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A New Approach to the Synthesis of Podophyllotoxin Based on Epimerization Reactions

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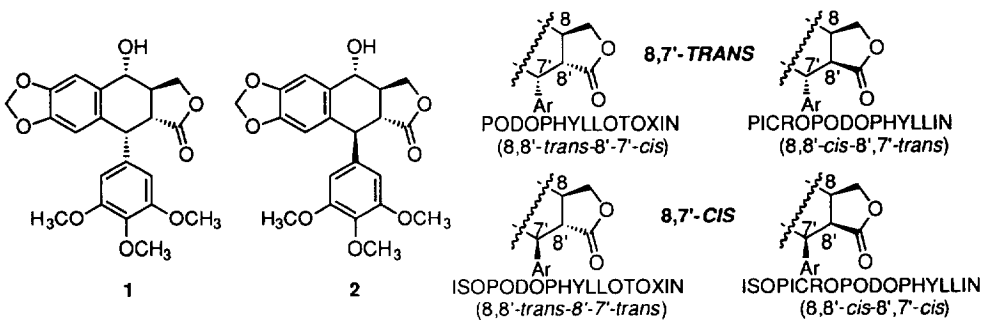
Abstract.- A formal synthesis of podophyllotoxin has been achieved by means of the well known conjugate addition-alkylation of 5*H*-furan-2-one, followed by cyclization and controlled epimerizations. This approach represents a useful new route to the 8,7'-*trans*-stereochemistry of aryltetralin lactones, that in other methodologies requires the opening and reclosure of the lacton ring.

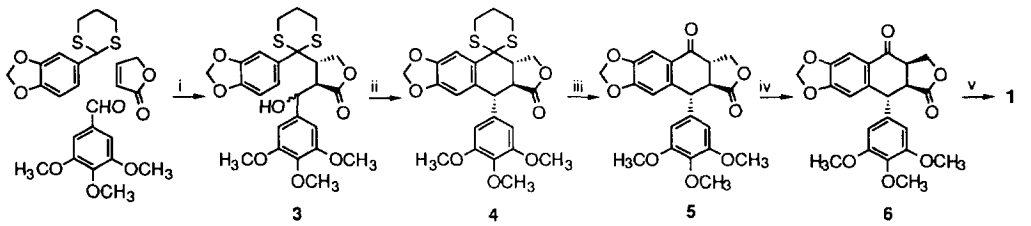
The synthesis of lignans[1] has attracted the attention of many research groups because of their interesting pharmacological activities.[2] Among these compounds, aryltetralin lactones with 8,8'-*trans*-8',7'-*cis* stereochemistry are the most interesting. Podophyllotoxin (**1**) is the best known lignan of this class, as a result of its antitumor and antiviral activities and those of many of its derivatives.[3]

The total synthesis of racemic or enantiomerically pure podophyllotoxin and other related aryltetralin lactones has been achieved by using several methodologies for the assembly of the carbon framework, the most common are based on: Diels-Alder,[4] oxidative coupling[5] and ionic cyclization[6] reactions. The control of the 8,8'-*trans*-8',7'-*cis* stereochemistry is the major difficulty in these synthesis. As an example, the cyclization process gives the 8,7'-*cis*-relationship between the lactone and the phenyl moieties,[6,7] that is represented by isopodophyllotoxin (**2**). To overcome this unwanted result, the cyclization has been carried out with open synthetic equivalents of the lactone ring[8] or the stereochemistry has been changed in open derivatives of the lactone followed by relactonization.[9]

In this communication we present a new approach, based on epimerizations, without lactone opening-relactonization reactions. With this methodology, it is possible to obtain the 8,7'-*trans*-relationship in a high yielding process from the easily obtained cyclization products. Surprisingly, the well known cyclization and the epimerization of aryltetralin lactones have not been combined in such a convenient way, to achieve the stereocontrolled synthesis of this class of compounds.



The epimerization of aryltetralin lactones with podophyllotoxin stereochemistry (8,8'-*trans*-8',7'-*cis*) by bases is known to produce compounds with picropodophyllin stereochemistry (8,8'-*cis*-8',7'-*trans*), by epimerization at C-8'.[10] The same treatment of isopodophyllotoxin derivatives, also produces the epimerization at C-8' to 8,8'-*cis*-fused lactones, thus yielding the isopicropodophyllin stereochemistry (8,8'-*cis*-8',7'-*cis*).[11] In order to convert the cyclization products, with isopodophyllotoxin stereochemistry (**8,7'-*cis***), into the desired compounds with podophyllotoxin (or picropodophyllin) stereochemistry (**8,7'-*trans***), the epimerization at C-8 or at C-7' is required, instead of the usual C-8' epimerization. As there are no close functionalities to accomplish the C-7' epimerization, we chose C-8 as the candidate for the key epimerization. The presence of a carbonyl function at C-7 is suitable for producing this transformation, with the advantage that it is present as a masked functionality (dithiane, dithioketal or protected cyanohydrin) in the starting uncyclized materials and also in the cyclization products. Accordingly, we planned the synthesis of podophyllotoxin (**1**), based on the epimerization of isopodophyllotoxone (**5**) to picropodophyllone (**6**), as depicted in scheme 1.



Scheme 1: i: 1) BuLi, THF, -78°C; 2) 5*H*-furan-2-one; 3) 3,4,5-trimethoxy-benzaldehyde. ii: $SnCl_4$, CH_2Cl_2 iii: HgO, BF_3-Et_2O, THF-H_2O. iv: AcOH, EtOH or p-TsOH, $CHCl_3$. v: Reference 19

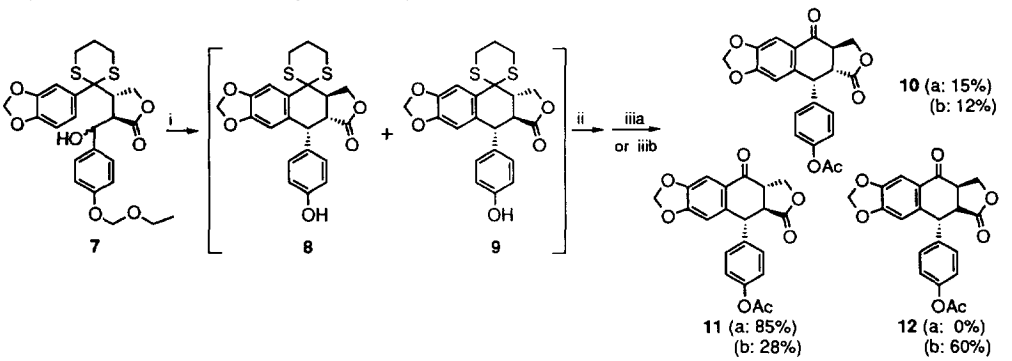
Following this synthetic strategy, we first obtained the dibenzylbutanolide **3**,[12] which was cyclized under standard conditions to produce the isopodophyllotoxin derivative **4**. The cyclization of compounds with the dithiane moiety at C-7 is more difficult than the cyclization of non-functionalized derivatives at C-7, but the use of stannic chloride produced a clean cyclization in high yield[13] (>80%). The deprotection of the keto group under standard conditions, gave the expected isopodophyllotoxone (**5**),[14] that is the substrate adequate for the stereochemical inversion at C-8.

The epimerization of cyclolignanolides under basic conditions, yields products of the epimerization at C-8', unsuitable for our purposes. However, the epimerization under acidic conditions appears as an alternative to achieve the adequate process. In fact, a similar transformation has been described for the conversion of podophyllotoxone (8,8'-*trans*-8',7'-*cis*) into isopicropodophyllone (8,8'-*cis*-8',7'-*cis*),[15] which implies the epimerization at C-8 from a *trans*-fused lactone to a *cis*-fused lactone. So, it was expected that the acidic conditions also would be convenient for the epimerization of aryltetralin lactones at C-8, from a *trans*-fused lactone (8,7'-*cis*) to a *cis*-fused lactone (8,7'-*trans*), that is between the isopodophyllotoxone, produced in the cyclization process, and picropodophyllone stereochemistries.

Using acetic acid at room temperature in the described conditions only partial epimerization was produced, but the quantitative transformation of isopodophyllotoxone (**5**) into picropodophyllone (**6**) was observed when *p*-toluenesulphonic acid in chloroform was used. This transformation has also been produced with 7-oxo-aryltetralin lactone analogs containing other aromatic residues.[16] The stereochemistry of this epimerization can be easily followed by the coupling constants of protons close to the epimerized position (H-7', H-8', H-8 and H-9),[17] furthermore, structures **5** and **6** are well established in the literature. In this way, the key epimerization step of our stereocontrolled approach to the synthesis of podophyllotoxin was achieved under acid conditions in very high yield (90% of isolated product),[18] without appearance of products of epimerization at C-8'.

As the transformation of picropodophyllone (**6**) into podophyllotoxin (**1**) has been described by means of: reduction to the 7α-OH, protection as TBDMS derivative, epimerization at C-8' (enolate formation followed by kinetic reprotonation) and deprotection,[19] our synthetic approach represents a new formal synthesis of podophyllotoxin. This methodology is being used for the synthesis of other new aryltetralin lactones with similar results. The application of enantioselective variations for the assembly of the starting material with dibenzylbutanolide skeleton, in the first step of the synthesis, could produce the corresponding enantioselective synthesis of podophyllotoxin in a high yielding process.

The isolation of aryltetralin lactones with the podophyllotoxin stereochemistry in a paper of Gonzalez *et al*[20] is a striking fact that needs to be confirmed, and it has been pointed out in a recent review on this subject (Ward, 1992).[1] In our opinion, these results can be explained after our transformation of the initially formed 8,7'-*cis* product **4** into the 8,7'-*trans* derivative **6** after the acidic treatment. Nevertheless, the transformation of the 8,8'-*cis*-lactone of the picropodophyllone type into the less stable 8,8'-*trans*-lactone of the podophyllotoxone type is difficult to explain. In order to check the results of that paper in the light of our results with acidic epimerization, we have repeated the synthetic scheme using as starting material the ethoxy-methyl ether of 4-hydroxybenzaldehyde.



Scheme 2: i: TFA, CH_2Cl_2. ii: Ac_2O, Pyr. iii: a: HgO, BF_3·Et_2O, THF-H_2O, 2 h.; b: HgO, BF_3·Et_2O, THF-H_2O, 4h.

The cyclization of **7** in the conditions described by Gonzalez *et al* produced an insoluble material, very difficult to handle in common solvents, that was successively acetylated and deprotected. The resulting reaction product is a mixture of **10** (15%) and **11** (85%), when the deprotection is quenched after two hours, but a mixture of **10** (12%), **11** (28%) and **12** (60%), when the deprotection is maintained for four hours. These results are more in agreement with those described in the literature and with those obtained by us, for the stereochemistry of the cyclization, and do not reproduce exactly the unexpected results of the aforecited paper. In consequence, the usual *trans-trans* fused lactone **9** must be the main reaction product of the reaction, that once acetylated and deprotected directly produces the final product **11**, which evolves to the isomerization product at C-8 (**12**) if the deprotection reaction is maintained for longer periods of time.[21] The minor amount (12-15%) of the 8,8'-*trans*-8',7'-*cis* fused material, described by Gonzalez *et al* as 40% of the reaction product, must be obtained from **8**, which is produced in the cyclization process. In consequence, it is not possible to control the stereochemistry of the cyclization by changing the nature of the oxygenated substituents in the aromatic ring, and compounds with the podophyllotoxone stereochemistry are only obtained in minor amounts.[22]

The methodology described in this communication for the synthesis of aryltetralin lactones with 8,7'-*trans* relationship, such as podophyllotoxin (**1**) or picropodophyllotoxin, represents a new approach for the stereochemical control of the cyclization products obtained from the readily available conjugate addition-alkylation starting materials.

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