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Article

Diastereoselective Synthesis of β-Piperonyl-γ-Butyrolactones from Morita-Baylis-Hillman Adducts. Highly Efficient Synthesis of (±)-Yatein, (±)-Podorhizol and (±)-*epi*-Podorhizol

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Descrevemos nesse trabalho um método simples e eficiente para a preparação diastereosseletiva de β-piperonil-γ-butirolactonas hidroxiladas, a partir de um aduto de Morita-Baylis-Hillman. Para exemplificar a eficiência dessa abordagem descrevemos também as sínteses das lignanas biologicamente ativas, (±)-yateína, (±)-podorizol e (±)-*epi*-podorizol.

Starting from a Morita-Baylis-Hillman adduct we describe a simple and very efficient method for the diastereoselective preparation of hydroxylated β-piperonyl-γ-butyrolactones. To exemplify the efficiency of this approach we also describe a highly efficient synthesis for the biologically active lignans (±)-yatein, (±)-podorhizol and (±)-*epi*-podorhizol.

Keywords: Morita-Baylis-Hillman, lignans, diastereoselectivity

Introduction

Lignans are natural products originated from a coupling reaction between C6-C3 units (phenylpropionate). These secondary metabolites are widely encountered in plant kingdom and present a huge structural diversity normally associated with interesting biological effects, such as anti-tumoral, fungicide and anti-viral.[1,2] Furthermore, they also show other biological activities against insects and some vertebrates (Figure 1).[3]

Trachelogenin amide A (**1**, Figure 1) is a dibenzylbutane lignan, isolated from the leaves and stems of *Trachelospermum jasminoides*. This plant is used in chinese folk medicine to treat rheumatic arthralgia, aching of loins and knees, and traumatic injuries.[4] Actaelactone (**2**, Figure 1), is a dibenzylbutyrolactone lignan isolated from back cohosh (*Actaea racemosa*).[5] Actaealactone showed antioxidant activity in the 1,1-diphenyl-2-picrylhydrazyl (DPPH) free-radical assay, with an IC_{50} value of 26 μmol L^{-1}. It also exhibited a small stimulating effect on the growth of MCF-7 breast cancer cells. 9α-Angloyloxypinoresinol (**3**) has displayed inhibitory activity against HIV reverse transcriptase and was isolated from the roots and rhizomes of the chinese plant *Ligularia kanaitizensis*.[6,7] Kadsuralignan J (**4**) was isolated from roots of the chinese plant *Kadsura coccinea* and presents a moderate nitric oxide inhibitory activity.[8] Beilschmin A (**5**) was isolated from the stems of chinese plant *Beilschmiedia tsangii*. This lignan was found to exhibit significant *in vitro* cytotoxicity against P-388 and HT-29 cell lines, with IC_{50} values of 1.2 and 5.0 μg mL^{-1}, respectively.[9] The most prominent member of the aryltetralin lignan class is podophyllotoxin (**6**). This compound and some analogues have been isolated from American Mayapple (*Podophyllum peltatum*).[10] Podophyllotoxin (**6**) has long been known to possess anti-mitotic activity with early clinical trials showing it to be highly efficacious but also quite toxic. Driven by the desire to enhance this biological profile, there have been many synthetic modifications to the podophyllotoxin structure, including the generation of potent anticancer agents. It is possible to include the following agents, as the actually marketed medicines Etoposide and Teniposide.[10]

The structural diversity and complexity associated with biological effects exhibit by lignans have stimulated the development of several synthetic approaches to prepare them, both in racemic and enantiomeric pure forms.[11] Most of the synthetic methodologies are based on a β-aryl-γ-butyrolactone. This key intermediate is very important in the synthesis of butyrolactone lignans, which are used as plataform for the preparation of other lignans.[12]

Some years ago, Enders *et al.*[13] elegantly demonstrated that hydroxylated β-aryl-γ-butyrolactone is a central

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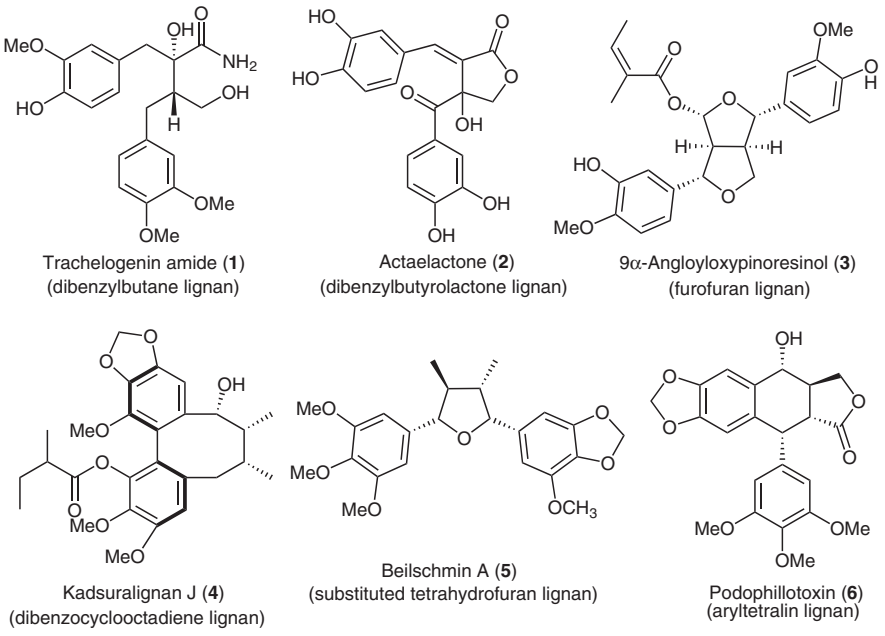


Figure 1. Types and examples of biological active lignans.

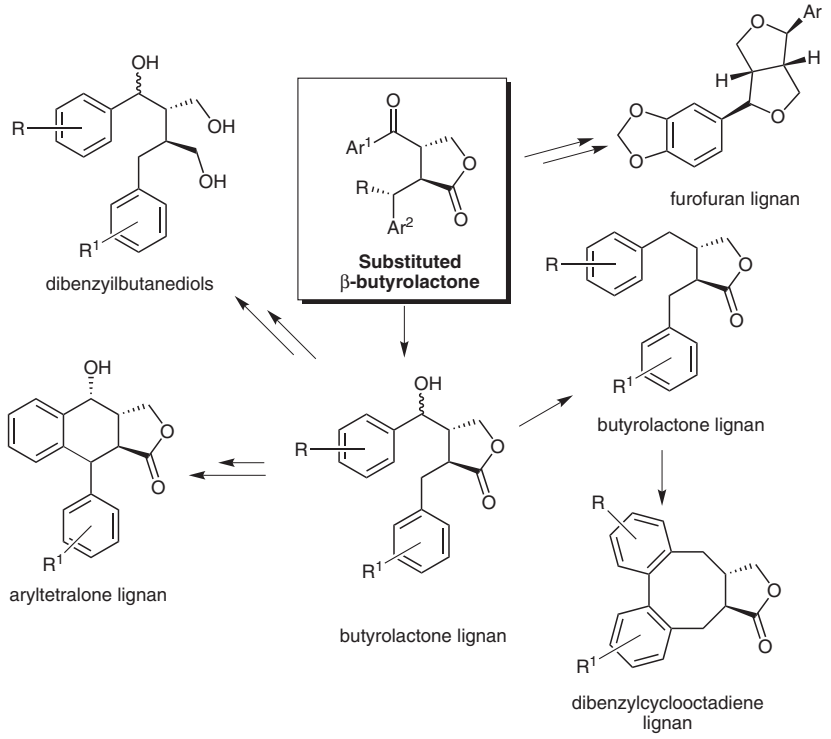


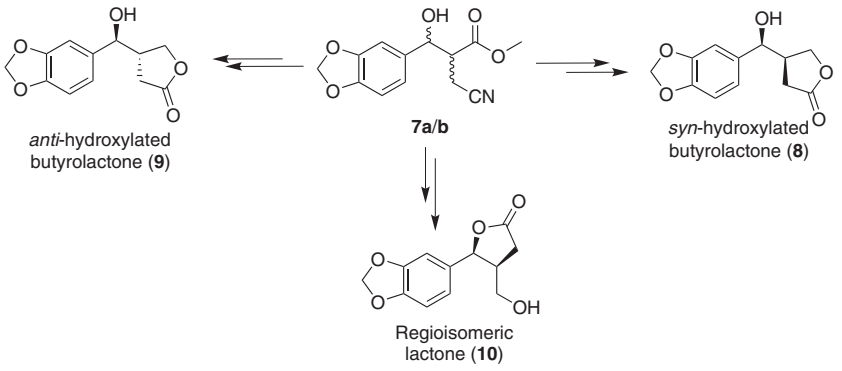
Figure 2. β-Aryl-γ-butyrolactone as key intermediates for lignans synthesis.

intermediate from which several different types of lignans can be synthesized (Figure 2).[13,14]

Results and Discussion

Morita-Baylis-Hillman is an amazing chemical transformation capable of efficiently providing highly functionalized β-hydroxy-α-methylene carbonyl derivatives.[15,16] The adducts formed in this reaction have been used as substrate for the synthesis of natural products and drugs.[17]

Some years ago we reported, for the first time, a strategy which allowed the preparation of β-aryl-γ-butyrolactone using Morita-Baylis-Hillman adduct as



Scheme 1. Butyrolactones from Morita-Baylis-Hillman adducts.

intermediates.[14] This simple and straightforward strategy provided access to *syn*- and *anti*-hydroxylated β-aryl-γ-butyrolactone (**8** and **9**, respectively) in good yield. The diastereoselectivity for the *syn* isomer was acceptable (4:1), but for the *anti* was very poor (1:1.5). In this case, the presence of regioisomeric lactone **10** was also detected, thus compromising the whole efficiency of the synthetic methodology (Scheme 1).

Basically, a diastereoselective Michael addition of a cyanide to the double bond of a Morita-Baylis-Hillman gave **7a/b**, as a mixture of diastereoisomers. Reduction of the ester group followed by basic hydrolysis of the nitrile group and *in situ* cyclisation, afford the desired butyrolactones in good yield. Unfortunately, this strategy had two major drawbacks. The first one was concerning the poor diastereoselectivity observed for the *anti* isomer. This isomer is particularly important for the synthesis of aryltetralin lactones, such as podophillotoxin. Second, an undesired regioisomeric butyrolactone (**10**) is formed, which renders the chromatographic separation laborious.

With the aim of overcoming afore mentioned drawbacks, we describe herein an alternative diastereoselective approach for the preparation of *syn*- and *anti*-hydroxylated β-aryl-γ-butyrolactone. To demonstrate the versatility of our aproach we also describe a highly efficient total synthesis of (±)-yatein (**11**), (±)-podorhizol (**12**) and (±)-*epi*-podorhizol (**13**) (Figure 3).

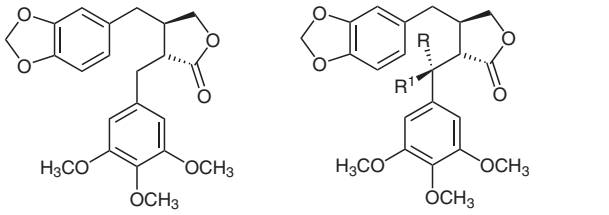


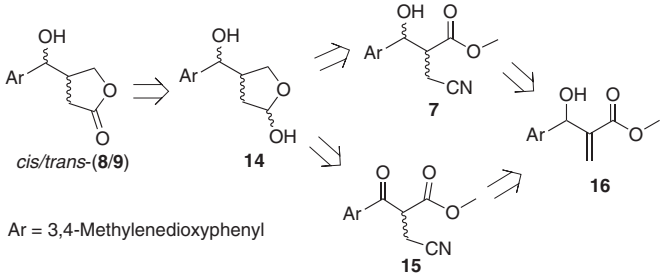
Figure 3. Lignans from a Morita-Baylis-Hillman addduct.

Yatein (**11**) is a biologically active butyrolactone lignan. This natural compound has strong insect feeding deterrent,[18] and anti-viral activity.[19] Podorhizol (**12**) presents a moderate anti-tumor activity,[20] while *epi*-podorhizol (**13**) shows antibacterial activity.[21]

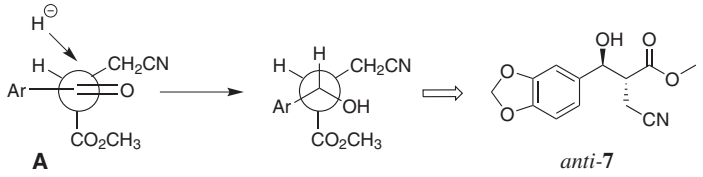
Hydroxylated β-aryl-γ-butyrolactones can be prepared from a Morita-Baylis-Hillman using the synthetic strategy depicted in scheme below (Scheme 2).

The butyrolactones can be prepared by direct oxidation of lactol **14**, which in turn can be synthesized in one step from cyanide-ester **7**, using reductive conditions. The preparation of **7** can be secured by a diastereoselective Michael addition reaction with a suitable Morita-Baylis-Hillman adduct, such as **16**. Based on our previous results, we anticipated good diastereoselective control could be achieved in the Michael step, mainly in the preparation of the *syn* diastereoisomer.[14]

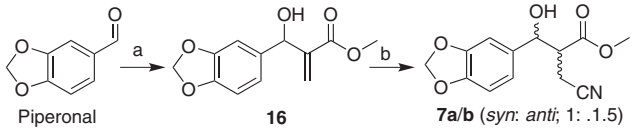
In order to improve the diastereoselectivity in the preparation of *anti* isomer, we thought that β-ketoesters **15**



Scheme 2. Retrosynthetic approach for the preparation of hydroxylated butyrolactones from Morita-Baylis-Hillman adduct.



Scheme 3. Stereochemical racionalization to obtain *anti* isomer **7**.



Scheme 4. Preparation of cyanide **7**. Reagents and conditions: (a) methyl acrylate (30 equiv.), DABCO, [bmim]PF_6, ultrasound, 80 h, 89%; (b) NaCN, NH_4Cl, DMF:H_2O (3:1), 12 h, 87%.

could be used as substrate in a diastereoselective reduction step. Based on a careful conformational analysis of **15**, we likely assume that A is the most stable conformer (Scheme 3). We can thus expect that hydride attack should preferentially occur on the less hindered side, leading to the *anti* diastereoisomer as the major product.

Taking in to account these preliminary considerations, we commenced with the synthesis of β-hydroxy-ester **16** by coupling of methyl acrylate with piperonal. Electron-rich aldehyde piperonal is very resistant to Morita-Baylis-Hillman reaction and normally rate, conversion and yield are very low. Searching to circumvent this problem we carried out a reaction using an excess of acrylate (30 equiv.) in the presence of catalytic amount of an ionic liquid [bmim]PF_6 (1-butyl-3-methylimidazolium hexafluorophosphate) and ultrasound. Under these conditions, adduct **16** was obtained after 80 h, in 89% yield (Scheme 4).

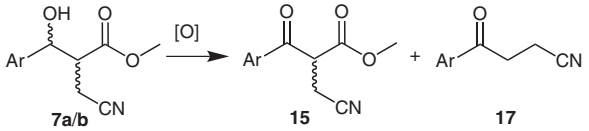
Michael addition reaction between sodium cyanide and adduct **16** afforded **7** in 87% yield but in a poor diastereoisomeric ratio (*syn*:*anti*; 1:1.5), as previously observed (Scheme 4).

The mixture was easily characterized by measuring the coupling constant (*J*) of the carbinolic proton in ^{1}H NMR spectrum. A doublet resonance at 5.10 ppm (*J* 4.4 Hz) was attributed to the *syn* diastereomer, while the doublet resonance at 4.95 ppm (*J* 7.6 Hz) was attributed to the *anti* isomer. The spectral data are consistent with those previously reported in literature.[14]

The preparation of β-ketoester **15** was unexpectedly troublesome. We tested several different oxidizing reagents. The results are summarized in Table 1.

Depending on experimental conditions used the β-ketoester **15** was contaminated with the decarboxylation product **17** (entries 1 and 2, Table 1). It is known that hypervalent reagent can hydrolyse esters and acetals.[23] Then, we believe that the large excess of 2-iodoxybenzoic acid (IBX) used in the reaction has favored the hydrolysis of our keto ester, which subsequently loss CO_2. The best result was achieved when Jones reagent was used in acetone at 0 °C.[24] Under these conditions, β-ketoester **15** was obtained as a sole product in 94% yield (entry 6, Table 1).

Table 1. Preparation of β-keto ester **15**



Ar= 3,4-Methylenedioxyphenyl

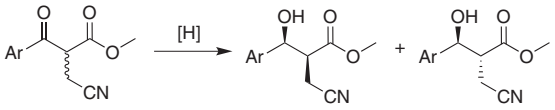
Entry	Reaction conditions	time	Products, (%)[a,b]
1	IBX/CH_3CN (reflux)[c]	12 h	**15** + **17**, 55
2	IBX (3 equiv.)/AcOEt (reflux)	12 h	**15** + **17**, 40
3	IBX (1.2 equiv.)/AcOEt (reflux)	12 h	**15**, 55
4	IBX (1.2 equiv.)/acetone	12 h	**15**, 45
5	PDC/CH_2Cl_2, r.t.	8 h	**15**, 65
6	CrO_3-H_2SO_4/acetone, 0 °C	15-20 min	**15**, 94

[a] Yields refer to isolated and purified products; [b] all spectral data (^{1}H NMR, ^{13}C NMR, IR, HRMS) are compatible with the proposed structures; [c] see reference 22.

Having ketoester **15** in our hands, we subjected it to a set of different reductive conditions. The results are summarized in Table 2.

In all cases, diastereoselectivity was better than that achieved by conjugate addition of cyanide to the double bond of Morita-Baylis-Hillman adduct. Moreover, the highest selectivity was attained when employing $NaBH_4$ at room temperature and using methanol as solvent (*syn*:*anti*;1:10). The difference between the diastereoselectivity for the oxidation-reduction approach and the Michael addition of sodium cyanide Michael addition is remarkable (Figure 4). After a simple chromatographic purification, *anti*-(±)-**7b** was obtained as a sole diastereoisomer in 75% yield. To accomplish our goal, it was necessary to protect the secondary

Table 2. Diastereoselective reduction of β-keto ester **17**



(±)-**15** (*syn*)-±-**7a** (*anti*)-±-**7b**

Ar= 3,4-Methylenedioxyphenyl

Entry	Reaction conditions	time (h)	Products, %[a,b] *syn*:*anti* ratio
1	$NaBH_4/CH_2Cl_2$/ –63 °C[c]	3	**7a/b**, -, -
2	$NaBH_4/CH_2Cl_2$/ r.t.	3	**7a/b**, 56, 1:7.5
3	$NaBH_4$/MeOH/ r.t.	1.5	**7a/b**, 75, 1:10
4	$NaBH_4$/*i*-PrOH/ r.t.	12	**7a/b**, 45, 1:4[27]
5	$PhMe_2SiH$, HMPA, 0 °C[d]	2	**7a/b**, 50, 1:3

[a] Yields refer to isolated and purified products; [b] all spectral data (^{1}H NMR, ^{13}C NMR, IR, HRMS) are compatible with the proposed structures; [c] see reference 25; (d) see reference 26.

hydroxyl group of *anti*-cyanide **7b**. Then, compound **7b** was treated with *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole in anhydrous dimethylformamide (DMF) to afford the silylether **18** in 78% yield.

A dichloromethane solution of **18** was then treated with a solution of diisobutylaluminium hydride (DIBAL-H) (3 equiv.), at –78 °C for 3 h to give the lactol **14** in 91% (Scheme 5). DIBAL-H reduces the ester group to the primary alcohol and nitrile to an imine, which is quenched at this stage. During the aqueous workup, imine is hydrolyzed to the aldehyde, which reacts with the alcohol to give lactol **14** (Scheme 5). The NMR analysis of lactol **14** was tedious, since the temporary appearance of a third stereogenic center excessively complicates the spectrum. Thus, **14** was directly treated with tetrapropylammonium perruthenate (TPAP) in the presence of *N*-methylmorpholine-*N*-oxide (NMO) and molecular sieve (MS, 4 Å) to afford silylated *anti*-butyrolactone **19** in 92%.[28]

Removal of the protecting group with tetra-n-butylammonium fluoride (TBAF) in MeOH gave *anti*-β-piperonyl-γ-butyrolactone **9** in 94% (Scheme 5).

All spectroscopic data are compatible with the proposed structure. The *anti*-β-piperonyl-γ-butyrolactone **9** was prepared in a highly diastereoselective approach in 36% overall yield, in 8 steps starting from piperonal.

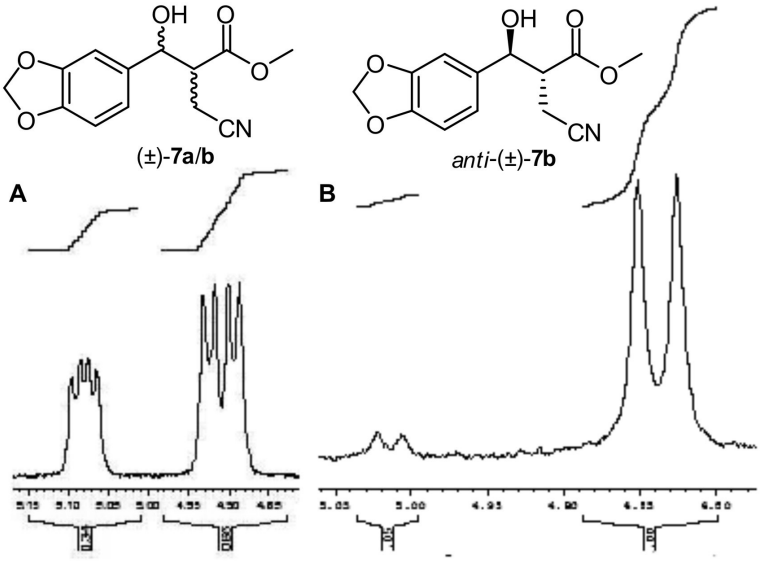
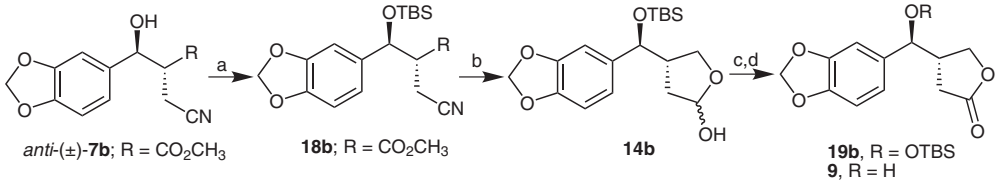
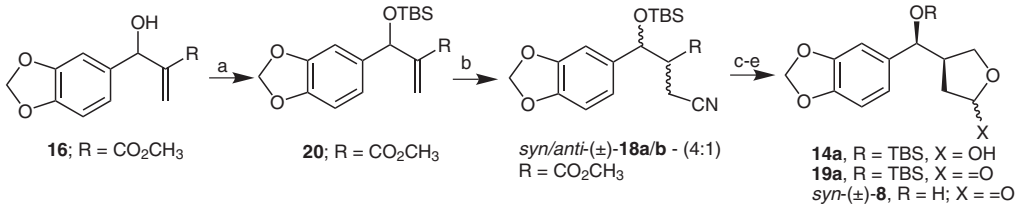


Figure 4. Determining the stereochemical ratio of cyano-ester **7a/b**. A. Diastereoisomeric ratio (*syn*:*anti*; 1:2) obtained by direct addition of cyanide on the double bond of the adduct. Signal centered at 5.08 ppm was atributted to the *syn* isomer (*J* 2.8 and 5.1 Hz), while that centered at 4.92 ppm (*J* 3.5 and 7.8 Hz) was atributted to the *anti* one. In both cases the minor coupling constants are due to the coupling with the hydroxyl hydrogen. B. Diastereoisomeric ratio obtained just after ketoester reduction with $NaBH_4$.



anti-(±)-**7b**; R = CO_2CH_3 **18b**; R = CO_2CH_3 **14b** **19b**, R = OTBS **9**, R = H

Scheme 5. Diastereoselective preparation of *anti*-butyrolactone. Reagents and conditions: (a) TBSCl, imidazole, DMF (drops), 18 h, r.t., 78%; (b) DIBAL-H, CH_2Cl_2, –78 °C, 3 h, 91%; (c) TPAP, NMO, MS (4 Å), 1 h, 92%; (d) TBAF, MeOH, 0 °C, 2 h, 95%.

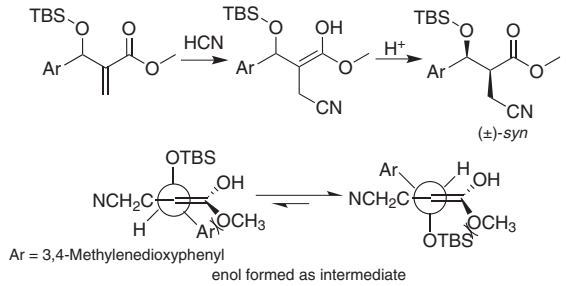


Scheme 6. Diastereoselective preparation of *syn*-butyrolactone **8a**. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, r.t., 2 h, 95%; (b) KCN, NH_4Cl, DMF:H_2O (3:1), 18 h, 83%; (c) DIBAL-H, CH_2Cl_2, −78 °C, 3 h, 91%; (d) TPAP, NMO, MS (4 Å), 1 h, 92%; (e) TBAF, MeOH, 0 °C, 2 h, 95%.

To demonstrate the feasibility of this strategy we also prepared *syn*-butyrolactone (**8**), using a similar synthetic sequence. To direct the diastereoselectivity towards the formation of the *syn* isomer, the secondary hydroxyl group of Morita-Baylis-Hillman adduct should be protected before the cyanide addition. The enhanced presence of the silyl group alters the course of the Michael addition leading to the *syn* isomer as the major product (Scheme 6).

Initially adduct **16** was silylated to afford the silyl ether **20** in 95%. Michael addition reaction yielded cyanide-esters **18a/b** as a mixture of diastereoisomers in which the *syn* isomer is the major one (4:1). This stereochemical ratio is certainly defined during the protonation of the enol intermediate formed after the addition of cyanide (Scheme 7). This protonation should likely occur in the enol face in opposite to the silyl group. However, the preference for this face seems to be not so high. A careful analysis of the proposed conformers clearly shows that we have a steric enhancement in both faces, although one side (opposite to TBDS group) being most accessible than other. This observation can explain the moderate selectivity attained.

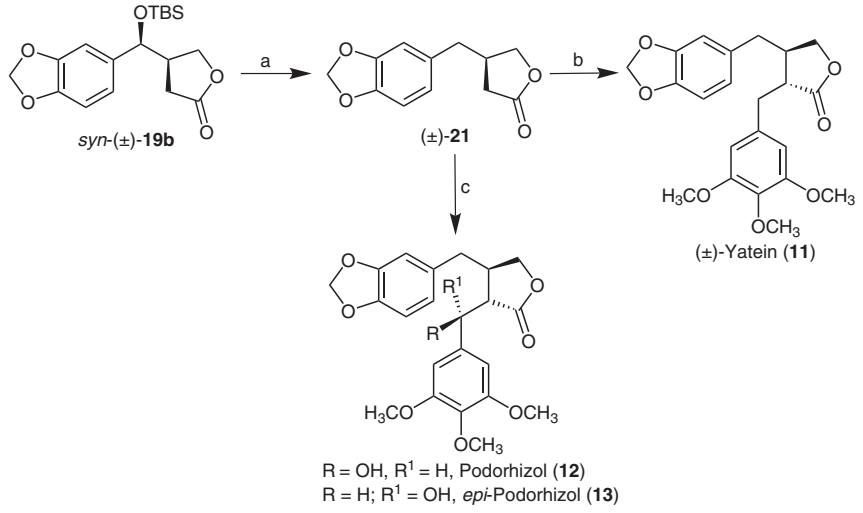
We made several attempts to separate these diasteroisomers by column chromatography at this stage,



Scheme 7. Explaining the diastereoselectivity observed during the Michael addition over the silylated Morita-Baylis-Hillman (MBH) adduct.

however, only slight enrichment of the mixture in favor of the *syn* isomer was realized. DIBAL-H reduction afford the lactol, which was immediately oxidized to the corresponding silylated lactone in 84% yield over two steps. The silyl group was removed to provide *syn*-hydroxylated β-piperonyl-γ-butyrolactone (**8**) in 95%. Unfortunately, lactone *syn* was already contaminated with a small amount of the *anti* isomer (7:1). The *syn*-butyrolactone was prepared in an overall yield of 56% in 7 steps from piperonal.

The optimized synthetic sequence was now employed for the synthesis of (±)-yatein (**11**), (±)-podorhizol (**12**) and (±)-*epi*-podorhizol (**13**), through a common intermediate.



Scheme 8. Reagents and conditions: (a) Pd/C 5%, H_2, 60 psi, 4 h, r.t., 92%; (b) LDA, THF, −78 °C, then bromide **22**, 6 h, 80%; (c) LDA, THF, −78 °C, aldehyde, 1 h, chromatographic separation, 80%.

To perform the lignan syntheses we have decided to use the sequence depicted in Scheme 8. Hydrogenolysis of **19b** in the presence of hydrogen and palladium on carbon at 60 psi provide β-piperonyl-γ-butyrolactone **21**, after 4 h, in 92% yield. Alkylation of **21** with the 3,4,5-trimethoxybenzyl bromide (**22**)[29] in the presence of LDA at −78 °C gave (±)-yatein (**11**) in 80% yield (Scheme 8). To synthesize podorhizol and *epi*-podorhizol we simply change the electrophile at the condensation step. Instead of bromide we use commercially available 3,4,5-trimethoxy-benzaldehyde in an aldolic condensation. The diastereoisomers (1:1 ratio) were easily separated by column chromatography, as previously reported (Scheme 6).[30] All spectroscopic data for epimeric lignans are completely compatible to those available in literature.[31]

The lignans were prepared in 6 steps from Morita-Baylis-Hillman adduct **16**. (±)-Yatein (**11**) was prepared in 49% overall yield. (±)-Podorhizol (**12**) and (±)-*epi*-podorhizol (**13**) were prepared both in 6 steps from Morita-Baylis-Hillman adduct **16** in 24.5 and 24% overall yield, respectively. All spectroscopic data are compatible with the proposed structures.

Conclusions

In summary we have described an alternative and efficient strategy for the synthesis of lignans from Morita-Baylis-Hillman adduct. This simple and straighforward sequence allows the diastereoseletive synthesis of *anti* and *syn* hydroxylated β-piperonyl-γ-butyrolactone in good overall yield. As far as we know this is the first report concerning the total synthesis of lignans from a Morita-Baylis-Hillman adduct. Due to the ease to which different Morita-Baylis-Hillman adducts were obtained, this approach can be used to furnish lignans of greater molecular diversity. Finally, we have demonstrated that Morita-Baylis-Hillman adducts can be considered as a valuable substrate to prepare lignans.

Experimental

General

The ^{1}H and ^{13}C NMR spectra were recorded with a Varian GEMINI BB at 300 and 75.4 MHz and Bruker at 250 and 62.5 MHz, respectively, or on an Inova Instrument at 500 and 125 MHz, respectively. The mass spectra were recorded using a HP model 5988A GC/MS with a High Resolution Autospec/EBE. IR were obtained with a Nicolet model Impact 410. Diastereoselectivities were determined from GC analysis on a HP6890 with flame ionization detector, using a HP-5 capillary (cross linked 5% phenyl methyl siloxane, 28 m) column or by NMR. Manipulations and reactions were not performed under a dry atmosphere or employing dry solvents, unless otherwise specified. Purifications and separations by column chromatography were performed on silica gel, using normal or flash chromatography. Thin-layer chromatography (TLC) visualization was achieved by spraying with 5% ethanolic phosphomolybdic acid and heating. Morita-Baylis-Hillman reactions were sonicated in an UNIQUE model GA 1000 ultrasonic bath (1000 W, 25 kHz). Ice was added occasionally to avoid increasing the temperature of the water of the ultrasonic bath, which was maintained between 30 and 40 °C. Reagents were purchased from Aldrich, Acros or Lancaster, and were used without prior purification.

*(±)-Methyl 2-[1,3-benzodioxol-5-yl(hydroxy)methyl]prop-2-enoate (**16**)*

A mixture of piperonal (12 g, 79.9 mmol), methyl acrylate (54 mL, 0.6 mol), 1-methyl-3-butylimidazolium hexafluorophosphate [bminPF$_6$] (0.23 g, 0.79 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (5.83 g, 52 mmol) was kept in an ultrasound bath for 20 h. Next, a new portion of methyl acrylate was added (54 mL, 0.6 mol) and the reaction was kept on the ultrasound for 20 h. This procedure was repeated twice to complete 80 h. The reaction medium was then evaporated and the acrylate was almost totally recuperated. The crude was diluted with dichloromethane (100 mL), washed with distilled water (100 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane:AcOEt, 4:1, v/v) to provide 16.8 g of adduct **16** in 89% yield, as yellow tinged oil, which crystalise on standing. mp 40-42 °C; IR ν_{max}/cm^{-1} 3490, 2954, 2897, 1703, 1630, 1487, 1438, 1295, 1246, 1037 (film); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.85-6.74 (m, 3H aromatics), 6.32 (d, 1H, *J* 0.9 Hz), 5.93 (s, 2H), 5.86 (d, 1H, *J* 0.9 Hz), 5.46 (d, 1H, *J* 5.3 Hz), 3.71 (s, 3H), 3.06 (d, 1H, *J* 5.3 Hz, exchangeable with D_2O); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 166.8, 147.8, 147.2, 141.9, 135.3, 120.2, 108.2, 107.2, 101.1, 72.9, 51.9; HRMS (70 eV, *m/z*) Calc. for $C_{12}H_{12}O_5$: 236.06847. Found: 236.0685.

*(±)-Methyl 2-[(tert-butyldimethylsilyloxy)(1,3-benzodioxol-5-yl)methyl]prop-2-enoate (**20**)*

To a solution of **16** (3 g, 12.7 mmol) in dichloromethane (100 mL) was added, at 0 °C and under an inert gas

atmosphere, Et_3N (3.5 mL, 25.5 mmol) and TBSOTf (3.5 mL, 16.5 mmol). The resulting solution was stirred at room temperature for 1 h. After that, the reaction medium was diluted with dichloromethane (100 mL) and the organic phase was washed a saturated solution of $NaHCO_3$ (200 mL) and distilled water (100 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane: AcOEt, 9:1, v/v) to provide **20** (4.35 g), in 98% yield, as a viscous oil. IR ν_{max}/cm^{-1} 2954, 2888, 2860, 2833, 1720, 1634, 1495, 1438, 1246, 1152, 1070, 1041 (film); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.85-6.79 (m, 2H aromatics), 6.70 (d, 1H, *J* 8.4 Hz), 6.22 (dd, 1H, *J* 1.7 and 1.2 Hz), 6.05 (dd, 1H, *J* 1.7 and 1.7 Hz), 5.92 (d, 1H, *J* 1.5 Hz), 5.91 (d, 1H, *J* 1.5 Hz), 5.51 (bs, 1H), 3.67 (s, 3H), 0.9 (s, 9H), 0.04 (s, 3H), –0,10 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 166.3, 147.3, 146.7, 136.6, 120.6, 107.7, 107.4, 100.9, 72.3, 51.6, 25.7, 18.1, –4.9, –5.13; HRMS (ESI, *m/z*) Calc. for $C_{18}H_{26}O_5Si$: 350.15495. Found: 294.09234 [M-57]$^+$.

*(±)-Methyl 3-(1,3-benzodioxol-5-yl)-2-(cyanomethyl)-3-hydroxypropanoate (**7a/b**)*

To a solution of **16** (3 g, 12.7 mmol) in a mixture of dimethylformamide and water (3:1) was added potassium cyanide (2.79 g, 42.8 mmol) and ammonium chloride (2.29 g, 42.8 mmol). The resulting mixture was stirred at room temperature for 12 h. After that, the medium was diluted with distilled water (200 mL) and the aqueous phase was extracted twice with ethyl acetate (100 mL each). The organic phases were combined and washed with distilled water (2 × 100mL) and brine (100 mL). The organic phase was then dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane:AcOEt, 7:3, v/v) to give **7a/b** (2.51 g), in 75% yield, as a viscous tinged yellow oil, in a mixture of diastereoisomers (*anti*:*syn*; 1.5:1). mp 50-52 °C; IR ν_{max}/cm^{-1} 3459, 2958, 2901, 2251, 1736, 1487, 1434, 1239, 1037 (film); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.85-6.75 (m, 3H aromatics), 5.97 (s, 2H), 5.09 (dd, 1H, *J* 2.9 and 5.1Hz, *syn* diastereoisomer), 4.90 (dd, 1H, *J* 3.5 and 7.7 Hz, *anti* diastereoisomer), 3.79 (s, 3H), 3.72 (s, 3H), 3.10-2.92 (m, 2H), 3.08-3.03 (m, 1H), 3.03-3.0 (m, 1H), 2.82 (dd, 1H, *J* 9 and 17 Hz, CH_2CN, *anti*), 2.62 (d, 1H, *J* 4.4 Hz, CH_2CN, *syn*), 2.56 (d, 1H, *J* 4.9 Hz, CH_2CN, *syn*), 2.42 (dd, 1H, *J* 8 and 17 Hz, CH_2CN, *anti*); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 171.8, 171.5, 148.2, 147.9, 147.6, 133.9, 133.3, 120, 119.9, 118, 117.1, 108.4, 108.3, 106.3, 106.1, 101.3, 101.2, 73.7, 72.6, 52.7, 52.6, 49.4, 48.8, 16.9, 14.9; HRMS (ESI, *m/z*) Calc. for $C_{13}H_{13}NO_5$: 263.07937. Found: 263.07892.

*(±)-Methyl 3-(tert-butyldimethyl silyloxy)-3-(1,3-benzodioxol-5-yl)-2-(cyanomethyl)propanoate (**18a/b**)*

To a solution of **20** (4.45 g, 12.7 mmol) in a mixture of dimethylformamide and water (4:1) was added potassium cyanide (2.79 g, 42.8 mmol) and ammonium chloride (2.29 g, 42.8 mmol). The resulting mixture was stirred at room temperature for 12 h. After that, the medium was diluted with distilled water (200 mL) and the aqueous phase was extracted twice with ethyl acetate (100 mL each). The combined organic phases were washed with distilled water (2 × 100 mL) and brine (100 mL). After removal of the solvent under reduced pressure, the residue was purified by flash silica gel column chromatography (hexane:AcOEt, 4:1, v/v) to afford 3.69 g of a colorless viscous oil, in 83% yield, as a mixture of diastereoisomer (*anti*:*syn*; 1:4). IR ν_{max}/cm^{-1} 2954, 2924, 2883, 2854, 2241, 1735, 1444, 1492, 1248, 1076, 1040 (film); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.90-6.60 (m, 3H aromatics), 5.97 (bs, 2H), 5.10 (d, 1H, *J* 4.3 Hz, diastereoisomer *syn*), 4.82 (d, 1H, *J* 7.6 Hz, diastereoisomer *anti*), 3.78 (s, 3H, *anti*), 3.76 (s, 3H, *syn*), 3.05-2.70 (m, 2H), 2.50-2.36 (m, 1H), 0.97 (s, 9H, *syn*), 0.96 (s, 9H, *anti*), 0.01 (s, 3H, *anti*), 0.0 (s, 3H, *syn*), –0.02 (s, 3H, *anti*), –0.25 (s, 3H, *syn*); ^{13}C NMR ($CDCl_3$, 75.4 MHz) diastereoisomer *syn*: δ 170.7, 147.7, 147.3, 133.9, 119.3, 118.5, 108.1, 106.3, 73.9, 52.3, 51.4, 25.6, 17.9, 14.2, –4.7, –5.4; diastereoisomer *anti*: δ 171.3, 148, 147.8, 133.8, 120.9, 117.6, 108.1, 106.5, 74.8, 52.3, 51, 25.5, 17.9, –4.7, –5.5; HRMS (EI, *m/z*) Calc. for $C_{19}H_{27}NO_5Si$: 377.16585. Found: 377.16319.

*(±)-Methyl 3-(1,3-benzodioxol-5-yl)-2-(cyanomethyl)-3-oxopropanoate (**15**)*

To a solution of **7a/b** (0.5 g, 1.9 mmol) in acetone (50 mL) was added drop by drop, at 0 °C, a freshly prepared solution of the Jones reagent[24] (5 mL). The reaction was monitored by TLC until the complete disappearance of the starting material. If necessary a tiny amount of the Jones reagent was added again. After the completion, an excess of isopropanol was added and the mixture was stirred just to become green. Then, the reaction was diluted with ethyl acetate (150 mL) and the organic phase was washed with water (2 × 150 mL) and brine (150 mL). The organic phase was dried over Na_2SO_4 and removed under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane:AcOEt, 1:1, v/v) to give **15** in 94% yield, as a

tinged yellow viscous oil. IR ν_{max}/cm^{-1} 2970, 2953, 2238, 1740, 1679, 1437, 1254, 1037 (film); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (d, 1H, *J* 3 Hz), 7.48 (s, 1H), 6.90 (d, 1H, *J* 3 Hz), 6.05 (s, 2H), 4.65 (apt, 1H, *J* 12 Hz), 3.75 (s, 3H), 3.18-2.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189, 167.3, 153, 148.6, 129.5, 126, 117.3, 108.5, 108.1, 102.2, 53.4, 49.5, 16.9; HRMS (EI, *m/z*) Calc. for $C_{13}H_{11}NO_5$: 261.06372. Found: 261.063351.

*anti-(±)-Methyl 3-(1,3-benzodioxol-5-yl)-2-(cyanomethyl)-3-hydroxypropanoate (**7b**)*

To a stirred solution of ketoester **15** (0.173 g, 0.67 mmol) in methanol (3 mL) was added, at 0 °C, sodium borohydrate (0.025 g, 0.66 mmol). The reaction was stirred at room temperature for 90 min. The solvent was then removed under reduced pressure and the residue was diluted with ethyl acetate (30 mL). The organic phase was washed with distilled water (2 × 30 mL) and a saturated solution of ammonium chloride (30 mL). The organic phase was then filtered over a pad of Celite® and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography to provide **7b**, in 75% yield, as a colorless oil and high diastereoisomeric purity (*anti*:*syn*;10:1). IR ν_{max}/cm^{-1} 3462, 2958, 2916, 2247, 1736, 1602, 1504, 1489 (film); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.87 (m, 3H), 6.0 (s, 2H), 4.95 (d, 1H, *J* 7.5 Hz), 3.80 (s, 3H), 3.08-3.03 (m, 1H), 2.62 (dd, 1H, *J* 9 and 17 Hz), 2.42 (dd, 1H, *J* 8 and 17 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3, 148.2, 147.9, 133.2, 120, 117, 108.4, 108.1, 106.3, 101.3, 52.8, 48.9, 17.1; HRMS (EI, *m/z*) Calc. for $C_{13}H_{13}NO_5$: 263.07937. Found: 263.07921.

*anti-(±)-Methyl 3-(tert-butyldimethyl silyloxy)-3-(1,3-benzodioxol-5-yl)-2-(cyanomethyl)propanoate (**18b**)*

To a mixture of cyano-ester **7b** (0.27 g, 1 mmol), *tert*-butyldimethylsilyl chloride (0.2 g, 1.3 mmol) and imidazole (0.17 g, 2.5 mmol), under an inert gas atmosphere, was added 2 drops of anhydrous DMF. The resulting mixture was vigorously stirred for 18 h, at room temperature. After that, the reaction was diluted with ethyl acetate (25 mL). The organic phase was washed with distilled water (25 mL) and brine (25 mL). After solvent removal, the residue was purified by flash silica gel column chromatography (hexane:AcOEt, 70:30) to provide **18b**, in 78% yield, as a colorless viscous oil. IR ν_{max}/cm^{-1} 2949, 2925, 2888, 2851, 2251, 1740, 1491, 1442, 1241, 1172, 1086, 1033 (film); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.80-6.60 (m, 3H), 5.96 (s, 2H), 4.85 (d, 1H, *J* 7.6 Hz), 3.76 (s, 3H), 2.98 (m, 1H), 2.33 (d, 2H, *J* 6.4 Hz), 0.92 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6, 148.2, 147.9, 133.2, 120, 117.4, 108.4, 106.3, 101.3, 73.7, 52.8, 48.9, 17.1; HRMS (EI, *m/z*) Calc. for $C_{19}H_{27}NO_5Si$: 377.16585. Found: 377.16319.

*anti-(±)-4-[1,3-Benzodioxol-5-yl(tert-butyldimethyl silyloxy)methyl]tetrahydrofuran-2-ol (**14b**)*

To a solution of cyano-ester **18b** (0.18 g, 0.48 mmol) in anhydrous dichloromethane (15 mL), at –78 °C, in an inert gas atmosphere, was added diisobutyl aluminum hydride (DIBAL-H, 1 mol L^{-1} solution in toluene, 1.56 mL, 1.56 mmol). The resulting mixture was stirred at –78 °C after 3 h. Then, a saturated solution of sodium acetate was added at –78 °C and the reaction was warmed at room temperature. After that, the reaction was dropped over a mixture of ethyl acetate (15 mL) and saturated solution of ammonium chloride (5 mL) and stirred after 1 h. The resulting gel was filtered over a pad of Celite®. The cake was washed with an additional amount of ethyl acetate (25 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane:AcOEt, 7:3, v/v) to afford 0.155 g of **14b**, in 91% yield, as a viscous light yellow oil. IR ν_{max}/cm^{-1} 3411, 2953, 2925, 2884, 2855, 1491, 1437, 1237, 1074, 1045 (film); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.90-6.60 (m, 3H), 5.95 (s, 2H), 5.60-5.30 (m, 1H), 4.70-4.30 (m, 1H), 4.20-3.40 (m, 2H), 4.15 (bs, 1H), 3.05 (bs, 1H), 2.90-2.40 (m, 1H), 2.20-1.40 (m, 2H), 0.92-0.82 (2s, 2 × 9H), 0.10-0.0 (2s, 2 × 3H), –0.12 - –0.26 (2s, 2 × 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 147.6, 147.5, 146.8, 146.7, 138, 137.9, 119.8, 119.6, 107.7, 107.6, 106.7, 106.6, 100.9, 98.7, 98.6, 77.4, 77.2, 70.3, 69.6, 47.4, 46.2, 25.7, 25.6, 18.03, 18, –4.48, –5.1, –5.2; HRMS (ESI, *m/z*) Calc. for $C_{18}H_{28}O_5Si$ + Na: 375.1604 $[M + Na]^+$. Found: 375.1557 $[M + Na]^+$.

*anti-(±)-4-[1,3-Benzodioxol-5-yl(tert-butyldimethyl silyloxy)methyl]dihydrofuran-2(3H)-one (**19b**)*

To a solution of lactol **14b** (0.18 g, 0.52 mmol) in anhydrous dichloromethane (20 mL), at room temperature under an inert gas atmosphere, was added molecular sieves (4 Å, 0.27 g), N-Methyl morpholine (NMO, 0.12 g, 1.04 mmol) and tetrapropylammonium ruthenate (TPAP, 0.0184 g, 0.04 mmol). The resulting mixture was stirred after 1 h. Then the crude was filtered over a pad of Celite® and the solvent removed under reduced pressure. The residue was purified by flash silica gel column chromatography to afford 0.165 g of **19b**, in 92% yield, as colorless viscous oil. IR ν_{max}/cm^{-1} 2953, 2929, 2892,

2851, 1777, 1491, 1437, 1241, 1172, 1078, 1033, 1008 (film); ^{1}H NMR (CDCl3, 250 MHz) δ 6.80-6.65 (m, 3H), 5.95 (s, 2H), 4.48 (d, 1H, *J* 6.8 Hz), 4.28 (m, 2H), 2.76 (m, 1H), 2.31 (m, 1H), 0.87 (s, 9H), 0.03 (s, 3H), -0.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 176.7, 147.8, 147.2, 136.1, 119.4, 108, 106.3, 101, 75.5, 70, 44.1, 31.2, 25.7, 17.9, –4.53, –5.26; HRMS (ESI, *m/z*) Calc. for $C_{18}H_{26}O_5Si$: 351.1648 $[M + H]^+$. Found: 351.1628 $[M + H]^+$.

*anti-(±)-4-[1,3-Benzodioxol-5-yl(hydroxy)methyl] dihydrofuran-2(3H)-one (**7b**)*

To a solution of **19b** (0.1 g, 0. 38 mmol) in methanol (5 mL) was added, at 0 °C and in an inert gas atmosphere, tetrabutylammonium fluoride (solution 1 mol L^{-1} in THF, 0.45 mL, 0.45 mmol). The resulting mixture was stirred at the same temperature after 2 h. Then, the solvent was removed under reduced pressure and the residue was diluted with ethyl acetate (25 mL). The organic phase was washed with distilled water (2 × 10 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4. After solvent removal, the residue was purified by flash silica gel column chromatography to give **7b** as colorless viscous oil, in 95% yield. IR ν_{max}/cm^{-1} 3429, 2900, 1771, 1492, 1444, 1248, 1040 (film); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.90-6.70 (m, 3H), 5.95 (s, 2H), 4.38 (d, 1H, *J* 8.0 Hz), 4.16 (dd, 1H, *J* 7.8 and 9.3 Hz), 4.03 (dd, 1H, *J* 6.4 and 9.3 Hz), 2.20-2.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 177.4, 148, 147.5, 135.8, 119.6, 108.2, 106.2, 101.2, 74.4, 69.9, 42.4, 30.7; HRMS (EI, *m/z*) Calc. for $C_{12}H_{12}O_5$: 236.06847. Found: 236.06831.

*(±)-4-(1,3-Benzodioxol-5-ylmethyl)dihydrofuran-2(3H)-one (**21**)*

To a solution of **18a/b** (0.55 g, 1.57 mmol) in methanol (50 mL) was added 5% Pd/C (0.034 g, 0.16 mmol) and two drops of concentrated hydrochloric acid. The resulting mixture was placed in a hydrogenation bottle, which was maintained in a shaker equipment, under hydrogen pressure (60 psi, 4 atm) after 4 h. Then, the mixture was neutralized with solid sodium bicarbonate and filtered over a pad of Celite®. The cake was washed with ethyl acetate (10 mL). The combined organic phases were removed and the crude was redissolved in ethyl acetate (50 mL). The organic phase was washed with distilled water (25 mL), brine (25 mL) and finally dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography to afford **21**, as a yellow tinged fluid oil, in 92% yield. IR ν_{max}/cm^{-1} 2909, 1769, 1487, 1438, 1248, 1037 (film); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.75 (d, 1H, *J* 7.8 Hz), 6.63 (d, 1H, *J* 1.7 Hz), 6.59 (dd, *J* 1.7 and 7.8 Hz), 5.94 (s, 2H), 4.33 (dd, 1H, *J* 6.8 and 9.2 Hz), 4.02 (dd, 1H, *J* 6.0 and 9.2 Hz), 2.80 (m, 1H), 2.69 (m, 2H), 2.60 (dd, 1H, *J* 8.0 and 17 Hz), 2.27 (dd, 1H, *J* 6.8 and 17 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 176.5, 147.8, 146.2, 131.7, 121.5, 108.7, 108.3, 100.9, 72.5, 38.7, 37.3, 34.2; HRMS (EI, *m/z*) Calc. for $C_{12}H_{12}O_4$: 220.07356. Found: 220.07341.

*Preparation of (±)-yatein (**11**)*

To a solution of **21** (0.12 g, 0.54 mmol) in anhydrous THF (5 mL), at –78 °C and in an inert gas atmosphere, was added a freshly prepared 1mol L^{-1} LDA solution (0.6 mL, 0.6 mmol). The temperature was raised until the room one and then the system was cooled again to –78 °C and stirred for 30 min. After that, a solution of 5-(bromomethyl)-1,2,3-trimethoxybenzene (0.71 g, 2.72 mmol) in anhydrous THF (0.5 mL) was added. The final mixture was stirred after 6 h. Then, a saturated solution of ammonium chloride (1 mL) was added and the reaction was extracted with ethyl acetate (30 mL). The organic phase was washed with distilled water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. After solvent removal, the residue was purified by flash silica gel column chromatography (hexane:AcOEt, 8:2, v/v) to provide (±)-yatein (**11**) as a fluid tinged yellow oil, in 80% yield. IR ν_{max}/cm^{-1} 2994, 2941, 2839, 1768, 1593, 1507, 1486, 1458, 1417, 1331, 1245, 1127, 1037, 1017 (film); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.68 (d, 1H, *J* 6.9 Hz), 6.47 (dd, 1H, *J* 1.6 and 6.9 Hz), 6.44 (bs, 1H), 6.35 (s, 2H), 5.92 (m, 2H), 4.18 (dd, 1H, *J* 7.1 and 9.3 Hz), 3.90-3.84 (m, 1H), 3.84 (s, 3H), 3.82 (s, 6H), 2.95-2.85 (m, 2H), 2.70-2.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 178.1, 153, 147.7, 146.2, 136.7, 133.1, 131.3, 121.4, 108.6, 108.2, 106.2, 101, 71.4, 60.9, 56.1, 46.5, 41, 38.4, 35.3; HRMS (EI, *m/z*) Calc. for $C_{22}H_{24}O_7$: 400.15220. Found: 400.15198.

*Preparation of (±)-podorhizol (**12**) and (±)-epi-podorhizol (**13**)*

To a solution of **21** (0.1 g, 0.44 mmol) in anhydrous THF (5 mL), at –78 °C and under an inert gas atmosphere, was added a solution of freshly prepared lithium diisopropylamine (LDA, 0.2 mol L^{-1}, 0.26 mL, 0.42 mmol). The resulting solution was allowed to warm to 0 °C during 30 min. After the solution was cooled again to –78 °C and stirred after 30 min. Then a solution of 3,4,5-trimethoxybenzaldehyde (0.08 g, 0.44 mmol) in anhydrous THF (2 mL) was added. The resulting solution was stirred after 1 h, at –78 °C. Then the reaction was

quenched with a saturated solution of ammonium chloride (10 mL) and warmed to the room temperature. The medium was extracted with ethyl acetate (30 mL) and the organic phase was washed with distilled water (2 × 10 mL) and dried over anhydrous Na_2SO_4. The isomers were separated by flash silica gel column chromatography (CH_2Cl_2:MeOH, 98:2, v/v) to afford **12** and **13** in a combined yield of 80%.

*(±)-Podorhizol (**12**)*: Yield: 41%; mp 123-125 °C (124-126 °C)[29]; IR ν_{max}/cm^{-1} 3500, 1762, 1590, 1490 (KBr); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 (s, 2H), 6.59 (d, 1H, *J* 7.7 Hz), 6.30 (dd, 1H, *J* 7.8 and 1.5 Hz), 6.22 (d, 1H, *J* 1.5 Hz), 5.92 (dd, 2H, *J* 1.4 and 1.4 Hz), 5.25 (d, lH, *J* 2.9 Hz), 4.39 (dd, lH, *J* 8.7 and 8.0 Hz), 3.97 (dd, lH, *J* 8.7 and 8.9 Hz), 3.83 (s, 3H, 3.82 (s, 6H), ca. 2.80 (m, lH), 2.62 (dd, lH, *J* 6.1 and 2.9 Hz), 2.47 (dd, lH, *J* 13.7 and 7.7 Hz), 2.25 (dd, lH, *J* 3.7 and 8.1Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 178.3, 153.4 (2 × C), 147.9, 146.3, 137.6, 136.8, 131.5, 121.5, 108.6, 107.9, 102.6, 101.1, 72.8, 72.1, 60.8, 56.2 (2 × OCH_3), 52.8, 39.4, 36.4

*(±)-epi-Podorhizol (**13**):* Yield: 39%; mp 132-133 °C (133-134 °C)[29]; IR[29c] ν_{max}/cm^{-1} 3500, 3010, 2780, 1760, 1600, 1510, 1490, 1230, 1120, 925 (film-$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (d, 1H, *J* 8.2 Hz), 6.65(s, 2H), 6.34 (dd, 1H, *J* 8.21 and 7 Hz), 6.33(d, 1H, *J* 1.7Hz), 5.92 (dd, 2H, *J* 1.4 and 1.4 Hz,-OCH_2O-) ,4.79 (d, 1H, *J* 7.9 Hz), 4.18 (dd, 1 H, *J* 9.3 and 7.8 Hz), 3.92 (dd, 1H, *J* 9.3 and 8.4 Hz), 3.88 (s, 6H), 3.83 (s, 3H), 2.62 (dd, 1H, *J* 9.1 and 7.8 Hz), *ca*. 2.50 (m, lH), 2.20 (dd, 1H, *J* 13.8 and 8.9 Hz), 2.12 (dd, 1H, *J* 13.7 and 5.4Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 153.8 (2 × C), 148.1, 146.6, 138.7, 135.8, 131.6, 121.5, 108.7, 108.4, 104.1 (2 × C), 101.1, 74.7, 72, 61, 56 (2 × C), 51.7, 38.9, 38.3.

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