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Heterolignanolides. Synthesis of a New Family of *Thienolignanolides*

Manuel Medarde*, Angel C. Ramos, Esther Caballero, Jose Luis López,
Rafael Peláez-Lamamié de Clairac and Arturo San Feliciano

Dpto. de Química Orgánica y Farmacéutica. Facultad de Farmacia. Av. Campo Charro s/n. E-37007 SALAMANCA. Spain.

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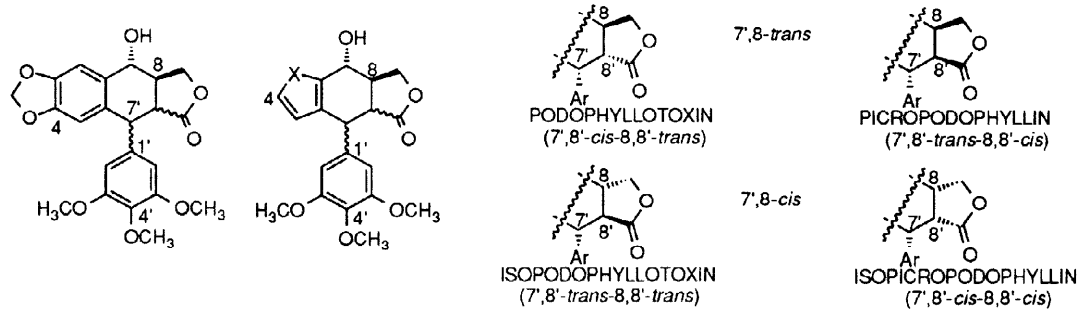
Abstract.- A new family of thienolignanolides has been synthesized by means of conjugate addition-alkylation of 5*H*-furan-2-one, followed by cyclization and controlled epimerizations. The applicability of this versatile methodology is extended to the preparation of heteroaromatic analogues of biologically relevant cyclolignanolides.

Lignans have attracted the attention of many research groups because of their interesting pharmacological activities.[1] Among these compounds, aryltetralin lactones are the best known as a result of their antitumoral and antiviral activities and those of many of their derivatives. Representative aryltetralin-lactones are the naturally occurring Podophyllotoxin and Picropodophyllin and the clinically used derivatives Etoposide and Teniposide.[1a]

Heterolignans are an interesting class of analogues characterized by the substitution of carbon atoms of the basic skeleton by heteroatoms or heterocyclic systems. Azatoxin is the most promising of this novel type of synthetic antitumoral compounds.[2]



Scheme 1: Numbering and relative stereochemistry of podophyllotoxins and heteropodophyllotoxins.[3]

The total synthesis of racemic or enantiomerically pure lignanolides and related heteroanalogues has been achieved *via* several methodologies for the assembly of the carbon framework, the most common being based on: Diels-Alder,[4] conjugate addition-alkylation-cyclization strategies,[5] oxidative coupling[6] and ionic cyclization reactions.[7] The well known conjugate addition-alkylation to 5*H*-furan-2-one followed by cyclization methodology has recently been described for the synthesis of 7´,8-*trans* -aryltetralin lactones *via* a convenient epimerization at C-8, allowing easy access to the Podophyllotoxin and Picropodophyllin series.[8]

In this communication we apply the conjugate addition-alkylation strategy to the synthesis of

FAX-34-23-294515, e-mail: medarde@gugu.usal.es

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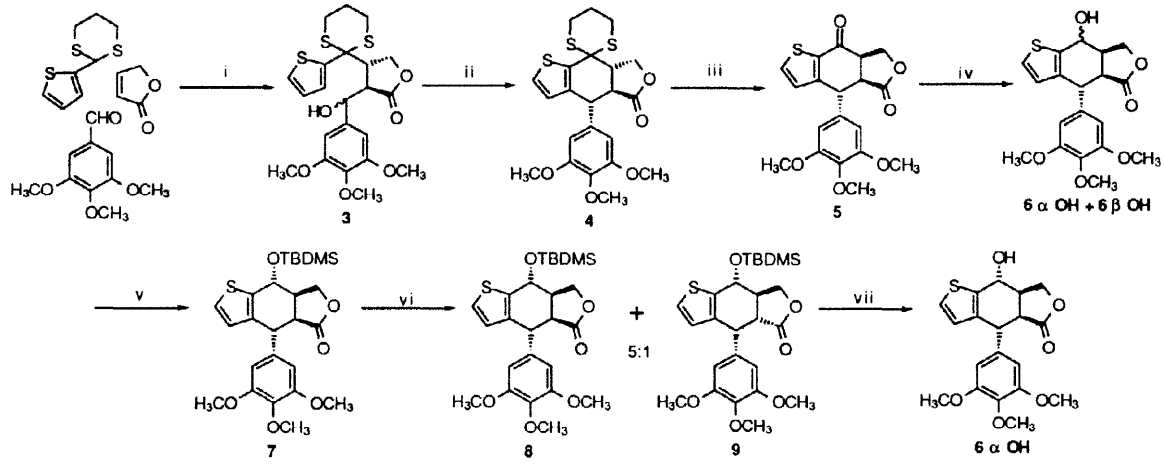
a new family of heterolignanolides carrying a thiophene ring instead of the benzodioxole moiety present in most of the biologically relevant lignanolides.[1a] This methodology produces the 7-keto-heterolignanolides in very good yields, whose epimerization at C-8 affords the desired 7′,8-*trans*-heterolignanolides in such a way to achieve the stereocontrolled synthesis of this class of compounds.



Reagents and Conditions: i: 1) BuLi, THF; 2) 5*H*-furan-2-one; 3) 3,4,5-trimethoxybenzaldehyde. ii: $SnCl_4$, CH_2Cl_2 or TFA, EtOH. iii: HgO, BF_3·Et_2O, THF-H_2O. iv: (^{t}BuO)$_3$LiAlH, THF. v: TBDMSTf, ^{i}Pr$_2$NEt, CH_2Cl_2. vi: 1) LHMDS, THF, -78°C; 2) AcOH, THF. vii) TBAF, CH_3CN.

Scheme 2

The first stage of the synthetic strategy involved the conjugate addition of 2-thiophene-1,3-dithiane to 5*H*-furan-2-one followed by alkylation with 3,4,5-trimethoxybenzaldehyde of the resulting enolate anion. As previously described,[9] the conjugate addition proceeds in excellent yields. Under optimized conditions (temp. <-50°C, two equivalents of TMEDA. Yield >80%) a 5:1 *erythro:threo* mixture of both epimeric alcohols at C-7' was obtained, a fact that implies a higher facial stereoselectivity for these heteroanalogues than those previously described for related lignanolides. Acid promoted cyclization of the unresolved mixture using TFA/Benzene/reflux or $SnCl_4/CH_2Cl_2$/r.t. exclusively yields the intermediate lactone **4** (62-74%).[10] The relative *trans-trans* stereochemistry of C-8, C-8′ and C-7′ in **4** was unambiguously established based on the NMR data, in agreement with most of the earlier reports.

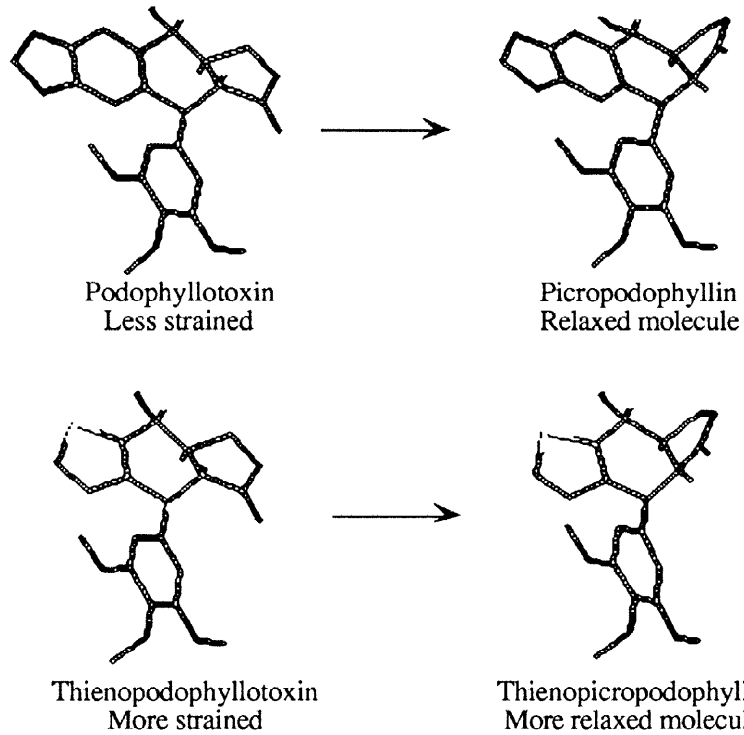
In order to reverse the undesired *cis* relative stereochemistry between C-7′ and C-8, the protecting 1,3-dithiane moiety was hydrolyzed, unmasking the carbonyl group at C-7 which renders C-8 sensitive to epimerization reactions. Basic epimerization of 7-ketocyclolignanolides typically yields products of epimerization at C-8′ (isopicropodophyllin type), unsuitable for our purposes. However, acidic epimerization of such derivatives produces *cis* lactones (isopodophyllotoxin type)*via* epimerization at C-8.[11] Tandem deprotection-epimerization reactions are carried out in "one pot" just by increasing the reaction time under the deprotecting conditions at room temperature, yielding the desired lactone **5** in very good yield (90%).

Lactone **5** is a thiophene analogue of picropodophyllone[12] which is the key intermediate in Kende's synthesis of podophyllotoxin[6a] based on the reduction to the 7α-OH, protection as TBDMS derivative, epimerization at C-8′ under kinetic control and deprotection. Thiophene analogues of podophyllotoxin should then be accessible from this key synthetic intermediate. (^{t}BuO)$_3$LiAlH reduction of **5** in THF yields a mixture of the two epimeric alcohols **6** at C-7. The 3:1 α:β ratio is similar to those

obtained by other groups with analogous ketolignans.[13] These compounds are the thiophene analogues of picropodo- and epipicropodophyllin. Attempts to protect the unresolved mixture of the two isomers with TBDMS triflate exclusively yield product **7** from the more accessible α alcohol, and unreacted β isomer. This selectivity allowed us to isolate and fully characterize the otherwise unresolvable alcohols.

The TBDMS derivative was deprotonated using either LDA or LiHMDS in THF at -78°C followed by kinetic reprotonation with dilute acetic acid, to afford a 5:1 mixture of the *cis* and *trans* protected lactones, **8** and **9**.[14] Other conditions and/or use of different deprotonating reagents did not improve the epimerization yield or produced several reaction products. Attempts to deprotect the unresolvable mixture with TBAF in acetonitrile only yielded the previously described α-picroalcohol **6** due to lactone epimerization caused by the weakly basic fluoride ion.[15]

The preference for a *cis* 8-8′ stereochemistry is higher in the case of this heteroanalogue than in related lignans, whose *trans* isomer can be isolated by the TBAF standard procedure without epimerization at C-8'. The structural strain introduced by the substitution of a six atom ring by a five-membered one can explain the difference in stability of both stereoisomers and the easier epimerization.[16]



Scheme 3: Molecular models of the (thieno)podophyllotoxins and (thieno)picropodophyllins.

The successful synthesis of the thienopodophyllotoxin compounds by the conjugate addition-alkylation-cyclization-epimerization methodology opens new possibilities for the preparation of many unnatural analogues of lignans. Structural variations for the study of structure-activity relationships with these compounds can be easily achieved by this procedure, because many new heterocyclic analogues of lignanolides carrying heterocyclic rings instead of one or both of the benzenic rings of natural lignans are accessible. The synthesis of furane, 5-methylfurane, 5-methylthiophene and other analogues are now under way following a similar procedure.

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10. The TFA catalyzed reactions also gives a minor product (c.a 15%) arising from a cationic rearrangement of the 1,3-dithiane ring which takes place to reduce steric congestion at C-8 (the so called Thorpe-Ingold effect, Jung, M.E.; Gervay, J. *Tetrahedron Lett.*, **1988,** *29*, 2429 and references therein), that is not observed in the $SnCl_4$ treatment. No aromatization products were observed for thiophene derivatives in any case.
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12. The ^{1}H-NMR spectrum of **5** shows C-7′ and C-8′ as two broad singlets, in agreement with a *trans* relationship between this pair of protons and a *cis* relationship between C-8 and C-8′.
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14. Representative ^{1}H RMN data of compounds **8** and **9** are given below:
8 ^{1}H RMN ($CDCl_3$, 200 MHz) δ 7.17 (d, *J* = 5.1, 1H); 6.58 (d, *J* = 5.1, 1H); 6.43 (s, 2H); 4.85 (d, *J* = 9.1, 1H); 4.78 (d, *J* = 7.4, 1H); 4.33 (dd, *J* = 4.7, 9.1, 1H); 4.32 (d, *J* = 2.2, 1H); 3.83 (s, 3H); 3.80 (s, 6H); 3.04 (dd, *J* = 2.2, 7.6, 1H); 2.84-2.73 (m, 1H); 0.98 (s, 9H); 0.29 (s, 3H); 0.22 (s, 3H).
9 ^{1}H RMN ($CDCl_3$, 200 MHz) δ 7.27 (d, *J* = 5.1, 1H); 6.67 (d, *J* = 5.1, 1H); 6.37 (s, 2H); 4.97 (d, *J* = 7.7, 1H); 4.60 (d *J* = 4.0, 1H); 4.50 (dd, *J* = 6.6, 8.4, 1H); 4.01 (dd, *J* = 6.8, 8.7, 1H); 3.02-2.86 (m, 2H); 0.94 (s, 9H); 0.27 (s, 3H); 0.11 (s, 3H)
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16. Angles R-C_2-C_3 and R'-C_2-C_3 in 2,3-disubstituted thiophene are 125.68° and 123.28° respectively, higher than those for benzene (120° each), further increasing the strain of the 7',8-*cis*-8,8'-*trans* cyclolignanolides.