Pergamon

Tetrahedron 57 (2001) 5137–5148

TETRAHEDRON

Cycloisomerization of 1,6-enynes in organoaqueous medium: an efficient and eco-friendly access to furan derivatives. Synthesis of a key intermediate of podophyllotoxin

Jean-Christophe Galland, Sonia Dias, Monique Savignac and Jean-Pierre Genêt*

Ecole Nationale Supérieure de Chimie de Paris, Laboratoire de Synthèse Sélective Organique et Produits Naturels, UMR CNRS 7573, 11, rue Pierre et Marie Curie, 75231 Paris, France

Dedicated to Professor Barry M. Trost on the occasion of his 60th birthday

Received 5 February 2001; revised 28 February 2001; accepted 1 March 2001

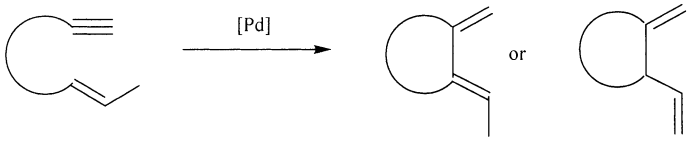
Abstract—The first cycloisomerization of enynes catalyzed by $Pd(TPPTS)_3$ catalyst in aqueous medium to give functionalized furans is described. This new reaction has been applied to the synthesis of podophyllotoxin analog.

1. Introduction

Green chemistry has emerged as a major concern in the field of chemistry and especially organic chemistry. In academic and industrial laboratories, the idea to devise new processes that are at the same time efficient, straightforward and respectful of the environment has slowly asserted itself as a natural way to conduct organic synthesis. Trost has given a determining contribution to this new 'eco-friendly' way of thinking by introducing the principle of 'atom economy';[1] optimizing a chemical process by utilizing simple substrates and minimizing the number of reactants can obviously lead to a dramatic decrease of the wastes and effluents. A striking example of an 'atom-economical' reaction is the palladium-catalyzed cycloisomerization of enynes.[2] In this process, 1,6- or 1,7-enynes can be directly converted to the corresponding cyclic dienes as depicted in Scheme 1.

This reaction offers an efficient access to five- or six-membered rings by using easily accessible starting materials. Both Pd(II)[3] and Pd(0)[4] can catalyze the cycloisomerization; in the latter case, a catalytic amount of acetic acid and of a phosphine is frequently required to run the reaction correctly. Palladium-catalyzed cycloisomerization can be applied to a large variety of 1,6-enynes substituted in the four position by a carbon[5] or another heteroelement such as nitrogen[6a] or oxygen.[6b] Enediynes,[7a] triynes[7b] and polyenynes[7c] may also be used to generate polycyclic compounds. The reaction is tolerant towards various functional groups including esters, alcohols, ethers and ketals. Therefore, several natural products have been synthesized using palladium-catalyzed cycloisomerization as a key step and taking advantage of the resulting 1,3-dienic framework.[8] The most recent developments of the reaction deal with the use of other transition metals including rhodium,[9] ruthenium,[10] platinum[11] and titanium[12] or the use of chiral ligands to control the stereoselectivity.[13]

In the course of our studies on homogeneous catalysis in organoaqueous medium,[14] we thought it would be advantageous to run the palladium-catalyzed cycloisomerization of 1,6-enynes using a water-soluble catalyst. Indeed, the use



Scheme 1.

Keywords: carbohydroxypalladation; organoaqueous medium; enynes; palladium; podophyllotoxin.
* Corresponding author. Tel.: +33-1-4427-6743; fax: +33-1-4407-1062; e-mail: genet@ext.jussieu.fr

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00368-4

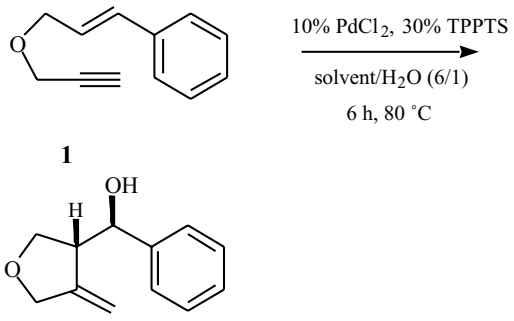
of an 'eco-friendly' solvent such as water and the ability to recover the catalyst by a simple decantation offer two supplementary economical and ecological assets.

The use of the trisulfonated phosphine TPPTS[15] is a widespread way to make a catalyst soluble in an aqueous medium. A remarkable example is the Rh/TPPTS 'Rhurchemie—Rhône Poulenc' hydroformylation process.[16] In the case of Pd/TPPTS catalytic systems, many industrial applications such as carbonylation[17b] or oligomerization[17c] have also been published recently.[17a] Our major contribution in this field has rather focused on the use of in situ water-soluble palladium catalysts in fine chemical organic reactions. We have developed a large number of cross-coupling reactions such as Suzuki–Miyaura,[18] 'copper free' Sonogashira,[19] Tsuji–Trost[20] or Heck reactions in inter-[19] and intramolecular[21] versions under mild conditions. The catalyst was proved to be a true Pd(0) species.[22] Water-soluble palladium catalysts have also been successfully utilized in order to remove allyloxycarbonyl protective group (Alloc) from acids, alcohols or amines.[23]

All these examples illustrate the possibility to conduct classical organometallic reactions in aqueous media. By applying this methodology to the cycloizomerization of 1,6-enynes, we thought it would be possible to associate an environmentally benign process with an environmentally friendly solvent.

2. A new 'carboxydroxypalladation' reaction[24]

Our first attempt to carry out a cycloisomerization reaction in an organoaqueous medium was directed towards the easily accessible cinnamylpropargyl ether **1**. The water-soluble palladium catalyst was preformed from $PdCl_2$ and TPPTS in water (1 h at 80°C) and the reaction was conducted at 80°C in a homogeneous mixture of acetonitrile and water. After 6 h of reaction, we were pleased to find that the starting material had been mainly converted into a new polar product which apparently was not the expected diene. Careful NMR analysis showed that this new product was the 4-α-hydroxyfuran derivative **2**. The experimental conditions were optimized in order to improve the yield of the reaction. As can be seen in Table 1, the 3-exomethylene-4-α-hydroxyfuran turned out to be very sensitive to acidic media and consequently to the purification conditions. Silica gel or neutral alumina were too aggressive and led to an extensive decomposition of the product. Fortunately, Florisil® was sufficiently neutral to isolate the furan in good conditions. The solvent used concomitantly with water appeared to have a great influence on the activity of the catalyst. The reaction turned out to be very sluggish using DMF or THF (entries 1–3). A dramatic improvement was obtained by using acetonitrile (entry 4) or 1,4-dioxane. In the latter case, a temperature of 80°C allowed us to complete the reaction within 3 h and to obtain the expected product in 85% yield after purification on Florisil® (entry 6).



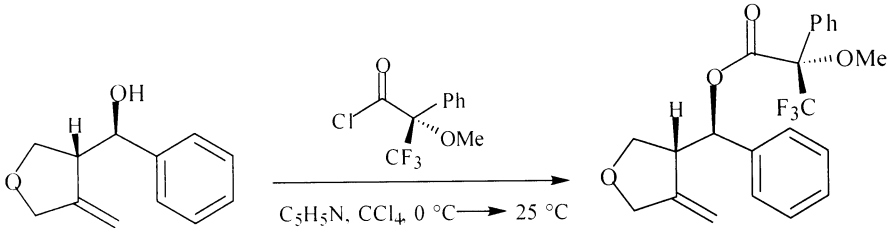
1 **2**

3. Structure determination

Compared to the classical cycloisomerization, several features are noteworthy: the carbohydroxypalladation is highly diastereoselective; the NMR spectra were consistent with the presence of a unique diastereomer. This could be confirmed by derivatization of the crude alcohol with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic chloride

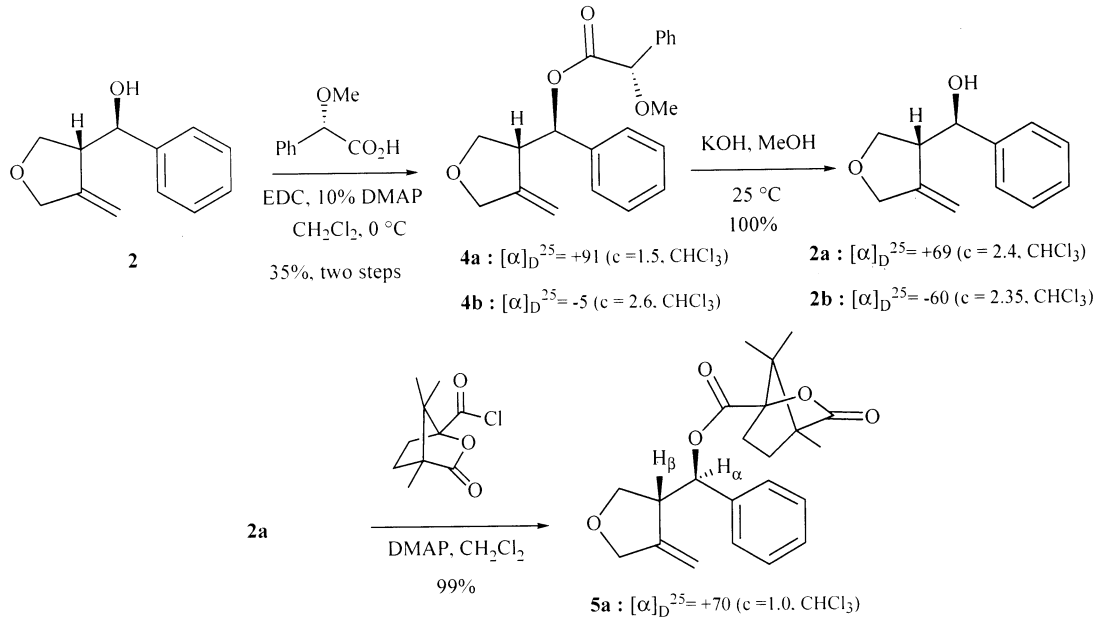
Table 1.

Entry	Solvent	Temperature (°C)	Time (h)	Purification	Yield (%)
1	DMF	65	48	–	<10
2	THF	65	45	Silica gel	28
3	THF	65	72	Neutral alumina	62
4	CH_3CN	65	7	Silica gel	44
5	CH_3CN	80	6	Neutral alumina	66
6	1,4-Dioxane	80	3	Florisil®	85



2 **3** (84%)

Scheme 2.



Scheme 3.

(Mosher's acid chloride). ^{1}H and ^{13}C NMR spectra of the resulting ester **3** were characterized by two sets of signals of equal intensity (Scheme 2). Unfortunately these two diastereomers were inseparable by chromatography.

The carbohydroxypalladation reaction gives rise to 3-exo-methylene-4-α-hydroxyfurans with a high level of stereoselectivity. In order to take advantage of this diastereoselectivity in synthesis applications, the absolute configuration of the furan had to be unambiguously established. Since Mosher's esters **3** could not be separated by column chromatography, we looked for a more convenient chiral auxiliary. (*S*)-(+)-α-Methoxyphenylacetic acid[25] furnished after coupling with **2** the oily diastereomers **4a** and **4b** separable by careful silica gel chromatography. In order to obtain crystallized derivatives, these diastereomers were cleanly saponified to the corresponding optically pure alcohols **2a** and **2b**. Derivatization of the liquid alcohol **2a** using (*S*)-(−)-camphanic acid chloride afforded the optically pure ester **5a** as a crystalline derivative (Scheme 3). X-ray diffraction studies showed an *anti* relationship for the two hydrogen atoms α and β to the hydroxy group and an (*R*,*R*) absolute configuration could be deduced for **2a** from the (*S*) configuration of the chiral camphanic moiety (Fig. 1).

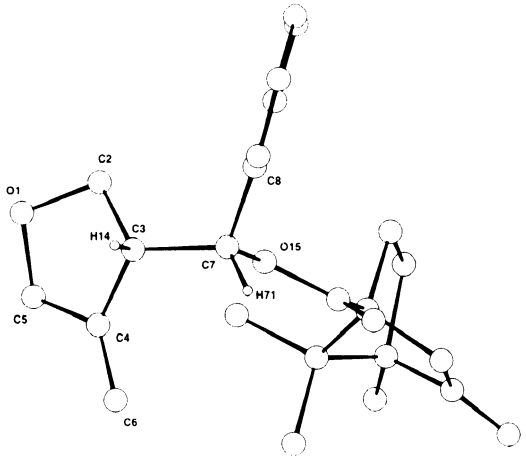


Figure 1.

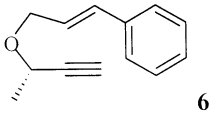
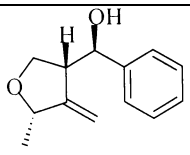
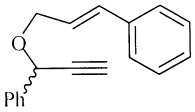
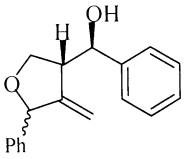
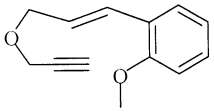
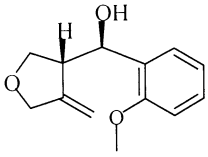
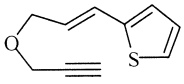
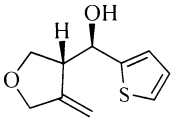
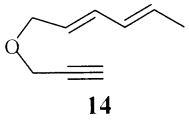
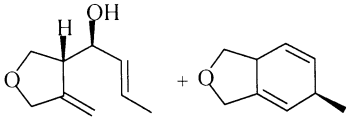
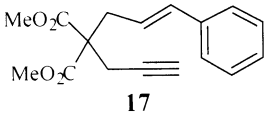
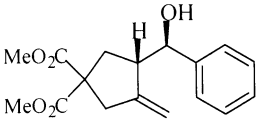
4. Scope and limitations

In order to evaluate the scope of this new reaction, various 1,6-enynes were tested using the optimized experimental conditions (3 h in 1,4-dioxane, purification on Florisil®). The results are summarized in Table 2. The reaction can be applied to a wide variety of propargylic ethers with aromatic or ethylenic groups on the double bond, leading to the corresponding hydroxyfurans with good yields and diastereoselectivities. The starting materials may be substituted on the propargylic position although the reaction times may be longer (entries 1 and 2). It is possible to use substrates bearing a functionalized aromatic ring (entry 3) or even a heteroaromatic nucleus such as thiophene (entry 4). In the case of compound **14** bearing an ethylenic group, the reaction takes place but competes with a palladium-catalyzed [4+2] cycloaddition process[26] leading to the bicyclic product **16**.

Carbocycles such as compound **18** can also be obtained using a carbohydroxypalladation but yields appear to be moderate (entry 6). The reaction entails two major limitations:

- Substrates with an aliphatic chain on the double bond did not give the expected secondary alcohol but a number of unidentified by-products: we assume that a complexation between the palladium and an unsaturated group is necessary to insure an efficient catalytic cycle.
- Propargylic amines did not undergo the reaction

Table 2.

Entry	Substrate	Product	Time (h)	Yield (%)[a]
1	 **6**	 **7**	10	85[b] (58/42)
2	 **8**	 **9**	7	82[b] (58/42)
3	 **10**	 **11**	5	47[c]
4	 **12**	 **13**	5	63[c]
5	 **14**	 **15** **16** (23%)	4.5	18[c]
6[d]	 **17**	 **18**	10	35[c]

[a] Isolated yields.
[b] Two diastereomers (ratio).
[c] Single diastereomer.
[d] Performed in CH_3CN, purification by flash chromatography on silica gel.

properly. Deallylation often competes as well as deactivation of the Pd(0) species by the nitrogen atom.

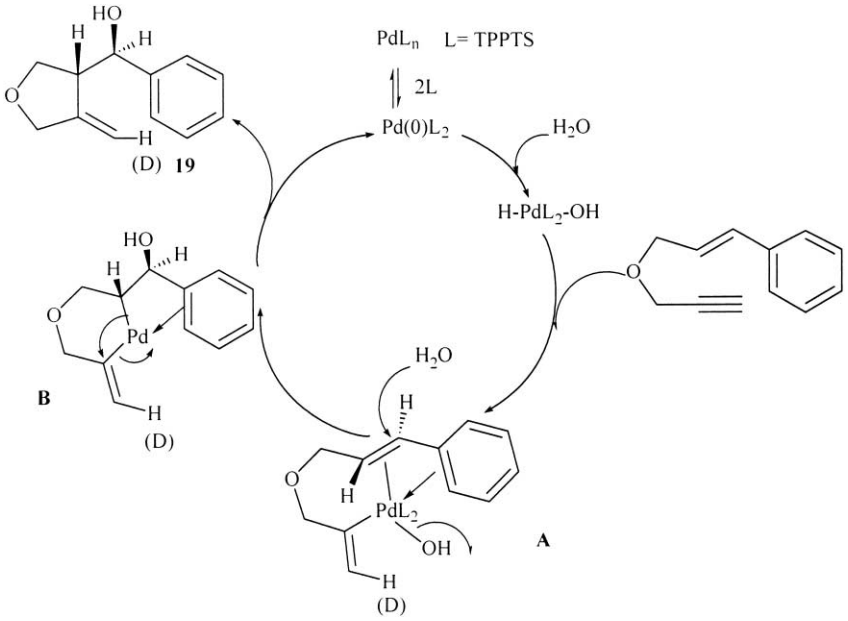
Besides these two limitations, the new carbohydroxypalladation offers an efficient and 'atom-economical' access to valuable cyclic skeletons with a high level of diastereoselectivity.

5. Mechanistic proposals

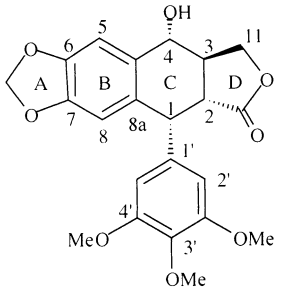
The mechanism of the carbohydroxypalladation reaction is not yet established. However, it is clear that it differs in the last step from the catalytic cycle usually adopted for Trost's cycloisomerizations in anhydrous medium. Carbohydroxypalladation does not require the use of acetic acid. We envisaged the formation of a hydroxypalladate species 'H-Pd-OH' in the first step. This observation is consistent with the formation of deuterated product **19** when the reaction was carried out in D_2O (see catalytic cycle). *Syn* addition on the triple bond of the enyne and subsequent coordination of the vinylpalladate give the intermediate **A**. The formation of a secondary alcohol is obviously related to the use of water. However, a classical cycloisomerization to a cyclic diene followed by a hydration cannot explain the diastereoselectivity of the reaction. One proposal which is consistent with the stereoselective introduction of the hydroxy group could be a 'Wacker-type' process in which intermediate **A** undergoes a nucleophilic attack of water α to the aromatic ring and *anti to the palladium*. Reductive elimination on intermediate **B** yields the expected hydroxyfuran and allows the regeneration of the starting Pd(0) catalyst (Scheme 4).

6. Application to the synthesis of the podophyllotoxin isomer

Podophyllotoxin is the aglycone moiety of etoposide,[27] an important agent commonly used for the treatment of many human malignancies. It is a powerful cytotoxic lignan extracted from the roots and the rhizomes of *Podophyllum peltatum* and *Podophyllum emodi*.[28] Its chemical structure is characterized by an aryltetralin skeleton including four contiguous cycles A–D.



Scheme 4.



Since podophyllotoxin analog is currently used in the treatment of severe forms of lung or testicle cancers, its synthesis has continuously been a challenging matter of interest for organic chemists.[29]

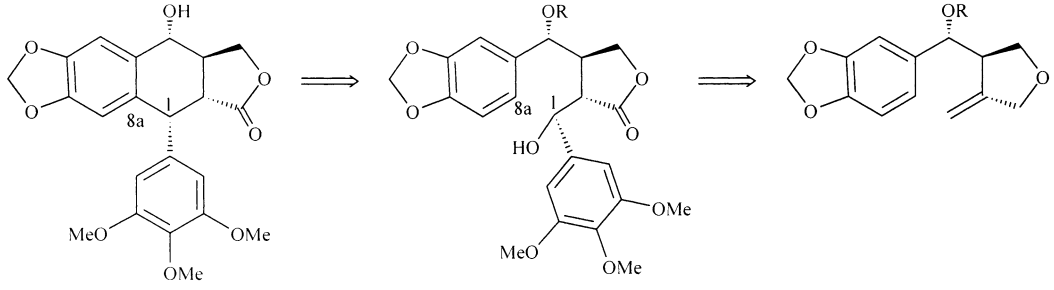
7. Disconnection strategy

Our new carbohydroxypalladation of propargyl cinnamyl ether giving functionalized hydroxyfuran in good yield with the correct *trans* relative configuration of the hydrogen at the C3 and C4 positions present in podophyllotoxin, we envisaged a straightforward approach to this important molecule as shown in the retrosynthetic Scheme 5. The first key step may be achieved by applying Mukaiyama's procedure to oxidize furan ring α to the oxygen atom.[30] Concerning the C ring, we decided to adopt a strategy based on an intramolecular Friedel–Crafts reaction. This kind of cyclization has been thoroughly studied[31] and used successfully by many authors in the synthesis of podophyllotoxin derivatives[32] (Scheme 5).

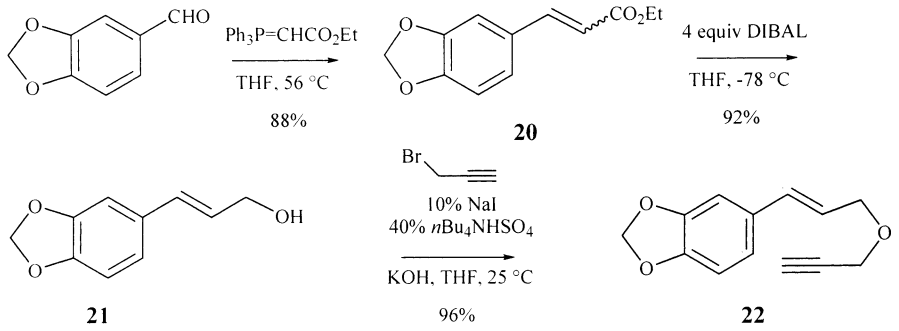
8. Synthesis of the precursor to the Friedel–Crafts reaction

The requisite propargyl ether for the carbohydroxypalladation reaction was prepared in three steps from piperonal in 78% overall yield. Wittig reaction using commercial (carbethoxymethylene)triphenylphosphorane led to the expected unsaturated ester which was conveniently reduced using diisobutylaluminum hydride (DIBAL) in excess. *O*-Alkylation of the resulting primary alcohol under phase transfer conditions furnished the appropriate propargyl ether with an excellent yield (Scheme 6).

The optimized carbohydroxypalladation conditions were successfully applied to substrate **22**. The sensitive hydroxyfuran was isolated in good yield of 84%. As expected, only one diastereomer could be detected by NMR. The hydroxy group was cleanly protected using triisopropylsilyl (TIPS)



Scheme 5.



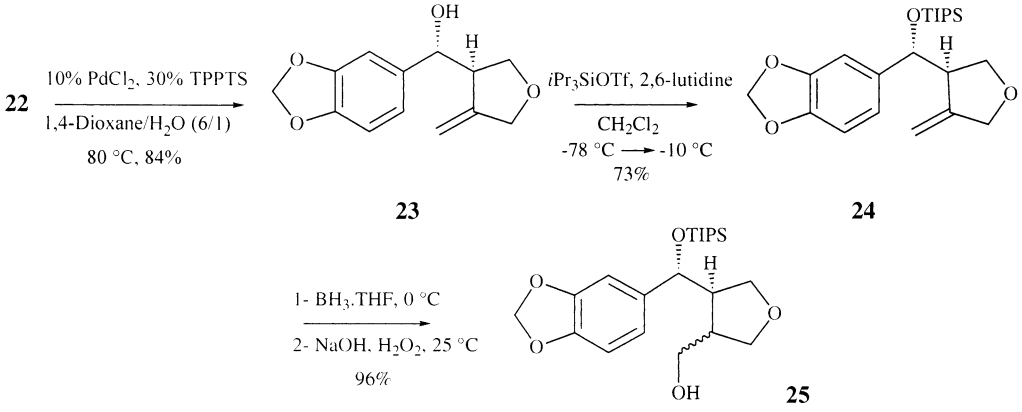
Scheme 6.

trifluoromethanesulfonate under mild conditions The *exo*-double bound was converted into primary alcohol using a classical hydroboration–oxidation sequence (Scheme 7).

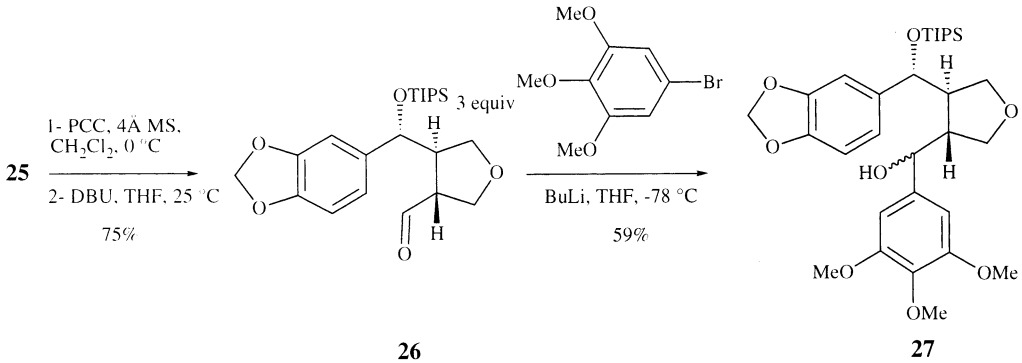
Treatment with PCC in the presence of 4 Å molecular sieves yielded 81% of the corresponding aldehyde as a mixture of two diastereomers (43/57). In accordance with Hannessian's results, the C2 carbon could be partly epimerized under basic conditions (DBU) to give an 84/16 mixture in favor of the more stable C2,C3-*trans* furan ring. At this stage, it was possible to introduce the E ring and generate the precursor to the Diels–Alder reaction by condensation of 3,4,5-trimethoxyphenyllithium on aldehyde **26**. The lithio derivative was prepared by halogen exchange from 1-bromo-3,4,5-trimethoxybenzene[33] using butyllithium at low temperature. Under stoichiometric conditions, only 35% of the expected secondary alcohol could be isolated. This moderate yield was increased to 59% by using three equivalents of 3,4,5-trimethoxyphenyllithium (Scheme 8).

9. Cyclization attempts using an intramolecular Friedel–Crafts reaction

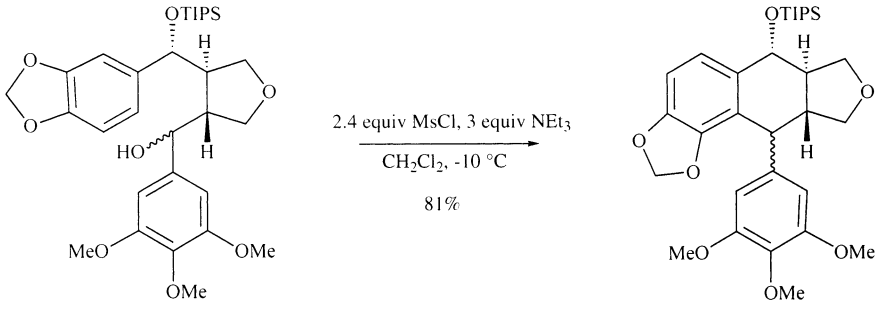
The intramolecular Friedel–Crafts reaction on alcohol **27** was first attempted under acidic conditions. Unfortunately, the use of a strong protic acid (CF_3CO_2H) or a Lewis acid such as $SnCl_4$ resulted in the decomposition of the starting material without any trace of the cyclized product. The Burgess reagent, successfully employed by Vandewalle[34] in the synthesis of (±)-podophyllotoxin and (±)-epi-podophyllotoxin, did not give satisfactory results. It seemed likely that our secondary alcohol **27** was too sensitive to acidic media since only degradation by-products resulting



Scheme 7.



Scheme 8.



27 28

Scheme 9.

from deprotection of the TIPS group could be observed. Taking into account this feature, we tried to undergo the cyclization under basic conditions by using mesyl chloride and triethylamine[34] (Schemes 9 and 10).

Indeed, the intramolecular Friedel–Crafts took place with a good yield. Surprisingly, careful analysis of the NMR spectra showed that the cyclization had occurred on the C5 position of the aromatic ring leading to compound **28** with the methylenedioxy group in the wrong position.

The reason for this unexpected regioselectivity is not established yet, but we may assume that a steric hindrance due to the bulky triisopropylsilyl group and the methylenedioxy moiety brings about the rotation of the B ring and favors the cyclization on the C5 position.

10. Conclusions

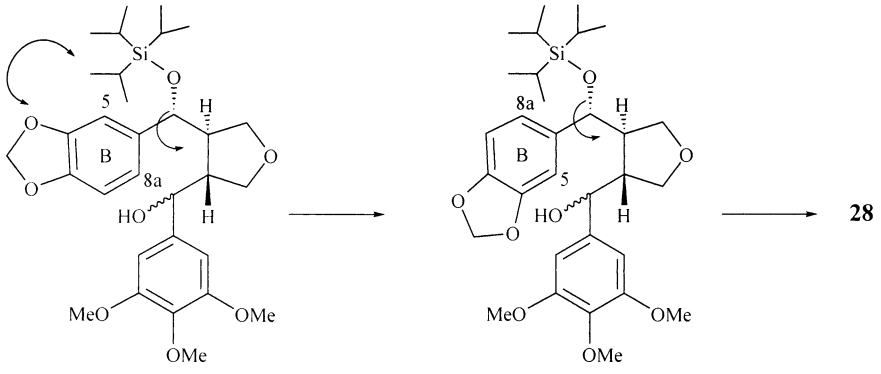
In this paper, we discuss a new reaction named carbohydroxypalladation which could have many applications in synthesis of natural products containing a furan ring. We have illustrated the interest of this methodology in an economical approach of an analog of podophylotoxin. However, the Friedel–Crafts cyclization affords the wrong isomer. Other routes for the production of podophyllotoxin itself which could have interesting biological activity are underway using the valuable hydroxyfuran intermediate **23**.

11. Experimental

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium–benzophenone. Dichloromethane (CH_2Cl_2) and dimethylformamide (DMF) were distilled over CaH_2. The other solvents (dioxane, acetonitrile, etc.) were used without further purification. All reactions were conducted under argon atmosphere, unless obviously unnecessary or otherwise specified. Column chromatography was performed using silica gel and thin-layer chromatography was carried out on E. Merck ref. 5554 precoated silica gel 60 E_{254} plates. Melting points are uncorrected and were measured on a Kofler melting point apparatus or on a Buchi apparatus. ^1H and ^{13}C NMR spectra were recorded on a Brucker AM 200 using $CDCl_3$ as solvent, unless otherwise indicated (δ ppm). Infrared spectra (IR, cm^{-1}) were recorded on a Brucker IFS 48 Fourier transform infrared spectrometer. Mass spectra were obtained on a Hewlett–Packard HP 5989 A coupling with a Hewlett–Packard HP 5890 gas chromatographs fitted with a Chrompack CPSi 15. Regional Microanalysis Service of P. et M. Curie University performed elemental analyses.

11.1. General procedure for carbohydroxypalladation in aqueous medium

All the solvents were degassed before used. A mixture of $PdCl_2$ (mol 10%), sodium triphenylphosphinosulfonate (TPPTS) (mol 30% in water) and H_2O (0.25 mL for 10^{-3} mol) was heated at 80°C for 30 min. The dark red solution was cooled to 50°C and a solution of propargyl ether



Scheme 10.

(1 equiv.) in dioxane (1.5 mL per 10^{-3} mol) was added dropwise. The mixture was heated at 80°C under stirring and the evolution was monitored by TLC. After cooling to room temperature, it was diluted with H_2O (3 mL per 10^{-3} mol) and extracted with Et_2O (4×10 mL). Organic layer was dried on Na_2SO_4, filtered and concentrated in vacuo. The residue was filtered or subjected to flash chromatography on Florisil (eluent, EtOAc/cyclohexane: 1/9).

11.1.2. 4-Exomethylene-3-(hydroxy)(phenyl)methyltetrahydrofuran (2). 161 mg, 85% as orange oil; ^{1}H NMR δ: 2.41 (1H, d, ^3J=3.2 Hz, OH), 3.1–2.9 (1H, m, HC), 4.13 and 3.86 (2H, 2dd, ^2J=9 Hz, ^3J=4.9 Hz and ^3J=6.8 Hz, CH_2), 4.4–4.2 (2H, m, CH_2), 4.59 (2H, 2q, ^4J=2.1 Hz, H_2C=), 4.78 (1H, dd, ^3J=6.5 Hz, ^3J=2.1 Hz, HC-OH), 4.96 (1H, q, ^4J=2.1 Hz, H_2C=), 7.4–7.2 (5H, m, H_{arom}); ^{13}C NMR δ: 51.0, 70.27, 71.82, 74.58, 106.23, 126.35, 127.64, 128.26, 142.38, 147.98; IR (neat): 3420, 1663, 1630, 1091, 1077, 1066; MS (DCI/NH_3 m/z): 208 $(M+NH_4^+)$, 190 $(M+NH_4-H_2O)^+$, 173 $(M-H_2O+H)^+$. Anal calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 72.82; H, 6.90.

11.1.3. 4-Exomethylene-3-[(*S*)-2-methoxy-2-trifluoromethyl-2-phenylacetoxy](phenyl)methyltetrahydro-furan (3). To a solution of **2** (138 mg, 0.72 mmol) in CCl_4 (5 mL) were added pyridine (2.9 mL, 36.3 mmol) and Mosher acid chloride (270 μL, 1.45 mmol) at 0°C. After stirring overnight at room temperature, the solution was neutralized with 3-dimethylamino-1-propargylamine (0.5 mL) and diluted with Et_2O. The organic layer was washed with 1 M HCl solution, dried on Na_2SO_4, filtered, and concentrated in vacuo to afford 247 mg of **3** (84%). R_f=0.42 (AcOEt/cyclohexane: 3/7); ^{1}H NMR δ diastereomers: 3.3–3.1 (1H, m, CH), 3.42 (3H, d, J=1.3 Hz, CH_3O) and 3.51 (3H, d, J=1.3 Hz, CH_3O), 3.9–3.7 (1H, m, CH_2) and 3.95 (1H, d, ^3J=6.2 Hz, CH_2), 4.21 (2H, s), 4.28 (2H, s), 4.85 (2H, d, ^4J=2.1 Hz, CH_2=) and 4.92 (2H, d, ^4J=2.1 Hz, CH_2=), 5.93 (1H, d, ^3J=7.8 Hz, CHO) and 5.95 (1H, d, ^3J=8.6 Hz, CHO), 7.5–7.1 (8H, m, H_{arom}), 8.62 (2H, d, ^3J=4.2 Hz, H_{arom}).

11.1.4. (3*R*)-4-Exomethylene-3-[(*R*)-[(*S*)-2-methoxy-2-phenylacetoxy](phenyl)methyl]tetrahydrofuran (4a). (3*S*)-4-Exomethylene-3-[(*S*)-[(*S*)-2-mehoxy-2-phenylacetoxy]-(phenyl)methyl] tetrahydrofuran (4b). To a solution of alcohol **2** (292 mg, 1.54 mmol), DMAP (19 mg, 0.15 mmol) and (*S*)-(+)-α-methoxyphenylacetic acid in CH_2Cl_2 (3 mL) was added EDC (323 mg, 1.69 mmol) at 0°C. The solution was stirred for 1 h at 0°C then concentrated in vacuo. The residue was hydrolyzed with H_2O (10 mL) and extracted with Et_2O (3×30 mL). The combined organic layers were washed successively with saturated $NaHCO_3$ and saturated NaCl solutions, dried (Na_2SO_4) and concentrated in vacuo. The crude product was filtered on silica gel chromatography (eluent, EtOAc/cyclohexane) to afford 85 mg of **4a** and 109 mg of **4b**; ^{1}H NMR δ: diastereomer **4a**: 3.05–3.15 (1H, m, CH), 3.40 (3H, s, CH_3O), 3.51 (1H, dd, ^2J=9.1 Hz, ^3J=5.9 Hz, CH_2), 3.65 (1H, dd, ^2J=9.1 Hz, ^3J=7.0 Hz, CH_2), 3.90 (1H, dd, ^2J=13.1 Hz, ^4J=2.1 Hz, CH_2), 4.12 (1H, d, ^2J=13.1 Hz, CH_2), 4.36 (1H, dd, ^4J=4.4 Hz, ^4J=2.3 Hz, CH_2=), 4.71 (1H, dd, ^4J= 4.1 Hz, ^4J=2.1 Hz, CH_2=), 4.77 (1H, s, CHO-CH_3), 5.87 (1H, d, ^3J=7.4 Hz, CHO), 7.5–7.25 (10H, m, H_{arom}); diastereomer **4b**: 3.2–3.1 (m, 1H), 3.40 (3H, s, CH_3O), 3.86 (2H, d, ^3J=6.8 Hz, CH_2), 4.26 (2H, s, CH_2), 4.48 (1H, dd, ^4J=4.4 Hz, ^4J=2.3 Hz, CH_2=), 4.80 (1H, s, CHO-CH_3), 4.88 (1H, dd, ^4J=2,0 Hz, CH_2=), 5.85 (1H, d, ^3J=7.3 Hz, CHO), 7.4–6.9 (10H, m, H_{arom}); ^{13}C NMR δ: diastereomer **4a**: 49.0, 57.6, 70.5, 72.0, 76.4, 82.9, 107.2, 127.4, 127.7, 128.6, 128.7, 128.9, 129.2, 136.5, 138.6, 146.5, 169.9; diastereomer **4b**: 49.3, 57.7, 70.7, 72.1, 76.6, 82.9, 107.4, 127.0, 127.5, 128.3, 128.4, 128.9, 129.0, 136.2, 138.4, 146.6, 169.8; IR (neat): 3064, 3033, 1754, 1198, 1172, 1114, 1076; MS (DCI/NH_3 m/z): 356 $(M+NH_4)^+$, 339 $(M+H)^+$.

11.1.5. 4-Exomethylene-3-(hydroxy)(phenyl)methyltetrahydrofuranyl (*S*)-(−)-camphanic ester (5a). To a solution of alcohol **2a** (48 mg, 0.252 mmol) and DMAP (308 mg, 2.52 mmol) in CH_2Cl_2 (1 mL) was added (*S*)-camphoric acid chloride (82 mg, 0.378 mmol). The solution was stirred overnight at room temperature and hydrolyzed with saturated $NaHCO_3$ solution (4 mL) and H_2O (6 mL). After extraction with Et_2O (3×20 mL), the combined organic layers were washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified on silica gel chromatography (eluent, EtOAc/cyclohexane: 3/7) to afford 89 mg of **5a** (99%). Recrystallization from CCl_4; R_f=0.28 (AcOEt/cyclohexane: 3/7); m.p. 132°C; $[\alpha]_D^{25}$=+70 (c=1.03; $CHCl_3$); ^{1}H NMR δ: 0.98, 0.81 (6H, 2s, $2CH_3$), 1.09 (3H, s, CH_3), 1.8–1.6 (1H, m, CH_{2cycle}), 2.1–1.85 (2H, m, CH_{2cycle}), 2.55–2.3 (1H, m, CH_{2cycle}), 3.35–3.2 (1H, m, CH), 3.98 (2H, d, ^3J=6.7 Hz, CH_2), 4.3 (2H, s, CH_2), 4.46 (1H, m, ^4J=2.3 Hz, ^4J=2.1 Hz, CH_2) 4.91 (1H, q, ^4J=2.1 Hz, CH_2), 5.91 (1H, d, ^3J=8.0 Hz, CHO), 7.28 (5H, s, H_{arom}); ^{13}C NMR δ: 9.5, 16.5, 28.8, 30.7, 48.8, 54.2, 54.7, 70.6, 71.7, 76.8, 90.8, 107.4, 127.2, 128.3, 138.0, 146.0, 166.5, 178.2; IR (KBr): 1778, 1747, 1065, 1045. MS (DCI/NH_3 m/z): 388 $(M+NH_4)^+$.

11.1.6. (5*S*)-4-Exomethylene-5-methyl-3-(hydroxy)(phenyl)-methyltetrahydrofuran (7). 175 mg, 85% as yellow oil as diastereomers; ^{1}H NMR δ: 2.91 (1H, d, ^3J=3.2 Hz, OH), 3.0–3.15 (1H, m, HC), 4.12 and 3.94 (2H, 2dd, ^2J=9.1 Hz, ^3J=4.8 Hz and ^3J=6.7 Hz, CH_2), 4.15–4.4 (2H, m, CH_2), 4.68 (1H, dd, ^2J=2 Hz, and ^4J=2.4 Hz, H_2C=), 4.9–5.05 (2H, 2m, H_2C= and HC), 7.2–7.4 and 6.8–7.1 (3H, 2m, H_{arom}); ^{13}C NMR δ: 51.00, 70.48, 71.00, 71.76, 106.49, 124.49, 124.79, 126.46, 146.51, 147.49; IR (neat): 3394, 2855, 1734, 1664, 1439, 1302, 1235, 1066; MS (DCI/NH_3 m/z): 214 $(M+NH_4)^+$, 196 $(M+NH_4-H_2O)^+$, 179 $(M-H_2O+H)^+$. Anal calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.09; H, 7.64.

11.1.7. 4-Exomethylene-3-(hydroxy)(phenyl)methyl-5-phenyltetrahydrofuran (9). 176 mg, 82% as yellow oil as diastereomers; ^{1}H NMR δ: major diastereomer 2.4 (1H, s, OH), 3.15–3.40 (1H, m, HC), 4.14 (2H, d, ^3J= 7.4 Hz, CH_2), 4.70–4.85 (2H, m, CH_2=), 4.93 (1H, d, ^3J= 5.9 Hz, HC-OH), 5.24 (1H, ^4J=2.0 Hz, HC), 7.7–7.0 (10H, m, H_{arom}); minor diastereomer 3.10–3.25 (1H, m, HC), 4.00 (1H, ^2J=9.2 Hz, ^3J=6.7 Hz, CH_2), 4.60 (1H, ^2J=9.2 Hz, ^3J=3.1 Hz, CH_2), 4.52 (1H, t, ^4J=2.2 Hz, CH_2=), 4.70–4.85 (1H, m, CH_2=), 4.70–4.85 (1H, HC-OH); ^{13}C NMR δ: 51.5 and 51.3, 68.8 and 69.3, 74.4 and 75.0, 84.0, 108.8, 126.2, 127.0, 127.8, 128.4, 140.7 and 140.9, 142.2 and 142.3, 151.9 and 151.1; MS (m/z): 248 $(M-H_2O)^+$.

11.1.8. 4-Exomethylene-3-(hydroxy)(2-methoxyphenyl)-methyletrahydrofuran (11). 260 mg, 47% as orange oil; ^{1}H NMR δ: 2.73 (1H, d, ^3J=6.3 Hz), 3.1–3.3 (1H, m, CH), 3.7–3.9 (4H, m, CH_2, CH_3), 4.16 (1H, dd, ^2J= 9.0 Hz, ^3J=4.6 Hz, CH_2), 4.27 (1H, d, ^2J=13.3 Hz, CH_2), 4.4 (1H, dq, ^2J=13.3 Hz, ^4J=1.9 Hz, CH_2), 4.63 (1H, q, ^4J=2.2 Hz, HC), 4.9–5.05 (2H, m, H_2C=CHOH), 6.7–7.0 (2H, m, H_{arom}), 7.2–7.4 (2H, m, H_{arom}); ^{13}C NMR δ: 49.2, 55.1, 70.4, 71.7, 71.8, 105.6, 110.2, 120.4, 127.7, 128.4, 130.1, 148.8, 156.3; IR (neat): 3410, 1605, 1590, 1050, 1070, 1066; MS (m/z): 220 $(M)^+$, 202 $(M-H_2O)^+$. Anal calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 69.68; H, 7.09.

11.1.9. 4-Exomethylene-3-(hydroxy)(thien-2-yl)methyl-tetrahydrofuran (13). 142 mg, 63% as orange oil; ^{1}H NMR δ: 2.91 (1H, d, ^3J=3.9 Hz, OH) 3.0–3.15 (1H, m, CHOH), 3.94 (1H, dd, ^2J=9.1 Hz, ^3J=6.7 Hz, CH_2), 4.12 (1H, dd, ^2J=9.1 Hz, ^3J=4.8 Hz, CH_2), 4.15–4.4 (2H, m, CH_2), 4.68 (1H, dd, ^4J=2.0 Hz, ^4J=2.2 Hz, H_2C=), 4.9–5.05 (2H, m, H_2C=, CHOH), 6.8–7.1 (2H, m, H_{arom}), 7.2–7.4 (1H, m, H_{arom}); ^{13}C NMR δ: 51.3, 70.5, 71.0, 71.8, 106.6, 124.8, 126.6, 146.6, 147.5; IR (neat): 3394, 1664, 1535, 1066; MS (DCI/NH_3 m/z): 214 $(M+NH_4)^+$, 196 $(M+NH_4-H_2O)^+$. Anal calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16. Found: C, 62.14; H, 6.02.

11.1.10. 4-Exomethylene-3-[(*E*)-1-hydroxybut-2-en-1-yl]-tetrahydrofuran (15). 22 mg, 18% as a yellow oil. ^{1}H NMR δ: 1.15 (3H, d, ^3J=7.4 Hz, CH_3), 2.75–3.0 (1H, m, CH), 3.2–3.3 (1H, dd, ^2J=7.1 Hz, ^3J=10.9 Hz, CH_2), 4.21 (1H, t, ^2J= ^3J=7.1 Hz, CH_2), 4.27 (1H, d, ^2J=12.1 Hz, CH_2), 4.44 (1H, dm, ^2J=12.1 Hz, CH_2), 5.43 (1H, s, HC=), 5.71 (2H, s, HC=); ^{13}C NMR δ: 21.6, 29.6, 39.4, 69.2, 72.1, 73.3, 120.9, 121.9, 133.7, 137.8.

11.1.11. 3-Methyl-8-oxabicyclo[4.3.0]nona-1(2),4-diene (16). 25 mg, 23% as yellow oil; ^{1}H NMR δ: 1.75 (3H, d, ^3J=6.3 Hz, CH_3), 2.75–2.9 (1H, m, CH), 4.0 (2H, dd, ^3J= 5.7 Hz, ^4J=2.2 Hz, CH_2), 4.2–4.4 (3H, m, CH_2, CHOH), 5.05–5.15 (2H, m, H_2C=), 5.53 (1H, ddm, $^3J_{trans}$=15.3 Hz, ^3J=6.7 Hz, HC=), 5.65–5.9 (1H, m, HC=); ^{13}C NMR δ: 22.0, 49.5, 70.0, 71.9, 73.3, 148.6, 131.6, 128.1, 105.8; IR (neat): 3425, 1667, 1078; MS (DCI/NH_3 m/z): 172 $(M+NH_4)^+$, 154 $(M+NH_4-H_2O)^+$.

11.1.12. 1,1-Bis(methoxycarbonyl)-4-exomethylene-3-(hydroxy)(phenyl)methylcyclopentane (18). 37 mg, 35% as a yellow oil; ^{1}H NMR δ: 2.16 (1H, s, OH), 2.24 (1H, d, ^3J=7.4 Hz, CH_2), 2.28 (1H, d, ^3J=9.2 Hz, CH_2), 2.9–3.15 (1H, m, CH), 3.0 (2H, s, CH_2), 3.69 (3H, s, CH_3), 3.73 (3H, s, CH_3), 4.93 (1H, q, ^4J=2.3 Hz, CH_2=), 5.0 (1H, d, ^4J=4.0 Hz, CHOH), 5.15 (1H, q, ^4J=2.3 Hz, H_2C=), 7.3–7.5 (5H, m, H_{arom}); ^{13}C NMR δ: 33.6, 42.0, 49.6, 52.7, 58.6, 73.9, 108.2, 125.7, 127.2, 128.2, 142.5, 148.8, 172.0; IR (neat): 3582, 1734, 1661, 1602, 1261, 1066; MS (m/z): 286 $(M-H_2O)^+$, 227 $(M-C_6H_5)^+$. Anal calcd for $C_{17}H_{20}O_6$: C, 67.09; H, 6.62. Found: C, 66.14; H, 6.47.

11.1.13. Ethyl (2*E*)-3-[(3,4-methylenedioxy)phenyl]prop-2-enoate (20). A solution of piperonal (3 g) in THF was added to 3 g of (ethoxycarbonylmethylene)triphenylphosphorane. The mixture was refluxed for 6 h, cooled to room temperature, diluted with Et_2O and filtered. The organic layer was washed, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (eluent CH_2Cl_2) to afford 3.88 g of a yellow solid (88%), m.p. 62°C; ^{1}H NMR δ: 1.26 (t, ^3J= 7.1 Hz, 3H), 4.18 (q, ^3J=7.1 Hz, 2H), 5.91 (s, 2H), 6.18 (d, $^3J_{trans}$=15.9 Hz, 1H), 6.71 (d, ^3J=7.9 Hz, 1H), 7.6–8.0 (m, 2H), 7.50 (d, $^3J_{trans}$=15.9 Hz, 1H); ^{13}C NMR δ: 14.2, 60.1, 101.4, 106.3, 108.3, 116.0, 124.2, 128.7, 144.0, 148.2, 149.4, 166.9; IR (KBr): 3052, 3031, 1703, 1642, 1611, 1504, 1175, 929. MS (m/z): 220 (M^+), 175 $(M-OCH_2CH_3)^+$, 148 $(M-CO_2Et+H)^+$.

11.1.14. (2*E*)-3-[(3,4-Methylenedioxy)phenyl]prop-2-en-1-ol (21). To a solution of ester **20** (3.68 g, 16.7 mmol) in dry THF (60 mL) was added dropwise a DIBAL molar solution (66.8 mL, 66.8 mmol) at −78°C. After stirring the mixture for 2 h 30 min, it was hydrolyzed dropwise with H_2O (20 mL) stirring for 30 min at room temperature. The gel was filtered and washed with Et_2O. After extraction of aqueous layer with Et_2O, the combined organic layers were washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated in vacuo. The crude product was filtered on silica gel chromatography to afford 2.74 g of **21** as a natural solid. R_f=0.11 (AcOEt/cyclohexane: 2/8), m.p. 82°C. ^{1}H NMR δ: 2.01 (s, 1H), 4.27 (d, ^3J=5.8 Hz, 2H), 5.94 (s, 2H), 6.18 (dt, $^3J_{trans}$=15.8 Hz, ^3J=5.8 Hz, 1H), 6.51 (d, $^3J_{trans}$=15.8 Hz, 1H), 6.7–7.0 (m, 3H). ^{13}C NMR δ: 63.4, 1100.9, 105.5, 108.1, 120.9, 126.5, 130.7, 130.9, 147.1, 47.8; IR (KBr) 3363, 3073, 3023, 1650, 1608, 1502, 1119, 1086, 1037, 1006, 926. MS (m/z): 178 (M^+), 135 $(M-CH-CH_2OH+H)^+$, 77 $(C_6H_5)^+$. Anal calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.65. Found: C, 67.27; H, 5.72.

11.1.15. (*E*)-3-[(3,4-Methylenedioxy)phenyl]prop-2-en-1-yl propargyl oxide (22). 2.73 g of alcohol **21** (15.53 mmol) was added dropwise to a solution of NaI (229 mg), nBu$_4$NHSO$_4$ (2.08 g), and 1.88 mL of propargyl bromide (16.8 mmol, 80% in toluene) in THF (30 mL). Amounts of KOH were rapidly added in 1 h. After reaction was completed (TLC control), the mixture was quenched with H_2O and the solution was extracted with AcOEt. The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash chromatography (AcOEt/cyclohexane: 2/8) to afford 3.17 g of **22** (96%). R_f=0.5 (AcOEt/cyclohexane: 2/8); ^{1}H NMR δ: 2.47 (1H, t, ^4J= 2.3 Hz, ≡CH), 4.15–4.3 (4H, m, CH_2), 5.95 (2H, s, O-CH_2-O), 6.11 (1H, dt, $^3J_{trans}$=15.8 Hz, ^3J=6.3 Hz, CH=), 6.56 (1H, d, $^3J_{trans}$=15.8 Hz, CH=), 6.7–7.0 (3H, m, H_{arom}); ^{13}C NMR δ: 56.9, 70.1, 74.4, 79.7, 101.0, 105.7, 108.2, 121.2, 123.1, 130.9, 133.1, 147.3, 147.9; IR (neat): 3291, 2116, 1653, 1607, 1251, 1193; MS (m/z): 216 (M^+), 177 $(M-CH_2C{\equiv}CH)^+$, 119 $(M-HC{\equiv}C\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH{=}CH_2 + H)^+$. Anal calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.08; H, 5.48.

11.1.16. 4-Exomethylene-3-(hydroxy)[(3,4-methylenedioxy)phenyl]methyltetrahydrofuran (23). As general procedure described for carbohydroxypalladation, 108 mg (0.5 mmol) of ether **21**, 9 mg (mol 10%) of $PdCl_2$ and 284 mg of TPPTS (mol 30%, 0.15 mmol) afforded 99 mg of **23** as an orange oil (86%). R_f=0.13 (AcOEt/cyclohexane:

2/8); ^{1}H NMR δ: 2.12 (1H, d, ^3J=3.1 Hz, OH), 3.1–2.9 (1H, m, CH), 3.89 (1H, dd, ^2J=9.1 Hz, ^3J=6.8 Hz, CH_2), 4.12 (1H, dd, ^2J=9.1 Hz, ^3J=4.7 Hz, CH_2), 4.2–4.45 (2H, m, CH_2), 4.64 (1H, q, ^4J=2.1 Hz, CH_2=), 4.71 (1H, dd, ^3J= 6.7 Hz, ^3J=3.1 Hz, CHOH), 4.98 (1H, q, ^4J=2.0 Hz, CH_2=), 5.97 (2H, s, O-CH_2-O), 6.75–6.9 (3H, m, H_{arom}); ^{13}C NMR δ: 51.0, 70.4, 71.8, 74.5, 100.9, 106.4, 106.8, 107.9, 119.8, 136.5, 146.9, 147.6, 147.8; IR (neat): 3413, 1653, 1096, 1039, 930; MS (DCI/NH_3 m/z): 252 $(M+NH_4)^+$, 234 $(M+NH_4-H_2O)^+$, 217 $(M+H-H_2O)^+$.

11.1.17. 4-Exomethylene-3-[(3,4-methylenedioxy)phenyl]-(triisopropylsilyloxy)methyltetrahydrofuran (24). To a solution of **23** (2.3 g, 9.82 mmol) in CH_2Cl_2 (40 mL) were added dropwise 2.3 mL of 2,6-lutidine then 3.95 mL (14.7 mmol) of triisopropylsilyl triflate. After stirring for 1 h at −78°C then for 3 h at −10°C, the mixture was quenched with MeOH (2 mL) and concentrated in vacuo. The crude product was purified by flash chromatography (AcOEt/cyclohexane 1/9 and 2% NEt_3) to give 2.8 g of **24** in 73% yield as yellow oil. R_f: 0.62 (AcOEt/cyclohexane: 3/7); ^{1}H NMR δ: 0.8–1.1 (21H, m, *i*Pr_3), 2.8–3.0 (1H, m, CH), 3.92 (1H, dd, ^2J=8.9 Hz, ^3J=6.5 Hz, CH_2), 4.1–4.25 (3H, m, CH_2), 4.43 (1H, q, ^4J=1.9 Hz, CH_2=), 4.64 (1H, d, ^3J=7.6 Hz, CHO), 4.84 (1H, q, ^4J=1.9 Hz, CH_2=), 5.95 (2H, s, O-CH_2-O), 6.72 (2H, s, H_{arom}), 6.85 (1H, s, H_{arom}); ^{13}C NMR δ: 12.4, 17.9, 53.1, 71.0, 71.8, 75.9, 100.8, 106.8, 107.3, 107.6, 120.8, 137.4, 146.7, 147.2, 147.5; IR (neat): 3079, 1665, 1610, 1245, 1061, 1042, 935; MS (DCI/NH_3 m/z): 408 $(M+NH_4)^+$, 391 $(M+H)^+$, 217 $(M-OSi$*i*$Pr_3)^+$.

11.1.18. 4-Hydroxymethyl-3-[(3,methylenedioxy)phenyl]-(triisopropylsilyloxy)methyltetrahydrofuran (25). To a solution of **24** (1.06 g, 2.71 mmol) in THF (8.5 mL) was added dropwise a molar solution of BH_3·THF (2.71 mL, 2.71 mmol) in THF at 0°C. After stirring the mixture for 1 h at 0°C, an additional amount of BH_3·THF (1.35 mL, 1.35 mmol) was added. The solution was stirred for 1 h at 0°C, quickly treated by 3N NaOH (2.84 mL) and a hydrogen peroxide solution (30% in water) was added dropwise. The mixture was stirred for 1 h at room temperature, quenched with water (100 mL) and the aqueous layer was extracted with Et_2O (3×150 mL). The combined organic layers were washed with saturated NaCl (150 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by silica gel flash chromatography (eluent AcOEt/cyclohexane: 4/6) to afford 1.06 g of **25** in 96% yield as a transparent oil. R_f=0.31 (AcOEt/cyclohexane: 1/1); ^{1}H NMR δ: 0.75–1.1 (21H, m, *i*Pr_3), 1.8 (1H, s, OH), 1.8–1.95 (1H, m, CH), 2.7–3.0 (1H, m, CH), 3.5–3.7 (2H, m, CH_2-O), 3.7–3.9 (m, 1H, CH_2), 3.94 (2H, t, ^2J=^3J=8.9 Hz, CH_2), 4.16 (1H, t, ^2J= ^3J=8.4 Hz, CH_2), 4.76 (1H, d, ^3J=10.1 Hz, CH-O), 5.96 (2H, s, O-CH_2-O), 6.7–7.0 (3H, m, H_{arom}); ^{13}C NMR δ: 12.4, 17.8, 18.0, 42.3, 50.8, 61.1, 71.6, 71.9, 74.7, 100.9, 107.3, 107.7, 120.7, 137.9, 147.1, 147.6; IR (neat): 3420, 1245, 1084, 1041, 929; MS (DCI/NH_3 m/z): 407 $(M-H)^+$, 365 $(M-iPr)^+$, 234 $(M-OSi$*i*$Pr_3-H)^+$, 217 $(M-OSi$*i*$Pr_3-H_2O)^+$; Anal calcd for $C_{22}H_{36}O_5Si$: C, 64.67; H, 8.88. Found: C, 64.60; H, 8.87.

11.1.19. (3*R*)-3-Formyl-4-[(3,4-methylenedioxy)phenyl]-(triisopropylsilyloxy)methyltetrahydrofuran (26). To a solution of alcohol **25** (333 mg, 0.82 mmol) in CH_2Cl_2 (6.5 mL) with 4 Å molecular sieves in powder (200 mg) was added PCC (352 mg, 1.63 mmol). The mixture was stirred for 1 h at 0°C and an additional amount of PCC was added. After stirring 1 h at 0°C, the mixture was filtered on silica gel and eluted with CH_2Cl_2. The organic phase was concentrated in vacuo to afford 270 mg of crude product as a yellow oil (81%). The oil was dissolved in THF (2 mL) and DBU (148 mL, 1 mmol) was added. The solution was stirred for 24 h at room temperature, quenched with saturated NH_4Cl solution and extracted with Et_2O (3×30 mL). The combined organic layers were washed with saturated NaCl solution (30 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by silica gel flash chromatography (eluent AcOEt/cyclohexane 25/75 and 1.5% NEt_3) to afford 250 mg of **26** in 93% yield as a yellow oil. R_f=0.31 (AcOEt/cyclohexane: 1/1); ^{1}H NMR δ (diastereomers): 0.9–1.1 (21H, m, *i*Pr_3), 2.8–3.0 (2H, m, CH), 3.75–3.95 (2H, m, CH_2), 3.95–4.1 (2H, m, CH_2), 4.69 (1H, d, ^3J=7.4 Hz, CH-O-), 5.98 (2H, s, OCH_2O), 6.77 (2H, s, H_{arom}), 6.87 (1H, s, H_{arom}), 9.28 (1H, d, ^3J=2.2 Hz, CHO), ^{13}C NMR δ: 12.3, 17.8, 17.9, 50.8, 53.7, 69.9, 71.0, 101.0, 107.0, 107.8, 120.2, 136.6, 147.2, 147.8, 200.0; IR (neat): 1726, 1610, 1504, 1488, 1244, 1099, 1064; MS (m/z): 405 $(M-H)^+$; 135 $(M-ArCH+H)^+$; Anal calcd for $C_{22}H_{34}O_5$: C, 64.99; H 8.43. Found: C, 64.80; H, 8.41.

11.1.20. (3*R*)-3-(Hydroxy)[(3,4,5-trimethoxy)phenyl]-methyl-4-[(3,4-methylenedioxy)phenyl](triisopropylsilyloxy)methyltetrahydrofuran (27). To a solution of 182 mg of 1-bromo-3,4,5-trimethoxybenzene in THF (5.3 mL) were added dropwise BuLi (285 μL, 0.713 mmol, 2.5 M hexane solution) at −78°C. The mixture was stirred for 1 h at −78°C then 100 mg of **26** (0.246 mmol) in THF (4.5 mL) were added dropwise for 10 min. After stirring 1 h at −78°C, the solution was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by silica gel flash chromatography (AcOEt/cyclohexane 35/65+1% NEt_3) to give 83 mg of **27** in 59% yield as a yellow oil. $R_{f\mathbf{27a}}$=0.29; $R_{f\mathbf{27b}}$=0.22 (AcOEt/cyclohexane: 4/6); ^{1}H NMR δ: diastereomer **27a**: 0.8–1.1 (21H, m, *i*Pr_3), 1.67 (1H, s, OH), 2.3–2.5 (1H, m, CH), 2.55–2.8 (1H, m, CH), 3.82 (3H, s, *p*-CH_3O), 3.85 (6H, s, CH_3O), 3.4–4.1 (4H, m, CH_2), 4.46 (1H, d, ^3J=7.8 Hz, CHOSi), 4.76 (1H, d, ^3J=4.9 Hz, CHOH), 5.98 (2H, d, J=2.4 Hz, O-CH_2-O) 6.49 (2H, s, H_{arom}), 6.71 (2H, s, H_{arom}), 6.86 (1H, s, H_{arom}); diastereomer **27b**: 0.8–1.1 (21H, m, *i*Pr_3) 1.9–2.4 (2H, 2m, CH, OH), 2.5–2.7 (1H, m, CH), 3.79 (6H, s, CH_3O), (3H, s, *p*-CH_3O), 3.8–4.1 (4H, m, CH_2), 4.18 (1H, d, ^3J=7.2 Hz, CHOH), 4.34 (1H, d, ^3J=8.1 Hz, CHOSi), 5.9–6.0 (2H, m, O-CH_2-O), 6.25 (2H, s, H_{arom}), 6.9–6.5 (3H, m, H_{arom}); ^{13}C NMR δ: diastereomer **27a**: 12.3, 17.8, 17.9, 48.3, 51.2, 55.8, 60.7, 70.7, 71.4, 75.3, 77.1, 101.1, 107.3103.1, 107.6, 120.4, 135.7, 137.4, 138.5, 146.9, 147.5, 153.0; diastereomer **27b**: 12.4, 17.8, 17.9, 49.2, 51.3, 55.8, 60.7, 69.5, 70.6, 75.6, 76.7, 101.1, 102.7, 106.9, 107.0, 120.1, 137.1, 137.6, 138.8, 146.8, 147.6, 153.0; IR (neat): 3417, 1593, 1244, 1129, 1040, 924; MS DCI/NH_3 m/z): 592 $(M+NH_4)^+$, 574 $(M+NH_4-H_2O)^+$, 557 $(M+H-H_2O)^+$, 401 $(M-i$*i*$Pr_3SiO)^+$.

11.1.21. [3,4]-[[(3,4)-Methylenedioxy]benzo]-2-triisopropyloxy-5-[(3,4,5)-trimethoxyphenyl]-8-oxabicyclo[4.3.0]-nonane (28). To a solution of alcohol **27** (27.5 mg, 0.048 mmol) in CH_2Cl_2 (0.7 mL) were added dropwise 20 μL of NEt_3 (0.143 mmol) then 9 μL of mesyl chloride (0.116 mmol) at −10°C. After stirring for 1 h at −10°C, the mixture was hydrolyzed with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified on Florisil (eluent AcOEt/cyclohexane: 95/5) to provide 21 mg (81%). R_f=0.5 (AcOEt/cyclohexane: 4/6); ^{1}H NMR δ: major diastereomer 0.8–1.1 (21H, m, *i*Pr$_3$), 2.15–2.3 (1H, m, CH), 2.3–2.45 (1H, m, CH), 3.80 (6H, s, 2CH$_3$O), 3.84 (3H, s, *p*-CH$_3$O), 3.90 (1H, t, ^2J=^3J=2.5 Hz, CH$_2$), 3.8–3.9 (1H, m, CH$_2$), 4.03 (1H, dd, ^2J=4.7 Hz, ^3J=2.5 Hz, CH$_2$), 4.10 (1H dd, ^2J=4.6 Hz, ^3J=2.2 Hz, CH$_2$), 4.32 (1H d, ^3J=4.1 Hz, CH), 4.42 (1H, d, ^3J=4.2 Hz, CHOSi), 5.9–6.05 (2H, m, O-CH$_2$-O), 6.25 (2H, s, H$_{arom}$), 6.4–6.8 (2H, m, H$_{arom}$); ^{13}C NMR δ: major diastereomer 12.4, 17.8, 17.9, 50.7, 52.3, 55.9, 60.7, 66.2, 70.1, 70.7, 76.3, 101.2, 104.3, 106.7, 120.1, 135.5, 137.2, 137.7, 146.9, 147.7, 152.8, 153.2; IR (neat): 1592, 1242, 1127, 1040, 922; MS (DCI/NH$_3$ m/z): 557 $(M-H)^+$, 401 $(M+NH_4-iPr_3SiO)^+$, 383 $(M-iPr_3SiO)^+$.

References

1. (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259. (b) Trost, B. M. *Science* **1991**, *254*, 1471.
2. (a) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. (b) Trost, B. M.; Krische, M. J. *Synlett.* **1998**, 1. (c) Negishi, E.; Copéret, C.; Ma, S.; Liou, S. Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (d) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635.
3. (a) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781. (b) Trost, B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; McPherson, D. T. *J. Am. Chem. Soc.* **1994**, *116*, 4255.
4. (a) Trost, B. M.; Lee, D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651. (b) Trost, B. M.; Romero, D. L.; Rise, F. J. *J. Am. Chem. Soc.* **1994**, *116*, 4268.
5. Trost, B. M.; Lautens, M. *Tetrahedron Lett.* **1985**, *26*, 4887.
6. (a) Trost, B. M.; Chen, S. F. *J. Am. Chem. Soc.* **1986**, *108*, 6053. (b) Trost, B. M.; Edstrom, E. D.; Carter-Petillo, M. B. *J. Org. Chem.* **1989**, *54*, 4489.
7. (a) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 12491. (b) Negishi, E.; Harring, L. S.; Owczarczyk, Z.; Mohamud, M. M.; Ay, M. *Tetrahedron Lett.* **1992**, *33*, 3253. (c) Trost, B. M.; Shi, Y. J. *J. Am. Chem. Soc.* **1993**, *115*, 9421.
8. (a) Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625. (b) Trost, B. M.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1924. (c) Trost, B. M.; Fleitz, F. J.; Watkins, W. J. *J. Am. Chem. Soc.* **1996**, *118*, 5146. (d) Yamada, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **1996**, *118*, 1054.
9. Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2000**, *122*, 6490.
10. (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 714. (b) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **1999**, *121*, 11680.
11. Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4913.
12. Okamoto, S.; Livinghouse, T. *Organometallics* **2000**, *19*, 1449.
13. (a) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 249–253. (b) Cao, P.; Zhang, X. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 4104. (c) Trost, B. M.; Haffner, C. D.; Jebaratnam, D. J.; Krische, M. J.; Thomas, A. P. *J. Am. Chem. Soc.* **1999**, *121*, 6183. (d) Trost, B. M.; Krische, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 6131. (e) Goeke, A.; Sawamura, M.; Kuwano, R.; Ito, Y. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 662.
14. Reviews: (a) Genêt, J. P.; Savignac, M.; Lemaire-Audoire, S. In *Transition Metal Catalysed Reactions*; Murahashi, S.-I., Davies, S. G., Eds.; Academic Press, 1999; pp. 55–79. (b) Genêt, J. P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305–317.
15. Kuntz, E. G.; Thorpe, T.; Brown, S. M.; Crosby, J.; Fitzjohn, S.; Muxworthy, J. P.; Williams, J. M. J. *Tetrahedron Lett.* **2000**, *41*, 4503; German Patent No. DE 2627354 (and references cited therein).
16. (a) Kuntz, E. G. *Chem. Tech.* **1987**, 520. (b) Hermann, W. A.; Kohlpainter, C. W. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1524. (c) Cornils, B.; Kuntz, E. G. *J. Organomet. Chem.* **1995**, *502*, 177.
17. (a) Cornils, B. *J. Mol. Catal. A: Chemical* **1999**, *143*, 1. (b) Verspui, G.; Moiseev, I. I.; Sheldon, R. A. *J. Organomet. Chem.* **1999**, *586*, 196. (c) Brunet, J. J.; Sivade, A.; Tkatchenko, I. *J. Mol. Catal.* **1989**, *50*, 291.
18. Genêt, J. P.; Linquist, A.; Blart, E.; Mouriès, V.; Savignac, M.; Vaultier, M. *Tetrahedron Lett.* **1995**, *36*, 1443.
19. Genêt, J. P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715.
20. Blart, E.; Genêt, J. P.; Safi, M.; Savignac, M.; Sinou, D. *Tetrahedron* **1994**, *50*, 505.
21. Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genêt, J. P. *Tetrahedron Lett.* **1996**, *37*, 2003.
22. Amatore, C.; Blart, E.; Genêt, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.* **1995**, *60*, 6829.
23. (a) Genêt, J. P.; Blart, E.; Savignac, M.; Lemeune, S.; Lemaire-Audoire, S.; Paris, J. M.; Bernard, J. M. *Tetrahedron* **1994**, *50*, 497. (b) Lemaire-Audoire, S.; Savignac, M.; Pourcelot, G.; Genêt, J. P.; Bernard, J. M. *J. Mol. Catal. A: Chemical* **1997**, *116*, 247.
24. Galland, J. C.; Savignac, M.; Genêt, J. P. *Tetrahedron Lett.* **1997**, *38*, 8695.
25. This resolving agent has already been employed successfully by Hanessian on similar substrates: Hanessian, S.; Léger, R. *Synlett* **1992**, 402. EDC=1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride.
26. Such simultaneous Pd(0)-catalyzed cycloadditions have already been observed recently. See for example: Kumar, K.; Jolly, R. S. *Tetrahedron Lett.* **1998**, *39*, 3047.
27. Meresse, P.; Bertounesque, E.; Imbert, T.; Monneret, C. *Tetrahedron* **1999**, *55*, 12805–12818 (and references cited therein).
28. Jardine, I. In *Anticancer Agents based on Natural Products Models, Chapter 9*; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; pp. 319–350.
29. (a) Berkowitz, D. B.; Choi, S.; Maeng, J.-H. *J. Org. Chem.* **2000**, *65*, 847–860. For reviews on podophyllotoxin synthesis, see: (b) Ward, R. S. *Synlett* **1992**, 719. (c) Ward, R. S. *Tetrahedron* **1990**, *46*, 5029. (d) Ward, R. S. *Chem. Soc. Rev.* **1982**, *11*, 75.
30. Hata, E.; Takai, T.; Mukaiyama, T. *Chem. Lett.* **1993**, 1513.
31. Angle, S. R.; Louie, M. S. *J. Org. Chem.* **1991**, *56*, 2853.

32. (a) Pelter, A.; Ward, R. S.; Pritchard, M. C.; Kay, I. T. *J. Chem. Soc., Chem. Commun.* **1988**, 1603. (b) Pelter, A.; Ward, R. S.; Pritchard, M. C.; Kay, I. T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1615. (c) Ziegler, F. E.; Schwartz, J. A. *J. Org. Chem.* **1978**, *43*, 985. (d) Gonzalez, A. G. *Tetrahedron* **1986**, *42*, 3899.
33. (a) Hoye, T. R.; Kaese, P. A. *Synth. Commun.* **1982**, *12*, 49–52. (b) Rose-Munch, F.; Chavignon, R.; Tranchier, J. P.; Gagliardini, V.; Rose, E. *Inorganica Chimica Acta* **2000**, 693.
34. Van der Eycken, J.; De Clercq, P.; Vandewalle, M. *Tetrahedron* **1986**, *42*, 4297.