a rotary evaporator. The reaction flask was washed with 200 mL of water and a minimal amount (ca. 40 mL) of ethanol and the liquids were added to the solid residue in the 1 L flask. The obtained dark solution was placed on a rotary evaporator in a water bath at 60 ^{o}C and rotated without vacuum for 1h to completely hydrolyze the remaining ethyl esters. After the indicated time, vacuum was applied carefully to evaporate ethanol and ca. 40 mL of the water. The dark aqueous solution was cooled to room temperature and transferred to a separatory funnel. The flask was washed with a total of ca 40 mL of water and 100 mL of AcOEt. The mixture was extracted with small portions of AcOEt until the extracts were completely colorless. All extracts were discarded, and the aqueous layer was acidified to ca. pH 2 with small portions of concentrated HCl. The precipitating diacid was extracted with small portions (ca. 25 mL) of AcOEt until the obtained extracts were colorless (typically 6-10 times). The aqueous layer was discarded and the combined organic layers were washed once with distilled water, once with brine and then dried over anhydrous sodium sulphate. After filtration and solvent removal a dense yellow gum was formed. The product was used for the next reaction without further purification. HRMS (ESI-TOF) m/z: calcd for $C_{12}H_{10}O_6Na$ $[M+Na]^+$, 273.0375; found, 273.0367

Dimethyl 2*E*-(3,4-methylenedioxybenzylidene)butanedioate (6)

In a round bottom flask of 250 mL, equipped with a stirring bar and under argon atmosphere, 18.2 g (1 eq, 72.8 mmol) of crude diacid **5** were placed and 150 mL of dry MeOH was added. The vigorously stirred suspension was cooled in a water-ice bath, and 30 mL of AcCl was added dropwise. After addition of a few mL of AcCl the solid has dissolved completely, and the solution changed its color from yellowish to orange. The ice bath was replaced with an oil bath, and the flask was equipped with a reflux condenser protected from moister. The temperature of the oil bath was set to 80 ^{o}C. The reaction mixture was refluxed for 12 h, and was then transferred into a 500 mL round bottom flask. Most of the solvent was removed on a rotary evaporator and the residue was cooled in ice-water bath. The reaction flask was washed with 100 mL of ice-cold distilled water, which was then added to the cooled residue, shaken until all the solids had dissolved and was transferred into a separatory funnel. The flasks were washed with 2 more portions (50 mL each) of ice-cold water. The joined liquids were extracted four times with small portions of AcOEt, and the combined organic layers were washed once with distilled water, once with brine and then dried over anhydrous magnesium sulphate. After filtration and solvent removal, the resulting oil was purified on a silica gel column, using AcOEt in n-hexane (gradient, from 0% to 12%) as an eluent. The product was crystallized from mixture of *n*-hexane and 2-propanol (10:1 v/v) and 13.33 g (0.048 mol, 66 % over 2 steps) of yellowish crystalline solid was obtained. M.p. 72.8 – 73.7 ^{o}C. **^{1}H NMR** ($CDCl_3$ with 0.03% v/v TMS, 500 MHz): δ 7.79 (s, 1H), 6.87 – 6.84 (m, 2H), 6.82 (dd, *J* = 7.6, 0.9 Hz, 1H), 5.98 (s, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 3.54 (s, 2H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 171.6, 167.9, 148.3, 147.9, 141.9, 128.8, 124.4, 124.0, 109.1, 108.6, 101.4, 52.2, 52.2, 33.5. HRMS (ESI-TOF) m/z: calcd for $C_{14}H_{14}O_6Na$ $[M+Na]^+$, 301.0688; found, 301.0694

2*E*-(3,4-methylenedioxybenzylidene)-3*E*-(3,4,5-trimethoxybenzylidene)butanedioic acid monomethyl ester (7)

To an oven dried 250 mL three-neck round-bottom flask, equipped with a stirring bar and flushed with argon, 2.22 g (1.1 eq, 19.77 mmol) of t-BuOK were inserted, and was suspended in 65 mL of dry toluene. To the vigorously stirring suspension, a solution of 3.53 g (1 eq, 17.97 mmol) of 3,4,5-trimethoxybenzaldehyde and 5.0 g (1 eq, 17.97 mmol) of ester **6** in 50 mL of dry toluene were added dropwise. The color of the suspension changed immediately from white to yellow, and later to brown. After complete addition, the suspension was stirred for another 1.5 h. The reaction mixture was then poured into ice and the reaction flask was washed with ice-cold distilled water, which was then added to the cooled residue and was transferred into a separatory funnel. The mixture was extracted three times with small portions of AcOEt. All those extracts were discarded, and the aqueous layer was acidified to ca. pH 2 with small portions of concentrated HCl. The precipitating acid was extracted with small portions of AcOEt until the obtained extracts were colorless. The aqueous layer was discarded and the combined organic extracts were washed once with distilled water, once with brine and then dried over anhydrous sodium sulphate. After filtration and solvent removal, the resulting oil was purified on a short silica gel column, using MeOH in $CHCl_3$ (gradient, from 0% to 1%) as an eluent. The product was dissolved in 100 mL of diethyl ether and was precipitated from n-hexane. The precipitated solid was filtered and dried in a desiccator to give 6.04 g (13.66 mmol, 76 %) of a white crystalline solid. M.p. 154.3 – 156.1 ^{o}C. **^{1}H NMR** ($CDCl_3$ with 0.03% v/v TMS, 500 MHz): δ 7.91 (s, 1H), 7.85 (s, 1H), 7.05 (d, *J* = 1.7 Hz, 1H), 7.03 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.78 (s, 2H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.96 (d, *J* = 1.4 Hz, 1H), 5.95 (d, *J* = 1.4 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.73 (s, 6H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 172.2, 167.2, 153.0, 149.6, 148.2, 144.1, 142.9, 139.6, 129.6, 128.4, 126.8, 124.9, 123.8, 108.8, 108.6, 107.3, 101.6, 60.9, 55.9, 52.6. HRMS (ESI) m/z: calcd for $C_{23}H_{22}O_9Na$ $[M+Na]^+$, 465.1161; found, 465.1180

Monomethyl (*S*)-(+)-2-pyrrolidinemethanol-2*E*-(3,4-methylenedioxybenzylidene)-3*E*-(3,4,5-trimethoxybenzylidene)butanediate amide ester (8)

Warning: oxalyl chloride is corrosive and forms toxic vapors. Special attention should be granted when working with this reagent. In a Schlenk tube of 50 mL, equipped with a stirring bar, 500 mg (1.0 eq, 1.13 mmol) of the monoester **7** were placed and put under argon atmosphere. The substrate was

dissolved in 20 mL of dry DCM and cooled on a water-ice bath with vigorous stirring. To the cooled solution, 195 µL (2.0 eq, 2.26 mmol) of oxalyl chloride was added in one portion. The reaction was allowed to reach room temperature and was stirred for 2 h. After this time, the solvent was removed on a rotary evaporator, which was vented with argon. The oily residue was dissolved in 10 mL of dry DCM and added dropwise, under argon, to a stirring solution of L-prolinol (120 mg, 1.05 eq, 1.19 mmol) and triethylamine (0.47 mL, 340 mg, 3.00 eq, 3.4 mmol) in 5 mL of dry DCM. The resulting solution was allowed to stir for 1 h and the solvent was evaporated. The residue was dissolved in 20 mL of AcOEt and washed with 10 mL of water, and back-extracted with 10 mL of AcOEt. The combined organic layers were washed with 10 mL of 10% citric acid solution, 10 mL of a 5% solution of $NaHCO_3$ and 10 mL of brine. The organic layer was dried with anhydrous sodium sulphate and filtered. After removal of the solvent on a rotary evaporator, 593 mg (1.12 mmol, 99%) of an amorphous solid was obtained. The product had a purity of at least 97% according to the ^{1}H NMR spectrum and can be used for the next step without further purification. Trace impurities however, can be removed on a silica gel column, using MeOH in $CHCl_3$ (gradient, from 0% to 2%) as an eluent. $[\alpha]_D^{25}$ = +423.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$ with 0.03% v/v TMS, 500 MHz): δ 7.72 (s, 1H), 6.95 – 6.46 (m, 6H), 5.92 (s, 2H), 4.15 (br s, 2H), 3.83 (s, 3H), 3.80 (br s, 9H), 3.68 (s, 3H), 3.27 (br s, 1H), 2.02 (s, 1H), 1.80 (br d, 2H), 1.44 (br s, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 167.3, 166.8, 153.0, 147.9, 147.6, 143.8, 130.4, 130.3, 129.7, 126.9 126.5, 123.9, 123.8, 108.3, 108.2, 106.7, 101.3, 61.7, 61.3, 60.9, 56.1, 52.4, 31.6, 25.3, 22.6. HRMS (ESI-TOF) m/z: calcd for $C_{28}H_{31}NO_9Na$ $[M+Na]^+$, 548.1896; found, 548.1879.

(*S*)-(+)-2-pyrrolidinemethanol-2*E*-(3,4-methylenedioxybenzylidene)-3*E*-(3,4,5-trimethoxybenzylidene)butanedioic acid amide (9)

In a 50 mL round bottom flask, 1.24 g (1 eq, 2.36 mmol) of amide ester **8** was dissolved in 15 mL of MeOH. The solution was stirred magnetically, and a solution of 1,63 g (5 eq, 11.8 mmol) of K_2CO_3 in 20 mL of water was added dropwise, which resulted in the formation of a yellowish suspension. After complete addition, the dropping funnel was replaced with a reflux condenser and the flask was kept in an oil bath at 80 °C for 3 h. During this time, the suspension turned into a clear orange solution. After complete reaction, the solution was cooled and the MeOH was removed on a rotary evaporator. The aqueous solution was transferred into a separatory funnel. The aqueous layer was extracted twice with AcOEt, and the extracts were discarded. The aqueous layer was acidified by slow addition of 15 mL of 10% citric acid during which the product precipitates as an oil. The product was extracted 5 times with 10 mL of AcOEt, and the combined organic fractions were washed with brine and dried with anhydrous sodium sulphate. After filtration and removal of the solvent, 1.20 g (2.34 mmol, 99%) of the acid **9** were obtained in the form of a yellowish, amorphous solid. The product contains only trace impurities and can be used in the next step without further purification. $[\alpha]_D^{25}$ = +151.7 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$ with 0.03% v/v TMS, 300 MHz): δ 7.81-7.54 (m, 2H), 7.18-6.84 (m, 2H), 6.79 (d, J = 11.0 Hz, 1H), 6.75-6.59 (m, 2H), 5.89 (s, 2H), 4.85 (br s, 1H), 3.98 (br d, 1H), 3.87-3.75 (m, *3*H), 3.69 (dd, J = 10.9, 2.9 Hz), 3.34 (s, 3H), 3.16 (br s, 1H), 2.22 – 1.54 (m, 4H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 166.3, 165.9, 152.8, 147.7, 146.6, 140.9, 130.3, 130.2, 128.4, 127.0, 124.3, 119.6, 117.6, 109.1, 107.3, 106.9, 106.7, 101.3, 61.5, 61.1, 60.9, 56.1, 56.0, 55.7, 25.2, 22.6. HRMS (ESI-TOF) m/z: calcd for $C_{27}H_{28}NO_9$ $[M-H]^-$, 510.1764; found, 510.1780.

2*E*-(3,4-methylenedioxybenzylidene)-3*E*-(3,4,5-trimethoxybenzylidene)butanediate (*S*)-(+)-2-pyrrolidinemethanol cyclic amide ester (10)

To a solution of 6.05 g (29.4 mmol, 1.5 equiv) of DCC and 2.65 g (21.6 mmol, 1.1 equiv) of DMAP in 80 mL of dry DCM, a solution of 10.0 g (19.6 mmol) of **9** in 40 mL of DCM was added dropwise using a syringe pump. The addition was completed during approx. 4 h and the reaction mixture was allowed to stirr for 1 h. After this time, the resulting suspension was filtered at atmospheric pressure and the filtrate was concentrated under vacuum. The residue was dissolved in AcOEt and filtered. The resulting filtrate was washed twice with 0.5 N HCl and twice with saturated aqueous $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The resulting oil was purified by column chromatography (isocratic elution, $CHCl_3$). The product was precipitated from *n*-hexane to give 7.16 g (14.5 mmol, 74 %) of a yellowish crystalline solid. M.p. 103.8 – 104.2 °C. $[\alpha]_D^{25}$ = +949.4 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$ with 0.03% v/v TMS, 500 MHz): δ 7.54 (s, 1H), 7.47 (s, 1H), 7.11 (d, *J* = 1.8 Hz, 1H), 7.05 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.03 (s, 2H), 6.76 (d, *J* = 8.1 Hz, 1H), 5.95 (d, *J* = 1.4 Hz, 1H), 5.93 (d, *J* = 1.4 Hz, 1H), 4.62 (dd, *J* = 13.9, 4.9 Hz, 1H), 4.31 (d, *J* = 13.8 Hz, 1H), 4.05 (dq, *J* = 11.5, 5.9 Hz, 1H), 3.88 (s, 6H), 3.85 (s, 3H), 3.58 – 3.40 (m, 2H), 2.29 (dt, *J* = 12.1, 5.3 Hz, 1H), 1.91 (dt, *J* = 11.6, 5.8 Hz, 1H), 1.78 – 1.51 (m, 2H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 168.13, 167.15, 153.14, 149.16, 148.14, 145.60, 140.94, 140.26, 128.65, 128.08, 126.57, 126.06, 124.37, 109.16, 108.56, 108.38, 101.51, 73.45, 60.85, 59.63, 56.34, 48.10, 34.54, 22.46. HRMS (ESI-TOF) m/z: calcd for $C_{27}H_{27}NO_8Na$ $[M+Na]^+$, 516.1635; found, 516.1648.

2*E*-(3,4-methylenedioxybenzylidene)-3*E*-(3,4,5-trimethoxybenzylidene)butanediate (*S*)-(+)-2-pyrrolidinemethanol cyclic amide ester (10)

6.3 g (12.3 mmol) of acid **9** was dissolved in 500 mL of DCM and the resulting yellow solution was stirring vigorously at room temperature. 8.17 g (18.5 mmol, 1.5 equiv) of BOP was added in a single portion, followed by the addition of 5.15 mL of triethylamine (3.74 g, 37 mmol, 3 equiv). After 1.5 h of stirring at room temperature the reaction mixture was concentrated under vacuum and the resulting residue was dissolved in DCM. This solution was extracted thrice with 10% aq citric acid, thrice with 5% aq $NaHCO_3$ and once with distilled water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The resulting oil was purified on

a short column, in the same conditions as described above, to give 3.88 g (7.87 mmol, 64 %) of compound **10**.

(1*R*,2*R*)-1-(3,4,5-trimethoxyphenyl)-6,7-methylenedioxy-1,2-dihydronaphthalene-2,3-dicarboxylate (*S*)-(+)-2-pyrrolidinemethanol cyclic amide ester (12)

In a 50 mL quartz cuvette, 25 mg (0.051 mmol) of compound **10** was dissolved in 50 mL of MeOH. The solution was flushed with dry argon for 10 minutes, and 38 µL (final concentration 0.01 M) of TFA was added. The reaction mixture was irradiated for 1 h, using a medium pressure mercury lamp. During the irradiation, the solution was vigorously flushed with dry argon, which guaranteed constant mixing of the solution. The color of the reaction mixture changed within the first 20 s of irradiation from colorless to yellow. During the irradiation the solution became strongly blue-fluorescent. After 1 h of irradiation, the TLC analysis showed complete disappearance of the starting material. The solution was transferred into a round bottom flask and the solvent was removed under vacuum. The resulting yellow oil was purified on a silica gel column under dry argon, using degassed AcOEt in degassed DCM (gradient, from 0% to 40%) as an eluent. 8 mg (0.016 mmol, 32 %) of product **12** was obtained in the form of a white, UV-fluorescent gum. $[\alpha]_D^{25}$ = +720.7 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$ with 0.03% v/v TMS, 500 MHz): δ 6.72 (br s, 2H, C-2', C-6'), 6.63 (s, 1H, C-5), 6.57 (d, *J* = 1 Hz, 1H, C-8), 6.50 (s, 1H, C-4), 5.92 (d, *J* = 1.4 Hz, 1H, -O-CH_2-O-), 5.90 (d, *J* = 1.4 Hz, 1H, -O-CH_2-O-), 4.42 (dd, *J* = 6.5, 1.0 Hz, 1H, C-1), 4.31 (dd, *J* = 11.1, 4.5 Hz, 1H, C-1''), 4.15 – 4.04 (m, 1H, C-2''), 3.88 (d, *J* = 6.5 Hz, 1H, C-2), 3.85 (s, 3H, -OCH_3), 3.80 (s, 6H, 2x -OCH_3), 3.61 (dd, *J* = 8.8, 5.3 Hz, 2H, C-5''), 3.23 (t, *J* = 11.2 Hz, 1H, C-1''), 2.17 – 1.90 (m, 3H, C-3'', C-4''), 1.69 – 1.59 (m, 1H, C-3''). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 171.1 (C-12), 169.5 (C-11), 153.2 (C-3', C-5'), 148.3 (C-7), 146.1 (C-6), 137.2 (C-1'), 134.6 (C-3), 131.0 (C-4'), 130.5 (C-9), 129.2 (C-4), 124.8 (C-10), 108.2 (C-5), 108.1 (C-8), 107.3 (C-2', C-6'), 101.2 (-O-CH_2-O-), 65.0 (C-1''), 60.8 (-OCH_3), 56.5 (C-2''), 56.0 (–OCH_3), 51.3 (C-2), 46.9 (C-1), 45.1 (C-5''), 26.9 (C-3''), 22.3 (C-4''). HRMS (ESI-TOF) m/z: calcd for $C_{27}H_{27}NO_8Na$ $[M+Na]^+$, 516.1635; found, 516.1627.

(1*R*,2*R*)-1-(3,4,5-trimethoxyphenyl)-6,7-methylenedioxy-1,2-dihydronaphthalene-2,3-dicarboxylate (*S*)-(+)-2-pyrrolidinemethanol cyclic amide ester (12)

In a 1 L flat bottom flask, 200 mg (1 eq., 0.405 mmol) of compound **10** was dissolved in 1.0 L of degassed MeOH and 740 µL of TFA (final concentration 0.01 M) was added. The solution was pumped through a multiply folded quartz tube, which was irradiated from the side with a medium pressure mercury lamp. To achieve a constant pumping speed, a HPLC pump was employed, and the flow rate was set to 0.7 mL/min. To avoid overheating of the solution inside the quartz tubing of the flow reactor, the solution was cooled with a stream of air. The irradiated solution was collected in a 2 L round bottom flask. After all the mixture had passed through the flow-reactor, the solvent was removed under vacuum. The resulting yellow oil was purified as described above 122 mg (0.247 mmol, 61 %) of product was obtained in the form of a white, UV-fluorescent gum.

Monomethyl (*S*)-(+)-2-pyrrolidinemethanol-(1*R*,2*R*)-1-(3,4,5-trimethoxyphenyl)-6,7-methylenedioxy-1,2-dihydronaphthalene-2,3-dicarboxylate amide ester (13)

In a round bottom flask of 50 mL, equipped with a stirring bar and under argon atmosphere, 135 mg (1 eq, 0.274 mmol) of compound **12** was dissolved in 20 mL of dry MeOH saturated with HCl. The solution was stirred for 45 min at 40 °C. The solvent was removed on a rotary evaporator. The residue was dissolved in a small portion of dry toluene, which was then also evaporated in vacuum, along with traces of HCl. The resulting oil was purified on a silica gel column, using EtOAc in DCM (gradient, from 0% to 45%) as an eluent. The product was precipitated from n-hexane to give 136 mg (0.258 mmol, 94 %) of a white, UV-fluorescent amorphous solid. M.p. 102.5 – 104.2 °C. $[\alpha]_D^{25}$ = -47.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$ with 0.03% v/v TMS, 500 MHz): δ 6.69 (s, 1H, C-5), 6.66 (d, *J* = 2.4 Hz, 1H, C-4), 6.58 (s, 1H, C-8), 6.32 (s, 2H, C-2', C-6'), 5.96 (d, *J* = 1.4 Hz, 1H, -O-CH_2-O-), 5.95 (d, *J* = 1.4 Hz, 1H, -O-CH_2-O-), 4.62 (s, 1H, -OH), 4.42 (d, *J* = 8.3 Hz, 1H, C-1), 4.38 (dd, *J* = 8.4, 2.4 Hz, 1H, C-2), 4.20 (dtd, *J* = 9.7, 7.6, 2.4 Hz, 1H, C-2''), 3.86 – 3.80 (br m, 1H, C-5''), 3.78 (s, 3H, -OCH_3), 3.78 (m, 1H, C-1''), 3.73 (s, 6H, 2x –OCH_3), 3.61 (m, 1H, C-1''), 3.49 (s, 3H, C-13), 3.56 – 3.43 (m, 1H, C-5''), 2.15 – 2.05 (m, 1H, C-3''), 1.90 – 1.76 (m, 1H, C-4''), 1.74 – 1.49 (m, 2H, C-3'', C-4''). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 172.7 (C-11), 171.6 (C-12), 152.9 (C-3', C-5'), 148.5 (C-7), 147.0 (C-6), 137.3 (C-1'), 135.2 (C-3), 130.5 (C-4'), 129.6 (C-9), 129.5 (C-4), 125.0 (C-10), 109.3 (C-8), 107.8 (C-5), 105.9 (C-2', C-6'), 101.4 (-O-CH_2-O-), 67.3 (C-1''), 61.0 (C-2''), 60.8 (-OCH_3), 56.0 (-OCH_3), 51.8 (C-13), 50.7 (C-5''), 49.1 (C-2), 46.7 (C-1), 28.5 (C-3''), 24.8 (C-4''). HRMS (ESI-TOF) m/z: calcd for $C_{28}H_{31}NO_9Na$ $[M+Na]^+$, 548.1896; found, 548.1914.

Monomethyl (*S*)-(+)-2-pyrrolidinemethanol-(1*R*,2*R*)-1-(3,4,5-trimethoxyphenyl)-6,7-methylenedioxy-1,2-dihydronaphthalene-2,3-dicarboxylate amide ester (13) – acidic work-up

The continuous flow irradiation was carried out as described above. After the whole solution left the microreactor, most of the solvent was removed under vacuum, to leave a volume of ca. 20 mL. This solution was transferred into 100 mL round bottom flask and supplemented with dry methanol saturated with HCl to a final volume of 30 mL.The flask was placed on an oil bath, and stirred for 1 h at 40 °C. The solvent was subsequently removed on a rotary evaporator and the residue was dissolved in a small amount of dry toluene, which was also evaporated in vacuum, along with traces of HCl. The resulting oil was purified on a silica gel column as described above, to give 125 mg (0.238 mmol, 59 %) of a white, UV fluorescent amorphous solid.

Monomethyl (*S*)-pyrrolidin-2-ylmethyl 3-bromobenzoate-(1*R*,2*R*)-1-(3,4,5-trimethoxyphenyl)-6,7-methylenedioxy-1,2-dihydronaphthalene-2,3-dicarboxylate amide ester (14)

To a stirring solution of 47 mg (0.089 mmol) of **13** in DCM, 12.4 µL (1 equiv) of TEA and 12.3 µL (1.05 equiv) of 3-bromobenzoyl chloride were added at room temperature. After 2 h of stirring, the reaction mixture was poured into an ice-water mixture. The organic phase was washed once with 10% citric acid and twice with water. After purification by column chromatography (SiO_2, EtOAc:DCM 15:85) 44 mg (0.062 mmol, 70 %) of product was obtained. Crystals suitable for X-ray analysis were grown by slow evaporation of the methanol solution. M.p. 181.0 – 182.5 °C. $[\alpha]_D^{25}$ = -46.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$ with 0.03% v/v TMS, 500 MHz): δ 8.18 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.71 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 6.67 (s, 1H), 6.63 – 6.58 (m, 1H), 6.57 (s, 1H), 6.32 (s, 2H), 5.96 (d, *J* = 1.4 Hz, 1H), 5.94 (d, *J* = 1.3 Hz, 1H), 4.53 (br s, 1H), 4.47 (br s, 2H), 4.41 (s, 2H), 3.78 (s, 4H), 3.73 (s, 6H), 3.55 (br s, 1H), 3.49 (s, 3H), 2.19 – 2.06 (m, 1H), 2.00 – 1.84 (m, 2H), 1.84 – 1.72 (m, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 172.2 (not observed), 171.7, 165.1, 152.9, 148.5, 147.0, 137.4, 136.0, 135.4, 132.6, 132.1, 130.6, 130.1, 129.9, 128.3, 125.2, 122.5, 109.3, 108.0 (not observed), 105.9, 101.4, 67.8 (not observed), 61.1 (not observed), 60.8, 56.1, 51.8, 50.7 (not observed), 49.1, 46.8, 28.9 (not observed), 24.9 (not observed). HRMS (ESI-TOF) m/z: calcd for $C_{35}H_{34}BrNO_{10}Na$ $[M+Na]^+$, 730.1264; found, 730.1279. The detailed structural parameters have been deposited with the Cambridge Crystallographic Data Centre under the number CCDC 1415848.

Monomethyl (*S*)-(+)-2-pyrrolidinemethanol-(1*R*,2*R*)-1-(3,4,5-trimethoxyphenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate amide ester (15)

62 mg (1 eq, 0.118 mmol) of product **13** and a stirring bar were placed in a 15 mL Schlenk tube under argon atmosphere. Dry THF (1.2 mL) was added, and the solution was stirred vigorously. Samarium Iodide solution (8,3 mL, 7 eq, 0.83 mmol) was added in a single portion, followed by the addition of 1035 µL of triethylamine (751 mg, 63 eq, 7.43 mmol) and 134 µL of water (63 eq, 7.43 mmol). Immediately after the addition of water, the color of the reaction mixture changed from dark brown to white. TLC analysis showed complete disappearance of the starting material. The reaction was stirred for 1 more h at room temperature and the suspension was then poured into 20 mL of 2.0 M hydrochloric acid. The product was extracted with chloroform three times, and the combined organic fractions were washed with brine and dried over anhydrous sodium sulphate. After filtration and removal of the solvent, the resulting oil was purified on a short column (silica gel, $CHCl_3$:MeOH 100:1). The product (35 mg, 0.066 mmol, 56 %) is a yellowish gum which foams upon solvent removal. $[\alpha]_D^{25}$ = -41.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$ with 0.03% v/v TMS, 300 MHz): δ 6.62 (s, 1H), 6.41 (s, 2H), 6.38 (s, 1H), 5.87 (d, J = 1.4 Hz, 1H), 5.86 (d, J = 1.4 Hz, 1H), 4.39 (br s, 1H), 4.29 – 4.13 (m, 2H), 3.83 (s, 3H), 3.78 (s, 7H), 3.74 – 3.63 (m, 2H), 3.63 – 3.46 (m, 2H), 3.41 (s, 3H), 3.24 (m, 2H), 2.74 (dd, J = 16.8, 4.8 Hz, 1H), 2.17 – 1.81 (m, 3H), 1.77 – 1.60 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 174.1, 173.3, 153.1, 146.2, 145.9, 137.1, 129.1, 128.7, 127.2, 108.7, 108.3, 106.8, 100.8, 66.4, 61.2, 60.9, 56.2, 51.3, 49.6, 48.2, 48.0, 42.8, 29.7, 28.2, 24.7. HRMS (ESI-TOF) m/z: calcd for $C_{28}H_{33}NO_9Na$ $[M+Na]^+$, 550.2053; found, 550.2075.

Monomethyl 3-formyl-(1*R*,2*R*)-1-(3,4,5-trimethoxyphenyl)-6,7-methylenedioxy-1,2-dihydronaphthalene-2-carboxylate ester (16)

The reaction was performed according to a literature protocol.[31] To a solution of 85 mg (0.16 mmol) of **13** in anhydrous THF was slowly added a 1 M THF solution of $LiAlH(O\text{-}tBu)_3$ (2.4 equiv). The reaction was carried out at room temperature and under argon atmosphere. The solution was stirred at room temperature for 5 min. A 0.24 M THF solution of Cp_2ZrCl_2 (1.4 equiv) was added rapidly. After stirring for 2 min, the reaction mixture was quenched by H_2O. Hydrochloric acid (0.5 M) was added to reach a pH of ca. 6 and the solution was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrate *in vacuo*. The residue was purified using flash column chromatography (silica gel, EtOAc/hexane, gradient from 0% to 20% of EtOAc) to yield 14 mg (0.032 mmol, 20 %) of product **16** as a yellowish gum. The analytical data for product **16** were identical to those reported in the literature.[35] $[\alpha]_D^{25}$ = +156.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$ with 0.03% v/v TMS, 500 MHz): δ 9.60 (s, 1H), 7.36 (s, 1H), 6.89 (s, 1H), 6.62 (s, 1H), 6.46 (s, 2H), 6.01 (d, *J* = 1.4 Hz, 1H), 5.99 (d, *J* = 1.4 Hz, 1H), 4.41 (d, *J* = 7.9, 1H), 3.98 (d, *J* = 7.9 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 6H), 3.40 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 191.0, 171.4, 153.3, 150.4, 147.1, 146.8, 137.4, 134.6, 134.3, 134.1, 125.6, 109.6, 109.2, 106.4, 101.7, 60.9, 56.1, 51.7, 48.3, 44.1. HRMS (ESI-TOF) m/z: calcd for $C_{23}H_{22}O_8Na$ $[M+Na]^+$, 449.1212; found, 449.1232.

Monomethyl 3-formyl-(1*R*,2*R*)-1-(3,4,5-trimethoxyphenyl)-6,7-methylenedioxy-1,2-dihydronaphthalene-2-carboxylate ester (16)

Compound **13** (150 mg, 0.285 mmol) was dissolved in 8 mL of anhydrous THF under argon. This solution is then added to 2 eq. of Schwartz's reagent at room temperature under argon. After 10 min of stirring, the Schwartz's reagent was dissolved completely, marking the completion of the reaction. The mixture was quenched by addition of 5 mL of H_2O. A solution of 0.5 N HCl was used to adjust the pH to ca. 6 and the product was extracted 3 times with small portions of EtOAc. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified as described above to yield 82 mg (0.192 mmol, 67 %) of product **16**.

Monomethyl 3-(hydroxymethyl)-(1*R*,2*R*)-1-(3,4,5-trimethoxyphenyl)-6,7-methylenedioxy-1,2-dihydronaphthalene-2-carboxylate ester (17)

58 mg (0.136 mmol, 1 equiv) of product **16** and a stirring bar were placed in a 25 mL round bottom flask. A volume of 3 mL of MeOH was added, and the solution was stirred vigorously at 0 °C. Sodium borohydride (7.5 mg, 1.46 eq, 0.198 mmol) was added in a single portion. The color of the solution changed

from orange to yellow. The reaction was allowed to reach room temperature and was stirred for 30 min. After this time, the reaction was quenched by addition of saturated aqueous NH_4Cl solution (ca. 15 mL) and diluted with EtOAc (ca. 50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The resulting oil was purified by column chromatography (EtOAc/hexane, gradient from 0% to 20% EtOAc) to yield 52.5 mg (0.123 mmol, 90 %) of product **17** as a white gum. ^{1}H NMR signals for product **17** were identical to those reported in the literature.[37] $[\alpha]_D^{25}$ = +112.9 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$ with 0.03% v/v TMS, 500 MHz): δ 6.65 (s, 1H), 6.53 (s, 1H), 6.52 (s, 1H), 6.49 (s, 2H), 5.90 (d, *J* = 1.5 Hz, 1H), 5.90 (d, *J* = 1.6 Hz, 1H), 4.34 (d, *J* = 7.3, 1H), 4.24 (s, 2H), 3.83 (s, 3H), 3.79 (s, 6H), 3.68 (d, *J* = 7.0, 1H), 3.51 (s, 3H), 2.31 (br s, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 172.5, 153.1, 147.1, 146.3, 137.2, 135.5, 133.7, 130.1, 127.0, 126.8, 108.4, 107.5, 106.1, 101.0, 65.3, 60.8, 56.1, 51.7, 48.9, 48.7. HRMS (ESI-TOF) m/z: calcd for $C_{23}H_{24}O_8Na$ $[M+Na]^+$, 451.1369; found, 451.1347.

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