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TOTAL SYNTHESIS OF PODOPHYLLUM LIGNANS : AN EXPLORATORY STUDY

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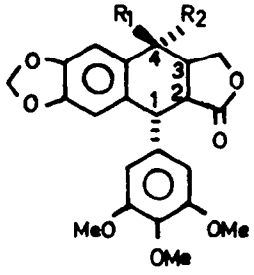
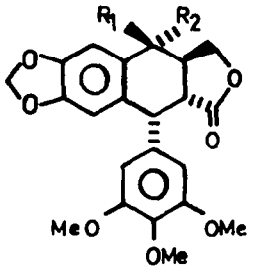
ABSTRACT - Approaches to podophyllotoxin 1c involving electrophilic ring closure as the crucial step have until now failed to produce the tetralin framework with the correct relative configuration. Stereochemical considerations allowed us to propose 18b as a precursor, in which the cis-substituted dioxane ring could be an essential stereocontrolling element. 18b was obtained with low selectivity via aldol condensation of 16. The crucial ring closure failed because of the high reactivity under Lewis acid conditions of the oxygen at C-4, when incorporated in a 2-phenyl-1,3-dioxane.

Podophyllotoxin (1c), a lignan isolated from Podophyllum peltatum and P. emodi[2], has stirred considerable interest in pharmacological and synthetic research due to its renowned antineoplastic activity[3]. At the present time, the eight possible diastereomers 1a-d and 2a-d



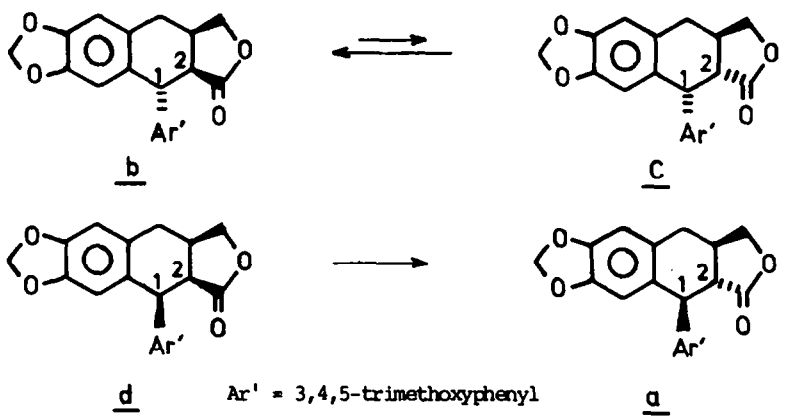


1 : R_1=H, R_2=OH	a : t-1,2-t-2,3	1c : podophyllotoxin
2 : R_1=OH, R_2=H	b : t-1,2-c-2,3	2c : epipodophyllotoxin
3 : R_1, R_2=O	c : c-1,2-t-2,3	3c : podophyllotoxone
4 : R_1, R_2=H_2	d : c-1,2-c-2,3	4c : 4-deoxypodophyllotoxin

Scheme 1

with the natural (R)-configuration at C-1, and also the corresponding 4-keto (3a-d) and 4-deoxy (4a-d) derivatives, have been obtained by partial synthesis from natural podophyllotoxin (1c) and isopicropodophyllone (3d)[2,4]. The thermodynamic relationships established via base-catalyzed isomerization of the γ-lactone within the 4 series a-d are shown in scheme 2. The equilibrium between podophyllotoxin (1c) and picropodophyllin (1b) is largely in favor of the latter (ratio 3:97)[5]. Base treatment (NaOH) of isopicropodophyllin (1d) has been reported to lead to the

carboxylic acid with inverted C-2 configuration via prior isomerization to the corresponding trans-lactone (1a)[4c]. Antitumor activity was found to be related to the thermodynamically unfavourable 1,2-cis-2,3-trans-configuration (c-series)[5,6].



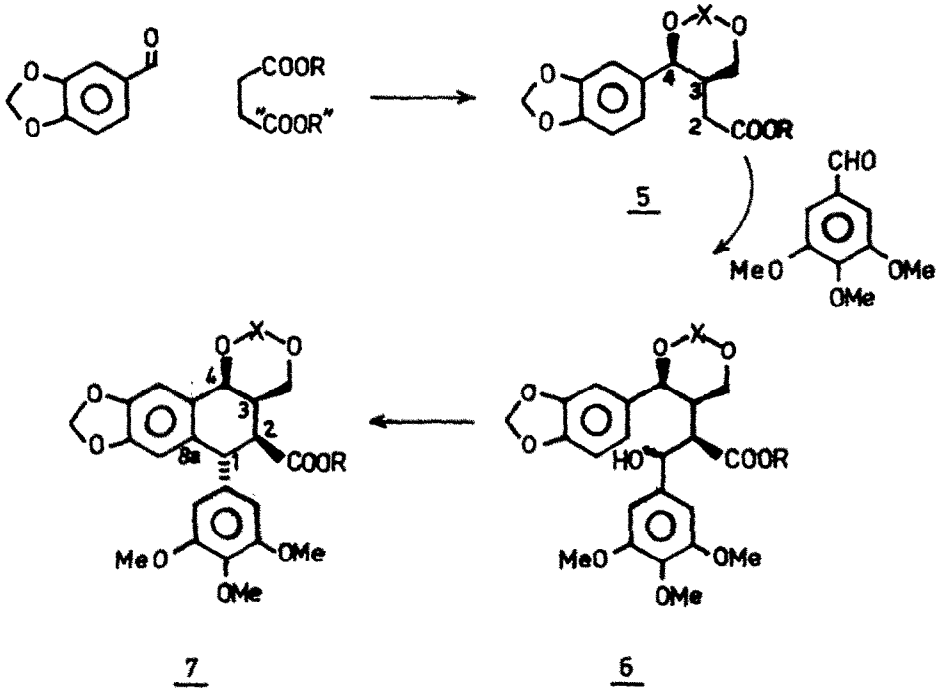
Scheme 2

Although several approaches towards podophyllum lignans have been reported[7-16], only Rodrigo's route[17] has so far been stereoselective in obtaining the requisite 1,2-cis-2,3-trans-configuration, typical for podophyllotoxin (1c) and epipodophyllotoxin (2c). Other approaches have led to lignan derivatives within the a-, b- or d-series. Although the partial conversion of picropodophyllin (1b) into podophyllotoxin (1c) has been realized via a kinetic deprotonation-protonation sequence[7d], the overall process, even under optimized conditions, proceeds in rather low yield. The early incorporation of an oxygen functionality at C-4 (cf. 1, 2 or 3) is highly recommended in view of the reported difficulties for the selective oxidation of corresponding 4-deoxy derivatives[8b]. Because of the known interconversion of 1c and 2c[18], both are adequate target molecules and therefore precursors with α or β stereochemistry at C-4 can be incorporated in a synthetic plan.

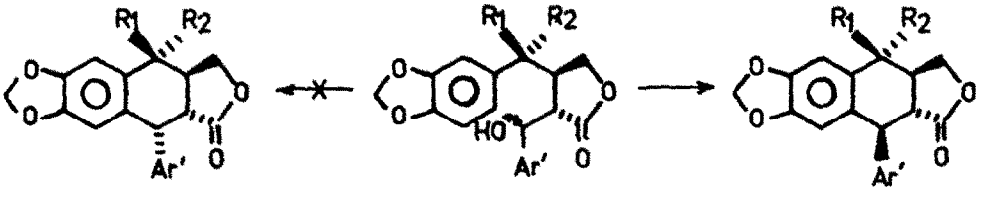
Retrosynthetic analysis and stereochemical implications

From the above considerations one may readily anticipate that the major problems related to a total synthesis of either podo- or epipodophyllotoxin will essentially be of a stereochemical nature. The proposed route for the construction of the required tetralin framework is shown in scheme 3. Central in our planning stands the electrophilic ring closure (C-1, C-8a) of the benzylic alcohol 6 to tetralin 7. Hydroxy-ester 6 would result from the aldol condensation of 5 and 3,4,5-trimethoxybenzaldehyde. The synthesis of ester 5 would proceed via condensation of a succinate equivalent with piperonal, followed by refunctionalization. The stereochemical implications of this proposed sequence led us to focus more particularly on the dioxane 6 with the indicated 2,3-cis-3,4-cis-configuration, as a substrate for the cyclization step during which the crucial trans-relationship between the 1,3-substituents is established. In previous syntheses where this type of ring closure has been investigated substrates either lacked a C-3 substituent or involved a trans-γ-lactone (structure 8 in scheme 4). Acid catalyzed cyclization led exclusively to the undesired trans-relation between C-1 and C-2 (a-series). Interestingly, this stereochemical result somehow corroborates the equilibration data shown in scheme 2, and indicates that the C-1, C-2 cis-relation is a major destabilizing conformational feature. Accordingly, the provision of a β-oriented ester group at C-2 might induce the desired α-orientation of the aryl group upon cyclization (6 → 7). The protection of the diol moiety as a cyclic ether (O-X-O; cf. 5, 6 and 7) with cis-3,4-disubstitution should subsequently allow

epimerization at C-2. Indeed, the latter event would relief the syn-diaxial interaction present in 7' (scheme 5), which should represent the preferred conformation of 7 when a β-oriented substituent R is incorporated in X (see arrow in 7").

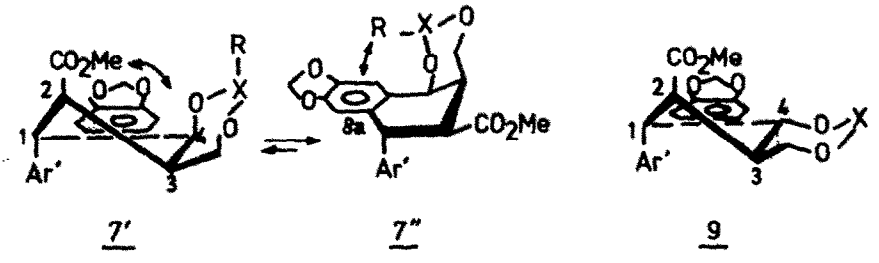


Scheme 3



Ar' = 3,4,5-trimethoxyphenyl; $R_1,R_2=H_2$ or $-SCH_2CH_2CH_2S-$

Scheme 4



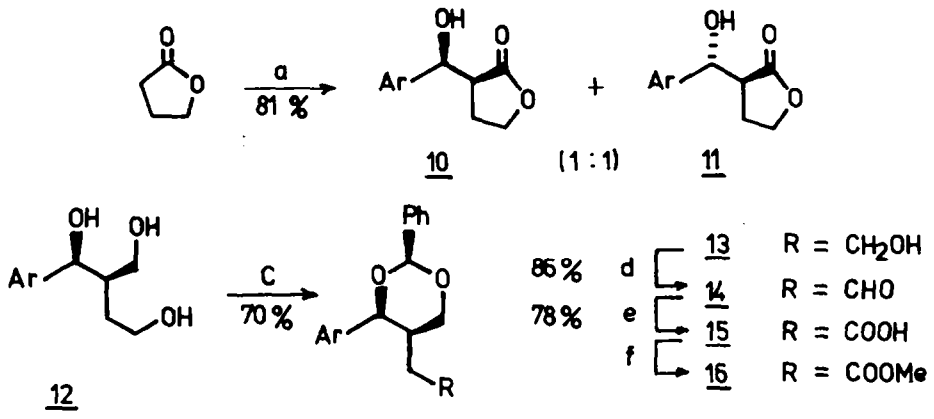
Ar' = 3,4,5-trimethoxyphenyl

Scheme 5

In the corresponding trans-3,4-derivative 9, however, no such clear-cut stereochemical bias between a β-oriented (and axial) and an α-oriented (gauche related with the 1-aryl group) methoxy-carbonyl group is apparent. Finally, once the cis-relation settled in 5, diastereoselective formation of 6 upon aldol condensation is normally tobe expected (vide infra).

The exploratory approach

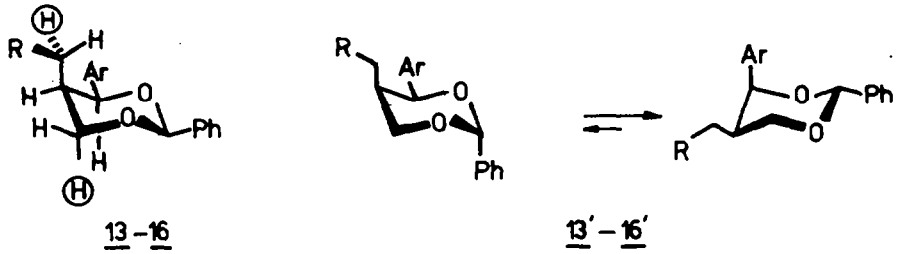
The potential of the projected route was first examined on the 2-phenyl-1,3-dioxane derivative 16, which was obtained via a 6-step sequence starting from γ-butyrolactone (scheme 6).



Ar = 3,4-methylenedioxyphenyl; a) LDA, THF, -78°C → -40°C; ArCHO, -78°C; NH_4Cl; b) LAH, THF, 0°C; c) C_6H_5CHO, $CHCl_3$, $CuSO_4$, r.t.; d) $CrO_3.Py_2$, CH_2Cl_2; e) Ag_2O, NaOH, MeOH-H_2O, 60°C; f) CH_2N_2, ether.

Scheme 6

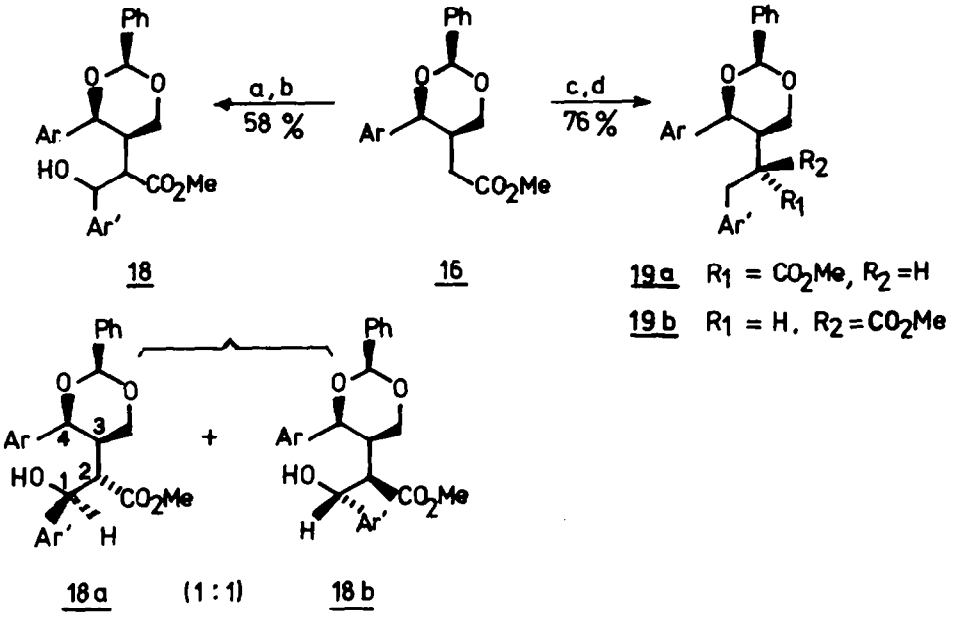
Condensation of the lithium enolate anion of butyrolactone with piperonal leads to a 1:1 mixture of hydroxylactones 10 and 11. After chromatographic separation, hydride reduction of 10 and acetalization of the resulting triol 12 with benzaldehyde gave the corresponding dioxane 13. Conversion of 13 into ester 16 involved consecutive oxidations to the aldehyde 14 and to the acid 15 followed by esterification. The sole formation of diastereomer 13 upon protection of the 1,3-diol is expected since the epimer 13' (1,3-trans-diaryl derivative; scheme 7) would necessarily involve an axial aryl group (A-value 2.87 Kcal/mol)[19]. Interestingly, the ^1H NMR coupling patterns (see experimental) found within the series 13-16 enables the identification of the preferred rotameric conformation, as depicted in scheme 7, from a long range W-type coupling between the indicated protons at C-2 and C-11 (^4J = 1.5 Hz in 16).



Ar = 3,4-methylenedioxyphenyl

Scheme 7

Early attempts to carry out the condensation of the lithium enolate anion (LDA or LICA in THF) of ester 16 with 3,4,5-trimethoxybenzaldehyde met with complete failure and only led to the recovery of starting material. Eventually it was discovered that the aldolate intermediate was extremely sensitive to retroreaction unless formed at -100°C and quenched at the same temperature (scheme 8). Under these conditions a 1:1 mixture of hydroxy-esters 18 was isolated in 58 % yield. Both diastereomers were separated by column chromatography. The structure of one of the isomers could unambiguously be assigned as 18b via single-crystal X-ray diffraction[20].



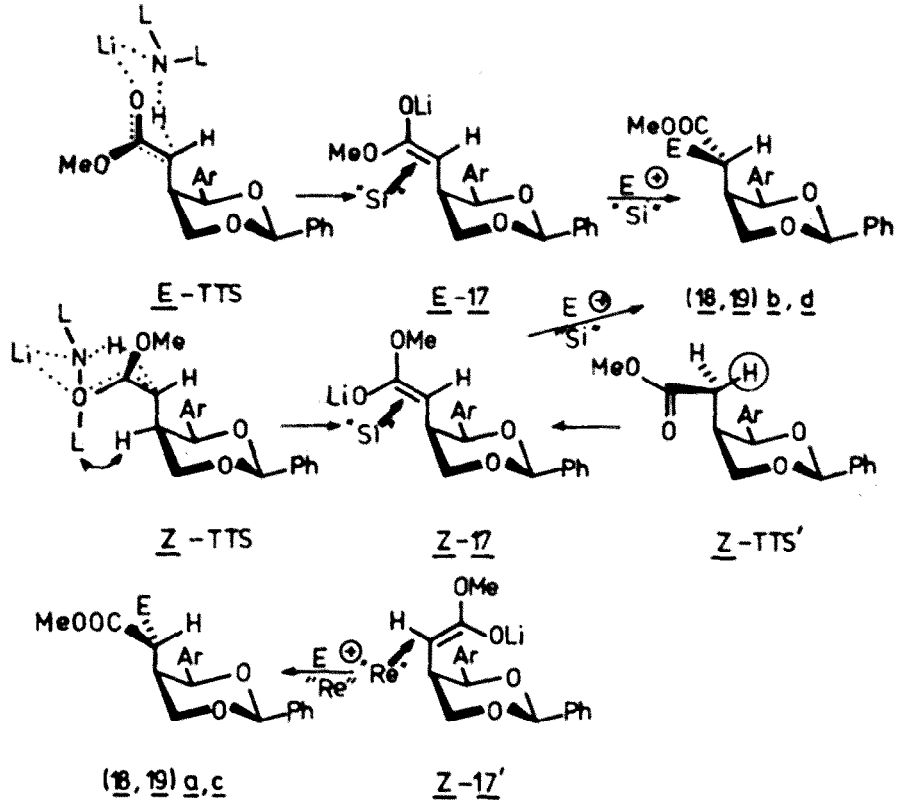
Ar = 3,4-methylenedioxyphenyl, Ar' = 3,4,5-trimethoxyphenyl

a) LICA, THF, -78°C → -40°C; b) Ar'CHO, -100°C, 5 min; 10 % HOAc-THF, -100°C; c) LICA, THF, -78°C → -40°C; d) $Ar'CH_2Br$, DMSO, 0°C, 15 min.

Scheme 8

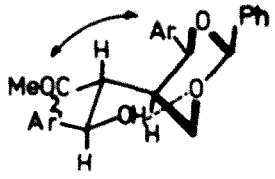
The formation of diastereomer 18b, which possesses the desired relative configuration at C-2, C-3 (see 6 in scheme 3), was expected for steric reasons (scheme 9).Indeed, attack of the electrophile on C-2 of the enolate anion 17 should occur exclusively from the less hindered Si-side and lead to 18b or 18d (epimeric at C-1). Interestingly, the syn-relation of the methoxycarbonyl group and the methylenedioxyphenyl substituent , as shown in the preferred rotamer of 18b (scheme 10), is reflected in the high field resonance of the methoxygroup in the ^1H NMR (3.08 compared to 3.57 ppm in 16). The almost parallel orientation of the methylenedioxyphenyl plane and the methoxycarbonyl plane is apparent in the solid state[20]. A rather eclipsed disposition of substituents is observed at the 2,3-bond (i.e., dihedral angle between H-C(2)-C(3)-H of 146°; J = 4 Hz); a near-staggered disposition is maintained, however, at the 1,2-bond (i.e., dihedral angle between H-C(1), C(2)-H of 165°; J = 9 Hz). The overall conformation of the C-3 side-chain on the dioxane results in a rather close spatial arrangement between the OH-group at C-1 and one of the oxygen ring atoms of the dioxane (scheme 10). In contrast to the high field resonance of the methoxycarbonyl group in 18b (3.08 ppm), the corresponding signal in the other diastereomer 18a which was isolated in equal amounts from the aldol condensation of 16 exhibits a normal value (i.e., 3.40 ppm) indicating the inverse configuration at C-2 for its structure[21]. This configuration must result from Re-side attack on the enolate anion 17. Since it is highly improbable that Re-side addition should occur on an enolate conformation E-17, as depicted in scheme 9, because of steric hindrance with the 3,4-

methylenedioxyphenyl group, the logical alternative explanation must reside in an attack from the least hindered side on a rotated enolate conformation, i.e., Z-17', in which complexation of the lithium counter ion with one (or both) oxygen(s) of the dioxane ring is possible (scheme 9).



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

Scheme 9



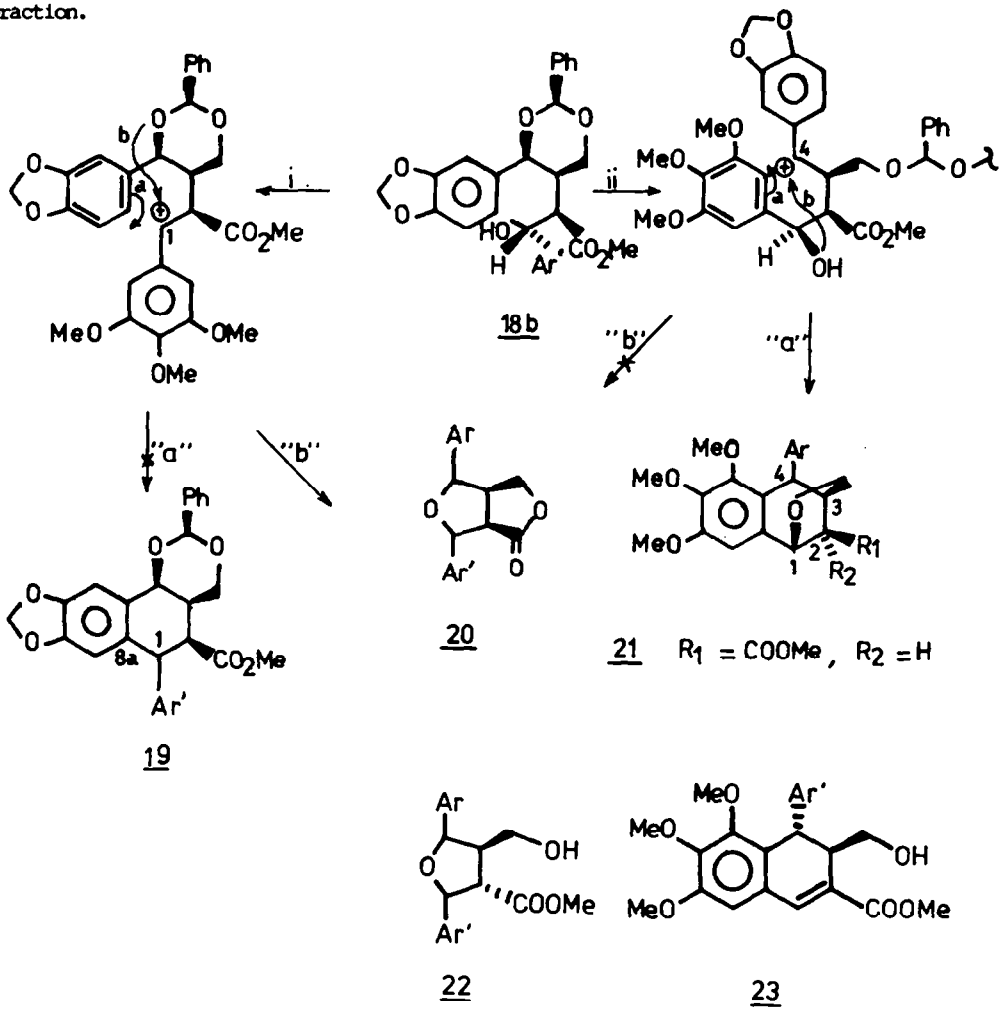
18b

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

Scheme 10

This stereochemical course of the addition of an electrophile to enolate anion 17 is further corroborated by the formation of two esters 19a and 19b (ratio 2:1) in 76 % yield upon alkylation with 3,4,5-trimethoxybenzylbromide in the presence of DMSO. In the absence of DMSO a low alkylation yield is observed (ca 15 %). Although both esters could not be separated, ^{1}H NMR analysis of the mixture allows for the assignment of structure 19a to the major isomer based on the observed chemical shift difference for the methoxycarbonyl group in both compounds (3.46 and 3.26 ppm for 19a and 19b, respectively). The question arises why the Z-enolate 17 is formed to such a large extent (ca. 30 % or more) under kinetic conditions (LICA in the absence of HMPA),

that normally yield the E-enolate[22] with high stereoselectivity[23]. Indeed, according to the TTS for enolate formation proposed by Ireland[23] (scheme 9), the Z-TTS should be destabilized as compared to the E-TTS to a considerable extent in view of the indicated (arrow) syn-diaxial interaction.



Scheme 11

A possible explanation would involve an alternative Z-TTS' in which the base would abstract the circled H at C-2 from above the dioxane ring (a consequence of the chelation of the lithium ion with the front-side dioxane oxygen atom). As a matter of fact it cannot be excluded that both 19a and 19b are formed from the exclusive Z-enolate. Note that the formation of 19a implies that the chelated conformation Z-17' should be maintained even in the presence of DMSO; theformation of 19a via equilibration of 19b is highly improbable.

With the desired 18b in hand we turned to investigate the possibility for electrophilic C-1, C-8a-bond formation under protic and Lewis acid conditions (scheme 11). The desired tetralin derivative 19, however, could never be isolated. Instead, treatment of 18b with trifluoroacetic acid (5 % soln in CH_2Cl_2, -20°C) led to a stereohomogeneous lactone 20 with unknown configuration at C-1 and C-4 (51 % isolated yield) next to the bridged ether 21 (a single isomer;19 % yield). On the other hand, with $SnCl_4$ (10 equiv in CH_2Cl_2, r.t.), a 55% yield of 21 (epimeric at C-4; ratio 8:3) was obtained. The relative configuration at C-4 in 21 could not be assigned unambiguously. The formation of 21 implies carbenium ion formation at C-4 (ii, path "a") rather

than at C-1 (i) which is necessary for obtention of 19. The absence of tetrahydrofuran 20 in the mixture obtained with $SnCl_4$ suggests that its formation under protic acid conditions originates from preferential carbenium ion formation at C-1 (i, path "b"). Under the same conditions, the other isomer 18a also suffered opening of the dioxane ring, leading to 22 and 23, thus indicating the high reactivity of the oxygen at C-4 when incorporated in a 2-phenyl-1,3-dioxane ring. Thus, from the above experiments it became clear that the dioxane protective group could not serve our purposes. We therefore decided to resume an analogous sequence with a more suitable protective group. The results are described in the subsequent paper.

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.

2-[Hydroxy-3',4'-methylenedioxyphenyl)-methyl]-butyrolactone (10)
To a soln of $(i.Pr)_2NH$ (67.2 ml, 0.48 mol) in dry THF (400 ml) was added at -40°C a soln of n.BuLi, (370 ml, 0.48 mol; 1.4 M in hexane). After stirring for 15 min the reaction mixture was cooled to -78°C, and a soln of butyrolactone (36.8 ml, 0.48 mol) in THF (400 ml) was added slowly. After stirring for 45 min at -78°C, a soln of piperonal (72 g, 0.48 mol) in THF (400 ml) was added; stirring was continued for 30 min at -78°C. The mixture was then poured into a cold sat. aq. NH_4Cl soln (200 ml). The water layer was extracted several times with ether; the combined organic phases were washed with a 10 % aq. HCl soln and with brine. After work-up, the residue was purified by HPLC (EtOAc/hexane 35:65), yielding syn-isomer 10 (52.6 g; 47 %) and anti-isomer 11 (39.9 g; 35 %) (total yield 82 %). M.p. : syn : 110°C (iso-octane:CH_2Cl_2); anti: 123°C; Rf (ether) : 0.42 (syn); 0.23 (anti); IR (KBr) : syn: 3800-3300, 1755, 1610, 1480, 1260, 1230, cm^{-1}; anti : 3700-3100, 1735, 1615, 1440, 1330-1110 cm^{-1}; ^1H NMR : syn: 6.87 (m, 1), 6.83 (ddd, 1, J = 8 and 1.5 Hz + LR), 6.79 (dd, 1, J = 8 Hz + LR), 5.96 (s, 2), 5.30 (dd, 1, J = 4.6 and 3.2 Hz), 4.35 (ddd(td), 1, J = 3.2, 8.6 Hz, ^2J = 8.6 Hz) and 4.18 (ddd(td), 1, J = 7.2, 8.6 Hz, ^2J = 8.6 Hz), 2.88 (ddd(td), 1, J = 2.8, 9.2 and 9.6 Hz), 2.65 (d, 1, J = 4.6 Hz), 2.43 (dddd(m), 1, J = 3.2, 7.2, 9.2 Hz, ^2J = 12.5 Hz), 2.01 (m, 1); anti : 6.91 (d, J = 1.5 Hz), 6.82 (dd + LR, 1, J = 8 and 1.5 Hz), 6.78 (d + LR, 1, J = 8 Hz), 5.968 (d, 1, ^2J = 1.5 Hz) and 5.963 (d, 1, ^2J = 1.5 Hz), 4.73 (d, 1, J = 8.5 Hz), 4.31 (m, 2), 4.16 (m, 1), 2.86 (m, 1), 1.98 (m, 2); MS : syn : m/z 236 ($M^{+\cdot}$, 7), 151 (75), 150 (87), 149 (100), 121 (31); anti: m/z 236 ($M^{+\cdot}$, 9), 151 (100), 150 (73), 149 (92), 121 (37), 93 (73); HRMS : calc. for $C_{12}H_{12}O_5$: 236.0685; found : 236.0701.

Syn-2-hydroxymethyl-1-(3',4'-methylenedioxyphenyl)-butane-1,4-diol (12).
A soln of 10 (34.5 g, 0.146 mol) in dry THF (400 ml) was added at 0°C to a stirred susp of $LiAlH_4$ (8.5 g, 0.219 mol) in THF (100 ml). After 2 h at 0°C, wet Et_2O was added, followed by a semi-saturated soln of $KHSO_4$, until a coarse-grained precipitate was obtained. The inorganic salts were continuously extracted with Et_2O during 48 h. After work-up triol 12 was obtained as an oil, which cristallyzed spontaneously on trituration with EtOAc (33.3 g; 95 %). M.p. : 104°C; Rf (ether) : 0.09; IR (KBr) : 3520, 3460-3000, 1645, 1500, 1435, 1250 cm^{-1}; ^1H NMR : 6.88 (d, 1, J = 1.5 Hz + LR), 6.82 (dd, 1, J = 8 and 1.5 Hz + LR), 6.78 (d, 1, J = 8 Hz + LR), 5.96 (s, 2), 4.86 (d, 1, J = 5 Hz), 3.81-3.66 (m, 4), 1.97 (m, 1), 1.84-1.67 (m, 2), 1.58 (s); MS : m/z 240 ($M^{+\cdot}$, 8), 222 (14), 179 (34), 151 (80), 150 (64), 149 (44), 105 (25), 93 (48), 91 (23), 32 (100); HRMS : calc. for $C_{12}H_{16}O_5$: 240.0998; found : 240.0975.

2-(r-2-Phenyl-c-4-(3',4'-methylenedioxyphenyl)-1,3-dioxan-c-5-yl)-ethanol (13).
To a susp of 12 (810 mg, 3.43 mol) in $CHCl_3$ (32 ml) was added PhCHO (1.6 ml, 15.7 mmol) and anhydrous $CuSO_4$ (3 g). The reaction mixture was stirred for 48 h at r.t. under N_2. After filtration over celite, the solvent was evaporated in vacuo. Purification by column chromatography (hexane for elution of PhCHO, then EtOAc/hexane 2:8) gave 13 (630 mg) next to some dimeric acetal. This byproduct was easily cleaved on treatment with a catalytic amount of PTSA in ether/MeOH, yielding the monoacetal 13 as a precipitate. The total yield was 760 mg (70 %). M.p. : 143°C (Et_2O); Rf (ether) : 0.53; IR (KBr) : 3490, 1500, 1440, 1245, 1035 cm^{-1}; ^1H NMR : 7.60-7.54 (m, 2), 7.44-7.35 (m, 3), 6.88 (m, 1), 6.81 (m, 2), 5.95 (d, 1, ^2J = 1.5 Hz) and 5.94 (d, 1, ^2J = 1.5 Hz), 5.72 (s, 1), 5.14 (d, J, J = 2 Hz + LR), 4.33 (dd, 1, J = 0.6 Hz, ^2J = 11.5 Hz) and 4.22 (ddd(m), 1, J = 2 and 0.8 Hz, ^2J = 11.5 Hz), 3.61 (m, 2), 1.98-1.87 (m, 2), 1.51 (m, 1), 1.6 (bs); MS : m/z 328 ($M^{+\cdot}$, 1), 151 (46), 150 (100), 149 (32), 131 (15), 107 (68), 105 (48); HRMS : calc. for $C_{19}H_{20}O_5$: 328.1311; found : 328.1263.

[r-2-Phenyl-c-4-(3',4'-methylenedioxyphenyl)-1,3-dioxan-c-5-yl]-acetaldehyde (14).
To a vigorously stirred soln of Collins reagent[24] (18.9 g, 73.3 mmol) in dry CH_2Cl_2 (90 ml), cooled on a water bath, was added in one portion a soln of 13 (3 g, 9.15 mmol) in CH_2Cl_2 (50 ml). After 15 min the reaction mixture was diluted with Et_2O, and the chromium salts removed by filtration on a celite path. Evaporation of the solvent under reduced pressure yielded crude

aldehyde 14 (2.59 g; 86 %), which was used without purification; Rf (ether/hexane 6:4) : 0.36; IR (neat) : 2730, 1720, 1485, 1440, 1365, 1235 cm^{-1}; ^1HNMR : 9.56 (s, 1), 7.53-7.46 (m, 2), 7.39-7.26 (m, 3), 6.78 (m, 1), 6.72 (m, 2), 5.87 (d, 1, ^2J = 1.5 Hz) and 5.86 (d, 1, ^2J = 1.5 Hz), 5.63 (s, 1), 5.04 (d, 1, J = 2.3 Hz), 4.18 (ddd, 1, J = 2 Hz, ^4J = 1Hz, ^2J = 11.5 Hz) and 4.13 (dd, 1, J = 1.25 Hz, ^2J = 11.5 Hz), 2.87 (ddd, 2, J = 9.75 Hz, ^2J = 19.5 Hz, ^4J = 1 Hz), 2.40-2.30 (m, 2); MS : m/z 150 (15), 121 (18), 119 (58), 117 (61), 107 (24), 106 (91), 105 (100).

Methyl(r-2-phenyl-c-4-(3',4'-methylenedioxyphenyl)-1,3-dioxan-c-5-yl)-acetate (16).
A mixture of crude aldehyde 14 (2.23 g, 6.84 mmol), Ag_2O (3.34 g, 14.4 mmol), NaOH (5.8 g), water (53 ml) and MeOH (45 ml) was stirred at 60°C during 4 h. The hot reaction mixture was filtered, and the solids were washed repeatedly with hot water. The combined filtrates were cooled to 0°C, and acidified under stirring with 20 % aq. HCl (35 ml). The precipitated acid 15 was filtered off, washed with water and vacuum-dried (yield 1.82 g; 78 %); m.p. 140°C (ether-hexane).
Treatment of 15 (1.57 g, 4.6 mmol) with ethereal CH_2N_2 at 0°C yielded ester 16 (1.63 g; 100 %). M.p. : 82°C (ether); Rf (ether/hexane 6:4) : 0.41; IR (KBr) : 1720, 1440, 1250, 1145 cm^{-1}; ^1H NMR : 7.60-7.54 (m, 2), 7.49-7.32 (m, 3), 6.86 (m, 1), 6.80 (m, 2), 5.95 (d, 1, J = 1.5 Hz) and 5.94 (d, 1, ^2J = 1.5 Hz), 5.71 (s, 1), 5.13 (d, 1, J = 2.5 Hz), 4.30 (dd, 1, J = 1.5 Hz, ^2J = 11.5 Hz) and 4.24 (ddd, 1, J = 2 Hz, ^2J = 11.5 Hz, ^4J = 1.5 Hz), 3.57 (s, 3), 2.81 (dd, 1, J = 10.5 Hz, ^2J = 17 Hz) and 2.23 (ddd, 1, J = 3.5 Hz, ^2J = 17 Hz, ^4J = 1.5 Hz), 2.32 (m, 1); MS : m/z 356 ($M^{+\cdot}$, 10), 220 (12), 206 (17), 150 (100), 149 (33), 131 (23), 105 (34), 101 (45), 100 (48); HRMS : calc. for $C_{20}H_{20}O_5$: 356.1260; found : 356.1132.

Aldol condensation of 16 with 3,4,5-trimethoxybenzaldehyde.
To a soln of N-isopropylcyclohexylamine (0.3 ml, 1.8 mmol) in THF (1.5 ml) was added at -30°C a soln of n.BuLi (1.15 ml, 1.5 mmol; 1.3 M in hexane). After 15 min the mixture was cooled to -78°C, and a soln of 16 (535 mg, 1.5 mmol) in THF (5 ml) was added dropwise over 10 min. When the addition was completed, stirring was continued for 30 min at -78°C. The mixture was allowed to warm up to -40°C over 30 min. After an additional 30 min of stirring, the mixture was cooled to -100°C, and a soln of 3,4,5-trimethoxybenzaldehyde (450 mg, 2.25 mmol) in THF (2.5 ml) was added. After 5 min at -100°C the aldolate was quenched by pooring it into 10 % HOAc/THF at -100°C. At r.t., solid $NaHCO_3$ was added and the organic phase was washed with water, 20 % aq. HCl and brine. After work-up, an oily residue was obtained, from which pure isomer 18a (240 mg; 29 %) cristallyzed upon trituration with ether. Purification of the mother liquor by column chromatography (ether/hexane 3:7) yielded isomer 18b (240 mg; 29 %).
β-hydroxy-ester 18a : m.p. : 156°C (ether/hexane); Rf (ether) : 0.36; IR (KBr) : 3800-3100, 1700, 1590, 1330, 1235, 1130 cm^{-1}; ^1H NMR : 7.54 (m, 2), 7.42-7.30 (m, 3), 6.66 (d, 1, ^2J = 8 Hz), 6.54 (dd, 1, J = 8 and 1.5 Hz), 6.38 (d, 1, J = 1.5 Hz), 6.17 (s, 2), 6.01 (d, 1, ^2J = 1.5 Hz) and 5.95 (d, 1, ^2J = 1.5 Hz), 5.65 (s, 1), 4.97 (d, 1, J = 2 Hz), 4.92 (d, 1, J = 2.5 Hz), 4.72 (dd, 1, J = 1.25 Hz, ^2J = 12 Hz) and 4.26 (dd, 1, J = 2.5 Hz, ^2J = 12 Hz), 4.13 (bs, 1), 3.85 (s, 3), 3.75 (s, 6), 3.40 (s, 3), 2.70 (bs, 1), 2.12 (bs, 1); MS : m/z 196 (42), 181 (24), 150 (100), 149 (42), 105 (55), 101 (42), 100 (47).
β-hydroxy-ester 18b: m.p. : 159°C (ether/hexane); Rf (ether) : 0.30; IR (KBr) : 3700-3200, 1720, 1590, 1330, 1240, 1130 cm^{-1}; ^1H NMR : 7.65-7.57 (m, 2), 7.49-7.37 (m, 3), 6.96 (d, 1, J = 1.5 Hz), 6.86 (dd, 1, J = 8 and 1.5 Hz), 6.82 (d, 1, J = 8 Hz), 6.52 (s, 2), 5.97 (d, 1, ^2J = 1.5 Hz and 5.96 (d, 1, ^2J = 1.5 Hz), 5.86 (s, 1), 5.33 (d, 1, J = 3 Hz), 5.10 (d, 1, J = 9 Hz), 5.08 (bd, 1, J ≈ 1 Hz, ^2J = 12.5 Hz) and 4.39 (dd, 1, J = 3 Hz, ^2J = 12.5 Hz), 2.93 (dd, 1, J = 4 and 9 Hz), 2.44 (m, 1), 3.08 (s, 3), 3.81 (s, 6), 3.76 (s, 3); MS : m/z 196 (100), 181 (54), 150 (68), 149 (32), 125 (70), 110 (54), 105 (39).

Alkylation of 16 with 3,4,5-trimethoxybenzaldehyde.
To a soln of the ester enolate derived from 16 (1.07 g, 3 mmol) in THF (12 ml), prepared as before was added at 0°C DMSO (2 ml), followed by a soln of 3,4,5-trimethoxybenzylbromide (1.17 g, 4.5 mmol) in THF (5 ml), added in one portion. After 15 min of stirring at 0°C, the mixture was poured into sat. aq. NH_4Cl soln (20 ml). The water layer was extracted (Et_2O), and the combined organic phases were washed (10 % aq. HCl and brine). After work-up and purification by column chromatography (ether/hexane 3:7), 1.22 g (76 %) of 19 was obtained as a mixture of 2 isomers (ratio 2:1). Rf (ether) : 0.43; IR (KBr) : 1730, 1590, 1490, 1240 cm^{-1}; ^1H NMR (200 MHz) : 7.75-7.50 (m, 2), 7.50-7.30 (m, 3), 6.98-6.78 (m, 3), 6.22 and 6.02 (s, 2), 5.96 (s, 2) and 5.95, 5.94 (d+d, 2, ^2J = 1.5 Hz), 5.77 and 5.67 (s, 1), 5.27 and 5.12 (d, 1, J = 3 Hz), 4.66 and 4.56 (dd, 1, J = 1.5 Hz, ^2J = 12 Hz), and 4.25, 4.15 (dd, 1, J = 3 Hz, ^2J = 12 Hz), 3.80 and 3.77 (s, 3), 3.76 (s, 6), 3.46 and 3.26 (s, 3), 2.98-2.84 (m), 2.78-2.66 (m), 2.28-2.18 (m), 1.89 and 1.59 (m, 1); MS : m/z 536 ($M^{+\cdot}$, 4), 253 (19), 182 (100), 105 (13); HRMS : calc. for $C_{30}H_{32}O_9$: 536.2046; found : 536.2052.

Electrophilic ring closure of 18a and 18b catalyzed by TFA.
A soln of β-hydroxy-ester 18b (100 mg, 0.18 mmol) in dry CH_2Cl_2 (20 ml) was treated at -20°C with anhydrous TFA (1 ml; distilled from 5 % TFA-anhydride). Two polar compounds (Rf 0.13 and 0.07, ether/hexane 8:2) were formed immediately, which upon warming up to 0°C were transformed slowly into the bridged tetraline 21 and the tetrahydrofuran lactone 20. After stirring overnight at r.t. a sat. aq. $NaHCO_3$ soln was added, and the mixture diluted with ether. The residue obtained after work-up was purified by HPLC (EtOAc/hexane 4:6), yielding lactone 20 (35 mg; 51 %) and the ether 21 (13 mg; 19 %).
- lactone 20 : m.p. : 130°C (ether); Rf (ether/hexane 4:6) : 0.22; IR (KBr) : 1765, 1595, 1510, 1495, 1360, 1255 cm^{-1}; ^1H NMR : 6.98 (d, 1, J = 1.5 Hz), 6.91 (dd, 1, J = 1.5 and 8 Hz), 6.83 (d, 1, J = 8 Hz), 6.78 (s, 1), 6.01 (s, 2), 5.18 (d, 1, J = 4.8 Hz), 4.65 (d, 1, J = 9 Hz), 4.43 (dd, 1, J = 6.2 Hz, ^2J = 10 Hz) and 4.35 (dd, 1, J = 1.2 Hz, ^2J = 10 Hz), 3.92 (s, 6), 3.87 (s, 3), 3.38 (dd, 1, J = 4.8 and 10 Hz), 3.12 (m, 1), 1.61 (bs); MS : m/z 414 ($M^{+\cdot}$, 32), 196 (92), 181 (29), 150 (26), 149 (41), 44 (100).

- the ether 21 : Rf (ether/hexane 4:6) : 0.27; IR (KBr) : 1730, 1490, 1265, 1235, 1130 cm^{-1}; ^1H NMR : 6.70 (d, 1, J = 8 Hz), 6.59 (s, 1), 6.52 (d, 1, J = 1.5 Hz), 6.38 (dd, 1, J = 8 and 1.5 Hz), 5.93 (d, 1) and 5.92 (d_2 1, ^2J = 1.5 Hz), 5.11 ((s), 1, J é 0.5 Hz), 4.27 (d, 1, J = 2.5 Hz), 4.19 (dd, 1, J = 6 Hz, ^2J = 8 Hz) and 3.69 ((d), 1, J é 0.5 Hz, ^2J = 8 Hz), 3.89 (s, 3), 3.79 (s, 3), 3.69 (s, 3), 3.44 (s, 3), 3.15 ((s), 1), 3.05 (m, 1); MS : m/z 428 ($M^{+\cdot}$, 11), 252 (7), 41 (100); HRMS : calc. for $C_{23}H_{24}O_8$: 428.1471; found : 428.1535.

Under the same conditons, 18a gives rise to a mixture of dihydronaphtalene 23 and tetrahydrofuran 22. An analytic sample of each was obtained after purification by column chromatography (EtOAc/hexane) and HPLC (ether/hexane 8:2).

- dihydronaphtalene 23 : Rf (ether/hexane 8:2) : 0.28; IR (KBr) : 3400 (br), 1700, 1660-1530, 1485, 1345, 1255 cm^{-1}; ^1H NMR : 7.57 (s, 1), 6.68 (s, 1), 6.64 (d, 1, ^2J = 8 Hz), 6.943 (ddd, 1, J = 1.5, 8 and 0.5 Hz), 6.490 (dd, 1, J = 1.5 and 0.5 Hz), 5.87 (d, 1, ^2J = 1.5 Hz) and 5.86 (d, 1, J = 1.5 Hz), 4.61 (bs, 1, J = 1 Hz), 3.90 (s, 3), 3.88 (s, 3), 3.75 (s, 3), 3.57 (s, 3), 3.68 (dd, 1, J = 5.7 Hz, ^2J = 10 Hz) and 3.42 (dd, 1, J = 8.5 Hz, ^2J = 10 Hz), 3.18 (ddd, 1, J = 1 Hz); MS : m/z 428 ($M^{+\cdot}$, 11), 365 (57), 307 (27), 276 (36), 205 (33), 147 (42), 135 (31), 115 (35); HRMS : calc. for $C_{23}H_{24}O_8$: 428.1471; found : 428.1520.
- tetrahydrofuran 22 : Rf (ether/hexane 8:2) : 0.17; ^1H NMR : 6.99 (d, 1, J = 1.5 Hz), 6.88 (dd, 1, J = 8 and 1.5 Hz), 6.80 (d, 1, J = 8 Hz), 6.65 (s, 2), 5.97 (s, 2), 5.42 (d, 1, J = 8.5 Hz), 4.97 (d, 1, J = 9 Hz), 3.86 (s, 6), 3.84 (s, 3), 3.75 (s, 3), 3.83 (dd, 1, J = 4.5 Hz, ^2J = 11 Hz) and 3.73 (dd, 1, J = 5.5 Hz, ^2J = 11 Hz), 3.18 (dd, 1, J = 8.5 and 10.5 Hz), 2.76 (m, 1); MS : m/z 386 (58), 247 (36), 165 (27), 141 (100).

Electrophilic ring closure of 18a and 18b catalyzed by $SnCl_4$.

To a stirred soln of 18b (20 mg, 0.036 mmol) in dry CH_2Cl_2 (3.6 ml) was added at r.t. $SnCl_4$ (42 ul, 0.36 mmol). After 1 h the reaction mixture was poured into sat. aq. $NaHCO_3$, and the water layer was extracted with CH_2Cl_2. The residue obtained after work-up was purified by column chromatography (ether/hexane 3:7), yielding 21 (8 mg; 55 %) as a mixture of two isomers (8:3); Rf (ether/hexane 8:2) : 0.33.

- major isomer : vide supra.
- minor isomer : ^1H NMR : 6.71 (d, 1, J = 8 Hz), 6.61 (s, 1), 6.53 (d, 1, J = 1.5 Hz), 6.39 (dd, 1, J = 8 and 1.5 Hz), 5.94 (s, 2), 5.12 (s, 1), 4.56 (d, 1, J = 5 Hz), 3.90 (s, 3), 3.77 (s, 3), 3.76 (s, 3), 3.46 (s, 3), 3.03 (s, 1), 3.1-3.03 (m, 1); the protons α to the hydroxyl group are obscured.

Under the same conditions, isomer 18a gives rise to a precipitate, probably a cyclic tin salt[10], from which the starting material was recovered on treatment with aq. $NaHCO_3$.

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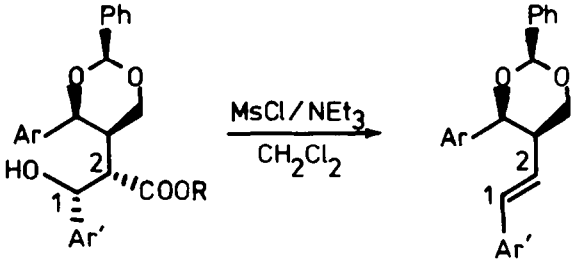
REFERENCES and NOTES

1. Senior Research Associate of the "Nationaal Fonds voor Wetenschappelijk Onderzoek".
2. For a review on the isolation and early chemistry of podophyllum lignans, see : J.L. Hartwell, A.W. Schrecker, Fortschr. Chem. Org. Naturst., 1958, 15, 83.
3. for reviews, see : a) I. Jardine, Med. Chem., 1980, 16, 319; b) G.R. Pettit, "Biosynthetic Products for Cancer Chemotherapy", Plenum Press, New York/London, 1977, vol. 1, pp. 97-104, and references cited therein.
4. a) V.N. Aiyar, F.C. Chang, J. Org. Chem., 1975, 40, 2384; b) F.C. Chang, C. Chang, V.N. Aiyar, Phytochem., 1975, 14, 1440; c) V. N. Aiyar, F.C. Chang, J. Org. Chem., 1977, 42, 246.
5. W.J. Gensler, C.D. Gatsonis, J. Org. Chem., 1966, 31, 3224.
6. C.F. Brewer, J.D. Loike, S.B. Horwitz, H. Sternlicht, W.J. Gensler, J. Med. Chem., 1979, 22 (3), 215.
7. a) W.J. Gensler, C.M. Samour, S.Y. Wang, J. Am. Chem. Soc., 1954, 76, 315; b) W.J. Gensler, S.Y. Wang, ibid., 1954, 76, 5890; c) W.J. Gensler, C.M. Samour, S.Y. Wang, F. Johnson, ibid., 1960, 82, 1714; d) W.J. Gensler, C.D. Gatsonis, J. Org. Chem., 1966, 31, 4004.
8. a) A.S. Kende, L.S. Liebeskind, J.E. Mills, P.S. Rutledge, D.P. Curran, J. Am. Chem. Soc., 1977, 99 (21), 7082; b) A.S. Kende, M.L. King, D.P. Curran, J. Org. Chem., 1981, 46, 2826.
9. a) W.S. Murphy, S. Wattanasin, J. Chem. Soc., Chem. Comm., 1980, 262; b) W.S. Murphy, S. Wattanasin, Tetrahedron Lett., 1980, 21, 3517.
10. F.E. Ziegler, J.A. Schwartz, J. Org. Chem., 1978, 43 (5), 985.
11. a) E. Brown, J.-P. Robin, R. Dhal, J. Chem. Soc., Chem. Comm., 1978, 556; b) J.-P. Robin, R. Dhal, E. Brown, Tetrahedron, 1982, 38 (24), 3667.
12. K. Tomioka, K. Koga, Tetrahedron Lett., 1979, 3315.
13. B.B. Snider, A.C. Jackson, J. Org. Chem., 1983, 48, 1471.
14. a) L.H. Klemm, K.W. Gopinath, Tetrahedron Lett., 1963, 1243; b) L.H. Klemm, D.R. Olson, D.V. White, J. Org. Chem., 1971, 36 (24), 3740.
15. S. Takano, S. Otaki, K. Ogasawara, J. Chem. Soc., Chem. Comm., 1985, 485.
16. M.B. Glinsky, T. Durst, Can. J. Chem., 1983, 61, 573.
17. a) H.P. Plaumann, J.G. Smith, R. Rodrigo, J. Chem. Soc., Chem. Comm., 1980, 354; b) R. Rodrigo, J. Org. Chem., 1980, 45 (22), 4540; c) D. Rajapaksa, R. Rodrigo, J. Am. Chem. Soc., 1981, 103, 6208.
18. a) W.J. Gensler, F. Johnson, A.D.B. Sloan, J. Am. Chem. Soc., 1960, 82, 6074; b) J.L. Hartwell, A.W. Schrecker, J. Am. Chem. Soc., 1951, 73, 2909.
19. E.J. Corey, N.F. Feiner, J. Org. Chem., 1980, 45, 765.
20. C. Piccinni-Leopardi, J.P. Declercq, G. Germain, M. Van Meerssche, J. Van der Eycken, M. Vandewalle, Bull. Soc. Chim. Belges, 1984, 93 (12), 1047.

21. The stereochemistry at C-1 in 18a was established as follows : aldol condensation of the TMS-ester of 15 with 3,4,5-trimethoxybenzaldehyde yielded β-hydroxy-acid i. The corresponding methylester i' (CH_2N_2) is different from both 18a and 18b. The normal methylester resonance (3.43 ppm) indicates that both 18a and i' have the same stereochemistry at C-2. The syn-relation in i between C-1 and C-2 follows from the dehydration-decarboxylation (MsCl), which gave trans-alkene ii (J(H-1,H-2) = 16 Hz) via syn-elimination (see subsequent paper; this journal). As i and 18a are epimeric at C-1, the structure of 18a is unequivocally established.



i : R = H, i' : R = Me ii

22. For assigning the stereochemical descriptor in ester enolates, the highest priority is always given to the oxygen atom bearing the metal ion (see : D.A. Evans in "Alkylation of chiral enolates", Asymmetric Synthesis, vol. 3, J.D. Morrison, Acad. Press, 1984, p. 1-110).
23. R.E. Ireland, R.H. Muller, A.K. Willard, J. Am. Chem. Soc., 1976, 98, 2868.
24. J.C. Collins, W.W. Hess, F.J. Frank, Tetrahedron Lett., 1968, 3363.