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TOTAL SYNTHESIS OF (±)-PODOPHYLLOTOXIN AND (±)-EPIPODOPHYLLOTOXIN

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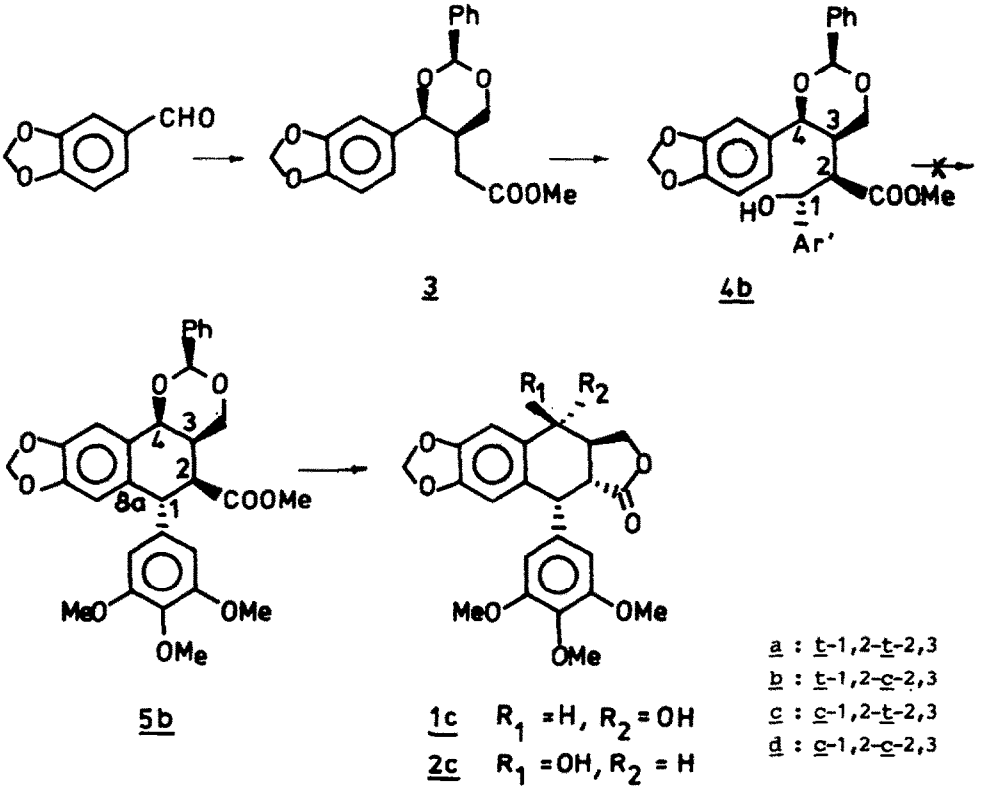
ABSTRACT - A novel approach to (±)-epipodophyllotoxin (2c) and hence also to (±)-podophyllotoxin (1c) is described, involving as a key-step the stereoselective ring closure of the TMS-ester derived from 17a to the tetralin derivative 30c with mesyl chloride.

In the preceding paper[2] we reported on an exploratory approach towards the podophyllum lignans podophyllotoxin (1c) and epipodophyllotoxin (2c). The plan was based on the conversion of piperonal into 3 which upon aldol condensation with 3,4,5-trimethoxybenzaldehyde gave 4b, next to an equal amount of a diastereomer (4a or 4c). For the sake of consistency configurations (a, b, c, d) will be designated as shown in scheme 1.

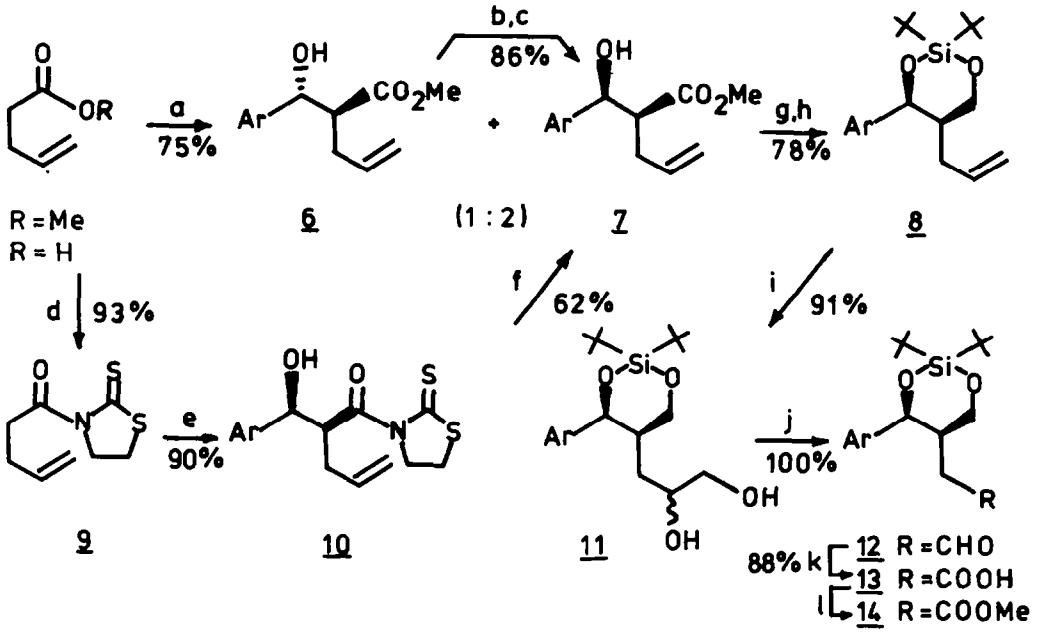


SCHEME 1

Electrophilic ring closure of 4b to the desired tetralin 5b (1-8a bond formation) did, however, not occur under Lewis acid conditions. Products were isolated resulting inter alia from carbenium ion formation at C-4 rather than at C-1. We therefore decided to study the projected sequence with an alternative 1,3-diol protective group which would resist the acid conditions for

electrophilic ring closure.

In the present paper we describe the successful route to epipodophyllotoxin (2c) involving the intermediacy of a 2-sila-1,3-dioxane instead of the 2-phenyl-1,3-dioxane[3]. The readily available di-t.butylsilylene ethers, recently introduced by Trost et al, have been reported to be stable under Lewis acid conditions[4]. Starting from 4-pentenoic acid two routes were developed leading to intermediate 14 (scheme 2).



Ar = 3,4-methylenedioxy. a) on R=Me : LICA, THF, -78°C → -30°C, piperonal, THF, -78°C, NH_4Cl; b) Swern oxidation; c) $Zn(BH_4)_2$; d) on R=H : DCC, DMAP, CH_2Cl_2, r.t.; e) $Sn(OSO_2CF_3)_2$, N-Et-piperidine, CH_2Cl_2; piperonal, -78°C; f) K_2CO_3, MeOH, r.t., 20 min; g) LAH, THF, 0°C, 1 h; h) $(t.Bu)_2Si(OSO_2CF_3)_2$, 2,6-lutidine, CH_2Cl_2, 2 h; i) OsO_4, NMMO, acetone-water, 16 h, r.t.; j) $NaIO_4$, acetone-water, r.t., 2 h; k) $NaClO_2$, 2-Me-2-butene, t-BuOH-water, pH 3, r.t., 30 min; l) CH_2N_2.

SCHEME 2

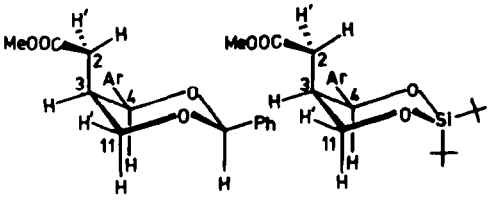
In the non-stereoselective approach aldol-condensation of methyl 4-pentenoate with piperonal gave a 2:1 mixture of diastereomers 7 and 6 (combined yield 75 %). After HPLC separation 6 can be recycled via Swern oxidation to the keto-ester and stereoselective reduction with zink borohydride to give exclusively the desired ester 7. The stereochemical assignment of 6 and 7 is in line with what is generally observed for this type of condensation[7]. An unambiguous structural assignment follows from the structure of 14 (vide infra). The stereoselective synthesis of 7 was accomplished using Mukaiyama's method[8]. Condensation of the tin(II)enolate of the activated amide 9[9] with piperonal followed by methanolysis gave exclusively hydroxy ester 7. After reduction, protection of the 1,3-diol was realized using Corey's conditions[10]. The direct oxidative cleavage of the double bond in 8 proved troublesome. Although the aldehyde 12 was formed upon ozonolysis (dimethylsulfide work-up) or osmium (IV) oxide - sodium periodate oxidation, the yields were low (< 56 %). Also, the direct conversion to acid 13 with ruthenium(IV)oxide-sodium periodate, followed by diazomethane esterification, only gave 31 % yield of ester 14, presumably due to overoxidation of the electron rich aromatic nucleus. Eventually, conversion of olefin 8 to aldehyde 12 could be achieved by a two-step procedure involving dihydroxylation to 11[11], followed by cleavage with sodium periodate. Sodium

chlorite oxidation[12] of 12 proceeded smoothly to the corresponding acid 13, which was then converted to ester 14.

At this point it is interesting to note that the preferred conformation of the di-t.butylsiladioxane ring in this series (8-14) is a chair conformation as indicated by the almost perfect similarity between the ^{1}H NMR J-values of 14 and the previously described 3 (Table 1). This also constitutes a proof for the cis-relation at C-3,C-4.

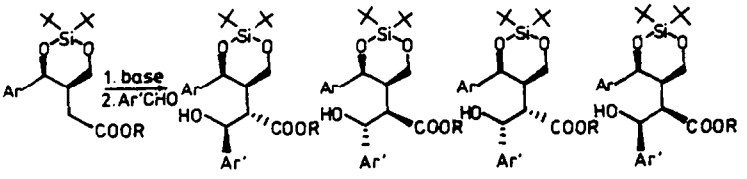
Table 1 : Relevant ^{1}H NMR shift values (ppm) and coupling constants (Hz) of 3 and 14

δ(ppm)	3	14	J(Hz)	3	14
H-2	2.81	2.73	(2,2')	17.0	16.8
H'-2	2.23	2.13	(2,3)	10.5	10.0
H-3			(2',3)	3.5	3.8
H-4	5.13	5.51	(3,4)	2.5	3.0
H-11	4.24	4.52	(3,11)	2.0	2.5
H'-11	4.30	4.09	(3,11')	1.5	1.8
CH_3	3.57	3.55	(11,11')	11.5	11.8
			(11,2')	1.5	1.3



3 14

Table 2 : Condensation of esters 14 and 16 with 3,4,5-trimethoxybenzaldehyde



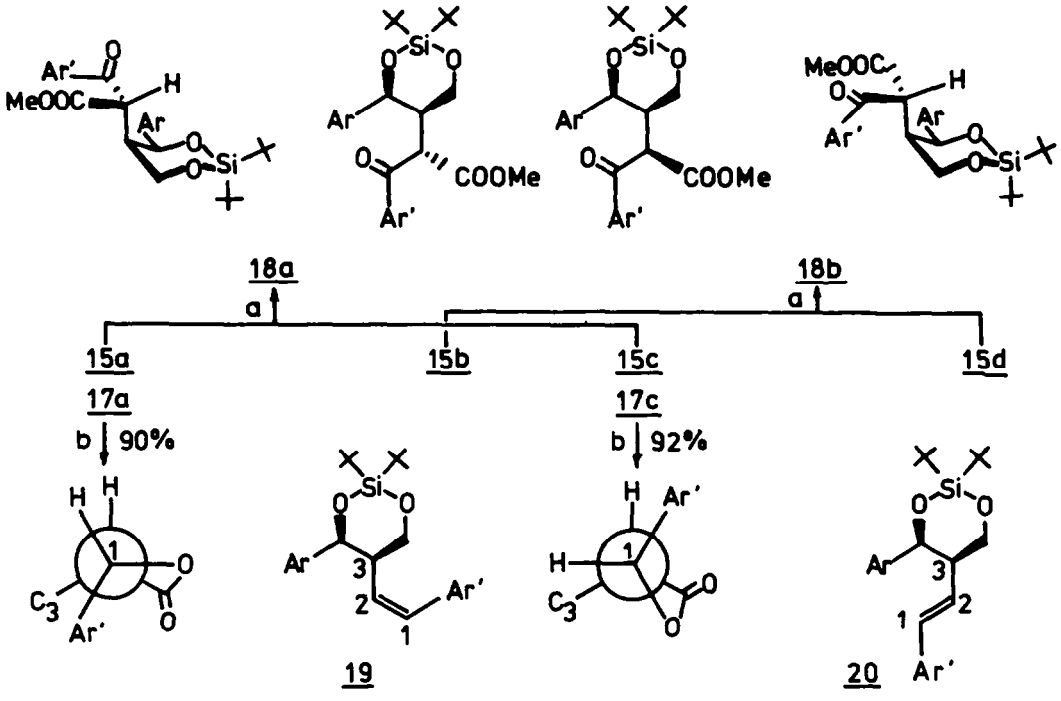
14 (R=Me) → 15 (R=Me) a b c d
16 (R=TMS) → 17 (R=H)

Entry	Substr.	Reaction conditions %	Isol.	a	b	c	d
1	14	LICA or LDA, ether; Ar'CHO, -100°C, 1 min; HOAc, -100°C	15 :	33 %	35 %	tr	tr
2	14	LICA or LDA, THF; Ar'CHO, -30°C → 10°C, 90 min; NH_4Cl	15 :	-	-	-	64 %
3	14	LDA, HMPA (23 vol %), THF; Ar'CHO, -100°C, HOAc, -100°C	15 :	tr	tr	tr	50 %
4	16	LDA, THF; Ar'CHO, -78°C, 3min; HOAc, -78°C	17 :	34 %	-	27 %	-
5	16	LDA, THF; Ar'CHO, -78°C → 0°C, 16 h; HOAc	17 :	34 %	-	27 %	-

Upon appropriate variation of reaction conditions it was possible to produce all four diastereomeric products 15a-15d from the condensation of the lithium enolate of 14 with 3,4,5-trimethoxybenzaldehyde. The results are summarized in table 2 and will be discussed briefly. The respective stereochemical assignments are based on chemical (scheme 3) and spectroscopic (table 3) grounds.

Upon oxidation of the aldol isomers 15 to the corresponding keto-esters, 18a was obtained from 15a or 15c, while the epimeric ester at C-2 (18b) was obtained from 15b or 15d. The assignment of the configuration at C-2 is deduced from the ^{1}H NMR resonance of the methyl ester protons (18a, J = 3.70 Hz and 18b, J = 3.10 Hz); the preferred rotameric conformations of both

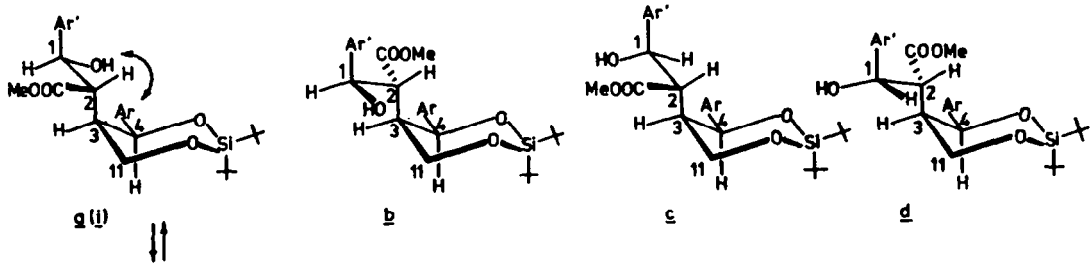
keto-esters (scheme 3), as revealed by the large ^3J value between H-2 and H-3 (10 and 11.5 Hz), indicate the methyl ester group to be located in the shielding cone of the aromatic nucleus[2].

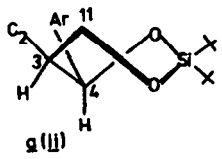


Ar = 3,4-methylenedioxyphenyl; Ar' = 3,4,5-trimethoxyphenyl.
a) PDC; b) MsCl, Et_3N or Burgess' reagent.

SCHEME 3

Table 3 : Relevant 1H NMR values and preferred rotameric population of a-d



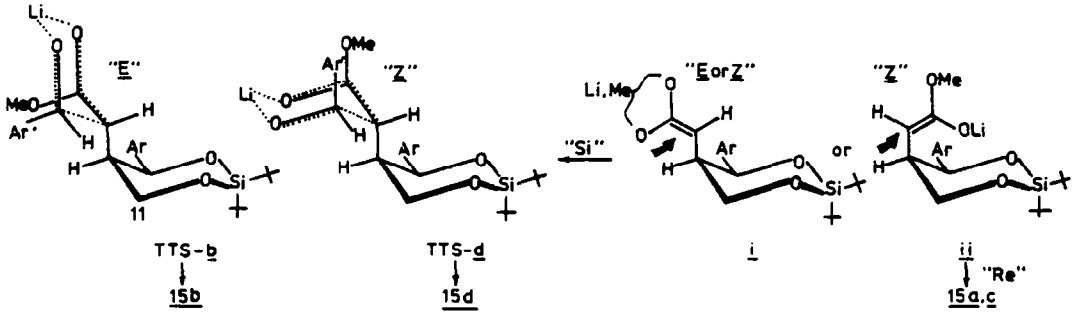


	^3J-values (Hz)							δ(ppm)
	(1,2)	(2,3)	(3,4)	(3,11)	(3,11')	(1,OH)	H1	COOMe
15a	6.3	3.5	6.8	10.0	3.0	-	4.80	3.19
15b	8.5	10.0	2.8	2.0	2.3	-	4.78	2.65
15c	3.5	9.0	3.5	2.5	3.8	10	3.90	2.41
15d	3.0	10.5	2.5	1.5	2.3	10	5.16	2.75

The assignment of the configuration at C-1 in 15a and 15c follows from the observation (vide infra) that upon treatment with mesyl chloride in triethylamine, acid 17a yields stereospecifically the Z-olefin 19 (J(H-1,H-2) : 11.5 Hz), while isomeric 17c leads exclusively to the corresponding E-derivative 20 (J(H-1,H-2) : 16 Hz). The olefins arise from β-lactone

formation via the mixed anhydride, followed by syn-decarboxylation[13]. The ^{1}H NMR spectral data obtained for 15a-d are also very informative (Table 3).Whereas the coupling patterns observed for H-3,H-4 and the geminal protons H-11 reveal a chair conformation for the siladioxane ring in isomers 15b, c and d (all vicinal values between 1 and 4 Hz; see also 14 in Table 1), the values found in 15a (^{3}J(H-3,H-4) : 6.8 Hz and ^{3}J(H-3,H-11) : 10.0 Hz) indicate a twist-boat-type conformation such as ii. Furthermore, whereas the preferred rotamers in 15b-d possess the H-2 oriented over the siladioxane ring (as indicated by J(H-2,H-3): 9-10.5 Hz), isomer 15a exhibits a much smaller value (3.5 Hz) for the same coupling. Finally, the consideration of a staggered conformation at C-2,C-1 with the largest groups (Ar' and C-3 substituent) in the antiperiplanar orientation leads to the preferred rotamers indicated in Table 3. In line with the indicated configurations at C-1 and C-2, a small ^{3}J(H-2,H-1) value is found in 15c and 15d (3.5 and 3.0 Hz, respectively) and a large value in 15b (8.5 Hz). The remarkably shielded H-1 proton in 15c (3.90 ppm compared to the value in the other isomers which ranges from 4.78 to 5.16 ppm) is in accord with its orientation above the methylenedioxyphenyl ring. A large (10 Hz) coupling of the hydroxyl proton in 15c and 15d indicating intramolecular hydrogen bonding, further substantiates both the assigned configurations and the indicated rotameric preferences of 15b-d. The corresponding all-staggered conformation of 15a with the siladioxane chair conformation now reveals a serious van der Waals interaction between the hydroxyl group at C-1 and the aryl group at C-4 (cf. arrow in i). Presumably, the anomalous conformational behavior of 15a (vide supra) originates here, since by adopting a twist-boat-type conformation for the heterocyclic ring, the latter interaction can be relieved as shown by molecular model examination.

We now comment upon the observed stereoselectivities obtained when performing the condensations with the methyl esters 14 and trimethylsilyl esters 16 under various conditions. The previous study on the analogue 3 has revealed that formation of the lithium enolate (LDA or LICA), under conditions which normally yield selectively the E-enolate[14], in fact produce both enolates (cf. scheme 9 in ref. 2). Under irreversible conditions, one may expect that, depending on the attack of the electrophile from the Re-side of the intramolecularly chelated Z-enolate or from the Si-side of the unchelated E- or Z-enolate, the aldol products of the a, c or b, d series will respectively be produced (scheme 4).



Ar = 3,4-methylenedioxyphenyl; Ar' = 3,4,5-trimethoxyphenyl

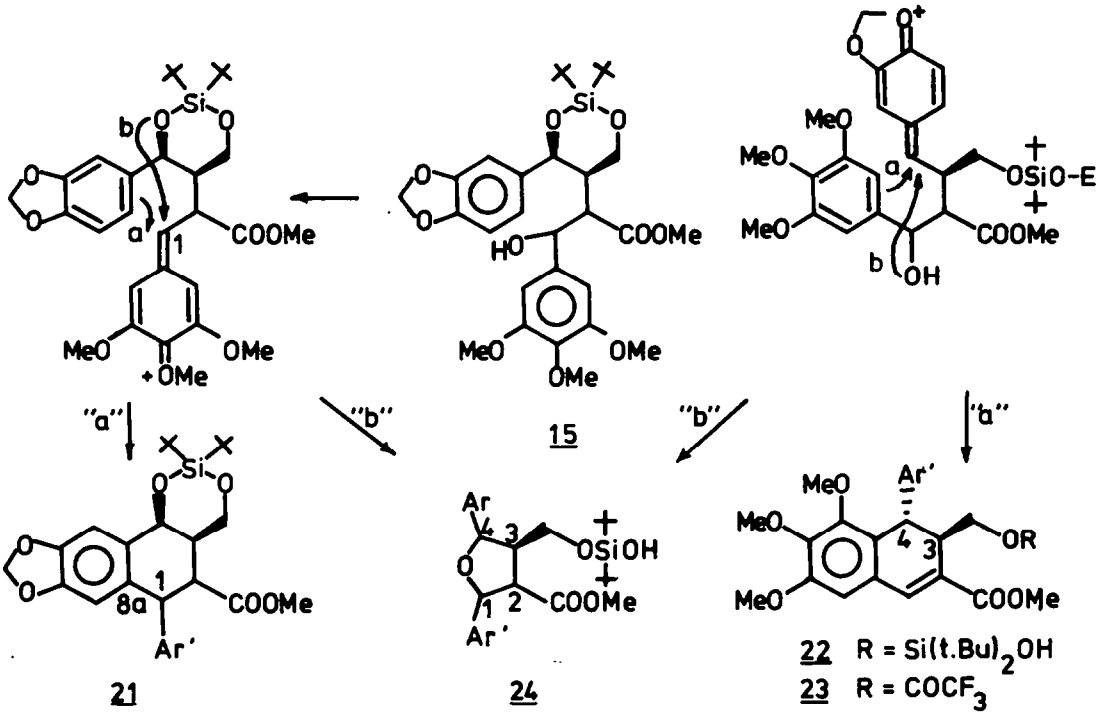
SCHEME 4

In line with the result obtained from 3, the enolate of 14 gave under kinetically controlled conditions (table 2; entry 1) a 1:1 mixture of 15a and 15b.

The preferred formation of 15b from the E-enolate is in line with the Zimmerman transition state as depicted in scheme 4; attack of the E-enolate on the aldehyde, with Ar' directed towards C-11, which would lead to 15d is disfavored due to a serious non-bonded interaction between Ar' and C-11 . However, when the enolate is formed in the presence of HMPA (table 2, entry 3) 15d is formed almost preferentially. Presumably, the unchelated Z-enolate (HMPA)[14] here reacts according to TTS-d, in which non bonded interactions between Ar' and C-11 are avoided. If the

reaction is allowed to equilibrate before acid quench, 15d is formed as the sole isolated product (entry 2). This is not surprising since the six-membered chelated aldolate would be the more stable in the d-configuration (cf. preferred rotamers in Table 3); the alternative c-aldolate chelate suffers from a C-1-C-4 gauche interaction. As will appear later we also needed to have directly access to the acids 17. Since the dianion of 13 failed to react with 3,4,5-trimethoxybenzaldehyde, the condensation was performed on the corresponding trimethylsilyl ester which, upon work-up, gave directly the acid 17 (table 2 and scheme 7). The crude suspension of the silyl ester 16 (from acid 13 and TMSCl in Et_3N-THF at 0°C) was added to the base since isolation of pure 16 proved unfeasable. Interestingly, a ca 1:1 ratio of 17a and 17c was obtained (61 % combined yield) both under presumed kinetic (table 2, entry 4) and thermodynamic (entry 5) conditions. Possibly, in this case, the equilibrium situation is obtained very rapidly due to the presence of large amounts of lithium salts and favors isomers a and c where the larger trimethylsilyloxycarbonyl group is disposed anti to the C-4 aryl group.

With the diastereoisomers 15 in hand we could now study the crucial C-1,C-8a ring closure. However, much to our dismay, electrophilic conditions (CF_3COOH or $SnCl_4$)[2] did not lead to the desired tetralin 21, but rather to products originating from closure at C-4, as we had previously experienced with the benzyl protected derivative 4b[2] (scheme 5).

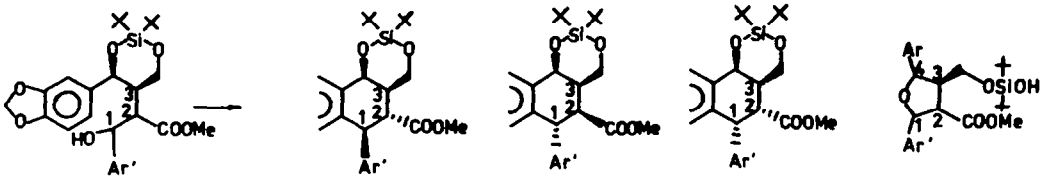


SCHEME 5

With tin(IV)chloride (CH_2Cl_2, -20°C - 0°C) the same dihydronaphtalene 22 resulted from the reaction of all four isomers 15a-d; in the case of trifluoroacetic acid (CH_2Cl_2, -20 - 0°C) isomers 15a and 15b each gave rise to a different tetrahydrofuran derivative 24 (unknown configuration; 53 % and 37 % yield, respectively), whereas 23 (53 % yield) was obtained selectively from 15c and 15d. This results indicate carbenium ion formation at C-4. The trans-diaxial disposition of the substituents at C-3 and C-4 in 22 and 23 follows from the observed ^3J(H-3,H-4) of 1.25 and 1 Hz.

Since it became clear that the siladioxane group in 15 is sensible to protic or Lewis acid conditions, we turned to the conversion of the hydroxyl group via the mesylate into a methyl sulfide in order to allow for selective C-1 carbenium ion generation under non acidic conditions (mercury on silver ions)[15].

Table 4 : Ring closure results obtained with 15

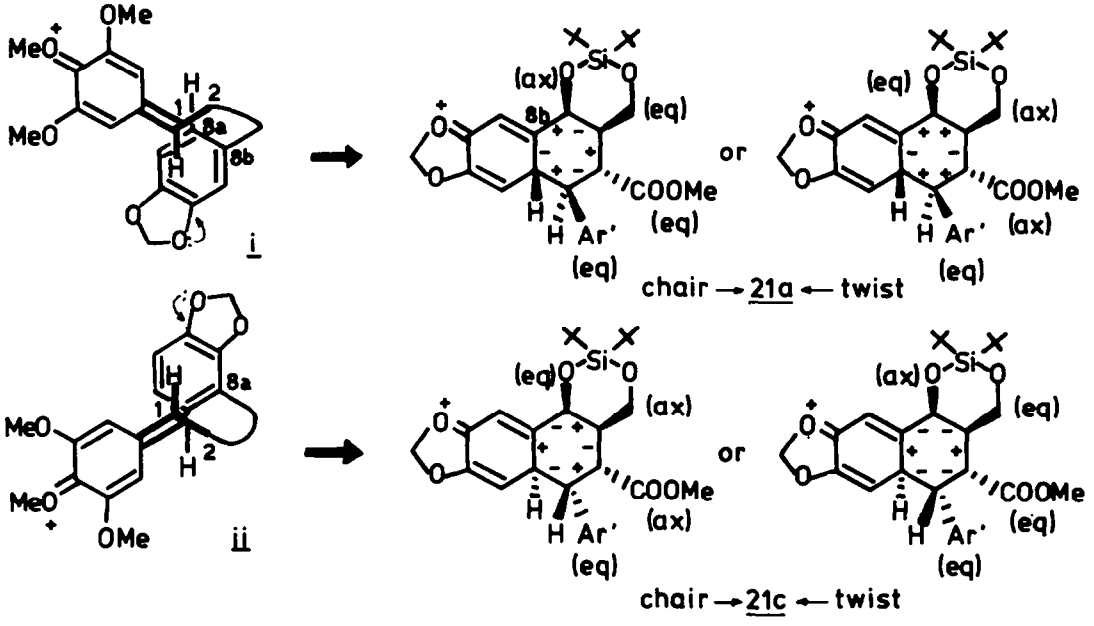


15 21a 21b 21c 24

a : t-1,2-t-2,3 c : c-1,2-t-2,3
b : t-1,2-c-2,3 d : c-1,2-c-2,3

Entry	Substr.	Reaction conditions	Ratio[a] (isolated yield)			
			21a	21b	21c	24
1	15a	MsCl, Et_3N	-	-	100(75 %)	-
2	15b	"	-	18	-	39+43(70 %)
3	15c	"	100(83 %)	-	-	-
4	15d	"	22	9	-	56+13[b]
5	15a	Burgess' reagent	-	-	100(97 %)	-
6	15b	"	-	67	-	33
7	15c	"	100(65 %)	-	-	-
8	15d	"	22	65	-	13

[a] Ratio's determined by ^1H NMR
[b] Mixture of two isomers



Ar' = 3,4,5-trimethoxybenzaldehyde; (ax) = axial; (eq) = equatorial or isoclinal

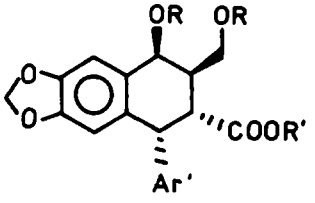
SCHEME 6

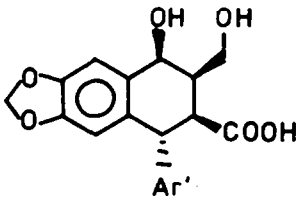
We were very fortunate to discover that attempted conversion of 15 into the corresponding mesylate directly led to the formation of tetralin derivatives 21 (table 4). Moreover, in the case of 15a and of 15c a stereoselective conversion to 21c and 21a, respectively, was observed (isolated yields : 75 % and 83 %). The same qualitative result was obtained when subjecting the alcohols 15a and 15c to Burgess' reagent[16]; in contrast, isomers 15b and 15d gave rise, next to tetralin derivatives 21, to substantial amounts of tetrahydrofurans 24. It should be mentioned that tetralin formation does not proceed via dehydration to a 1,2 double bond[17].

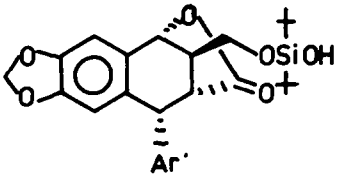
The configurational assignment of 21a, 21b and 21c follows from the ^{1}H NMR coupling patterns observed for the protons at C-1, C-2 and C-3 . The above results obtained with 15a and 15c suggest a neat S_N2-type displacement. However, upon careful model examination it seems quite unlikely that the steric requirements involved in this particular reaction type can be fulfilled. It would rather seem that capture of the incipient carbenium ion at C-1 occurs before conformational interconversion (scheme 6).

This would explain the exclusive formation of tetralins from 15a and 15c where, in the preferred ground state conformations, C-1 is situated in the immediate neighbourhoud of the 3,4-methylenedioxyphenyl ring. Assuming bond formations between C-1 and C-8a to occur via a staggered disposition (i or ii) with minimal steric interactions between both aromatic rings as depicted in scheme 6, reaction in the a- or c-series ($COOCH_3$ at C-2 α-oriented) should lead to formation of 21a via a chair-conformation and of 21c via a twist-conformation. The different conformation of the siladioxane ring in 15a compared to 15b-c may well be responsible for the exclusive formation of 21c from 15a.

The final steps to (+)-epipodophyllotoxin, in principle, involve the removal of the cyclic protective group, the saponification of the methyl ester and lactonization. As for the relative order of the steps it was known from Rodrigo's work[19] that whereas diol 25 leads to isomerized 27 upon alkaline treatment (scheme 7)(see also ref. 2 : trans-relation between C-1 and C-2), the corresponding acetonide 26 can be saponified without C-2 epimerization thus leading to 28 after acid removal of the protective group. Quite to our surprise we were unable to perform the hydrolysis of the methyl ester in 21c under a variety of basic conditions without affecting the siladioxane group. Invariably lactone 29 was found as the major product.







21c R=-Si(t.Bu)$_2$-, R'=Me
25 R=H, R'=Me
26 R=-CMe$_2$-, R'=Me
28 R=R'=H
30c R=-Si(t.Bu)$_2$-, R'=H

27

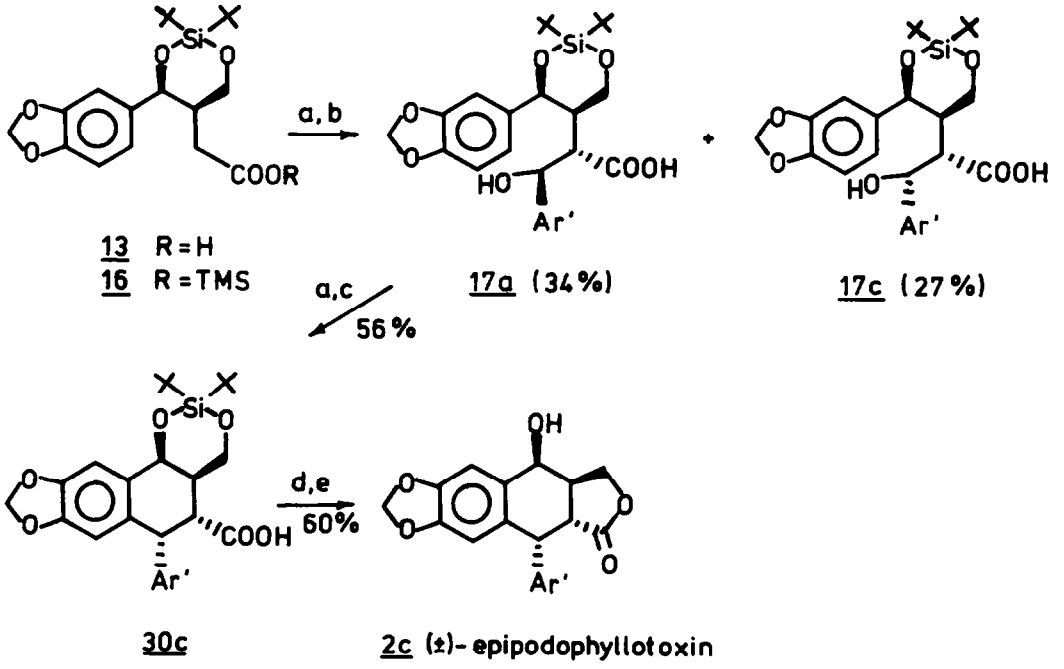
29

SCHEME 7

This set back led us to investigate the aldol condensation of the acid 13 instead of the corresponding methyl ester 14 (scheme 7). As described above hydroxy-acids 17a and 17b were obtained when performing the condensation on the trimethylsilyl ester 16.

The synthesis of the desired tetralin (30c) would involve treatment of isomer 17a with mesyl chloride and triethylamine or Burgess' reagent (vide supra). Instead, as already mentioned, Z-alkene 19 was formed. However, prior conversion of acid 17a to its trimethylsilyl ester and mesyl chloride treatment afforded upon work-up directly the expected 30c.

Eventually, (±)-epidopodophyllotoxin (2c) was obtained via the removal of the siladioxane group and direct lactonization of the resulting dihydroxy-acid. The racemic 2c exhibited the same TLC behavior and spectral properties as (-)-epipodophyllotoxin which was obtained from natural (-)-podophyllotoxin via a known procedure[20]. We thus succeeded in realizing the thermodynamically disfavored 1,2-c-2,3-t-configuration of 1c and 2c via a mild and efficient cyclization of hydroxy-acid 17a. An asymmetric synthesis of 1c and 2c is currently in progress.



Ar' = 3,4,5-trimethoxybenzaldehyde. a) TMSCl, Et_3N, CH_2Cl_2, 0°C; b) LDA, THF; Ar'CHO, -78°C, 3 min, HOAc-ether, -78°C; c) MsCl, Et_3N, -10°C; d) n.Bu_4NF, THF; e) DCC, DMAP, CH_2Cl_2, r.t.

SCHEME 8

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. $MgSO_4$, 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 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.s. are uncorrected.

Syn methyl 2-(hydroxy-(3',4'-methylenedioxyphenyl)-methyl)-4-pentenoate (7).
A mixture of 4-pentenoic acid (1 g, 10 mmol), thiazolidine-2-thione (1.31 g, 11 mmol), DCC (2.27 g, 11 mmol) and DMAP (122 mg, 1 mmol) in dry CH_2Cl_2 (50 ml) was stirred under N_2 for 48 h. The mixture was diluted with ether, and the solids filtered off. Column chromatography (ether/hexane 4:6) afforded 9 (1.87 g; 93 %) as a yellow oil. Rf (ether/hexane 4:6) : 0.21. A soln of 9 (100 mg, 0.50 mmol) in CH_2Cl_2 (0.7 ml) was added at -78°C over 5 min to a susp of $Sn(OTf)_2$ (rinced with absolute ether; 259 mg, 0.621 mmol) in dry CH_2Cl_2 (1 ml) and N-Et-piperidine (102 ul, 0.745 mmol). After 30 min at -78°C, piperonal (112 mg, 0.75 mmol) in CH_2Cl_2 (0.7 ml) was added. The mixture was stirred for 20 min at -78°C, and then poured into a phosphate buffer (pH 7). The residue obtained after work-up was purified by column chromatography (ether/hexane 6:4), yielding 10 (157 mg, 90 %). Rf (ether/hexane 6:4) : 0.15. A soln of 10 (90 mg, 0.256 mmol) in MeOH (3 ml) was treated with K_2CO_3 (71 mg) at r.t. for 10 min; then a phosphate buffer (pH 7) was added. Work-up and column chromatography (ether/hexane 3:7) gave 7 (42 mg; 62 %). Rf (EtOAc/hexane 2:8) : 0.19; IR (neat) : 3650-3200, 1730, 1645 cm^{-1}; ^1H NMR : 6.87 (m, 1), 6.80 (ddd, 1, J = 8, 1.5 and 0.5 Hz), 6.76 (dd, J = 8 and 0.5 Hz), 5.96 (s, 2), 5.74 (dddd(m), 1, J = 16.75, 10, 6.5 and 7.25 Hz), 5.05 (ddd, 1, J = 1.5, 3 and 16.75 Hz), 5.00 (dddd(m), 1, J = 1, 1, 3 and 10 Hz), 4.90 (dd, 1, J = 5.75 and 2.75 Hz), 3.60 (s, 3), 2.78 (ddd, 1, J = 5.75, 5 and 9.25 Hz), 2.72 (d, 1, J = 2.75 Hz), 2.49 (m, 1, J = 14.25 Hz), 2.40 (m, 1, J = 14.25 Hz); MS : m/z 264 ($M^{+\cdot}$, 23), 151 (100), 150 (83), 149 (100), 121 (30); HRMS : calc. for $C_{14}H_{16}O_5$: 264.0998; found : 264.0965.

Syn-5-allyl-2,2-di-t.butyl-4-(3',4'-methylenedioxyphenyl)-2-sila-1,3-dioxane (8).
To a susp of $LiAlH_4$ (3.3 g, 87.5 mmol) in dry THF (60 ml) was added at 0°C a soln of 7 (15.4 g, 58.3 mmol) in THF (200 ml). After 1 h at 0°C water (3.5 ml), 15 % aq. NaOH (3.5 ml) and water (10.5 ml) were added successively. The mixture was diluted with ether and the salts removed by filtration. Drying, solvent evaporation and column chromatography (EtOAc/hexane 2:8), yielded the diol (13.3 g; 97 %). Rf (ether/hexane 8:2) : 0.27.
To a soln of the diol (14.3 g, 60.6 mmol) in dry CH_2Cl_2 (200 ml) were added at 0°C 2,6-lutidine (dist. from CaH_2; 21.15 ml, 181.8 mmol) and $(t.Bu)_2Si(OTf)_2$ (23.5 ml, 72.7 mmol). The reaction mixture was slowly warmed up to r.t. After 2 h of stirring the solvent was removed in vacuo. Column chromatographic purification (EtOAc/hexane 5:95) afforded 8 (18.37 g; 81 %) as an oil. Rf (EtOAc/hexane 5:95) : 0.26; ^1H NMR : 6.88 (m, 1, LR), 6.81 (dd, 1, J = 8 Hz + LR), 6.78 (ddd, 1, J = 8 and 1.5 Hz + LR), 5.96 (s, 2), 5.55 (m, 1), 5.51 (bd, 1, J = 2.5 Hz + LR), 5.00-4.91 (m, 2), 4.40 (ddd, 1, J = 2.5 and 1.25 Hz, ^2J = 11.5 Hz) and 4.16 (dd, 1, J = 1.75 Hz, ^2J = 11.5 Hz), 2.41 (ddd, 1, J = 8.5, 11 and 14.5 Hz), 1.83-1.71 (m, 2), 1.14 (s, 9), 1.13 (s, 9); MS : m/z 376 ($M^{+\cdot}$, 15), 319 (100), 289 (53), 201 (28), 135 (33); HRMS : calc. for $C_{17}H_{23}O_4Si$: 319.1366; found : 319.1307.

3-(2',2'-Di-t.butyl-r-4'-(3",4"-methylenedioxyphenyl)-2'-sila-1',3'-dioxane-c-5'-yl)-propane-1,2-diol (11).
To a soln of 8 (16.44 g, 43.7 mmol) in acetone (490 ml) were added a soln of N-Me-morpholine-N-oxide (5.6 g, 48 mmol) in water (165 ml) and OsO_4 (100 mg, 0.39 mmol). The reaction mixture was stirred at r.t. for 16 h. Acetone was removed in vacuo, and the residue worked up. Column chromatography (EtOAc/hexane 1:1) afforded 16.2 g (91 %) diol 11 as a diastereomeric mixture. Rf (ether/hexane 8:2) : 0.15; IR (KBr) : 3700-3100, 1495, 1335, 1245, 1150, 1070 cm^{-1}; ^1H NMR : 6.89-6.75 (m, 3), 5.96 (m, 2), 5.53 and 5.47 (d, 1, J = 2.5 Hz), 4.51 (m, 2) and 4.21 (dd, 1, J = 1.5 Hz, ^2J = 12 Hz) and 4.17 (dd, J = 1.5 Hz, ^2J = 12 Hz), 3.68 and 3.22 (m, 1), 3.51 (dd, 1, J = 3 Hz, ^2J = 11 Hz) and 3.27 (dd, 1, J = 7.5 Hz, ^2J = 11 Hz), 3.37 (dd, 1, J = 2.5 Hz, ^2J = 10 Hz) and 3.16 (dd, 1, J = 7.5 Hz, ^2J = 10 Hz), 2.13-1.7 (m), 1.5-1.3 (m).

Methyl syn-(2,2-di-t.butyl-4-(3',4'-methylenedioxyphenyl)-2-sila-1,3-dioxan-5-yl)-acetate (14).
A soln of 11 (16.2 g, 39.5 mmol) in acetone (450 ml) was treated under stirring with a soln of $NaIO_4$ (27.9 g, 130.4 mmol) in water (150 ml). After 2 h at r.t. the solids were filtered off and the filtrate was concentrated in vacuo. Work-up of the residue yielded 15 g (100 %) of nearly pure 12. Rf (ether/hexane 8:2) : 0.71; IR (neat) : 1730 cm^{-1}; ^1H NMR : 9.50 (dd(bs), 1, J = 1.2 and 1.25 Hz); MS : m/z 378 ($M^{+\cdot}$, 1).
To a stirred and ice-cooled soln of 12 (15 g, 39.7 mmol) and 2-Me-2-butene (42.3 ml, 397 mmol) in t.BuOH (200 ml) was added during 10 min a soln of $NaClO_2$ (80 %; 5.65 g, 49.7 mmol) in a phosphate buffer (pH 3; 40 ml). After 15 min, t.BuOH was removed in vacuo. Work-up afforded an oil, which upon crystallization (EtOAc/hexane 3:10) yielded 13 (12.2 g; m.p. 164°C) in 2 crops. Purification of the mother liquors by column chromatography (EtOAc/hexane) afforded another 1.44 g (total yield : 13.64 g; 88 %). Treatment of 13 (11.7 g, 29.7 mmol) at 0°C with an ethereal soln of CH_2N_2, gave 14 (12.1 g; 100 %). M.p. : 89°C; Rf (ether/hexane 8:2) : 0.70; IR (neat) : 1735 cm^{-1}; ^1H NMR : 6.87 (m, 1), 6.79 (m, 2), 5.95 (d+d (s), 2, J = 1.5 Hz), 5.51 (d, 1, J = 3 Hz + LR), 4.52 (ddd, 1, J = 2.5 Hz, ^2J = 11.75 Hz, ^4J = 1.25 Hz) and 4.09 (dd, 1, J = 1.75 Hz, ^2J = 11.75 Hz), 3.55 (s, 3), 2.73 (dd, 1, J = 10 Hz, ^2J = 16.75 Hz), and 2.13 (ddd, 1, J = 3.75 Hz, ^2J

= 1.25 Hz, ^2J = 16.75 Hz), 2.39 (m, 1), 1.13 (s, 9), 1.12 (s, 9); MS : m/z 408 ($M^{+\cdot}$, 1), 352 (21), 351 (86), 321 (68), 173 (34), 135 (56), 115 (32), 91 (100); HRMS : calc. for $C_{17}H_{23}O_6Si$: 351.1263; found : 351.1286.

Aldol condensation of 14 with 3,4,5-trimethoxybenzaldehyde.
The same typical procedure was used as described for the condensation of 3[2]. Specific reaction conditions and product ratios are indicated in table 2.
15a: Rf (ether/hexane 8:2) : 0.41; m.p. : 72°C; IR (KBr) : 3560-3180, 1720, 1585 cm^{-1}; ^1H NMR : 6.88 (d, 1, J = 1.5 Hz), 6.79 (dd, 1, J = 1.5 and 8 Hz), 6.73 (d, 1, J = 8 Hz), 6.45 (s, 2), 5.933 (d, 1) and 5.926 (d, 1, J = 1.5 Hz), 4.92 (d, 1, J = 6.75 Hz), 4.80 (d, 1, J = 6.25 Hz), 4.45 (dd, 1, J = 10 Hz) and 4.25 (dd, 1, J = 3 and 11.5 Hz), 3.84 (s, 6), 3.81 (s, 3), 3.19 (s, 3), 3.16 (m, 1), 2.81 (bs, 1), 2.59 (dd, 1, J = 3.5 and 6.25 Hz), 1.08 (s, 9), 1.05 (s, 9); MS : m/z 408 (1), 351 (42), 196 (100), 181 (51), 125 (44), 110 (36), 91 (31).
15b: Rf (ether/hexane 8:2) 0.36; m.p. : 134°C; ^1H NMR : 6.84 (d (bs), 1, J_2= 1.5 Hz + LR), 6.73 (dd, 1, ^2J = 8 and 1.5 Hz), 6.70 (d, 1, J = 8 Hz), 6.48 (s, 2), 5.88 (d, 1, ^2J = 1.5 Hz) and 5.87 (d, 1, ^2J = 1.5 Hz), 5.57 (d, 1, J = 2.75 Hz + LR), 4.78 (d, 1, J = 8.5 Hz), 4.72 (dd, 1, J = 2 Hz) and 4.64 (dd, 1, J = 2.25 and 12.7 Hz), 4.74 (s, 1), 3.80 (s, 6), 3.76 (s, 3), 3.19 (dd, 1, J = 8.5 and 10 Hz), 2.76 (m, 1), 2.65 (s, 3), 1.27 (s, 9), 1.17 (s, 9).
15c: Rf (ether/hexane 8:2) : 0.28; ^1H NMR : 7.09 (d, 1, J = 1.5 Hz), 7.00 (dd, 1, J = 8 and 1.5 Hz + LR), 6.85 (d, 1, J = 8 Hz), 6.21 (s, 2), 5.97 (d, 1) and 5.95 (d, 1, ^2J = 1.5 Hz), 5.57 (bd, 1, J = 3.5 Hz + LR), 4.44 (dd, 1, J = 2.5 Hz, ^2J = 12.25 Hz) and 4.14 (dd, 1, J = 3.75 Hz, ^2J = 12.25 Hz), 3.90 (dd, 1, J = 3.5 and 10 Hz), 3.80 (s, 6), 3.79 (s, 3), 3.70 (bd, 1, J = 10 Hz), 3.41 (s, 3), 3.24 (dd, 1, J = 3.5 and 9 Hz), 2.79 (m, 1), 1.14 (s, 9), 1.11 (s, 9).
15d : Rf (ether/hexane 8:2) : 0.28; m.p. : 82°C; ^1H NMR : 6.87 (d (bs), 1, J = 1.5 Hz + LR), 6.76 (dd, 1, J = 8 and 1.5 Hz + LR), 6.71 (d, 1, J = 8 Hz), 6.39 (s, 2), 5.89 (d, 1, ^2J = 1.5 Hz) and 5.88 (d, 1, ^2J = 1.5 Hz), 5.64 (d, 1, J = 2.5 Hz + LR), 5.16 (ddd, 1, J = 10 and 3 Hz + LR), 4.81 (dd, 1, J = 1.5 Hz) and 4.62 (dd, 1, J = 2.25 and 12.25 Hz), 3.785 (s, 3), 3.783 (s, 6), 3.57 (bd, 1, J = 10 Hz), 3.31 (dd, 1, J = 3 and 10.5 Hz), 2.79 (s, 3), 2.62 (m, 1), 1.24 (s, 9), 1.17 (s, 9).
The isomers 15 gave almost identical IR and MS spectra.

Acid-catalyzed electrophilic ring closure of 15.
The cyclization reactions of 15 with $SnCl_4$ or TFA were carried out as described for 3[2].
- dihydronaphtalene 22 :Rf (ether/hexane 8:2) : 0.43; UV (MeOH) : λ_{max} = 310 nm; ^1H NMR : 7.55 (s, 1), 6.69 (s, 1), 6.64 (d, 1, J = 8 Hz), 6.50-6.45 (m, 2), 5.87 (d, 1, ^2J = 1.5 Hz) and 5.86 (d, 1, ^2J = 1.5 Hz), 4.82 (bs, 1, J = 1.25 Hz), 3.90 (s, 3), 3.88 (s, 3), 3.74 (s, 3), 3.59 (s, 3), 3.83 (dd, 1, J = 3.75 Hz, ^2J = 10 Hz) and 3.35 (dd (t), 1, J = 9.5 Hz, ^2J = 10 Hz), 3.19 (ddd, 1, J = 1.25, 3.75 and 10 Hz), 1.05 (s, 9), 1.02 (s, 9).
- dihydronaphtalene 23 (53 % from 15a and 15b with TFA) : for spectral data see ref. 2.
- tetrahydrofuran 24 (from 15a with TFA; 53 %) : Rf (ether/hexane 8:2) : 0.47; IR (neat) : 3700-3300, 1725, 1590, cm^{-1}; ^1H NMR : 6.89 (d, 1, J = 1.5 Hz), 6.83 (dd, 1, J = 8 and 1.5 Hz), 6.78 (d, 1, J = 8 Hz), 6.70 (s, 2), 5.96 (s, 2), 5.21 (d, 1, J = 7.5 Hz), 5.09 (d, 1, J = 8 Hz), 3.88 (s, 6), 3.86 (s, 3), 3.73 (s, 3), 3.53 (dd, 1, J = 5.5 Hz, ^2J = 10.5 Hz) and 3.42 (dd, 1, J = 9 Hz, ^2J = 10.5 Hz), 3.15 (dd, 1, J = 6 and 8 Hz), 3.06 (m, 1), 0.901 (s, 9), 0.895 (s, 9); MS : m/z 604 ($M^{+\cdot}$, 2), 351 (17), 181 (23), 135 (100), 91 (43).
isomer 24 (from 15b with TFA; 37 %) :Rf (ether/hexane 8:2) : 0.46; IR (neat) : 3700-3300, 1725, 1590 cm^{-1}; ^1H NMR : 6.99 (d, 1, J = 1.5 Hz), 6.92 (dd, 1, J = 8 and 1.5 Hz + LR), 6.80 (d, 1, J = 8 Hz), 6.69 (s, 2), 5.97 (s, 2), 5.23 (d, 1, J = 8.25 Hz), 4.95 (d, 1, J = 7.5 Hz), 4.00 (dd, 1, J = 6 Hz, ^2J = 10.5 Hz) and 3.96 (dd, 1, J = 5.5 Hz, ^2J = 10.5 Hz), 3.87 (s, 6), 3.84 (s, 3), 3.73 (s, 3), 3.22 (dd, 1, J = 8.25 and 10 Hz), 2.69 (m, 1), 1.01 (s, 9), 1.00 (s, 9); MS : m/z 604 ($M^{+\cdot}$, 1), 351 (22), 161 (14), 149 (18), 135 (100), 91 (32).

Ring closure of 15 with MsCl/NEt_3 : typical procedure.
A cooled (-10°C) soln of 15 (72 mg, 0.12 mmol) in dry CH_2Cl_2 (2.5 ml) was treated with MsCl (23 ul, 0.29 mmol) and NEt_3 (51 ul, 0.36 mmol), and stirred for 30 min. Then water was added, and the mixture was worked up. The residue was purified by HPLC (ether/hexane) (for the ratios of compounds formed, see table 4).

Ring closure of 15 with Burgess' reagent : typical procedure.
A soln of 15 (30 mg, 0.054 mmol) in dry benzene (0.5 ml) was added at r.t. to a susp of Burgess' reagent (39 mg, 0.163 mmol) in benzene (0.3 ml). The mixture was stirred for 30 min at 50°C. After addition of water and work-up, the residue was purified by HPLC (ether/hexane) (for the ratios of compounds formed, see table 4).
21a : Rf (ether/hexane 8:2) : 0.41; ^1H NMR : 6.83 (s, 1), 6.33 (bs, 2), 6.25 (bs, 1), 5.92 (d, 1, ^2J = 1.5 Hz) and 5.91 (d, 1, ^2J = 1.5 Hz), 5.25 (d, 1, J = 3.5 Hz), 4.41 (dd, 1, J = 3 Hz, ^2J = 12.5 Hz) and 3.91 (dd, 1, J = 2.3 Hz, ^2J = 12.5 Hz), 4.06 (d, 1, J = 11 + LR), 3.85 (s, 3), 3.78 (bs, 6), 3.62 (dd (t), 1, J = 11 and 12 Hz), 3.53 (s, 3), 2.20 (m, 1), 1.18 (s, 9), 1.06 (s, 9).
21b : M.p. : 200°C (ether/hexane); Rf (ether/hexane 1:1) : 0.27; IR (KBr) : 1735, 1595, cm^{-1}; ^1H NMR : 7.22 (bs, 1), 6.18 (bs, 1), 6.27 (s, 2), 5.92 (d, 1, ^2J = 1.5 Hz) and 5.89 (d, 1, ^2J = 1.5 Hz), 5.38 (bd, 1, J = 5.5 Hz), 4.12-4.03 (m, 3), 3.83 (s, 3), 3.78 (s, 6), 3.60 (s, 6), 3.06 (dd, 1, J = 3 and 12 Hz), 2.92 (m, 1), 1.08 (s, 9), 0.88 (s, 9).
21c: M.p. : 151°C (ether); Rf (ether/hexane 1:1) : 0.20; IR (KBr) : 1730, 1590 cm^{-1}; ^1H NMR : 6.98 (s, 1), 6.46 (s, 1), 6.13 (s, 2), 5.95 (s, 2), 5.33 (d, 1, J = 4.8 Hz), 4.41 (d, 1, J = 6 Hz), 4.25 (dd, 1, J = 3 Hz, ^2J = 11.8 Hz) and 4.13 (dd, 1, J = 4.8 Hz, ^2J = 11.8 Hz), 3.80 (s, 3), 3.74 (s, 6), 3.58 (s, 3), 3.48 (dd, 1, J = 6 and 10.8 Hz), 2.56 (m, 1), 1.15 (s, 9), 0.99 (s, 9); MS : m/z 586 ($M^{+\cdot}$, 10), 351 (33), 334 (20), 91 (100), 77 (80); HRMS : calc. for $C_{31}H_{42}O_9Si$: 586.2598; found : 586.2542.

Aldol condensation of TMS-ester 16 with 3,4,5-trimethoxybenzaldehyde.
A cooled (0°C) soln of 13 (400 mg, 1.02 mmol) in dry THF (10 ml) was treated with TMSCl (142 ul, 1.12 mmol) and NEt_3 (156 ul, 1.12 mmol). After 15 min of stirring at 0°C, the white susp was transferred over 10 min via a syringe, to a soln of LDA (3.05 mmol) in THF (4 ml) at -78°C. The mixture was stirred for 30 min at -78°C, then warmed up slowly till -40°C, and stirred for 1 h. The reaction mixture was then cooled to -78°C, and a soln of 3,4,5-trimethoxybenzaldehyde (240 mg, 1.22 mmol) in THF (8 ml) was added. After 3 min the soln was poured into a cooled (-78°C) 10 % HOAc soln in ether, and warmed up to r.t. Water was added, and the water layer extracted (ether). The combined organic phases were washed (10 % aq. HCl and brine) and dried. Purification by HPLC (ether/hexane/HOAc 55:45:1) yielded 17a (204 mg; 34 %) and 17c (164 mg; 27 %). Rf (ether/hexane/HOAc : 80:20:1) 17a : 0.22 and 17c : 0.16.
Both isomers 17a and 17c were characterized as the corresponding methyl esters 15a and 15c respectively (treatment with CH_2N_2).

Ring closure of 17a with mesyl chloride.
A soln of 17a (11 mg, 0.019 mmol) in dry CH_2Cl_2 (0.7 ml) was treated at 0°C with TMSCl (3.5 ul, 0.028 mmol) and NEt_3 (3.9 ul, 0.028 mmol) and stirred for 15 min at 0°C. Then the mixture was cooled to -10°C, and MsCl (3.4 ul, 0.044 mmol) and NEt_3 (7.6 ul, 0.055 mmol) were added. After 30 min at -10°C the reaction mixture was worked up. Purification by HPLC (ether/hexane/HOAc 35:65:1) afforded 30c (6 mg; 56 %). M.p. : 195°C (ether); Rf (ether/hexane/ HOAc 55:45:1) : 0.17; IR (KBr) : 3700-2400, 1700, 1585 cm^{-1}; ^1H NMR : 6.97 (s, 1), 6.48 (s, 1), 6.19 (s, 2), 5.93 (s, 2), 5.29 (d, 1, J = 5 Hz), 4.44 (d, 1, J = 5.7 Hz), 4.22 (dd, 1, J = 3 Hz, ^2J = 12 Hz) and 4.12 (dd, 1, J = 4.7 Hz, ^2J = 12 Hz), 3.77 (s, 3), 3.70 (s, 6), 2.61 (m, 1); H-2 is obscured.
Treatment of 30c with ethereal CH_2N_2 yielded 21c.

Epipodophyllotoxin (2c).
To a soln of 30c (13 mg, 0.023 mmol) in dry THF (0.3 ml) was added at r.t. a soln of $(n.Bu)_4NF$ (1 M in THF; 75 ul, 0.075 mmol). After stirring for 16 h at r.t. the mixture was diluted with ether, and water was added. The crude 28 (Rf (ether/HOAc) : 99:1) obtained after work-up was further transformed into (+)-epipodophyllotoxin (2c) as previously described[19] (overall yield : 4 mg; 44 %). M.p. : 158°C; Rf (ether/CH_2Cl_2/hexane) : 0.22; IR (KBr) : 3450 (br), 1770, 1590 cm^{-1}; ^1H NMR : 6.88 (s, 1), 6.55 (s, 1), 6.28 (s, 1), 6.00 (d, 1, ^2J = 1.5 Hz) and 5.98 (d, 1, ^2J = 1.5 Hz), 4.87 (d, 1, J = 3.25 Hz), 4.62 (d, 1, J = 5 Hz), 4.39 (dd, 1, J = 10.5 Hz, ^2J = 8 Hz), and 4.36 (dd (t), J = 8 Hz, ^2J = 8 Hz), 3.80 (s, 3), 3.74 (s, 6), 3.28 (dd, 1, J = 5 and 14 Hz), 2.84 (m, 1); MS : m/z 414 ($M^{+\cdot}$, 43), 246 (11), 201 (15), 169 (31), 105 (43), 93 (43), 91 (100); HRMS : calc. for $C_{22}H_{22}O_8$: 414.1315; found : 414.1295.

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