Tetrahedron Vol. 47, No. 26, pp. 4675-4682, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

Enantioselective Total Synthesis of (-)-Epipodophyllotoxin and (-)-Podophyllotoxin

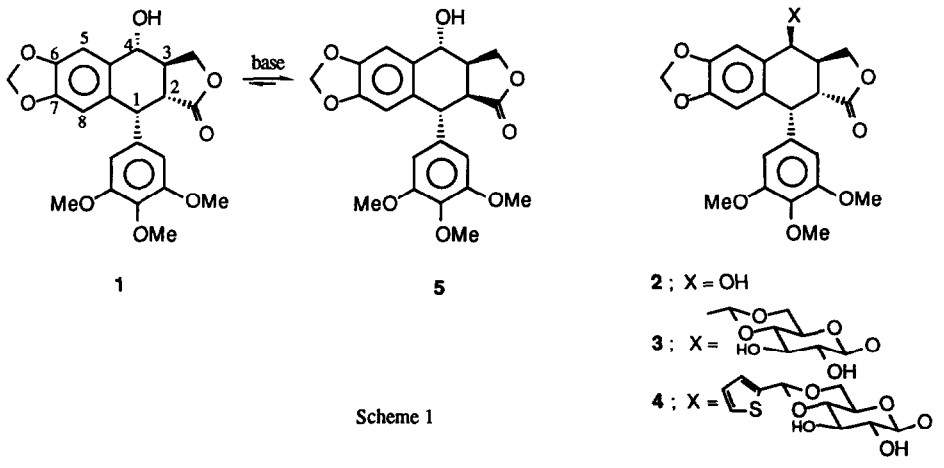
R. Van Speybroeck, H. Guo, J. Van der Eycken, and M. Vandewalle*

State University of Gent, Department of Organic Chemistry, Laboratory for Organic Synthesis, Krijgslaan, 281 (S.4), B-9000 GENT (Belgium)

(*Received in UK* 28 *February* 1991)

***Abstract** : An enantioselective total synthesis of (-)-epipodophyllotoxin (**2**) and hence of (-)-podophyllotoxin (**1**) is described, involving as key steps a conjugate addition on butenolide **13** as the chiral template, a stereoselective aldol condensation on **11a** and a stereoselective ring closure of **8**.*

The cytotoxic lignan lactone[1] podophyllotoxin (**1**), the major constituent of several plant species of the Podophyllum family, has stirred considerable interest in pharmacological and synthetic research. As a result, two semi-synthetic glucosides, derived from epipodophyllotoxin (**2**), etoposide (**3**) and teniposide (**4**)[2], have been developed as important antineoplastic drugs. The structure of **1** is only deceptively simple as the 1,2-cis-2,3-trans stereorelationship, which is of crucial importance for its biological activity[1], constitutes a real thermodynamic trap, due to facile epimerization to the less strained, but inactive cis-lactone picropodophyllin (**5**)[3]. It should be noted that the stereochemistry at C-4 is of less concern as **1** and **2** are easily interconvertible[4,5]. Furthermore for the synthesis of **3** and **4** the C-4 hydroxyl group can either be α or β oriented because in the glycosidation reaction only the C-4 β glycoside is obtained[6].



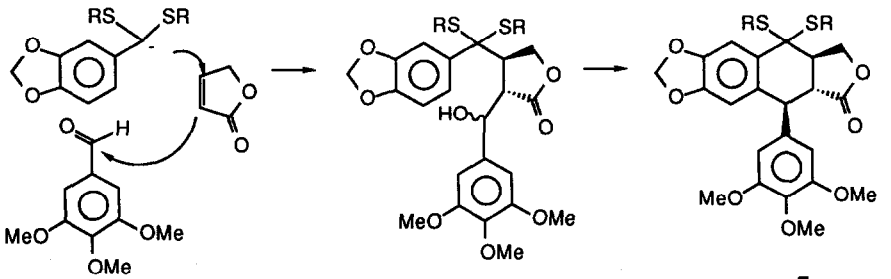
Scheme 1

Since the pioneering work of Gensler *et al.*[7], a number of synthetic chemists have studied this challenging problem and have reported work along three different strategies.

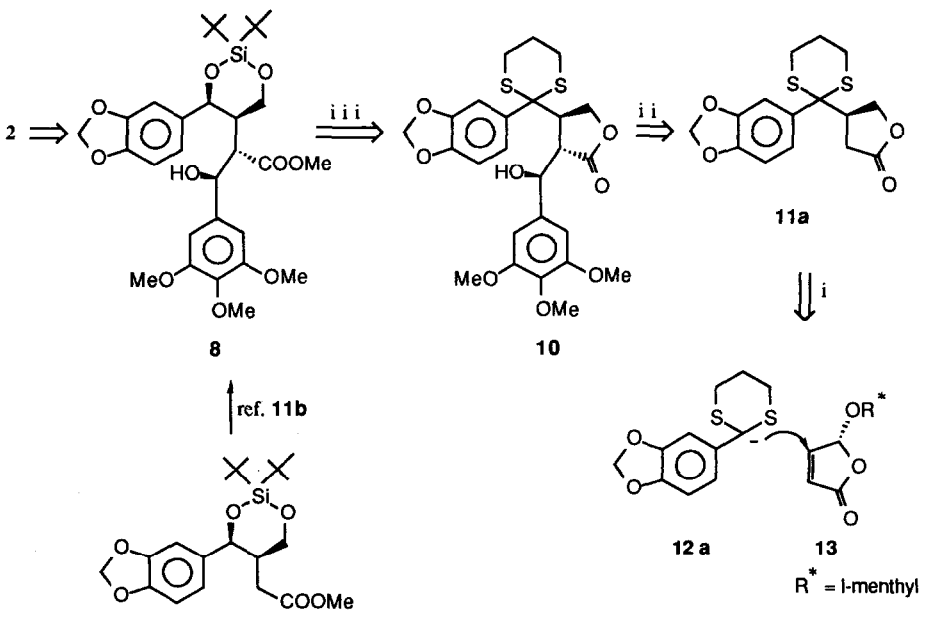
(1) Several approaches[8], including the first enantioselective synthesis reported by Meyers *et al.*[8d], are directed towards picropodophyllin **5** and rely on Gensler's observation of kinetic protonation of the enolate anion of **5**[7] yielding **1** and **5** in a 45:55 ratio. More recently, equilibration at an earlier stage of the sequence was found to be more efficient.[8c]

(2) The intermediacy of **5** was avoided first by Rodrigo *et al.*[9a], who constructed ring B via a Diels-Alder reaction involving a transient isobenzofuran. Also other groups have drawn on this strategy[9b-e].

(3) An interesting approach has been explored by Ziegler *et al.*[10]. In this approach, the carbon framework is assembled during a one-pot tandem Michael addition-aldol condensation (scheme 2), resulting in the desired 2,3-trans relationship. However, electrophilic ring closure (formation of the 1-8a bond) of **6** leads to the all-trans product **7**, belonging to the uninteresting isopodophyllotoxin series. Also a biomimetic ring closure has provided only the 1,2-trans substitution pattern[8a].



Scheme 2



Scheme 3

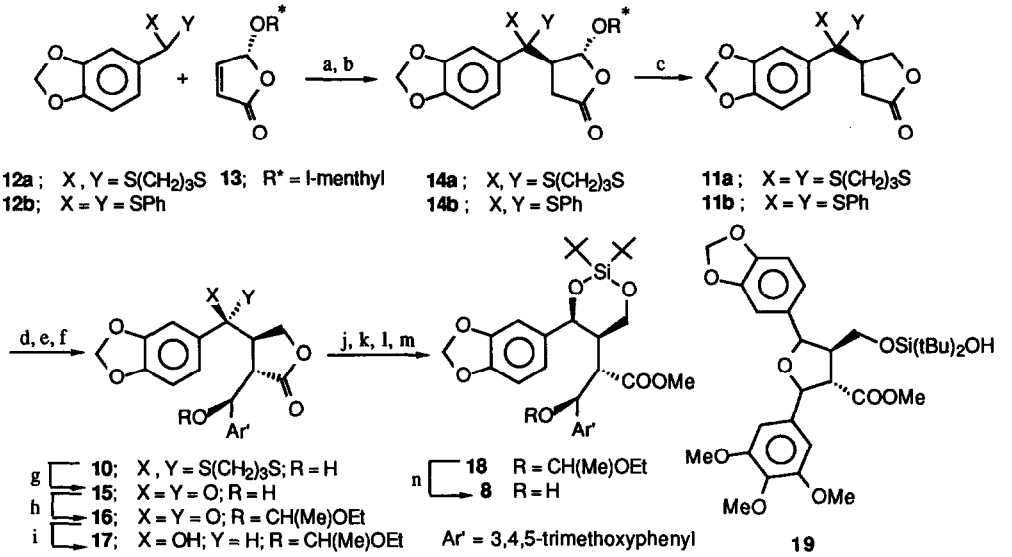
Because Ziegler's strategy is inherently straightforward and easily adaptable to enantioselective synthesis, the reinvestigation of a stereoselective 1-8a bond formation would be highly rewarding. Some time ago we reported an efficient solution to this problem, based upon the remarkably stereoselective electrophilic ring closure of **8** (scheme 3), leading exclusively to the required 1,2-cis-2,3-trans stereorelation[11]. The cis-substituted siladioxane ring in **8** is the stereocontrolling element for the intramolecular aromatic substitution (*vide infra*); however the presence of this ring is also responsible for the unselectivity observed during the aldol condensation of **9**[11b].

It is therefore obvious that, for a successful application of this strategy, the requisite syn relationship - 1(S),2(S) - in the acyclic precursor **8** has to be created prior to the formation of the stereocontrolling siladioxane ring. Presently we want to describe an enantioselective synthesis with excellent stereocontrol at all four stereogenic centers based on (i) asymmetric 1,4-addition to the optically pure butenolide **13**[12] as the template; (ii) a syn-selective titanium-mediated aldol condensation[13]; (iii) transformation of the lactone **10** in the key-intermediate silylene ether **8** (scheme 3).

Conjugate addition of the lithium anion of **12a** (scheme 4) to the butenolide **13** afforded the 1,4-adduct **14a** as a single isomer in 84 % yield. Removal of the chiral auxiliary via base-catalyzed lactone hydrolysis and subsequent reduction of the aldehyde function could be effected without racemization. After acidification and extractive work-up, the hydroxy-acid slowly cyclized to the lactone **11a** upon standing (81 % yield). The optical purity of **11a** was found to be higher than 95 % ee by ^{1}H NMR analysis in the presence of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato] europium(III) (Eu(hfc)$_3$). In contrast, removal of the l-menthyloxy group from the bis(phenylthio)-acetal **14b** (prepared in 82 % yield from **12b**), afforded lactone **11b**, in only 25 %, due to facile β-elimination of thiophenol during hydrolysis.

Treatment of the lactone **11a** with lithium diisopropylamide (THF, -78°C), followed by transmetallation with tris(diethylamino)-titaniumchloride[14] at -45°C, and subsequent addition of 3,4,5-trimethoxybenzaldehyde at -105°C, afforded 86 % of the desired isomer **10**, together with 6.5 % of the C_1-epimer. Hydrolysis of the thioketal[15], followed by protection of the 1-hydroxy-group as an ethoxyethyl ether and reduction of the 4-keto-function with sodium borohydride yielded the alcohol **17** as a single isomer in 80 % overall yield from **10**. The stereospecificity of the reduction is in line with Felkin's rule[16].

The stage is now set for the formation of the crucial silylene ether **8**. However, the transformation of the lactone **17** into **18** appeared to be very troublesome due to facile relactonisation of the intermediate γ-hydroxy-acid. For example, attempted lactone ring opening of **17** with lithium methoxide[17] in methanol only resulted in β-elimination of the ethoxyethyl group. After extensive experimentation, we found that the lactone could be opened under carefully controlled conditions with ethanolic potassium hydroxide (1.3 eq.) at ambient temperature, followed by acidification to pH 5.7 at -5°C with a phosphate buffer. The solution of the hydroxy-acid was immediately treated with ethereal diazomethane at -40°C in a two-phase system. Any trace of acid was neutralized by washing with bicarbonate, and after drying and removal of the solvents at low temperature, the resulting crude dihydroxy-methyl ester was immediately silylated with excess di-t.butylsilyldiitriflate[18] in the presence of 2,6-lutidine at -60°C, affording the desired silylene ether **18** in 56 % overall yield from **17**. It is crucial that this sequence of manipulations is carried out without interruption and at low temperature, in order to avoid fast relactonization and β-elimination. Finally, selective hydrolysis of the ethoxyethyl ether **18** could be accomplished in 94 % yield with pyridinium para-toluenesulfonate in THF.



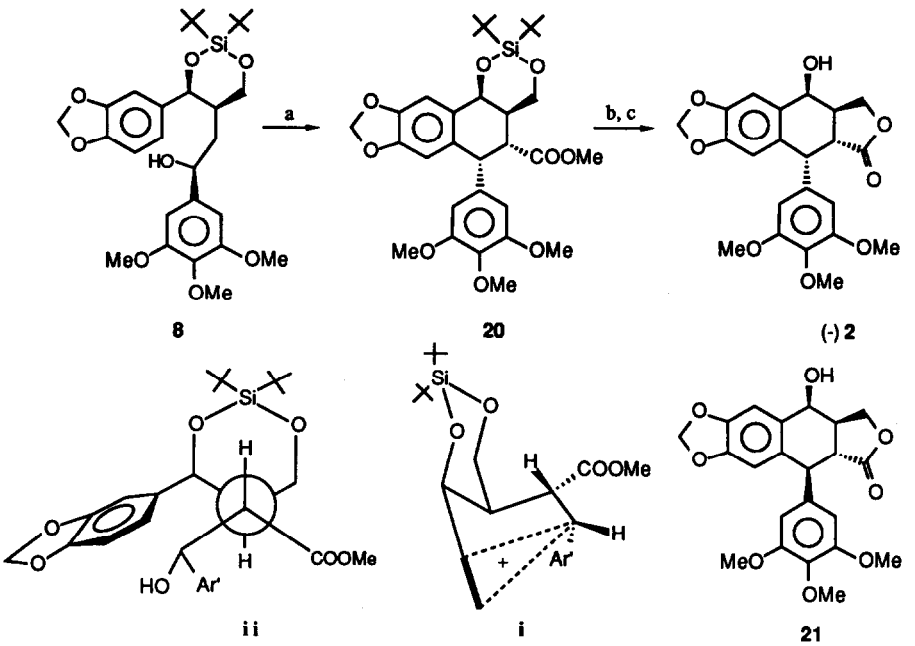
a) n.BuLi (1.2 eq.), THF, -78°C; b) **13**, THF, -84°C; c) $NaBH_4$ (4 eq.), KOH (4 eq), EtOH, rt, 1.5 h; d) LDA (1.2 eq.), THF, -78°C, 40 min; e) $ClTi(NEt_2)_3$ (3.1 eq.), -78°C; then -45°C, 50 min; f) 3,4,5-tri(OMe)-PhCHO (1.19 eq.), THF, -105°C, 3 h; g) $HgCl_2$ (4 eq.), $CaCO_3$ (4.2 eq.), CH_3CN/acetone/water 6:3:2, reflux, 12 h; h) CH_2=CHOEt, pTSA, THF, -15°C, 50 min; i) $NaBH_4$ (2 eq), MeOH, -0°C, 25 min; j) KOH (0.2 M in EtOH, 1.3 eq.), rt, 40 min; k) NaH_2PO_4 (1 M in H_2O), -5°C, to pH 5.7; l) CH_2N_2, EtOAc, -40°C; m) $t.Bu_2Si(OTf)_2$ (2.3 eq), 2,6-lutidine (7.7 eq), CH_2Cl_2, -60°C, 30 min; n) PPTS (1 eq.), THF, rt, 40 min.

Scheme 4

The use of an ethoxyethyl protective group is absolutely essential, although some of it was cleaved during the above described procedure. Other protective groups investigated (MOM, MEM) needed stronger acidic conditions for their removal. Key-intermediate **8** is very sensitive towards acid which catalyzes its transformation into the tetrahydrofurans **19** (scheme 4) via facile carbenium ion formation at C-4[11b].

As we reported earlier[11b], mesylation of **8** led, without detection of the intermediate mesylate, exclusively to the formation of the desired 1,2-cis-2,3-trans tetralin **20** (92 % yield) (scheme 5). On the other hand, the C_1-epimer of **8** only afforded the 1,2-trans-2,3-trans tetralin (**21**). Although these results suggest a neat S_N2-displacement, model examination reveals that the steric requirements cannot be fulfilled. We therefore believe that the incipient carbenium ion at C_1 is intercepted by the aromatic ring before rotation around the 1,2 bond can occur (**i**). This results in a non-classical carbenium ion, which eventually reacts with inversion of configuration at C_1. The silylene ether plays a crucial role during tetralin formation, as it holds the reacting centers (C_1 and C_{8a}) in close proximity, as illustrated in scheme 5. The ^1H NMR spectrum of **8** allows to prove the presence of only the thermodynamically most stable rotamer **ii**[11].

Further elaboration of **20** to (-)-epipodophyllotoxin (**2**) was carried out via desilylation, and subsequent Lewis-acid catalyzed lactonization[9d], affording (-)-**2** (97 %), identical in all respects with a sample of (-)-**2** prepared from natural (-)-podophyllotoxin (**1**) via a known procedure[19,20] The further transformation of **2** into **1** has been described[4].



a) MsCl (3.3 eq.), NEt_3 (6.7 eq.), CH_2Cl_2, -15°C, 15 min; b) TBAF (4.7 eq.), THF, rt, 20 min; c) $ZnCl_2$ (78 eq.), mol. sieves 4Å, THF, 65°C, 3 h.

Scheme 5

In summary, we succeeded in achieving an efficient enantioselective synthesis of (-)-epipodophyllotoxin (**2**) (and hence also of (-)-podophyllotoxin (**1**)) in 20 % overall yield from **12a** and **13**. Our strategy offers an efficient solution for the creation of the desired 1,2-cis relationship during the formation of the 1-8a bond, in contrast to the hitherto observed trans stereochemistry[10].

EXPERIMENTAL

General : All reactions were carried out under Ar with magnetic stirring unless otherwise specified. "Work-up" denotes extraction with an org. solvent, washing the org. phase with sat. aq. NaCl soln, drying over anh. Na_2SO_4, and removal of solvent by distillation in vacuo using a rotatory evaporator. HPLC separations were performed on Waters LC/System 500 or Waters 6.000 A, both with RI-detection. IR spectra were recorded on a Beckmann IR 4230 spectrometer, mass spectra on a AEI MS-50 or on a HP 5988a spectrometer. The ^1H NMR spectra were recorded at 360 MHz (WH-Brucker) with TMS as internal standard. Rf values are quoted for Merck silica gel 60 GF_{254} plates of thickness 0.25 mm. M.p. are uncorrected.

Formation of butenolide 14a

To a solution of **12a** (2.50 g, 10.40 mmol) in dry THF was added at -78°C, n.butyllithium (2.45 M in hexane, 5.20 mL, 12.74 mmol) under argon atmosphere. After 1 h of stirring a solution of **13** (2.50 g, 10.49 mmol) in dry THF (42 mL) was slowly added over a period of 1.5 h at -84°C. The reaction mixture was stirred for 2 h at -84°C and was then quenched with saturated NH_4Cl and extracted with Et_2O. Work-up and column chromatography (hexane/Et_2O 7:3) afforded **14a** (4.20 g, 84 %) as a colorless solid : mp 128°C (hexane/Et_2O); $[\alpha]_D^{25}$ -71.8 (c 0.96, $CHCl_3$); Rf (hexane/Et_2O 6:4) 0.48; IR (neat) ν 3060, 2960, 2920, 2870, 1785, 1500, 1480, 1240 cm^{-1}; ^1H NMR δ 7.45 (s, 1), 7.46 (d, J = 7.3 Hz, 1), 6.82 (d, J = 7.3 Hz, 1),

5.99 (s, 2), 5.72 (d, J = 1.5 Hz, 1), 3.40 (m, 1), 2.85 (dd, J = 3.3 Hz, J = 18.0 Hz, 1), 2.63 (dd, J = 9.8 Hz, J = 18.0 Hz, 1), 2.80-2.66 (m, 4), 2.05-1.79 (m, 4), 1.68-1.50 (m, 4), 1.35-1.25 (m, 1), 1.16-1.06 (m, 1), 1.00-0.62 (m, 1); MS m/e 479 ($M^{+\cdot}$, 18), 294 (10), 266 (8), 239 (100), 220 (21), 192 (13), 159 (14). Anal. calcd. for $C_{25}H_{34}S_2$: C, 62.27; H, 7.16; found : C, 62.45; H, 7.14.

Formation of 11a

A mixture of **14a** (4.20 g, 8.78 mmol), sodium borohydride (2.50 g, 66.1 mmol), KOH (0.4 M in ethanol, 36 mL, 14.4 mmol) in ethanol (98 %, 160 mL) was stirred at ambient temperature for 1.5 h. After adding phosphate buffer (1 M, pH 6, 40 mL), the mixture was acidified to pH 3.4 with hydrochloric acid (1 N) and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered and concentrated at reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL) and left overnight at r.t. Concentration and purification by column chromatography (hexane/Et_2O 1:1) afforded **11a** (2.30 g, 81 %) as a colorless solid : mp 158°C; $[\alpha]_D^{25}$ +10.2 (c 0.51, $CHCl_3$); Rf (hexane/Et_2O 1:1) 0.32; IR (neat) ν 3050, 2990, 2980, 2930, 2900, 2820, 2770, 1775, 1600, 1500, 1475, 1430, 1235 cm^{-1}; ^1H NMR (500 MHz) δ 7.47 (dd, J = 8.8 Hz, J = 2.0 Hz, 1), 7.46 (d, J = 2.0 Hz, 1), 6.83 (d, J = 8.8 Hz, 1), 6.01 (s, 2), 4.40 (dd, J = 9.5 Hz, J = 8.0 Hz, 1), 4.20 (dd, J = 8.0 Hz, J = 8.2 Hz, 1), 3.00 (m, 1), 2.86 (dd, J = 9.2 Hz, J = 3.5 Hz, 1), 2.8-2.6 (m, 4), 2.43 (dd, J = 3.5 Hz, J = 4.5 Hz), 2.07-1.80 (m, 2); MS m/e 324 ($M^{+\cdot}$, 17), 246 (11), 239 (100), 165 (31). Analy. calcd. for $C_{15}H_{16}O_4S_2$: C, 55.54; H, 4.97; found : C, 55.42; H, 4.98.

Aldol condensation of 11a with 3,4,5-trimethoxybenzaldehyde

To a solution of LDA (prepared from diisopropylamine (212 mg, 2.09 mmol) and n-butyllithium (2.40 M in hexane 1.1 mL, 2.64 mmol) in anhydrous THF (8 mL) at -25°C, 40 min) at -78°C was added a solution of **11a** (700 mg, 2.16 mmol) in anhydrous THF (17 mL) under argon atmosphere. After 40 min of stirring at -78°C, $ClTi(NEt_2)_3$ (2.1 mL, 6.7 mmol) was added. The mixture was allowed to warm up to -45°C and stirring was continued for 50 min. At -105°C a solution of 3,4,5-trimethoxybenzaldehyde (505 mg, 2.58 mmol) in anhydrous THF (6 mL) was slowly added over a period of 30 min. The mixture was stirred at -105°C for 1.5 h and was then diluted with ethyl acetate (60 mL) and washed with saturated NH_4F. Work-up and column chromatography (hexane/ethyl acetate 1:1) afforded **10** (952 mg, 86 %), and its C-1 epimer (72 mg, 6.5 %) as colorless solids. **10** : mp 183°C (hexane/ethyl acetate); $[\alpha]_D^{21}$ +53.6 (c 1, $CHCl_3$); Rf (hexane/ethyl acetate 1:1) 0.40; IR (neat) ν 3500, 3060, 3000-2820, 1757, 1700, 1585, 1495, 1485, 1450, 1415, 1330, 1230, 1120 cm^{-1}; ^1H NMR δ 7.22 (dd, J = 1.0 Hz, J = 8.2 Hz, 1), 6.96 (d, J = 1.0 Hz, 1), 6.59 (d, J = 8.2 Hz, 1), 6.30 (s, 2), 6.08 (d, J = 1.1 Hz, 1), 5.95 (d, J = 1.1 Hz, 1), 5.06 (bs, 1), 4.91 (d, J = 9.1 Hz, 1), 4.37 (t, J = 8.34 Hz, 1), 3.72 (s, 6), 3.71 (s, 3), 2.93 (m, 1H); 2.80 (m, 1), 2.71-2.48 (m, 5), 1.91-1.75 (m, 2); MS m/e 520 ($M^{+\cdot}$, 1.3), 501 (1), 335 (50), 324 (71), 239 (47), 196 (28), 45 (100).

Ketone 15

Dithiane **10** (540 mg, 1.04 mmol) was dissolved in a mixture of acetonitrile (22 mL), acetone (11 mL) and water (8 mL). After addition of $HgCl_2$ (1100 mg, 4.05 mmol) and $CaCO_3$ (435 mg, 4.35 mmol), the mixture was refluxed for 12 h at 85°C. After cooling, the reaction mixture was filtered, and the filtrate washed with saturated NH_4OAc. Work-up and column chromatography (hexane/ethyl acetate 1:1) afforded compound **15** (370 mg, 83 %) as a white solid : mp 198°C (hexane/ethyl acetate); $[\alpha]_D^{25}$ -50.3 (c 0.98, $CHCl_3$); Rf (hexane/ethyl acetate 1:1) 0.17; IR (neat) : ν 3500 (br), 3050, 2980, 2950, 2910, 2850, 1780, 1680, 1600, 1507, 1465, 1450, 1255, 1185 cm^{-1}; ^1H NMR (500 MHz) δ 7.23 (dd, J = 2.0 Hz, J = 8.2 Hz, 1), 7.11 (d, J = 2.0 Hz, 1), 6.76 (d, J = 8.2 Hz, 1), 6.47 (s, 2), 6.03 (s, 2), 5.45 (m, 1), 4.57 (t, J = 8.7 Hz, 1), 4.49 (dd, J = 8.3 Hz, J = 17.0 Hz, 1), 4.14 (t, J = 8.3 Hz, 1), 3.71 (s, 3), 3.70(s, 6), 3.68 (dd, J = 3.0 Hz, J = 8.7 Hz, 1), 2.56 (d, J = 4.5 Hz, 1); MS m/e 430 ($M^{+\cdot}$, 68), 236 (10), 234 (12), 197 (100), 196 (42), 181 (20), 169 (48). Anal. calcd. for $C_{22}H_{22}O_9$: C, 61.40; H, 5.15; found : C, 61.12; H, 5.21.

Compound 17

To a solution of **15** (169 mg, 0.393 mmol) and pTSA.H_2O (24 mg, 0.126 mmol) in dry THF (8 mL) was added, at -15°C, ethyl vinyl ether (0.5 ml, 5.23 mmol). The mixture was stirred at -15°C for 50 min, neutralized to pH 7.5 by adding KOH (0.2 M in ethanol) and concentrated at reduced pressure. Filtration through silica gel (hexane/ethyl acetate 6:4, 3 % triethylamine), afforded the epimers **16** (195 mg, 99 %) as a white solid. A mixture of crude **16** (140 mg, 0.279 mmol), $NaBH_4$ (15 mg, 0.4 mmol) and methanol

(30 mL) was stirred at 0°C for 25 min. After evaporation of the solvent at r.t., the residue was dissolved in Et_2O (50 mL). Work-up and column chromatography (hexane/ethyl acetate 1:1, 3 % triethylamine) afforded **17** (141 mg, 97 %) as a white solid; mp 170°C (hexane/ethyl acetate); Rf (hexane/ethyl acetate 1:1) 0.38. IR : ν 3500 (br), 3050, 2800, 1755, 1585, 1500, 1485, 1455, 1400, 1425, 1365, 1330, 1230, 1180, 1120, 1075, 1025, 925 cm^{-1}; ^1H NMR δ 6.56 (d, J = 2.3 Hz, 1) and 6.55 (d, J = 2.3 Hz, 1), 6.49 (t, J = 1.3 Hz, 1) and 6.46 (t, J = 1.3 Hz, 1), 6.29 (d, J = 1.6 Hz, 1) and 6.27 (s, 1), 6.35 (s, 2), 5.99 (app. t, J = 1.4 Hz, 2) and 5.93 (app. t, J = 1.4 Hz, 2), 5.16 (d, J = 2.2 Hz, 1) and 5.06 (d, J = 2.7 Hz, 1), 4.66 (br, 1), 4.69 (q, J = 5.3 Hz, 1) and 4.61 (q, J = 5.3 Hz, 1), 4.53 (m, 1) and 4.48 (m, 1), 4.35 (m, 1) and 4.32 (m, 1), 3.81 (s, 3) and 3.80 (s, 3), 3.79 (s, 6, both isomers), 3.51 (q, J = 7.0 Hz, 2) and 3.48 (q, J = 7.0 Hz, 2), 2.83 (m, 1), 2.80 (m, 1), 1.27 (d, J = 5.3 Hz, 3) and 1.25 (d, J = 5.3 Hz, 3), 1.20 (t, J = 7.0 Hz, 3) and 1.17 (t, J = 7.0 Hz, 3); MS m/e 505 ($M^{+\cdot}$, 15), 416 (7), 196 (15), 181 (10), 151 (20), 73 (100).

Formation of acyclic precursor 8

17 (150 mg, 0.3 mmol) was dissolved in a solution of KOH (0.2 M in ethanol, 2.0 mL, 0.4 mmol) and the mixture was stirred at r.t. for 40 min. After careful acidification to pH 5.7 with phosphate buffer (1 M, pH 4.5) at -5°C, ethyl acetate (30 mL) was added, and the mixture immediately treated with diazomethane at -40°C. The mixture was washed successively with ice cold saturated $NaHCO_3$ and brine, dried over Na_2SO_4 at -15°C for 15 min, filtered over dry Na_2SO_4 and concentrated at -15°C using an oil pump. The residue was dried azeotropically with toluene (2x8 mL) at -15°C with an oil pump and successively dissolved in anhydrous dichloromethane (3 mL) at -40°C.

At -60°C, 2,6-lutidine (270-µL, 2.32 mmol) and $t.Bu_2Si(OTf)_2$ (250 µL, 0.69 mmol) were added. The mixture was stirred at -60°C for 30 min, and then diluted with ethyl acetate (30 mL). Work-up and column chromatography (hexane/ethyl acetate 4:1, 3 % triethylamine) afforded compound **18** (112 mg, 56 %), as a colorless oil (mixture of 2 epimers) : Rf (hexane/ethyl acetate 7:3) 0.36.

A mixture of **18** (83 mg; 0.123 mmol, PPTS (30 mg, 0.120 mmol) and anhydrous THF (4 mL) was stirred at r.t. for 40 min, and then water (15 mL) was added. Work-up and column chromatography (hexane/ethyl acetate 7:3) afforded compound **8** (70 mg, 94 %) as a white solid : mp 80°C (hexane/ethyl acetate); $[\alpha]_D^{26}$ +29.0 (c 1.36, $CHCl_3$), Rf (hexane/ethyl acetate 7:3) 0.15; IR ν 3600 (br), 3040, 2930, 2880, 1730, 1596, 1505, 1492, 1460, 1449, 1421, 1390, 1365, 1330, 1240, 1190, 1130, 1090 cm^{-1}; ^1H NMR δ 6.88 (s,1), 6.78 (dt, J = 1.3 Hz, J = 8.1 Hz, 1), 6.73 (d, J = 8.0 Hz, 1), 6.48 (s, 2), 5.95 (d, J = 1.3 Hz, 1), 5.94 (d, J = 1.5 Hz, 1), 4.92 (dd, J = 3.8 Hz, J = 7.0 Hz, 1), 4.80 (dd, J = 2.7 Hz, J = 6.4 Hz, 1), 4.44 (m, 1), 4.25 (m, 1), 3.84 (s, 6), 3.81 (s, 3), 3.19 (d, J = 2.6 Hz, 3), 3.16 (m, 1), 2.59 (dd, J = 3.5 Hz, J = 6.2 Hz, 1), 2.80 (d, J = 2.5 Hz, 1), 1.08 (s, 9), 1.05 (s, 9); MS m/e 604 ($M^{+\cdot}$, 10), 529 (4), 407 (7), 379 (4), 351 (100), 334 (15), 197 (28), 196 (30).

Electrophylic ring closure of 8

To a solution of **8** (35 mg, 0.058 mmol) in anhydrous dichloromethane (1.7 mL) were added anhydrous triethylamine (54 µL, 0.39 mmol) and mesyl chloride (15 µL, 0.194 mmol) at -15°C. The mixture was stirred at -15°C for 15 min. Water (3 mL) was added and the mixture was extracted with ethyl acetate. Work-up and column chromatography (hexane/ethyl acetate 7:3) afforded **20** (31 mg, 92 %) as a white solid : mp 157°C (hexane/ethyl acetate); $[\alpha]_D^{25}$ -22.5 (c 0.99, $CHCl_3$), Rf (hexane/ethyl acetate 3:2) 0.41; IR ν 3060, 2980-2840 (br), 1730, 1600, 1505 (sh), 1480, 1437, 1420, 1395, 1375, 1365, 1330, 1300, 1265, 1230, 1170 cm^{-1}; ^1H NMR δ 6.98 (s,1), 6.46 (s, 1), 6.13 (s, 2), 5.95 (s, 2), 5.33 (d, J = 5.0 Hz, 1), 4.41 (d, J = 5.2 Hz, 1), 4.25 (dd, J = 3.1 Hz, J = 12 Hz, 1), 4.13 (dd, J = 4.9 Hz, J = 12 Hz, 1), 3.80 (s, 3), 3.71 (s, 6), 3.58 (s, 3), 3.47 (m, 1), 2.63 (m, 1), 1.11 (s, 9), 1.00 (s, 9); MS m/e 587 ($M^{+\cdot}$, 23), 586 (7), 529 (28), 418 (23), 397 (20), 379 (19), 365 (48), 361 (40), 358 (30), 335 (22), 333 (100); HRMS : calc. for $C_{31}H_{42}O_9Si$ 586.2598; found 586.2542.

Epi-podophyllotoxin (2)

To a solution of **20** (19 mg, 0.032 mmol) in anhydrous THF (2 mL) was added tetrabutylammonium fluoride (1 M in THF, 150 µL, 0.15 mmol). The mixture was stirred at rt for 20 min and then anhydrous $ZnCl_2$ (1 M in Et_2O, 2.5 mL, 2.5 mmol) and molecular sieves (4Å, 1 g) were added. The mixture was refluxed at 65°C for 3 h, then diluted with dichloromethane (80 mL), and filtered. Work-up and column chromatography

(dichloromethane/ethyl acetate 3:2) afforded compound **2** 11.8 mg, 88 %) as a white solid. Recrystallization from Et_2O gave colorless crystals of **2** : mp 182°C; $[\alpha]_D^{20}$ -72.0 (c 0.70, $CHCl_3$), Rf (hexane/ethyl acetate 1:4) 0.38; IR ν 3430, 3060, 2960, 2900, 2840, 1760, 1590, 1500, 1480, 1460, 1420, 1385, 1330, 1290, 1265, 1240, 1197, 1165, 1120 cm^{-1}; ^1H NMR δ 6.88 (s, 1), 6.55 (s, 1), 6.28 (s, 2), 6.05 (d, J = 1.2 Hz, 1), 5.98 (d, J = 1.2 Hz, 1), 4.87 (d, J = 3.4 Hz, 1), 4.62 (d, J = 5.4 Hz, 1), 4.38 (m, 2), 3.82 (s, 3), 3.75 (s, 6), 3.29 (dd, J = 5.1 Hz, J = 14.2 Hz, 1), 2.84 (m, 1); MS m/e 414 ($M^{+\cdot}$, 100), 399 (7), 396 (38), 394 (8), 346 (10), 181 (15); HRMS : calc. for $C_{22}H_{22}O_8$ 414.1315; found 414.1295.

Acknowledgements

We thank the "NFWO" and the "Ministerie voor Wetenschapsbeleid" for financial support to the laboratory. R.V.S. gratefully acknowledges the "IWONL" for a doctorate fellowship. We thank Prof. B. Feringa for the procedure of the preparation of butenolide **13**, prior to publication.

REFERENCES

1. Hartwell, J.L.; Schrecker, A.W.; *Fortschr. Chem. Org. Naturst.*, **1958**, *15*, 83.
2. Keller-Juslén, C.; Kuhn, M.; von Wartburg, A.; Stähelin, H.; *J. Med. Chem.*, **1971**, *14*, 936.
3. Gensler, W.J.; Samour, C.M., Wang, S.Y., Johnson, F.; *J. Am. Chem. Soc.*, **1960**, *82*, 1714.
4. Gensler, W.J.; Johnson, F.; Sloan, A.D.B.; *J. Am. Chem. Soc.*, **1960**, *82*, 6074.
5. Hartwell, J.L.; Schrecker, A.W.; *J. Am. Chem. Soc.*, **1951**, *73*, 2909.
6. Kuhn, M.; von Wartburg, A.; *Helvetica Chim. Acta*, **1969**, *52*, 948.
7. Gensler, W.J.; Gatsonis, C.D.; *J. Am. Chem. Soc.*, **1966**, *31*, 4004.
8. (a) Kende, A.S.; Liebeskind, L.S.; Mills, J.E.; Rutledge, P.S.; Curran, D.P.; *J. Am. Chem. Soc.*, **1977**, *99*, 7082; (b) Kende, A.S.; King, M.L.; Curran; D.P.; *J. Org Chem.*, **1981**, *46*, 2826; (c) Kaneko, T.; Wong, H.; *Tetrahedron Lett.*, **1987**, *28*, 517; (d) Andrews, R.C.; Teague, S.J.; Meyers, A.I.; *J. Am. Chem. Soc.*, **1988**, *110*, 7854.
9. (a) Rajapaksa, D.; Rodrigo, R.; *J. Am. Chem. Soc.*, **1981**, *103*, 6208; Forsey, S.P.; Rajapaksa, D.; Taylor, N.J.; Rodrigo, R.; *J. Org. Chem.*, **1989**, *54*, 4280; (b) Macdonald, D.I.; Durst, T.; *J. Org. Chem.*, **1988**, *53*, 3663; (c) Takano, S.; Otaki, S.; Ogasawara, K.; *J. Chem. Soc., Chem. Comm.*, **1985**, 485; Takano, S.; Otaki, S.; Ogasawara, K.; *Heterocycles*, **1985**, *23*, 2811; (d) Jones, D.W.; Thompson, A.M.; *J. Chem. Soc., Chem. Comm.*, **1987**, 1797; Jones, D.W.; Thompson, A.M.; *J. Chem. Soc., Chem. Comm.*, **1989**, 1370; (e) Jung, M.E.; Lam, P.Y.-S.; Mansuri, M.N.; Speltz, L.M.; *J. Org. Chem.*, **1985**, *50*, 1087; Jung, M.E.; Lowen, G.T.; *Tetrahedron Lett.*, **1986**, *27*, 5319.
10. Ziegler, F.E.; Schwartz, J.A.; *J. Org. Chem.*, **1978**, *43*, 985.
11. (a) Van der Eycken, J.; De Clercq, P.; Vandewalle, M.; *Tetrahedron*, **1986**, *42*, 4285; (b) Van der Eycken, J.; De Clercq, P.; Vandewalle, M.; *Tetrahedron*, **1986**, *42*, 4297.
12. Feringa, B.L.; De Jong, J.C.; *J. Org. Chem.*, **1988**, *53*, 1125.
13. Reetz, M.T.; *Top. Curr. Chem.*, **1982**, *106*, 1.
14. (a) Benzing, E.; Kornicker, W.; *Chem. Ber.*, **1961**, 142; (b) Reetz, M.T.; Urz, R.; Schuster, T.; *Synthesis*, **1983**, 540.
15. Corey, E.J.; Erikson, B.W.; *J. Org. Chem.*, **1971**, *35*, 3553.
16. (a) Chérest, M.; Felkin, H.; Prudent, N.; *Tetrahedron Lett.*, **1968**, 2199; (b) Anh, N.T.; Eisenstein, O.; *Nouv. J. Chim.*, **1977**, *1*, 61.
17. Hirama, M.; Vei, M.; *J. Am. Chem. Soc.*, **1982**, *104*, 4251.
18. Corey, E.J.; Hopkins, P.B.; *Tetrahedron Lett.*, **1982**, *23*, 4871.
19. Hartwell, J.L.; Schrecker, A.W.; *J. Am. Chem. Soc.*, **1951**, *73*, 2909.
20. Schreier, E.; *Helvetica Chim. Acta*, **1964**, *47*, 1529.