HETEROLIGNANS

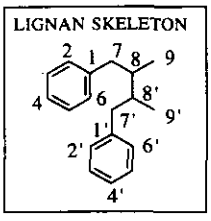
Angel C. Ramos, Rafael Peláez-Lamamié de Clairac, and Manuel Medarde*

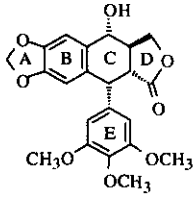
Departamento de Química Farmacéutica. Facultad de Farmacia. Universidad de Salamanca
Campus "Miguel de Unamuno", E-37007 Salamanca, Spain
Fax: 34-923-294515
E- Mail : medarde@gugu.usal.es

Abstract- Lignans are natural bis-phenylpropanoids having biological activities. Fully synthetic analogues carrying heteroatoms instead of C atoms on the basic skeleton have been grouped under the name heterolignans. In this review a classification and their structures, biological activities and synthesis are presented.

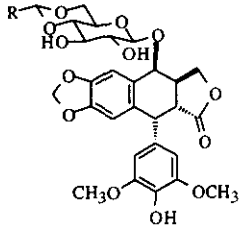
INTRODUCTION

Lignans are a well known family of natural products,[1, 2] characterized by the presence of two phenylpropane units bonded trough C8-C8' (Figure 1). Many such compounds have been isolated from natural sources[3-9] and different synthetic procedures have been described for their total synthesis.[10-12] Due to their interesting pharmacological activities,[5, 13-15] many of these compounds and their semisynthetic derivatives have been assayed in order to elucidate their mode of action and their structure-activity relationships.[16] Among them, podophyllotoxin, its derivatives etoposide (VP-16) and teniposide (Figure 1) are the most known as a consequence of their antitumoral activity.[17] VP-16 has been introduced in the clinic for the treatment of testicular cancer, small-cell lung cancer, leukemias and non Hodgkin's lymphoma.[18]





Podophyllotoxin



Etoposide (**VP-16**) R = CH_3
Teniposide R = 2-thienyl

Figure 1. Basic lignan skeleton and representative examples

The presence of additional C-C bonds and oxygen bridges in the bisphenylpropane structure has been used to structurally classify lignans in different groups (Figure 2). The three main skeletons correspond to: 1)

Acyclic lignans and other containing no additional C-C bonds (**I**), including different types such as substituted furans, furofurans, dibenzylbutyrolactones; 2) Arylnaphthalene derivatives (**II**), having a C6-C7' bond, which include the podophyllotoxins; and 3) Derivatives of dibenzocyclooctene skeleton (**III**), with a C6-C2' bond, which include the steganacins.

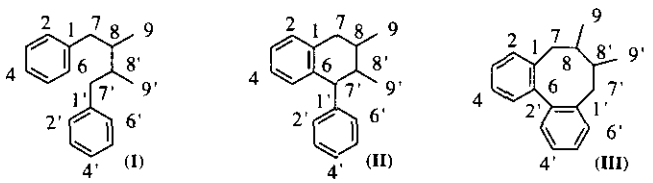


Figure 2. Lignanic main structural classes.

The variations introduced in the lignan structure have been mainly directed at the modification of the substituents on the basic skeleton. Modifications affecting the substitution pattern of the aromatic rings,[19, 20] the substituents at C7,[21-25] the change of the 9,9'-lactone into a 9,9'-lactam,[26] and many others modifications have been carried out.[27] In spite of all this work, less work has been done on the synthesis and pharmacological studies of nonnatural analogues of lignans. Examples of non natural lignans include several types of compounds, such as those with a cyclopentane ring instead of the cyclohexane ring of tetrahydronaphthalene podophyllotoxins[28] or those with a cyclopentanone instead of the lactone ring.[29]
One possibility for the structural modification of lignans, which could lead to the preparation of many derivatives, is the replacement of carbon atoms of the basic skeleton by heteroatoms. This modification is very interesting from the synthetic and pharmacological points of view. In this review we present the chemical and pharmacological aspects of those compounds described in the literature which can be grouped under the common name of "heterolignans".

DEFINITION AND CLASSIFICATION

The term "heterolignans" was first introduced by us[30] to define a class of compounds developed in a research line directed at the synthesis of new analogues of lignan.[31] "Heterolignans" are those synthetic analogues of lignans designed as a result of replacing one or more carbon atoms of the propane moieties (C7-C9 and/or C7'-C9') by heteroatoms and/or replacing one or both benzenic rings (C1-C6 and/or C1'-C6') by heteroaromatic systems. The number of possibilities is limitless, because to the previously known variations described among the natural lignans ("carbolignans") and their derivatives, it can be added the multiple variations introduced by the nature of heteroatoms and heterocyclic systems respectively replacing the carbon atoms and benzenic rings.
In order to systematize the description of already known compounds that can be grouped as heterolignans and also facilitate the inclusion of new derivatives into this family, it is necessary to classify the heterolignans in different groups. One possibility is to maintain the three groups of lignans: acyclic (only C8-C8' bond), aryltetralin naphthalenes (additional C6-C7' bond) and dibenzocyclooctenes (additional C6-C2' bond), but there is little simplification within each group. Another possibility, selected for this review, is to classify the heterolignans according to the number and position of heteroatoms or heteroaromatic

systems in the skeleton. The distinction between cyclization patterns of the skeleton is not used because, usually, acyclic and C6-C7' and C6-C2' cyclized derivatives are obtained by further cyclizations along the same synthetic sequence. The differentiation by the nature of the heteroatom (N, O, S) or the heterocyclic system (electron-rich, electron-deficient) is not significant in the broad classification, but it can be used for further subgroups within each group.

Accordingly, we have classified heterolignans as follows

HETEROLIGNANS WITH HETEROATOMS AT 7-9;7'-9'

A. Heterolignans with one heteroatom at 7-9;7'-9'

B. Heterolignans with two or more heteroatoms at 7-9;7'-9'

HETEROLIGNANS WITH HETEROAROMATIC SYSTEMS

C. Heterolignans with one heteroaromatic system

C-1 Replacing the 1-6 ring

C-2 Replacing the 1'-6' ring

D. Heterolignans with two heteroaromatic systems

MIXED HETEROLIGNANS

E. Heterolignans with heteroatoms at 7-9;7'-9' and heteroaromatic system

E-1 Replacing the 1-6 ring

E-2 Replacing the 1'-6' ring

LIGNAN HETERO DERIVATIVES

F. Heterolignans incorporating one of the benzenic rings into a more extended heterocyclic system

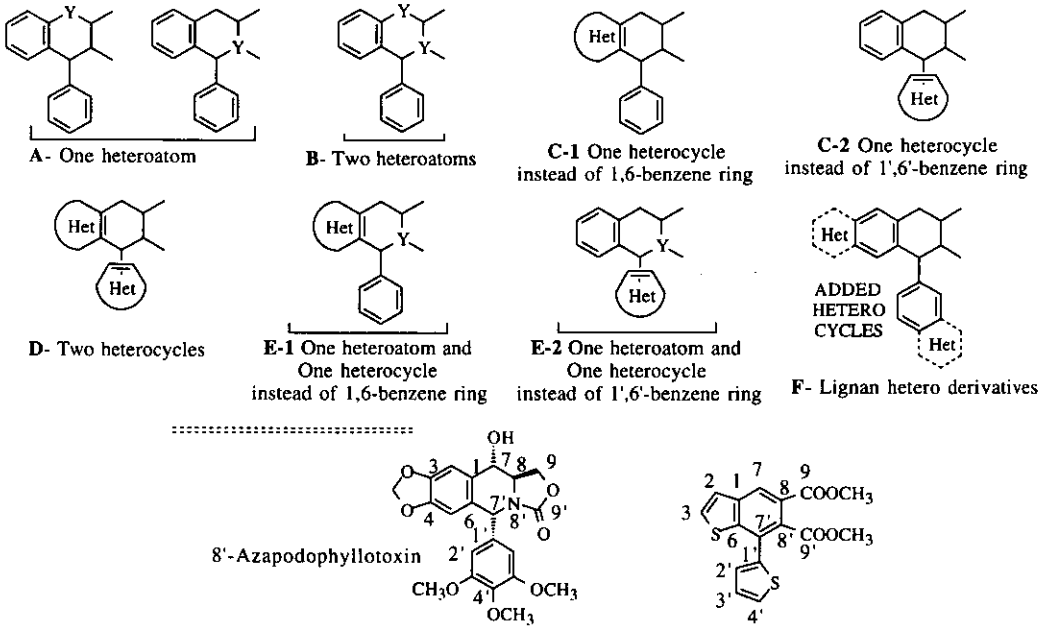


Figure 3. Aryltetralin heterolignans.

In Figure 3 a generic representation of each type of aryltetralin heterolignanic analogues is depicted. Two particular examples of such compounds are also drawn and numbered. Numbering follows the lignan

numbering, to keep the similarity between both classes of compounds. It is not systematic, but allows an easy comparison of the structural modifications. When five membered heterocyclic systems replace benzene rings, one atom is missed and it is assumed that the heteroatom corresponds with two positions of the parent lignan.

Lignan derivatives obtained by construction of heteroaromatic systems on the 7-9:7'-9' moieties of the lignan framework have been excluded from this classification, because they can just be considered as substituents. Only modifications of the benzenic rings, that maintain both 1-6 and 1'-6' rings are included in F group, because the construction of extended heteroaromatic systems modifies the nature of the benzenic rings of the basic skeleton.

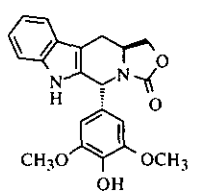
On the other hand, other compounds containing additional carbon atoms in the basic skeleton have been included, as far as they have been prepared as lignan analogues. For example, six membered piperidine rings replacing the lactonic D ring of podophyllotoxin can be found in type A heterolignans.

This classification is not exhaustive, but allows its adaptation to include many types of derivatives that can be obtained taking as model the structure of lignans. Among groups A-F other subgroups can be included, taking into account the classifications of lignans, but it is beyond the purpose of this review, mainly directed at the compilation of the existing material. Due to the limited number of compounds described until this moment the adopted classification is adequate for our purpose, and only in the future other subdivisions will be introduced for a better systematization.

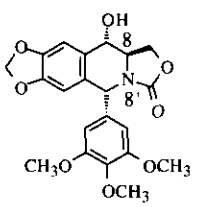
INTEREST

The reasons for the interest in the synthesis of heterolignans, can be grouped in two general aspects: a) those affecting their pharmacological activities, and b) those affecting their synthesis.

a) The presence of heteroatoms influences the structure and hence the chemical characteristics and behavior of these compounds. In this way, the replacement of carbon atoms by nitrogen atoms introduces a basic character into the molecule, that can influence their pharmacological properties. Another example is the change of one benzenic ring into an extended heterocyclic system, as it is the case of azatoxin,[32-35] in which the intercalating nature of elliptitoxin is added to the lignan by means of an indole moiety (Figure 4).



Azaelliptitoxin (Azatoxin)
Ellipticine based analogue



8'-Azapodophyllotoxin
Non epimerizable at 8'

Figure 4. Bioactive heterolignans.

The presence of the heteroatom can affect the structural properties preventing undesired transformations, that deactivate the compound. The 8'-azapodophyllotoxins[36-40] are representative of such an effect; the undesired epimerization at C8', which produces a reduction of the activity of *trans*-lactones when transformed into the most stable *cis*-lactones,[41] being not produced in the 8'-aza analogues (Figure 4).

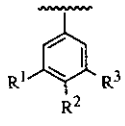
b) From a synthetic point of view formation of C-heteroatom bonds is easier than the formation of C-C bonds and the structural variability and synthetic versatility of heterocycles is higher than of benzenic rings. As a consequence, the number of analogues that can be prepared are higher and usually their synthesis is achieved in fewer steps.

The total syntheses of 8'-azapodophyllotoxins[36-40] are representative of the simplification of the synthetic process, that is effected in few high yielding steps, while the syntheses of podophyllotoxins require more steps and harder stereochemical control, producing the final products in lower yields.[12]

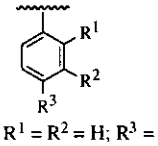
Synthetic strategies employed for the construction of different types of heterolignans have been "de novo" developed for this purpose. In other cases they are the logic adaptation of the existing methodologies for the preparation of natural or synthetic carbolignans.

STRUCTURES OF HETEROLIGNANS.

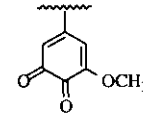
In the next section the structures of described heterolignans are presented according to their classification. In Figure 5, the abbreviations used for 1'-6' aryl groups are depicted.



Ar¹ $R^1 = R^2 = R^3 = H$
Ar² $R^1 = R^3 = H$; $R^2 = OCH_3$
Ar³ $R^1 = R^2 = OCH_3$; $R^3 = H$
Ar⁴ $R^1, R^2 = OCH_2O$; $R^3 = H$
Ar⁵ $R^1 = R^3 = OCH_3$; $R^2 = OH$
Ar⁶ $R^1 = R^2 = R^3 = OCH_3$
Ar⁹ $R^1 = OCH_3$; $R^2 = R^3 = H$
Ar¹² $R^1 = R^2 = Cl$; $R^3 = H$
Ar¹³ $R^1 = R^2 = Cl$; $R^3 = OCH_3$
Ar¹⁵ $R^1 = OCH_3$; $R^2 = OH$; $R^3 = H$
Ar¹⁶ $R^1 = R^3 = H$; $R^2 = OH$



Ar⁷ $R^1 = R^2 = H$; $R^3 = CH_3$
Ar⁸ $R^1 = OCH_3$; $R^2 = R^3 = H$
Ar¹⁰ $R^1 = R^2 = OCH_3$; $R^3 = H$
Ar¹¹ $R^1 = R^3 = OCH_3$; $R^2 = H$



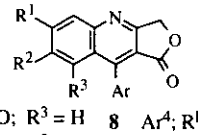
Ar¹⁴

Figure 5. Abbreviations for the aryl groups.

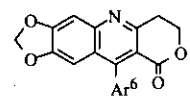
HETEROLIGNANS WITH HETEROATOMS AT 7-9;7'-9'

A. Heterolignans with one heteroatom at 7-9;7'-9'

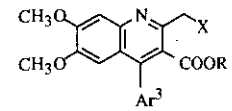
The largest number of heterolignans described up to the moment belong to this group. The carbon atoms have been replaced by N, O and S, mainly at positions 7 and 8', because of synthetic accessibility and also because they more directly affect the activity of most interesting lignans of the aryltetralinelactone type.



1 Ar^3; $R^1 = R^2 = OCH_2O$; $R^3 = H$
2 Ar^4; $R^1 = R^2 = OCH_2O$; $R^3 = H$
3 Ar^6; $R^1 = R^2 = OCH_2O$; $R^3 = H$
4 Ar^9; $R^1 = R^2 = OCH_2O$; $R^3 = H$
5 Ar^2; $R^1 = R^2 = OCH_2O$; $R^3 = H$
6 Ar^1; $R^1 = R^2 = OCH_2O$; $R^3 = H$
7 Ar^3; $R^1 = R^2 = OCH_3$; $R^3 = H$
8 Ar^4; $R^1 = R^2 = OCH_3$; $R^3 = H$
9 Ar^6; $R^1 = R^2 = OCH_3$; $R^3 = H$
10 Ar^3; $R^1 = R^2 = R^3 = OCH_3$
11 Ar^6; $R^1 = R^2 = R^3 = OCH_3$
12 Ar^2; $R^1 = R^2 = R^3 = H$
13 Ar^1; $R^1 = R^2 = R^3 = H$



14

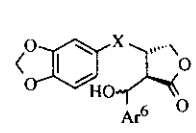


15 $R = CH_3$; $X = Cl$
16 $R = C_2H_5$; $X = COOC_2H_5$
17 $R = C_2H_5$;
$X = CH_2$-Heterocycle

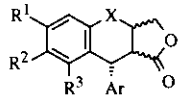
Figure 6. 7-Aza-heterolignans.

The 7-aza heterolignans are represented by the quinoline derivatives (**1-17**) (Figure 6), analogues of

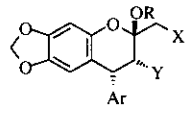
arylnaphthalene lignans.[42, 43] Synthesized 7-oxa and 7-thia heterolignans have structures of acyclic- (**18** and **19**) and cyclolignans (**20-46**) (Figure 7).[44, 45]



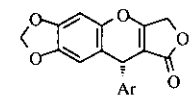
18 X = O
19 X = S



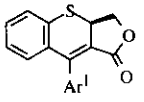
20 X = O; 8α,8'β; R^1,R^2 = OCH_2O; R^3 = H; Ar^6
21 X = S; 8α,8'β; R^1,R^2 = OCH_2O; R^3 = H; Ar^6
22 X = S; 8β,8'α; R^1 = R^2 = R^3 = H; Ar^1
23 X = S; 8β,8'β; R^1 = OCH_3; R^2 = R^3 = H; Ar^6
24 X = S; 8α,8'β; R^1 = OCH_3; R^2 = R^3 = H; Ar^6
25 X = S; 8α,8'β; R^1 = R^2 = H; R^3 = OCH_3; Ar^6



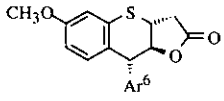
28 X = Y = R = H; Ar^6
29 X , Y = CH_2OCO; R = H; Ar^6
30 X , Y = CH_2OCO; R = CH_3; Ar^6
31 X , Y = $(CH_2)_3CO$; R = H; Ar^6
32 X , Y = CH_2OCO; R = CH_3; Ar^{11}
33 X , Y = CH_2OCO; R = CH_3; Ar^{10}
34 X , Y = CH_2OCO; R = CH_3; Ar^3
35 X , Y = CH_2OCO; R = CH_3; Ar^4
36 X , Y = CH_2OCO; R = CH_3; Ar^2
37 X , Y = CH_2OCO; R = CH_3; Ar^9
38 X , Y = CH_2OCO; R = CH_3; Ar^8



39 Ar^6 **40** Ar^{11}
41 Ar^{10} **42** Ar^3
43 Ar^4 **44** Ar^2
45 Ar^9 **46** Ar^8



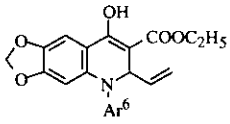
26



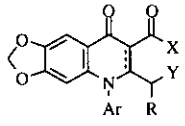
27

Figure 7. Oxa- and thia- heterolignans.

The 7'-heterolignans described in the literature are quinolones (**48-51**) (Figure 8), carrying extra carbon atom at C9 that have all been prepared from synthetic intermediate (**47**) with a vinyl group at C8.[46]



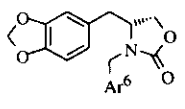
47



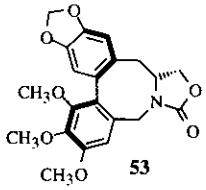
48 Ar^6; X, Y = O; R = CH_2OH; $\Delta^{8,8'}$
49 Ar^6; X, Y = OCH_2; R = H
50 Ar^5; X = OC_2H_5; Y = H; R = CH_2OH
51 Ar^5; X, Y = OCH_2; R = H

Figure 8. 7'-Azaheterolignans.

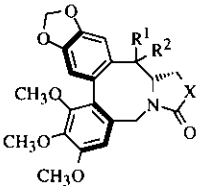
Many 8'-aza derivatives have been prepared as analogues of acyclic lignans, steganacins and podophyllotoxins, some of them with a piperidine ring instead of the lactonic ring of such natural lignans.



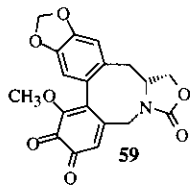
52



53



54 R^1 = R^2 = H; X = O
55 R^1 = H; R^2 = OH; X = O
56 R^1 = OH; R^2 = H; X = O
57 R^1 = R^2 = O; X = O
58 R^1 = R^2 = H; X = NH



59

Figure 9. 8'-Azaheterolignans.

As it happens with steganacins, two atropoisomeric structures can exist. By cyclization of 8'-azalignanolide (**52**), the more stable 8'-azaisopicrostegane (or 8'-azaisostegane) (**54**) and the less stable 8'-

azapicrostegane (or 8'-azastegane) (**53**) were isolated in a 60:1 ratio (Figure 9). Upon heating each isomer is converted into a mixture of **54** and **53** in a 40:1 ratio.[47, 48] It is noteworthy (Figure 10) that the analogous treatment of acyclic precursor of steganes produces the same atropoisomer, which in this case, is the less stable isomer that can be converted into the more stable one.[49] By related methodology, the oxidized derivatives (**55-57**) at the benzylic position, the imidazolidinone (**58**) or the *ortho*-quinone (**59**) can be prepared.

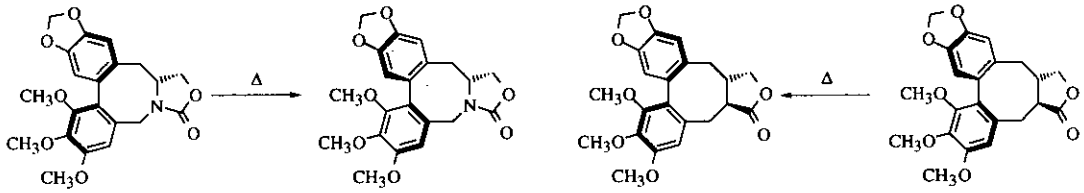


Figure 10. Atropoisomer interconversion in the stegane series.

Looking for enantiomerically pure 8'-aza analogues, Lienard *et al.*[50-52] have prepared compounds belonging to the three types of skeletons with a piperidine ring instead of the lactonic ring of lignanolides. Acyclic (**60-61**), steganacin analogue (**62**) and podophyllotoxin analogues (**63-66**), 8'-aza analogues carrying an additional carbon atom at the D-ring have been prepared (Figure 11).[50-52]

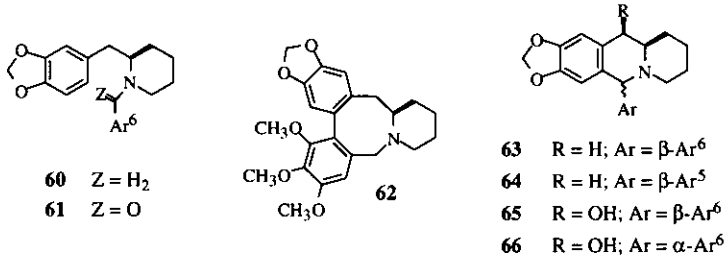


Figure 11. 8'-Azaheterolignans with a piperidine D ring.

Several 8'-aza analogues of tetrahydronaphthalenelactone lignans (**67-77**) (Figure 12) have been prepared.[36-40, 53] Among them, the most significant derivatives are 8'-azapodophyllotoxin (**74**) and 8'-aza-7-*epi*podophyllotoxin (**75**), which were easily obtained as non 8'-epimerizable analogues of the natural lignans.[36, 37] From the latest, the 8'-azaetoposide (**78**) has been also synthesized.[54] The easy access to 8'-azalignans has favored the synthesis of all these varied structures, as for example the naphthalene analogues (**79-80**) of 8'-aza-deoxypodophyllotoxin.[55]

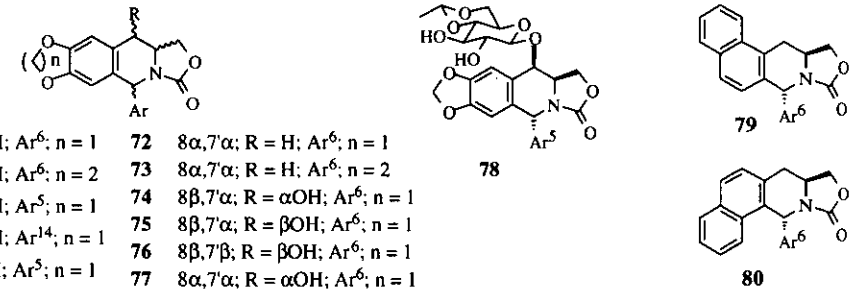
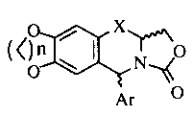


Figure 12. 8'-Azatetrahydronaphtalene lactone heterolignans.

B. Heterolignans with two heteroatoms at 7-9;7'-9'

This family is only represented by the 7,8'-dihetero analogues of podophyllotoxins, carrying N, O or S at position 7 and N at position 8', due to simple synthetic methodologies and the convenience of the N atom at 8'.



81 8β,7'α; X = NH; Ar^6; n = 1
82 8β,7'α; X = NH; Ar^6; n = 2
83 8β,7'α; X = NH; Ar^5; n = 1
84 8β,7'α; X = NH; Ar^5; n = 2
85 8α,7'α; X = NH; Ar^6; n = 1
86 8α,7'α; X = NH; Ar^6; n = 2
87 8α,7'α; X = NH; Ar^5; n = 1
88 8α,7'α; X = NH; Ar^6; n = 2
89 8β,7'α; X = O; Ar^6; n = 1
90 8β,7'α; X = S; Ar^6; n = 1

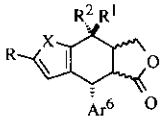
Figure 13. 7,8'-Diazapodophyllotoxins.

Several stereoisomers of 7,8'-diazapodophyllotoxins (**81-88**) (Figure 13) have been synthesized carrying 1,3-dioxolane and dihydro-1,4-dioxane rings on the 1,6-benzene ring.[56-59] By a different methodology the 7-oxa-8'-aza-podophyllotoxins (**89**)[60] and 7-thia-8'-aza-podophyllotoxins (**90**)[61] have been prepared (Figure 13).

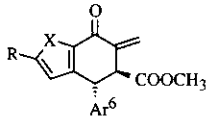
HETEROLIGNANS WITH HETEROAROMATIC SYSTEMS

C-1. Heteroaromatic systems replacing the 1,6-ring

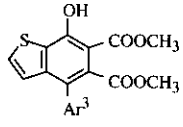
The replacement of the 1,6-benzene ring by a furan or thiophene ring, as it is the case of compounds (**91-103**), has proven to produce small modification in the spectroscopic properties or in the cytotoxic activity of these analogues.[62] From these compounds it was possible to synthesize the heteroanalogues (**104-107**) of thuriferic acid methyl esther.[31] A related thiophene analog (**108**) (Figure 14) of naphthalene lignans has also been described.[63]



91 8α,8'β; X = O; R = H; R^1,R^2 = O
92 8α,8'β; X = O; R = CH_3; R^1,R^2 = O
93 8α,8'β; X = S; R = H; R^1,R^2 = O
94 8α,8'β; X = S; R = CH_3; R^1,R^2 = O
95 8α,8'β; X = O; R = H; R^1 = R^2 = H
96 8β,8'β; X = O; R = H; R^1,R^2 = O
97 8β,8'β; X = O; R = CH_3; R^1,R^2 = O
98 8β,8'β; X = S; R = H; R^1,R^2 = O
99 8β,8'β; X = S; R = CH_3; R^1,R^2 = O
100 8β,8'β; X = O; R = H; R^1 = H; R^2 = OH
101 8β,8'β; X = S; R = H; R^1 = H; R^2 = OH
102 8β,8'β; X = S; R = H; R^1 = OH; R^2 = H
103 8β,8'α; X = S; R = H; R^1 = H; R^2 = OH



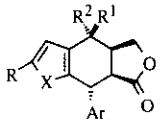
104 X = O; R = H
105 X = O; R = CH_3
106 X = S; R = H
107 X = S; R = CH_3



108

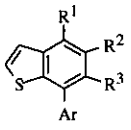
Figure 14. Furo and thiophene analogues of podophyllotoxins and thuriferic acid.

Other thiophene derivatives, which differ in the fusion of this ring to the rest of the molecules, were obtained. They are nonaromatic C-ring (**109-117**) (Figure 15)[64] and aromatic thiophene analogues (**118-124**) of cyclolignans (Figure 16).[63, 65, 66]

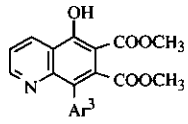


109 X = O; R = H; R^1, R^2 = O; Ar^3
110 X = O; R = CH_2OH; R^1, R^2 = O; Ar^3
111 X = O; R = R^2 = H; R^1 = OCH_3; Ar^3
112 X = S; R = R^1 = H; R^2 = OCH_3; Ar^2
113 X = S; R = R^1 = H; R^2 = OCH_2OCH_3; Ar^3
114 X = S; R = R^1 = H; R^2 = OCH_2COOCH_3; Ar^3
115 X = S; R = CH_2OCH_3; R^1 = H; R^2 = OCH_3; Ar^6
116 X = S; R = R^1 = H; R^2 = OCH_3; Ar^6
117 X = S; R = R^1 = H; R^2 = OCH_3; Ar^{13}

Figure 15. Non aromatic C-ring thiophene heterocyclolignans.



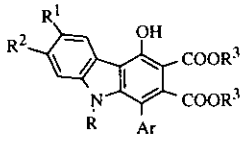
118 R^1 = OH; R^2 = R^3 = $COOCH_3$; Ar^3
119 R^1 = OH; R^2 = R^3 = $COOCH_3$; Ar^5
120 R^1 = OH; R^2 = R^3 = $COOCH_3$; Ar^7
121 R^1 = OH; R^2 = R^3 = $COOCH_3$; Ar^1
122 R^1 = OH; R^2 = R^3 = $COOCH_3$; Ar^{12}
123 R^1 = SC_2H_5; R^2, R^3 = COOCO; Ar^1
124 R^1 = SC_2H_5; R^2 = H; R^3 = $COOCH_3$; Ar^1



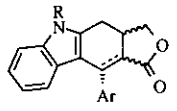
125

Figure 16. Aromatic C-ring thiophene and pyrido heterocyclolignans.

Only three additional types of C-1 group, with an *N*-heteroaromatic system, have been synthesized: the pyrido derivative (**125**),[63] the indolo (a formal carbazole system) derivatives (**126-128**)[63, 67] and the differently oriented indolo derivatives (**129-131**) (Figure 17).[68]



126 R =Ts; R^1 = R^2 = H; R^3 = CH_3; Ar^6
127 R =Ts; R^1 = R^2 = H; R^3 = CH_3; Ar^1
128 R =CH_3; R^1, R^2 = OCH_2O;
R^3 = C_2H_5; Ar^6

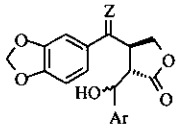


129 8β,8'α; R = H; Ar^5
130 8β,8'β; R = $PhSO_2$; Ar^6
131 $\Delta^{7,8'}$; R = Ts; Ar^5

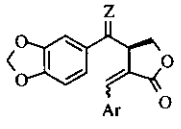
Figure 17. Indolo heterocyclolignans.

C-2. Heteroaromatic systems replacing the 1',6'-ring

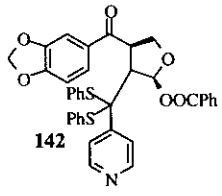
By the procedure employed by us for the synthesis of C-1 heterolignans, we prepared the diaryl derivatives (**132-137**) (Figure 18),[30] as heteroanalogues of dibenzylbutanolide lignans. Dehydration to benzyl heteroarylidenebutanolides yields **138-141**,[69, 70] which have structures related to the natural lignan nemerosin. Different uses of the conjugate-addition alkylation methodology for the assembly of the lignan skeleton produced the pyridyl derivative (**142**)[71] and the furyl derivative (**143**).[72] The latest can be also considered a C-1 heterolignan, but it is recompiled in this group due to the similarities with de aforecited **142**.



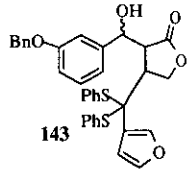
132 Z = H_2; Ar = 2-furyl
133 Z = H_2; Ar = 2-thienyl
134 Z = H_2; Ar = 4-pyridyl
135 Z = O; Ar = 2-furyl
136 Z = O; Ar = 2-thienyl
137 Z = H, OH; Ar = 2-furyl



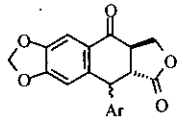
138 Z = H_2; Ar = 2-furyl
139 Z = H_2; Ar = 2-pyridyl
140 Z = O; Ar = 2-furyl
141 Z = O; Ar = 3-thienyl



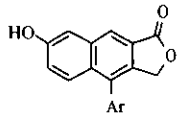
142



143



144 Ar = 2-furyl
145 Ar = 2-thienyl

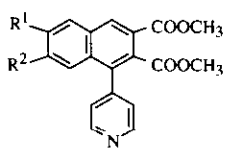


146 Ar = 2-furyl
147 Ar = 3-thienyl
148 Ar = 3-furyl

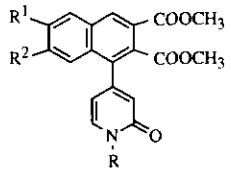
Figure 18. Diarylbutirolactone heterolignans and related cyclolignans.

Cyclization of compounds type (**132-137**) yields 1',6'-heterocyclolignanolides (**144-145**).[70] Other furyl and thienyl lignanolide analogues of C-2 type are the naphthalenic compounds (**146-148**) (Figure 18).[72]

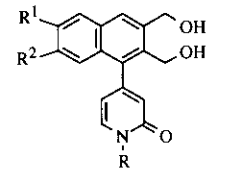
Pyridyl-naphthalenic derivatives (**149-165**) (Figure 19) were obtained in a structure-antirheumatic activity relationship study.[73]



149 $R^1 = R^2 = OCH_3$
150 $R^1 = OCH_3$; $R^2 = OC_2H_5$
151 $R^1 = R^2 = OC_2H_5$
152 $R^1 = OC_2H_5$; $R^2 = OCH_3$



153 R = H; $R^1 = R^2 = OCH_3$
154 R = N-nC_4H_9; $R^1 = R^2 = OCH_3$
155 R = N-$(CH_2)_2OCH_3$; $R^1 = R^2 = OCH_3$
156 R = N-nC_4H_9; $R^1 = OCH_3$; $R^2 = OC_2H_5$
157 R = N-nC_4H_9; $R^1 = R^2 = OC_2H_5$
158 R = N-$(CH_2)_2OCH_3$; $R^1 = R^2 = OC_2H_5$
159 R = N-$(CH_2)_2OCH_3$; $R^1 = OC_2H_5$; $R^2 = OCH_3$

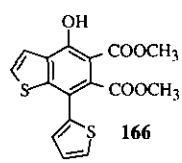


160 R = N-nC_4H_9; $R^1 = R^2 = OCH_3$
161 R = N-$(CH_2)_2OCH_3$; $R^1 = R^2 = OCH_3$
162 R = N-nC_4H_9; $R^1 = OCH_3$; $R^2 = OC_2H_5$
163 R = N-nC_4H_9; $R^1 = R^2 = OC_2H_5$
164 R = N-$(CH_2)_2OCH_3$; $R^1 = R^2 = OC_2H_5$
165 R = N-$(CH_2)_2OCH_3$; $R^1 = OC_2H_5$; $R^2 = OCH_3$

Figure 19. Naphthalenic heterolignans.

D. Heterolignans with two heteroaromatic systems

Only one example of this highly modified analogues has been found in the literature. It is the fully aromatized dithienyl derivative (**166**) (Figure 20),[63] related to the natural justicidins .



166

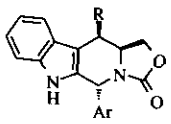
Figure 20. Justicidin analogue **166**.

MIXED HETEROLIGNANS

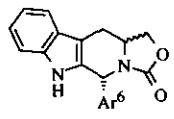
E-1. Heterolignans with heteroatoms at 7-9;7'-9' and a heteroaromatic system by replacing the 1-6 ring.

The most successful heterolignan, AZATOXIN (**167**) (Figure 21),[32, 35, 74-76] belongs to type E-1 heterolignans, carrying an heteroatom at 7-9; 7'-9' and an heterocyclic system instead of the 1-6 benzene ring. It was rationally designed by molecular modeling on preexisting topoisomerase II inhibitors, resulting in this molecule with interesting antitopoisomerase II and antitubulin activities.

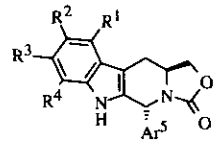
In consequence many studies have been carried out by replacement of the pendant phenyl group and C7 substituents, in order to improve the pharmacological properties of this fully synthetic type of compounds. Derivatives (**168-170**) differently substituted at the phenyl group[34, 76] and other with oxygen, nitrogen and aniline substituents at C7 (**171-182**),[75] have been obtained. Other changes have been directed at the effect of the stereochemistry, in compounds (**183** and **184**),[76] and the orientation of the heterocyclic system, that has been achieved in derivative (**185**) (Figure 21).[32]



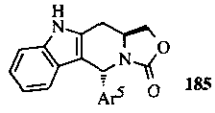
167 R = H; Ar^6
168 R = H; Ar^5 AZATOXIN
169 R = H; Ar^{15}
170 R = H; Ar^{16}
171 R = OH; Ar^5
172 R = OCH_3; Ar^5
173 R = $O(CH_2)_2OH$; Ar^5
174 R = $NH(CH_2)_2N(CH_3)_2$; Ar^5
175 R = *p*-$NH(C_6H_4)F$; Ar^5
176 R = *p*-$NH(C_6H_4)NO_2$; Ar^5
177 R = *p*-$NH(C_6H_4)CN$; Ar^5
178 R = NH-Ar^1; Ar^5
179 R = NH-Ar^{16}; Ar^5
180 R = NH-Ar^{15}; Ar^5
181 R = NH-Ar^5; Ar^5
182 R = NH-Ar^6; Ar^5



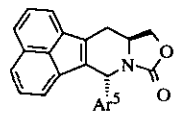
183 8β
184 8α



186 R^1,R^2 = CH=CH-CH=CH; R^3 = R^4 = H
187 R^2,R^3 = CH=CH-CH=CH; R^1 = R^4 = H
188 R^3,R^4 = CH=CH-CH=CH; R^1 = R^2 = H



185



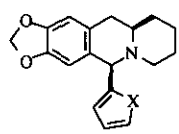
189

Figure 21. Azatoxin and related heterolignans.

To extend the aromatic system of azatoxin the benzoindole derivatives (**186-188**) have been also synthesized.[77] A related molecule (**189**), which has no heteroaromatic system but is related to azatoxins, was also described in these studies (Figure 21).[32]

E-2. Heterolignans with heteroatoms at 7-9;7'-9' and a heteroaromatic system by replacing the 1'-6' ring

Only two representatives of this group have been found in the literature.[50] They are the furyl and thienyl analogues (**190**) and (**191**), which also contain an extra carbon in the six membered ring replacing the lactone ring of lignanolides (Figure 22).



190 X = O
191 X = S

Figure 22. E-2 type heterolignans.

LIGNAN HETERO DERIVATIVES

F. Heterolignans incorporating one of the benzenic rings into a more extended heterocyclic system

As a logic modification in the search for lignan derivatives, that can enhance the activity or the pharmacokinetics of natural lignans, the extension of the benzenic rings by building heteroaromatic systems has been carried out. These are recent modifications, because the main work in the structural variation of lignans has been directed at the modification of the stereochemistry, substituents in the propane moieties or in the benzene rings.

Examples of the modification of the 1-6 benzene ring are the phenazine derivatives (**192-194**)[78] and the phthalazine derivative (**195**).[79] The other possibility is the extension of the 1'-6' benzene ring, carried out in acetoxypodophyllotoxin derivatives (**196-199**) (Figure 23).[80]

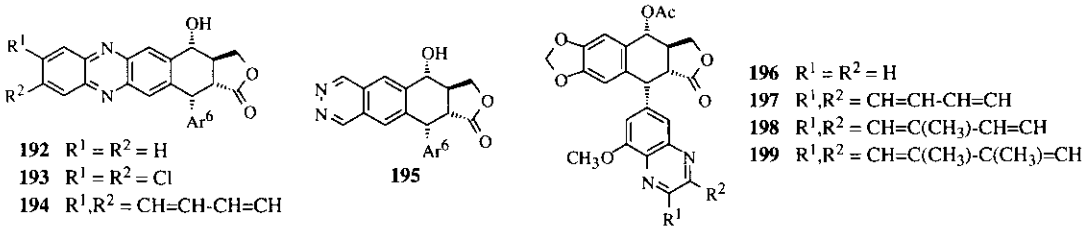


Figure 23. "Extended" heterolignans.

SYNTHESIS

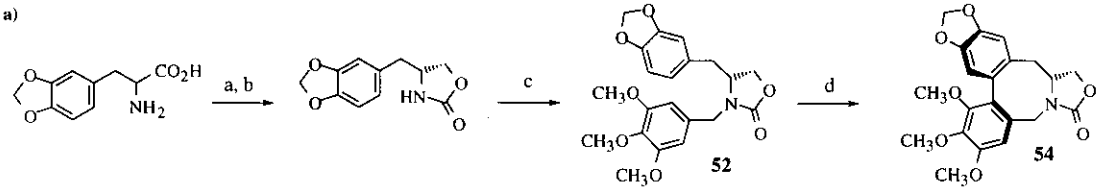
The synthesis of heterolignans has been carried out by different approaches, as it can be expected from the high number of structural variations that can be suggested for these compounds. In general, the methodologies are similar to those employed for the synthesis of lignans,[2, 10-12] using starting materials or reagents that contain the heteroatoms in the required position. In other cases, strategies non similar to those employed for lignan synthesis and mainly based in the synthesis and reactivity of heterocyclic systems, have been used, as it is the case for 7,8'-diazaanalogues (type B) and for heterocyclic derivatives of lignans (type F).

In this review we have grouped the different synthetic strategies in five general approaches: 1) From 2-phenethylamines, 2) Conjugate addition, 3) From diarylmethanes, phenylthioethers or anilines, 4) Diels-Alder, and 5) Miscellaneous, depending on the starting materials or the related methodologies used in each case. This classification is of interest, because it systematizes the main body of the synthetic effort carried out by different authors and suggests the methodologies that can be employed for the preparation of new designed members of this group of compounds.

1) From 2-phenethylamines

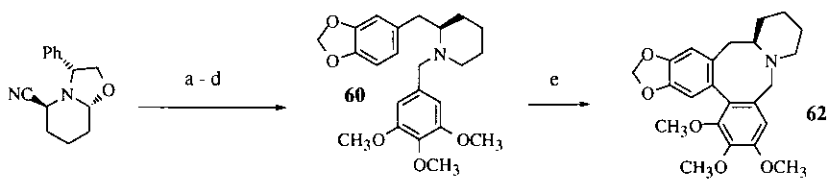
These starting materials have been used for the assembly of the skeleton of 8'-azalignans. The reaction of the amine group with an electrophilic reagent is conducted for the introduction of the pendant benzene ring.

a)



Reagents and conditions; (a) LAH, THF, reflux, 70%; (b) $OC(OC_2H_5)_2$, $NaOC_2H_5$ -C_2H_5OH, reflux, 89%; c) NaH, 3,4,5-trimethoxybenzyl bromide, THF, reflux, 96%; (d) VOF_3, CH_2Cl_2, TFA, -42°C, 96%.

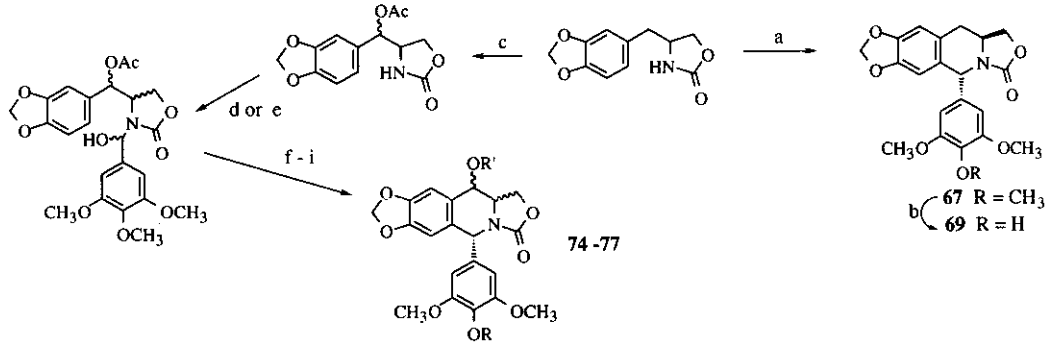
b)



Reagents and conditions: (a) LDA, THF, -78°C, piperonyl bromide; (b) $NaBH_4$, EtOH, reflux; c) H_2, 10% Pd(C), HCl, C_2H_5OH, 67%; d) 3,4,5-trimethoxybenzyl chloride, K_2CO_3, acetone, reflux, 65%; (e) VOF_3, CH_2Cl_2, TFA-TFAA, -78°C, 65%.

Scheme 1

Usually, the basic 2-phenethylamine moiety is included in a bigger structure containing the C9 and the oxygen atoms (Scheme 1), as it is the case of 3-phenyl-2-aminopropanol derivatives employed in the synthesis of 8'-azalignans (**67-77**). Oxazolidinones, carrying the C1-C9 subunit, the N8' and the C9' as a carboxylate, directly give the 8'-azalignan skeleton, for example in the synthesis of 8'-azadeoxypodophyllotoxin (**67**) (Scheme 2).



Reagents and conditions: (a) 3,4,5-trimethoxybenzaldehyde, H_2SO_4, CH_2Cl_2, 93%; (b) HBr, DCE, 0°C, 80%; (c) DDQ-AcOH, 60°, 70%; (d) CF_3SO_3H-AcOH, CH_2Cl_2, 4°, 34%; (e) CF_3SO_3H-CH_3OH, CH_2Cl_2, 94%; (f) K_2CO_3-CH_3OH, 95%; (g) 10% aq. HCl-dioxane, 82%; (h) HBr-DCE, $BaCO_3$, THF-H_2O, 60%; (i) $(C_2H_5)_3SiH$-CF_3SO_3H, 93%.

Scheme 2

Depending on the electrophilic reagent, the synthesis included in this general methodology have been grouped into three types.

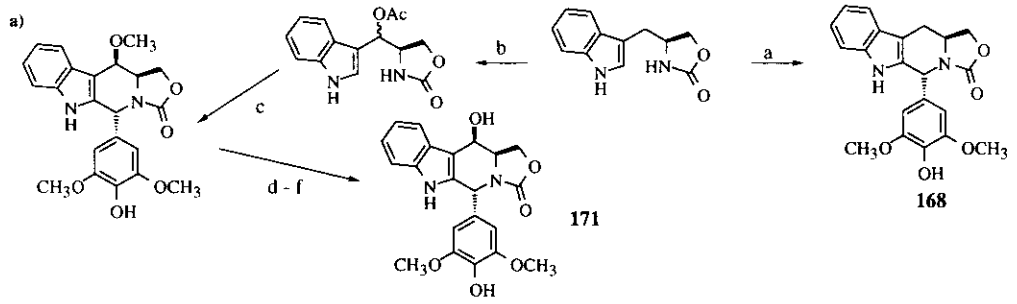
1a. With benzylic bromides

This approach is represented in Scheme 1a by the synthesis of 8'-azaisostegane (**54**), by treatment of 4-piperonyl-2-oxazolidinone with 3,4,5-trimethoxybenzyl bromide to yield 8'-azayatein (**52**), followed by its oxidative coupling with vanadium(V) oxytrifluoride to afford the most stable atropoisomer (**54**).[47, 48] By the same procedure the piperidine analogue (**62**) was prepared from 3,4,5-trimethoxybenzylamine (**60**) obtained from enantiomerically enriched 2-piperonylpiperidine (Scheme 1b).[52]

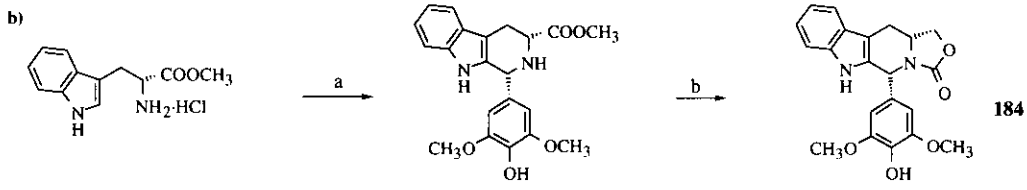
1b. With aromatic aldehydes

The treatment of 4-piperonyl-2-oxazolidine with 3,4,5-trimethoxybenzaldehyde in acidic medium (Scheme 2) directly gives the cyclized 8'-azadeoxypodophyllotoxin (**67**). By previous benzylic oxidation this process produces the 8'-azapodophyllotoxins (**74-77**), through the isolable uncyclized hydroxy derivative.[39, 40, 81]

The synthesis of azatoxins (**167-185**) (Scheme 3a) has been carried out by this methodology, starting from the required indolic precursors. The use of the 2-oxazolidine starting material yields azatoxin (**168**) and, by previous benzylic oxidation, the 7β-hydroxy derivative (**171**).[75] In order to obtain the *cis*-(8α,7'α)-stereoisomer, the reaction with syringaldehyde was achieved with methyltryptophan, thus producing the intermediate with *cis* disposition between the ester group and the aromatic Ar^6 residue, that was converted to the isoazatoxin (**184**) (Scheme 3b).[76]



Reagents and conditions: (a) syringaldehyde dimethyl acetal , TFA, THF, 91%; (b) DDQ, HOAc, THF, -78°C, 98%; (c) syringaldehyde dimethyl acetal, *p*TsOH, DCM-CH_3OH, 47%; (d) $ClCOOCH_3$, TEA, DCM, 94%; (e) *p*TsOH, dioxane-H_2O 9:1, 66%; (f) $NaOCH_3$, CH_3OH, 73%.



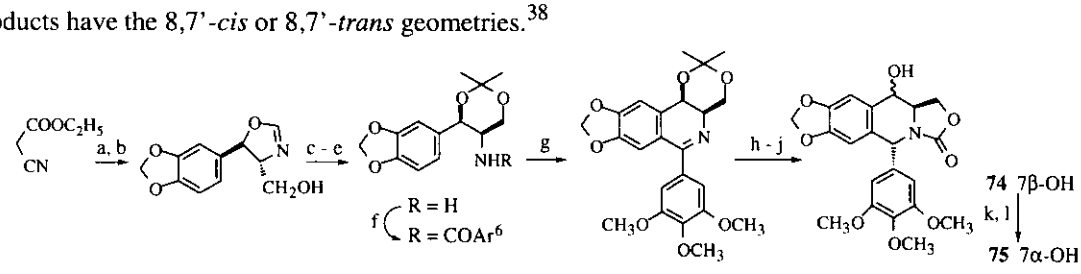
Reagents and conditions: (a) NH_4OH, syringaldehyde, TFA, CH_2Cl_2; (b) $NaBH_4$, dioxane-H_2O, carbonyldiimidazole.

Scheme 3

The benzo derivatives (**186-188**) of azatoxin were synthesized by the same procedure, by reaction of syringaldehyde dimethyl acetal with the corresponding 4-benzoindolylmethyl-2-oxazolidines, obtained from the benzo-[*e*] or [*f*] or [*g*]-indoles as starting materials.[77]

1c. With aromatic acyl derivatives

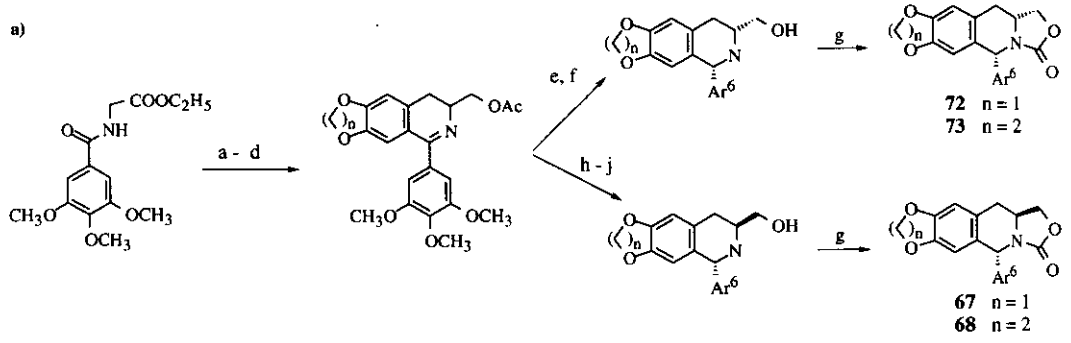
The cyclization to 8'-azapodophyllotoxins has also been carried out from the amides of 2-arylethanamines, which result in dihydroisoquinoline intermediates that must be reduced to the tetrahydroisoquinoline system of the final products. These syntheses are resumed in Scheme 4 for the preparation of 8'-azapodophyllotoxin (**74**) and 8'-azaepipodophyllotoxin (**75**).[37] Based on the same cyclization process, but using the alkylation of ethyl *N*-3,4,5-trimethoxybenzoylglycinate (Scheme 5a) for the assembly of the acyclic amide intermediate, the syntheses of 8'-azadeoxypodophyllotoxin (**67**), 8'-azadeoxyisopodophyllotoxin (**72**) and related compounds (**68**) and (**73**) were achieved. Depending on the reaction conditions and the use of intermediate dihydroisoquinoline produced by this methodology, the final products have the 8,7'-*cis* or 8,7'-*trans* geometries.[38]



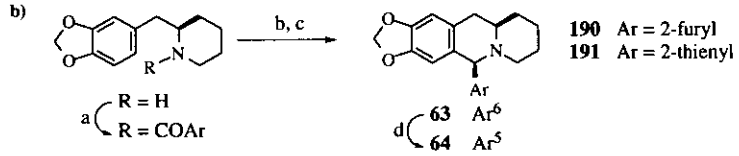
Reagents and conditions: (a) piperonal , NaCN, C_2H_5OH, 15°C, 89%; (b) $NaBH_4$, $^iC_3H_9OH$, 72%; (c) $(C_2H_5)_3N$, H_2O-C_2H_5OH 1:1, reflux; (d) $(CH_3)_2C(OCH_3)_2$, $(CH_3)_2CO$, HBr 1M in CH_3OH; (e) 85% $N_2H_4{\cdot}H_2O$, reflux, 63% (c-e); (f) 3,4,5-trimethoxybenzoyl chloride, pyridine, DMAP, 0°C, 96%; (g) PPSE, pyridine, reflux, 73%; (h) $Al(CH_3)_3$, THF, then LAH, 67%; (i) HCl, dioxane, H_2O; (j) $COCl_2$, CH_2Cl_2, $(C_2H_5)_3N$, 0°C, 48%; (k) PCC, CH_2Cl_2. (l) $Zn(BH_4)_2$, $(C_2H_5)_2O$, 65% (k-l)

Scheme 4

Quirion *et al.*[51, 52] also used this approach for the asymmetric synthesis of piperidine analogues (**63**) and (**64**) from amide (**61**).(Scheme 5b), obtained form enantiomerically pure 2-piperonylpiperidine. The same procedure was used for the synthesis of type E heterolignans (**190**) and (**191**).[50]



Reagents and conditions: (a) LDA, TMEDA, THF, -78°C, then 3,4,5-trimethoxybenzyl bromide, THF, -78°C, 70%; (b) $LiBH_4$, DME, reflux; (c) Ac_2O, pyridine, 94% in two steps; (d) PCl_5, DCM, then $AlCl_3$, 92%; (e) AlH_3, THF, -30°C, 97%; (f) HCl, acetone, H_2 (1 atm), 10% Pt/C, C_2H_5OH-CH_3OH 1:2, then $NaHCO_3$, 92%; (g) $COCl_2$, $N(C_2H_5)_3$, DCM, 0°C, 89%; (h) K_2CO_3, CH_3OH, 89%; (i) AlH_3·THF, reflux; (j) HCl 2N, THF, 31% in two steps.

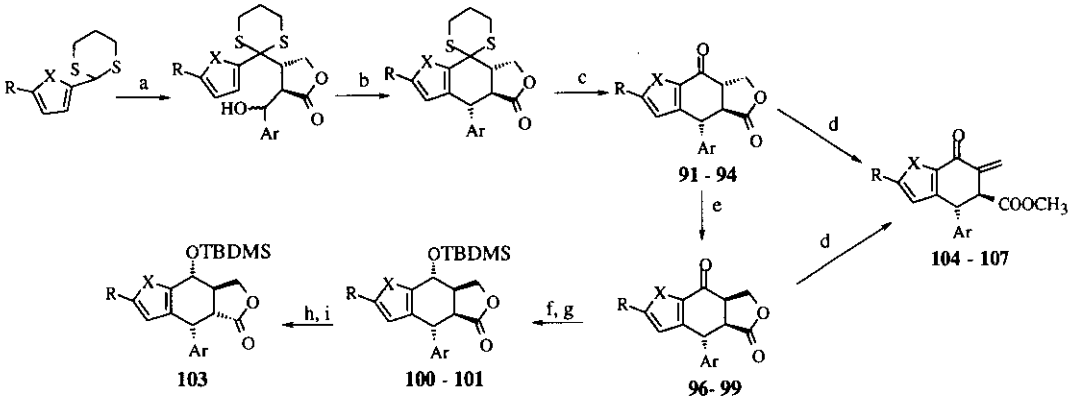


Reagents and conditions: (a) 3,4,5-trimethoxybenzoyl chloride, CH_2Cl_2, H_2O, NaOH, 98%; (e) $POCl_3$, toluene, reflux; (f) $NaBH_4$, CH_3OH, 0°C, 67% in two steps; (g) HBr, CH_2Cl_2, 47%.

Scheme 5

2. Conjugate addition

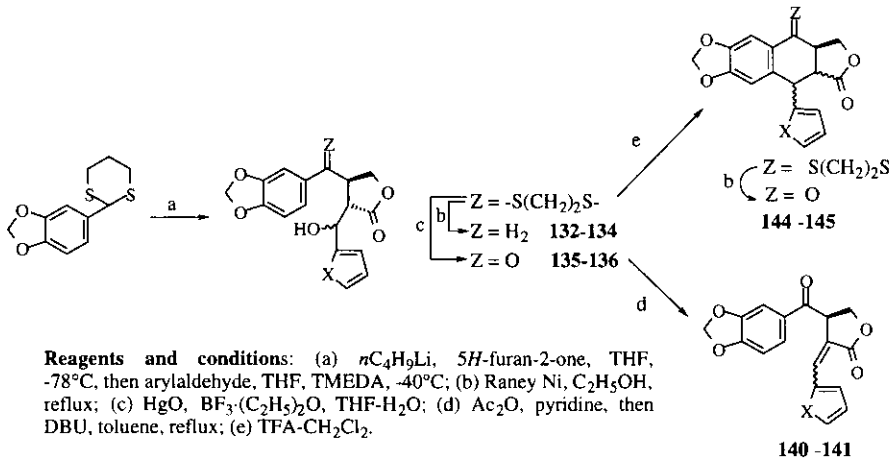
The sequence conjugate addition-alkylation of 5*H*-2-furanone is one of the most powerful approaches for the assembly of the lignan skeleton, thus rendering 2,3-dibenzylbutanolides that can be further transformed into cyclolignans of the arylnaphthalene or the dibenzocyclooctene types.



Reagents and conditions: (a) i; nC_4H_9Li, -78°C, THF. ii; 5*H*-furan-2-one, -78°C. iii; arylaldehyde, -40°C, THF, TMEDA; (b) TFA, benzene, reflux or $SnCl_4$, CH_2Cl_2; (c) HgO, BF_3·$(C_2H_5)_2O$, THF-H_2O; (d) i; KOH, CH_3OH; ii; CH_2N_2, ether; (e) AcOH, C_2H_5OH, reflux or *p*TsOH, $CHCl_3$, reflux; (f) $LiAlH(^tC_4H_9O)_3$, THF; (g) $(^iC_3H_7)_2(C_2H_5)N$, TBDMSTf, CH_2Cl_2; (h) i: LDA, THF, -78°C. ii: AcOH-THF, -78°C; (i) TBAF, CH_3CN

Scheme 6

By replacing one of the benzene rings by heterocycles, heterolignans of families C-1 and C-2 have been synthesized. This has been the methodology employed at our laboratory for the synthesis of compounds (**91-107**) (Scheme 6),[31, 62] belonging to family C-1, and compounds (**132-141**, **144** and **145**) (Scheme 7)[69, 70] of the family C-2.

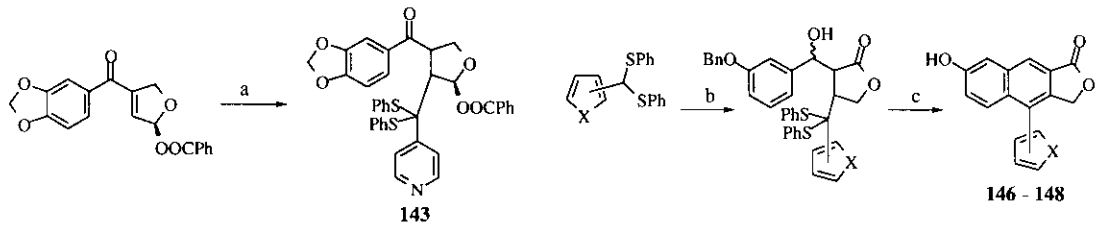


Reagents and conditions: (a) nC$_4$H$_9$Li, 5*H*-furan-2-one, THF, -78°C, then arylaldehyde, THF, TMEDA, -40°C; (b) Raney Ni, C_2H_5OH, reflux; (c) HgO, $BF_3{\cdot}(C_2H_5)_2O$, THF-H_2O; (d) Ac_2O, pyridine, then DBU, toluene, reflux; (e) TFA-CH_2Cl_2.

Scheme 7

Surprisingly, the stereochemistry of the major cyclization product in the second case (Scheme 7) is of the podophyllotoxin type (8,8-*trans*-7',8'-*cis*), instead of the observed for the major product of cyclization in lignan or for family C-2 (Scheme 6), which are of the isopodophyllotoxin type (8,8'-*trans*-7',8'-*trans*). Stereochemically controlled transformations allowed us to synthesize thienopodophyllotoxin (**103**) (Scheme 6) by the same sequence used for the synthesis of podophyllotoxin.[82] From intermediate furo- and thienoisopodophyllotoxones (**91-94**), it was possible to prepare the heteroanalogues (**104-107**) of thuriferic acid[31, 83, 84] or picropodophyllotoxones (**96-99**).[31]

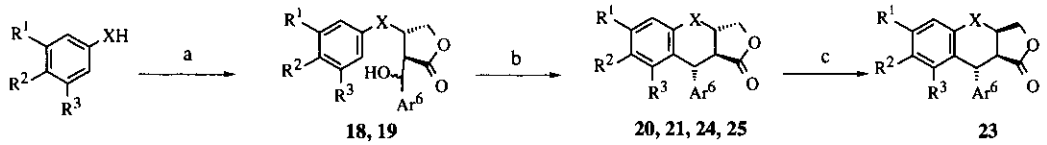
The addition of lithiated heterocyclic dithioacetals to conjugated systems has also been described for the preparation of compounds (**142**, **143**)[71] and (**144-148**)[72] (Scheme 8) belonging to family C-2.



Reagents and conditions: (a) 4-[bis(phenylthio)methyl]pyridine, nC$_4$H$_9$Li, THF, -78°C, 31%; (b) nC$_4$H$_9$Li, THF, -78°C, 5*H*-furan-2-one, 3-benzyloxybenzaldehyde; (c) TFA, $PhSCH_3$, 25%.

Scheme 8

Instead of the reaction with carbon nucleophiles, the use of oxygen and sulfur nucleophiles in the conjugate addition to 5*H*-2-furanone bring access to 7-oxa- and 7-thialignanolides (**18-19**) (Scheme 9) of the family A, which can be cyclized to 7-oxa- and 7-thiacyclolignanolides (**20-25**).[44]



18, 19 **20, 21, 24, 25** **23**

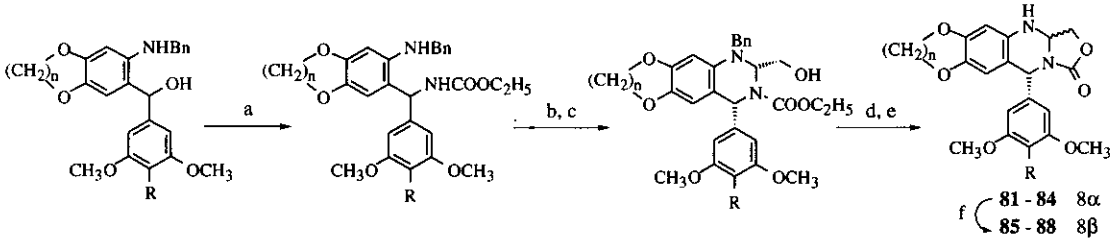
Reagents and conditions: (a) nC_4H_9Li, THF, -78°C, then 5*H*-furan-2-one and 3,4,5-trimethoxybenzaldehyde, THF, -78°C; (b) *p*TsOH, benzene, reflux; (c) DBU, THF.

Scheme 9

By a very different use of the conjugate addition it is also possible to synthesize 7'-azaheterolignans, of the family A. These lignan analogues (**48-51**) were prepared by conjugate addition of vinylmagnesium bromide to *N*-aryl-4-quinolones, thus yielding compound (**47**) which was transformed into the final products.[46]

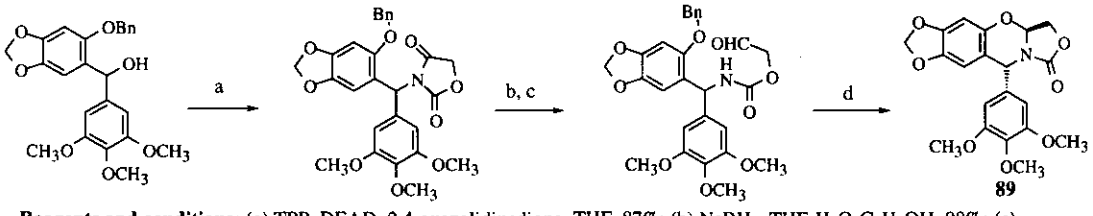
3. From diarylmethanes, aryl thioethers and anilines

The methods included in this group are chemically heterogeneous, but all of them share two common characteristics: 7-heterolignans A (or 7,8'-diheterolignans B) are obtained and the X7-C8 bond is formed between the heteroatom at position 7 and a carbonyl carbon or equivalent as C8.



Reagents and conditions: (a) ethyl carbamate, PPE, THF; (b) HCOCOOH, THF ; (c) $NaBH_4$, $BF_3{\cdot}(C_2H_5)_2O$, THF; (d) CH_3ONa, CH_3OH; (e) H_2, 10% Pd(C), DCM-CH_3OH-AcOH; (f) TFA, $CHCl_3$.

Scheme 10

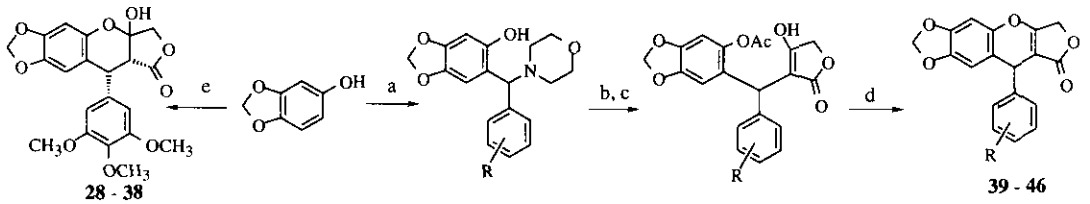


Reagents and conditions: (a) TPP, DEAD, 2,4-oxazolidinedione, THF, 87%; (b) $NaBH_4$, THF-H_2O-C_2H_5OH, 98%; (c) Dess-Martin, DCM, 81%; (d) H_2, 10% Pd(C), C_2H_5OH, then AcOH, 98%.

Scheme 11

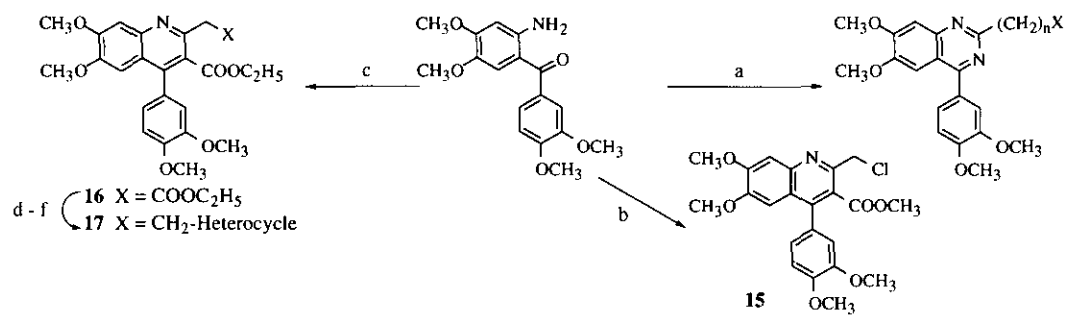
Diarylmethanes with and *ortho* nitrogen or oxygen atom are the starting or intermediate materials for the synthesis of 7,8'-diazapodophyllotoxins[58, 59] (Scheme 10), 7-oxa-8'-azapodophyllotoxins[60] (Scheme 11), 7-oxalignans[45] (Scheme 12) and quinazoline (7,8'-diaza) analogues[42] (Scheme 13). The synthesis of compounds (**81-88**) is achieved according to Scheme 10 and the synthesis of **89** by the procedure of Scheme 11, in both cases the six membered 1,3-diheterocyclic ring is formed by inter- or intramolecular reaction with suitable aldehyde. The use of tetronic acid as precursor of the lactone moiety (C8-C9-O-C9'-C8'), by reaction with *ortho* oxygenated diarylmethanes, is the straightforward route to 7-oxalignans (**28-**

46) depicted in Scheme 12. From readily prepared *ortho*-aminobenzophenones the synthesis of fully aromatic 7,8-diaza- and 7-aza-heterolignans, is easily carried out in few steps, as shown in Scheme 13.



Reagents and conditions: (a) Arylaldehydes, morpholine, H_2SO_4, CH_2Cl_2; (b) tetronic acid, AcOH-H_2O; (c) $(CH_3)_2SO_4$, K_2CO_3, acetone, then Ac_2O, pyridine; (d) NaOH 10%, CH_3OH-H_2O; (e) 3,4,5-trimethoxybenzaldehyde, tetronic acid, CH_3OH, reflux

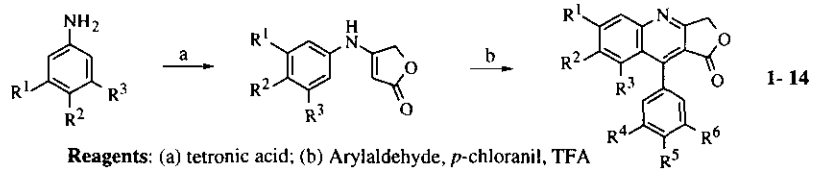
Scheme 12



Reagents and conditions: (a) $ClCH_2CN$, $AlCl_3$; (b) $ClCH_2COCH_2COOR$ (R = CH_3; C_2H_5), concetrated H_2SO_4, AcOH; (c) $CO(CH_2COOC_2H_5)_2$, concd H_2SO_4, AcOH; (d) $LiAlH_4$, ether; (e) PBr_3, ether; (f) Wittig reaction followed by hydrogenation.

Scheme 13

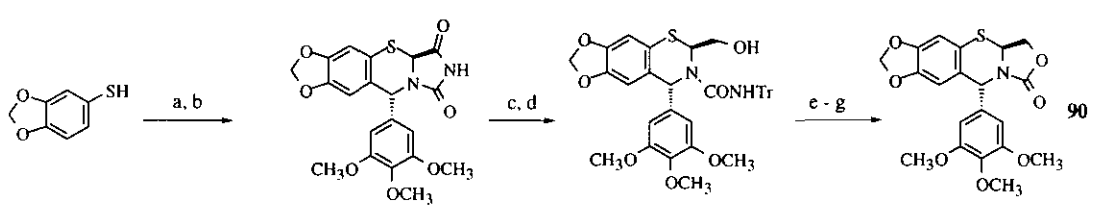
Although they are different strategies, those using aniline derivatives (Scheme 14) and aryl thioethers (Scheme 15) share related starting materials and the use of benzaldehydes for the assembly of the heterolignan skeleton, in a reaction that could also be included into methodologies type 1b.[43]



Reagents: (a) tetronic acid; (b) Arylaldehyde, *p*-chloranil, TFA

Scheme 14

In Scheme 14 the synthesis of quinolino analogues (**1-14**) of justicidins is shown and in Scheme 15 it is presented the synthesis of 7-thia-8'-azapodophyllotoxin (**90**).[61]



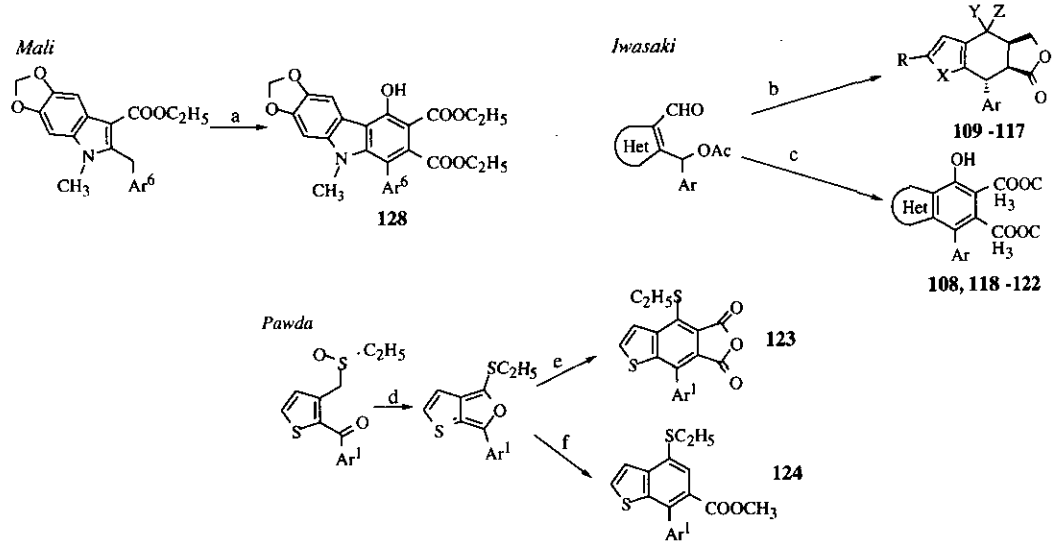
Reagents and conditions: (a) $CO(NH_2)_2$, HCOCOOH·H_2O, dioxane, HCl, 86%; (b) 3,4,5-trimethoxybenzaldehyde, CF_3SO_3H, CF_3CH_2OH, 88%; (c) TrCl, K_2CO_3, acetone, CH_2Cl_2; (d) $NaBH_4$, dioxane-H_2O, 97%; (e) diethyl azadicarboxylate, PPh_3, benzene, 85%; (f) TFA, C_2H_5OH; (g) $NaNO_2$, AcOH, 90%.

Scheme 15

4. Diels-Alder reaction

The Diels-Alder reaction, either in its intermolecular or in its intramolecular (IMDA) versions has been applied for the synthesis of heterolignans, as it has been used for the syntheses of lignans.

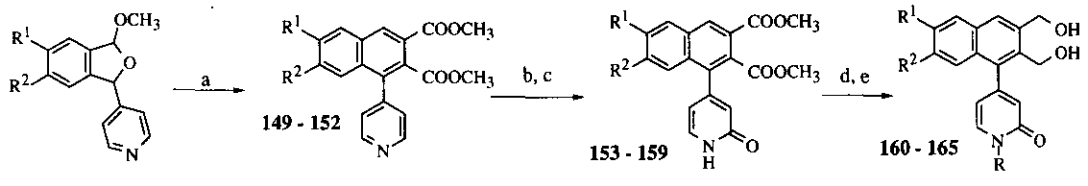
In some cases found in the literature the heterocycle contributes to the diene moiety with two carbon atoms or in others the heterocycle is a substituent of the diene, thus, they are homo Diels-Alder reactions with the heterocycle as substituent of -or fused to- the diene. No examples of heterolignan synthesis by means of hetero Diels-Alder reaction for the introduction of heteroatoms in the 1-6-7-8-8'-7' moiety have been found. Mali,[67] Iwasaky[63, 65] and Pawda[66] have employed heterocyclic equivalents of *ortho*-quinodimethanes of different structure for the reaction with dimethyl acetylenedicarboxylate (DMAD) or other dienophiles as depicted in Scheme 16, to synthesize type C-1 heterolignans (**108**, **118-124** and **128**).



Reagents and conditions: (a) LDA, THF, -78°C, then dimethyl acetylenedicarboxylate, 52%; (b) maleic anhydride, TFA, benzene, reflux; (c) DMAD, TFA, benzene, reflux; (d) Ac_2O, *p*TsOH; (e) maleic anhydride, *p*TsOH; (e) methyl acrylate.

Scheme 16

The use of 1-pyridylisobenzofurane as *ortho*-quinodimethane equivalent yielded pyridylnaphthalenelignans (**149-152**) (Scheme 17), which were transformed into differently substituted derivatives (**153-165**), all of them of the heterolignans family C-2.[73]

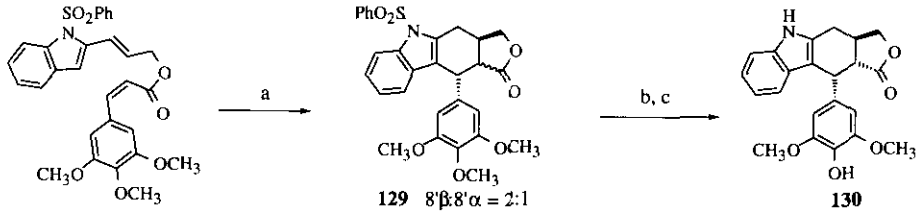


Reagents and conditions: *(a) dimethyl maleate, AcOH-toluene, reflux; (b) mCPBA, DCM; (c)* Ac_2O*, reflux, then* NH_4OH, CH_3OH; (d) NaH, alkyl iodide, DMF; (e) $NaBH_4$, THF, CH_3OH, reflux.

Scheme 17

The IMDA reaction has been used for the efficient synthesis of C-1 heterolignans carrying an indole moiety. As shown in Scheme 18, indolodeoxypicropodophyllin derivative (**129**) (8'β) and compound (**129**) (8'α) (a synthetic intermediate to demethyl indolodeoxypodophyllotoxin), were obtained as a mixture of

stereoisomers. The later one was demethylated and detosylated to **130**.[68]

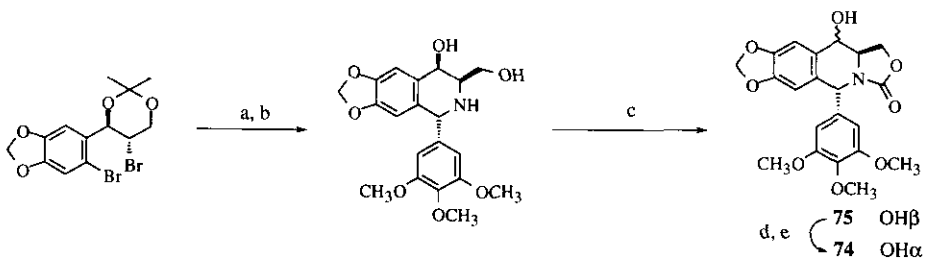


Reagents and conditions: (a) toluene, reflux, 71%; (b) TMSI, DCM, 79%; (c) Li-naphthalene, THF, -78°C.

Scheme 18

5. Miscellaneous

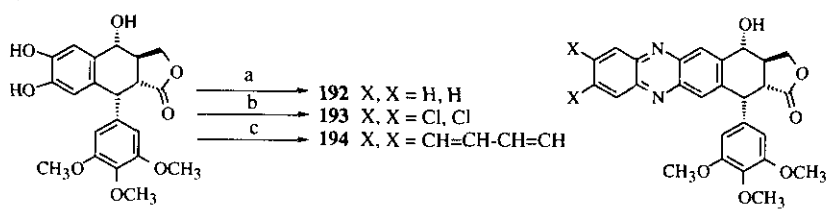
Here are included those methods that can not be grouped in one of the four previously described. The first one (Scheme 19) has been used for the synthesis of racemic 8'-azapodophyllotoxin (**74**) by isomerization of the initially prepared 8'-azaepipodophyllotoxin (**75**). The key step is the controlled lithiation of an alkylphenyl dibromide followed by treatment with an electron donor-acceptor benzylidene sulfonamide, which directly renders the tetrahydroisoquinoline intermediate (Scheme 19). Construction of the 2-oxazolidine moiety completes the synthesis of 8'-azapodophyllotoxins.[36]



Reagents and conditions: (a) nC_4H_9Li, THF, -75°C, then 3,4,5-trimethoxybenzylidenephenylsulfonamide, HMPA, 0°C, 71%; (b) Na/naphthalene, DME, THF, -75°C, then 2N HCl, 61%; (c) $COCl_2$, pyridine, CH_2Cl_2, 0°C, 75%; (d) PCC, CH_2Cl_2; (e) $(^tC_4H_9O)_3LiAlH$, THF, 65%.

Scheme 19

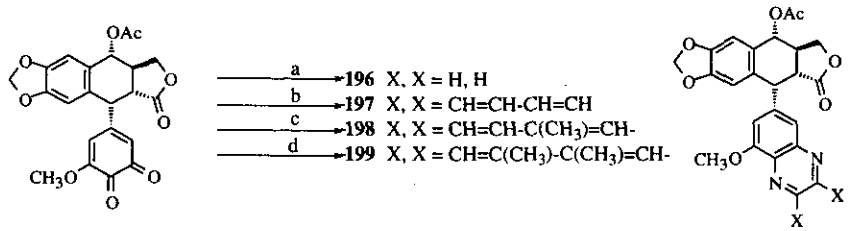
Other syntheses included in this group are those of the lignan heteroderivatives of family F. In order to prepare the heteroderivatives by extension of the 1-6-ring, with the aims of obtaining intercalating analogues, Lee *et al.*[78] have used the oxidation of demethylenepodophyllotoxin with silver carbonate in the presence of different diamino derivatives (Scheme 20). By this procedure the phenazine derivatives (**192-194**) of podophyllotoxin were obtained.



Reagents and conditions: (a) 1,2-phenylenediamine, Ag_2CO_3, celite, C_2H_5OH, 16%; (b) 4,5-dichloro-1,2-phenylenediamine, Ag_2CO_3, celite, C_2H_5OH, 45%; (c) 2,3-naphthalenediamine, Ag_2CO_3, celite, C_2H_5OH, 31%.

Scheme 20

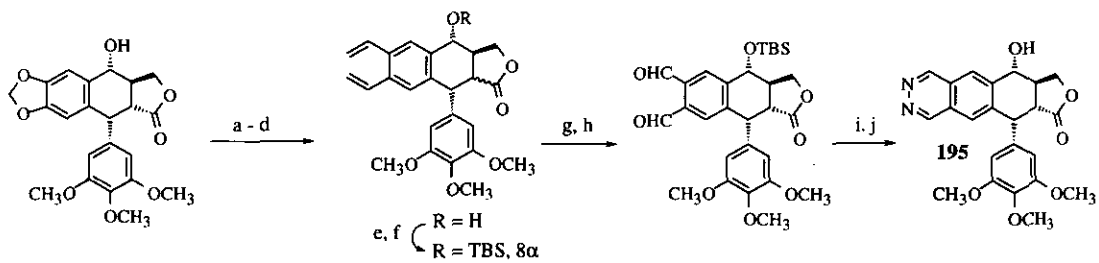
By a related procedure, the *ortho*-quinone obtained by oxidation of the 1'-6'-ring was treated with diamines to produce the quinoxaline derivatives (**196-199**) of acetylpodophyllotoxin[80] (Scheme 21).



Reagents and conditions: (a) ethylenediamine, C_2H_5OH, AcOH; (b) 1,2-diaminobenzene, C_2H_5OH, AcOH; (c) 4-methyl-1,2-diaminobenzene, C_2H_5OH, AcOH; (d) 4,5-dimethyl-1,2-diaminobenzene, C_2H_5OH, AcOH.

Scheme 21

For the synthesis of phthalazine derivative (**195**) (Scheme 22) a more elaborated approach is required, because two additional carbon atoms must be introduced at C3 and C4. A double Heck reaction of the 3,4-ditriflate with vinylstannane followed by ozonolysis yielded the phthalazine system by treatment with hydrazine.[79]



Reagents and conditions: (a) BCl_3, DCM, -78°C; b) $BaCO_3$, acetone, H_2O, reflux, 58%; (c) Tf_2O, 2,6-lutidine, DMAP, DCM, 0°C, 68%; (d) $Pd(Ph_3)_4CH{=}CHSn(C_4H_9)_3$, LiCl, dioxane, 95°C, 65%; (e) TBSOTf, 2,6-lutidine, DCM, 0°C; (f) LDA, THF, -78°C, then AcOH, 95%; (g) OsO_4, NMO, acetone, H_2O, 0°C, 90%; (h) $Pb(OAc)_4$, DCM, benzene, 91%; (i) NH_2NH_2, C_2H_5OH, -50°C, 79%; (j) $(C_2H_5)_3N$-HF, CH_3CN, 97%.

Scheme 22

BIOLOGICAL ACTIVITIES

Mirroring their lignanic counterparts and along with their great structural diversity heterolignans display a breadth of biological activities. Compounds with antitumour, antimitotic, antiinflammatory, immunomodulating, antiarthritic, antispasmogenic, hepatoprotectant and antihyperlipidemic activities and a variety of mechanisms of action have been described. Much interest has been focused on their use as antineoplastic agents and the modes of action by which they regulate the growth of mammalian cells. Amongst the lignans,[14] the most active antitumour compounds belong to the aryltetralin and dibenzocyclooctene series. The arylnaphthalenes display interesting properties against inflammatory diseases and accordingly the main changes into hetero analogues in the search for active compounds have been done in these structural classes.

Introduction of heteroatoms on the basic lignanic skeleton greatly affects the resulting biological activities, the underlying reasons being multiple: physicochemical properties, physiological or metabolic stability, pharmacodynamical properties or receptor binding due to altered complex formation, different dipole

moment, conformational preferences... The more frequent approach is the replacement of a carbon atom by an heteroatom (i.e. azapodophyllotoxin) intending to preserve the original shape and pharmacophore while modifying an undesired property such as conformational or stereochemical lability, solubility, molecular dipole... but also some less conservative approaches such as bioisosteric replacement of aromatic moieties (i.e. thienopodophyllotoxin) or molecular hybridization of two bioactive unrelated molecules have been undertaken with uneven results. These latter approaches have led to more diverse structures (i.e. azatoxin) which have become new leaders in the search for clinically useful compounds.

Antitumour activity

Some lignans, particularly of the podophyllotoxin series, display antitumour activities and most of the hetero analogues described belong to structural classes with such an activity. The actions as microtubule polymerization inhibitors *via* interaction with tubulin at the colchicine site and as inhibitors of DNA topoisomerase II are deemed to be the mean responsibles for such antitumour activity.[2] The pharmacophore for agents that inhibit tubulin polymerization by binding at the colchicine site includes two variable aromatic domains kept in a non-planar arrangement by different linkers (Figure 24a).[85] The structural requirements for antitopoII activity have led to the proposal of a composite pharmacophore that accounts for the structural diversity among several classes of inhibitors (Figure 24b).[77, 78] The model describes four domains: (A) a planar polyaromatic array responsible for DNA association; (B) a pendant group responsible for minor groove binding with a hydrogen bond donor roughly 5.5Å bellow the plane of the first domain; (C) the acyl functionality domain which dictates the conformational relationships available to the other three aforementioned domains and (D) an optional variable substituent domain also thought to bind in the DNA minor groove, not included in the basic lignan skeleton but appended in some of their synthetic derivatives. The fact that antitubulin and antitopoII pharmacophores have both structural resemblance and share the spatial arrangements for the homologous domains allow related compounds to target either one or simultaneously both of them as is the case for the lignans and the heterolignans. Carbon replacement by heteroatoms have been carried out in every domain of the pharmacophores helping to refine and corroborate the model (Figure 24).

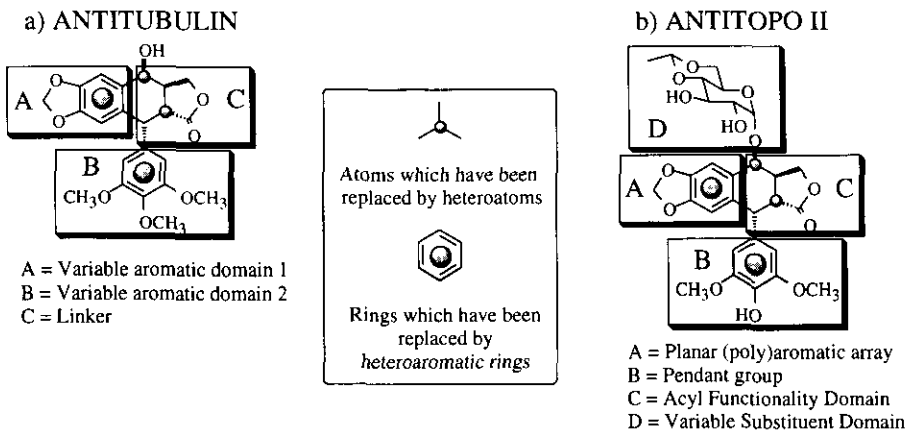


Figure 24. Proposed pharmacophores for antitubulin and antitopoII activities.

Within the podophyllotoxin series the most frequent replacements have been (Figure 24): (1) replacing C8´ by N suppressing the labile *trans* lactone while maintaining the active molecular conformation and/or (2) C7 substitution by several unsubstituted heteroatoms in the antitubulin agents (the deoxypodophyllotoxins were known to be more potent antitubulin agents than the corresponding hydroxylated series) or by substituted N in the topoisomerase II inhibitors, where a bulky substituent in such position was preferred for activity. Conversion of tetrahydronaphthalene lignans into tetrahydroisoquinolines (**63-77**,[37-40, 50-53] **81-90**[56-61]) maintains antitubulin activity. Surprisingly, azaetoposide (**78**) shows much less antitopoII activity than etoposide[86] while other series show important antitopoII activity with the same substitution (see bellow). Heteroatoms at position 7 seem not to decrease the activity, but much less data is available. Extension (**79-80**,[55] **192-195**[78, 79]) or replacement (**91-124**[31, 63-66]) of the polyaromatic ring system and changes on the pendant ring domain (**132-143**,[30, 62, 69, 70] **190-191**,[50] **196-199**[80]) has not led to substantial improvements in the biological potencies.

Molecular hybridization of etoposide with ellipticin has led to the synthesis of azatoxin (**167**), a highly potent dual antitubulin-antitopoisomerase inhibitor.[32, 33] The dual activity of azatoxin has highlighted and exploited the previously known structural relationship between the topoisomerase and tubulin pharmacophores. Azatoxin is currently under clinical trials and has became a new lead for the development of new antitumour compounds (**168-189**). Structural modifications on azatoxin have revealed a much closer SAR to podophyllotoxin than to ellipticin (Figure 25). Accordingly, introduction of a bulky substituted aniline group as the variable substituent domain (Figure 24), eliminates the antitubulin activity and enhances the antitopoII activity (**175-182**).[35, 75] The effect of the substituent on the aniline group is analogous to that observed for their lignanic counterparts, being the electron withdrawing substituents (CN, NO_2) the most favorable.[25, 87, 88] The planar polyaromatic domain seems to be very sensitive to structural modification, most of them being detrimental for the activities (**185-189**).[32, 76, 77] The pendant ring domain is also very sensitive to structural changes: the hydroxyl group at 4 is required for antitopoII activity while methylation is preferred for antitubulin drugs. Substitution patterns other than the 3,4,5-trimethoxyphenyl, including those of the antitopo drug amsacrine (mAMSA) lead to less active or inactive compounds.[32, 35, 76, 89] The stereochemical requirements are those determined for the lignanic analogues, and show similar stringency.[32]

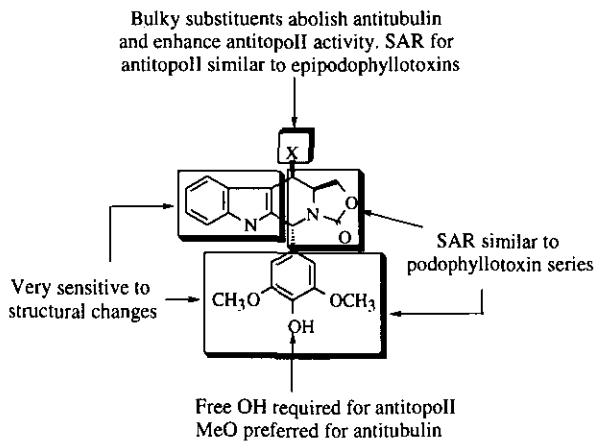


Figure 25. SAR for azatoxin derivatives.

The dibenzocyclooctene class of lignans also display antitubulin activity and the most active representatives present a boat-chair conformation locked by a trans lactone ring.[2, 14] Carbon by nitrogen substitution on the bridgehead (**53-59**) leads, in analogy to 8´-azapodophyllotoxin series, to compounds whose preferred conformations are the active ones and show no lactone epimerization.[47, 48]

Antirheumatic and antiasthmatic activity.

Taking the potent bone resorption inhibitors justicidins as the lead compounds, analogues in which the naphthalene ring has been replaced by a quinoline or a quinazoline ring were found to have potent anti-inflammatory effect in rats with adjutant arthritis. Their pharmacological profile suggests that they act as immunomodulators, differentially inhibiting cytokine production in different Th type clones. Such cytokines are deemed important in the late stages of rheumatoid arthritis and bone metabolism. Their activity, devoid of any effect on prostaglandin synthesis inhibition, points at them as an useful new type of disease-modifying antirheumatic drugs which may complement the symptomatic relief provided by nonsteroidal anti-inflammatory drugs (NSAIDs). Heteroaryl (azole) substituents on the side chain at C9 and alkoxy groups at C3, C4 and C3' and C4' at the pendant phenyl ring are required for potent antiinflammatory activity as exemplified by **17** whose effective dose to inhibit the rat´s left hind paw swelling by 50% is as low as 2.6 mg/kg).[42]

Other arylnaphthalene lignan lactones are selective and orally active inhibitors of 5-lipooxygenase.[90] They interact with the arachidonic acid binding site of 5-LO and inhibit the enzymatic reaction by a non redox mechanism. However, extensive metabolism reduces the potential for these inhibitors.[91] Reduced metabolic lability with no loss of *in vivo* inhibitory potency were combined in a series of modified heterolignans in which the pendant phenyl moiety has been replaced by five membered heteroaryls (**146-148**). The replacement of metabolically unstable groups improves their stability while preserving the *in vitro* potency.

The arylnaphthalene lignans as a class also show inhibitory activity against cyclic nucleotide phosphodiesterases IV (PDE IV) making them potential antiasthmatic agents. In the search for selective PDE IV inhibitors (PDE III inhibition is reported to correlate with the induction of cardiovascular side effects) 1-heteroaryl-2,3-bis(hydroxymethyl)naphthalenes bearing an *N*-alkylpyridone ring (**160-165**) have shown antispasmogenic activity comparable to rolipram (ED_{50} = 0.01 mg/Kg iv)[92] without significant undesired effects on the cardiovascular system and compound (**164**) was selected for further evaluation as antiasthmatic agent.[73]

This review of the structures, activities, and employed methodologies for the synthesis of A-F heterolignans, reveals that several approaches and classes of derivatives have been described, but there are a lot of unexplored possibilities for the synthetic work and for the rational design of new active molecules, as it was the successful preparation of azatoxin.

ACKNOWLEDGMENTS

Financial support by Junta de Castilla y León (SA-66/12/92; SA 18/95), Spanish DGICYT (SAF98-0103) and EU (BIO4-CT98-0451), is gratefully acknowledged. A.C. Ramos and R. Peláez thank the University of Salamanca and the Spanish M.E.C. their predoctoral and postdoctoral positions.

REFERENCES

1. C. B. S. Rao, '*Chemistry of lignans*,' Andhra University Press., Waltair, 1978.
2. D. C. Ayres, and J. D. Loike, '*Lignans: Chemical, biological and clinical properties*,' Cambridge University Press, Cambridge, 1990.
3. D. A. Whiting, *Nat. Prod. Reports*, 1985, **2**, 191.
4. D. A. Whiting, *Nat. Prod. Reports*, 1987, **4**, 499.
5. G. M. Massanet, P. E. F. Rodríguez-Luis, and E. Zubia, *Fitoterapia*, 1989, **40**, 3.
6. D. A. Whiting, *Nat. Prod. Reports*, 1990, **7**, 349.
7. R. S. Ward, *Nat. Prod. Reports*, 1993, **10**, 1.
8. R. S. Ward, *Nat. Prod. Reports*, 1995, **12**, 183.
9. R. S. Ward, *Nat. Prod. Reports*, 1997, **14**, 43.
10. R. S. Ward, *Chem. Soc. Rev.*, 1982, **11**, 75.
11. R. S. Ward, *Tetrahedron*, 1990, **46**, 5029.
12. R. S. Ward, *Synthesis*, 1992, 719.
13. I. Jardine, '*Anticancer Agents Based on Natural Products Models*,' ed. by J. M. Kassadi, and J. D. Douros. Academic Press, Inc., New York, 1980, pp. 319-351.
14. W. D. MacRae and G. H. N. Towers, *Phytochemistry*, 1984, **23**, 1207.
15. W. D. MacRae, J. B. Hudson, and G. H. N. Towers, *Planta Med.*, 1989, **55**, 531.
16. S. J. Cho, A. Tropsha, M. Suffness, Y. C. Cheng, and K. H. Lee, *J. Med. Chem.*, 1996, **39**, 1383.
17. H. Stähelin and A. von Wartburg, *Prog. Drug. Res.*, 1989, **33**, 169.
18. B. F. Issell, F. M. Huggin, and S. K. Carter, '*Etoposide (VP-16), Current Status and New Developments*,' Academic Press, Orlando, 1984.
19. S. D. Paisley, M. S. Wolfe, and R. T. Borchardt, *J. Med. Chem.*, 1989, **32**, 1418.
20. A. Pelter, R. S. Ward, and L. Quianrung, *J. Nat. Prod.*, 1993, **56**, 2204.
21. K. H. Lee, S. A. Beers, M. Mori, Z. Q. Wang, Y. H. Kuo, L. Li, S. Y. Liu, J. Y. Chang, F. S. Han, and Y. C. Cheng, *J. Med. Chem.*, 1990, **33**, 1364.
22. X. M. Zhou, Z. Q. Wang, J. Y. Chang, H. X. Chen, Y. C. Cheng, and K. H. Lee, *J. Med. Chem.*, 1991, **34**, 3346.
23. X. M. Zhou, K. J. H. Lee, J. Cheng, S. S. Wu, H. X. Chen, X. Guo, Y. C. Cheng, and K. H. Lee, *J. Med. Chem.*, 1994, **37**, 287.
24. Y. L. Zhang, A. Tropsha, A. T. McPhail, and K. H. Lee, *J. Med. Chem.*, 1994, **37**, 1460.
25. Y. L. Zhang, X. Guo, Y. C. Cheng, and K. H. Lee, *J. Med. Chem.*, 1994, **37**, 446.
26. J. F. Kadow, D. M. Vyas, and T. W. Doyle, *Tetrahedron Lett.*, 1989, **30**, 3299.
27. W. J. Gensler, C. A. Murthy, and M. H. Trannell, *J. Med. Chem.*, 1977, **20**, 635.
28. L. L. Klein, C. M. Yeung, D. T. Chu, E. J. McDonald, J. J. Clement, and J. J. Plattner, *J. Med. Chem.*, 1991, **34**, 984.
29. C. F. Brewer, J. D. Loike, and S. B. Horwiz, *J. Med. Chem.*, 1979, **22**, 215.
30. M. Medarde, R. Peláez-Lamamié de Clairac, F. Tomé, J. L. López, and A. San Feliciano, *Arch. Pharm. (Weinheim)*, 1995, **328**, 403.

31. A. C. Ramos, Ph. D. Dissertation, Universidad de Salamanca, 1997.
32. F. Leteurtre, J. Madalengoitia, A. Orr, T. Cuzi, E. Lehnert, T. Macdonald, and Y. Pommier, *Cancer Res.*, 1992, **52**, 4478.
33. E. Solary, F. Leteurtre, K. D. Paull, D. Scudiero, E. Hamel, and Y. Pommier, *Biochem. Pharmacol.*, 1993, **45**, 2449.
34. B. Eymin, E. Solary, S. Chevillard, L. Dubrez, F. Goldwasser, O. Duchamp, P. Genne, F. Leteurtre, and Y. Pommier, *Int. J. Cancer,* 1995, **63**, 268.
35. F. Leteurtre, D. L. Sackett, J. Madalengoitia, G. Kohlhagen, T. Macdonald, E. Hamel, K. D. Paull, and Y. Pommier, *Biochem. Pharmacol.*, 1995, **49**, 1283.
36. H. L. Pearce, N. J. Bach, and T. L. Cramer, *Tetrahedron Lett.*, 1989, **30**, 907.
37. J. P. Bosmans, J. Van der Eycken, and M. Vandewalle, *Tetrahedron Lett.*, 1989, **30**, 3877.
38. J. Van der Eycken, J. P. Bosmans, D. Van Haver, and M. Vandewalle, *Tetrahedron Lett.*, 1989, **30**, 3873.
39. K. Tomioka, Y. Kubota, and K. Koga, *Tetrahedron Lett.*, 1989, **30**, 2953.
40. K. Tomioka, Y. Kubota, and K. Koga, *J. Chem. Soc., Chem. Commun.*, 1989, 1622.
41. H. Enmenegger, H. Stähelin, J. Rutschmann, J. Renz, and A. von Wartburg, *Arzneim. Forsch.*, 1961, **11**, 327.
42. A. Baba, N. Kawamura, H. Makino, Y. Ohta, S. Taketomi, and T. Sohda, *J. Med. Chem.*, 1996, **39**, 5176.
43. Y. Hitotsuyanagi, M. Kobayashi, M. Fukuyo, K. Takeya, and H. Itokawa, *Tetrahedron Lett.*, 1997, **38**, 8295.
44. S. W. McCombie, J. R. Tagat, W. A. Metz, D. Nazareno, and M. S. Puar, *Tetrahedron*, 1993, **46**, 8073.
45. L. Jurd, *J. Het. Chem.*, 1996, **33**, 1227.
46. C. Clémencin-Le Guillou, S. Giorgi-Renault, J. C. Quirion, and H. P. Husson, *Tetrahedron Lett.*, 1997, **38**, 1037.
47. K. Tomioka, Y. Kubota, H. Kawasaki, and K. Koga, *Tetrahedron Lett.*, 1989, **30**, 2949.
48. Y. Kubota, H. Kawasaki, K. Tomioka, and K. Koga, *Tetrahedron,* 1993, **49**, 3081.
49. K. Tomioka, H. Mizuguchi, T. Ishiguro, and K. Koga, *Chem. Pharm. Bull.*, 1985, **33**, 121.
50. P. Lienard, J. C. Quirion, and H. P. Husson, *Tetrahedron Lett.*, 1991, **32**, 2489.
51. P. Lienard, J. C. Quirion, and H. P. Husson, *Tetrahedron,* 1993, **49**, 3995.
52. P. Lienard, B. Saint-Jalmes, and J. C. Quirion, *Tetrahedron Lett.*, 1995, **36**, 5895.
53. A. Iida, M. Kano, Y. Kubota, K. Koga, and K. Tomioka, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2565.
54. H. Pearce, N. Bach, T. Cramer, M. Danks, G. Grindey, D. Katterjohn, S. Rincel, and T. Beck, *Proc. Am. Cancer Res.*, 1990, **47**, 758.
55. J. R. Prous, *Annual Drug Data Report*, Prous, J.R. Science Publishers, Barcelona 1988, p. 510.
56. J. R. Prous, *Annual Drug Data Report*, Prous, J.R. Science Publishers, Barcelona 1991, p. 817.
57. J. R. Prous, *Annual Drug Data Report*, Prous, J.R. Science Publishers, Barcelona 1995, p. 949.
58. Y. Hitotsuyanagi, K. Yamagami, A. Fujii, Y. Naka, Y. Ito, and T. Tahara, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 1039.

59. Y. Hitotsuyanagi, T. Naka, K. Yamagami, A. Fujii, and T. Tahara, *J. Chem. Soc., Chem. Commun.*, 1995, 49.
60. Y. Hitotsuyanagi, Y. Ichihara, K. Takeya, and H. Itokawa, *Tetrahedron Lett.*, 1994, **35**, 9401.
61. Y. Hitotsuyanagi, M. Kobayashi, K. Takeya, and H. Itokawa, *J. Chem. Soc., Perkin Trans. I*, 1995, 1387.
62. M. Medarde, A. C. Ramos, E. Caballero, J. L. López, R. Peláez-Lamamié de Clairac, and A. San Feliciano, *Terahedron Lett.*, 1998, **39**, 2001.
63. T. Kuroda, M. Takahashi, T. Ogiku, H. Ohmizu, T. Nishitani, K. Kondo, and T. Iwasaki, *J. Org. Chem.*, 1994, **59**, 7353.
64. J. R. Prous, *Annual Drug Data Report*, Prous, J.R. Science Publishers, Barcelona 1991, p. 45.
65. T. Kuroda, M. Takahashi, T. Ogiku, H. Ohmizu, K. Kondo, and T. Iwasaki, *J. Chem. Soc., Chem. Commun.*, 1991, 1634.
66. C. O. Kappe and A. Padwa, *J. Org. Chem.*, 1996, **61**, 6166.
67. R. S. Mali and P. G. Jagtap, *Tetrahedron Lett.*, 1992, **33**, 1655.
68. J. S. Madalengoitia and T. L. Macdonald, *Tetrahedron Lett.*, 1993, **34**, 6237.
69. R. Peláez-Lamamié de Clairac, Ph. D. Dissertation, Universidad de Salamanca, 1994.
70. V. Ortiz de Urbina, Degree project, Universidad de Salamanca, 1996.
71. N. Rehnberg and G. Magnusson, *J. Org. Chem.*, 1990, **55**, 4340.
72. D. Delorme, Y. Ducharme, C. Brideau, C. C. Chan, N. Chauret, S. Desmarais, D. Dubé, J. P. Falgueyret, R. Fortin, J. Guay, P. Hamel, T. R. Jones, C. Lépine, C. Li, M. McAuliffe, C. S. McFarlane, D. A. Nicoll-Griffith, D. Riendeau, J. A. Yergey, and Y. Girard, *J. Med. Chem.*, 1996, **39**, 3951.
73. T. Iwasaki, K. Kondo, T. Kuroda, Y. Moritani, S. Yamagata, M. Sugiku, H. Kikkawa, O. Kaminuma, and K. Ikezawa, *J. Med. Chem.*, 1996, **39**, 2696.
74. J. R. Prous, *Annual Drug Data Report*, Prous, J.R. Science Publishers, Barcelona 1992, p. 745.
75. J. J. Tepe, J. S. Madalengoitia, K. M. Slunt, K. W. Werbovetz, P. G. Spoors, and T. L. Macdonald, *J. Med. Chem.*, 1996, **39**, 2188.
76. J. S. Madalengoitia, J. J. Tepe, K. A. Werbovetz, E. K. Lehnert, and T. L. Macdonald, *Bioorg. Med. Chem.*, 1997, **5**, 1807.
77. K. A. Miller, P. R. Vachaspati, M. A. Labroli, C. D. Thomson, A. L. Bulman, and T. L. Macdonald, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1065.
78. S. J. Cho, Y. Kashiwada, K. F. Bastow, Y. C. Cheng, and K. H. Lee, *J. Med. Chem.*, 1996, **39**, 1396.
79. E. Bertounesque, T. Imbert, and C. Monneret, *Tetrahedron*, 1996, **52**, 14235.
80. M. J. Alvarez, Degree project, Universidad de Salamanca, 1996.
81. K. Tomioka, Y. Kubota, and K. Koga, *Tetrahedron*, 1993, **49**, 1891.
82. M. Medarde, A. C. Ramos, E. Caballero, J. L. López, R. Peláez-Lamamié de Clairac, and A. San Feliciano, *Tetrahedron Lett.*, 1996, **37**, 2663.
83. J. L. López, E. Del Olmo, B. Pascual-Teresa, M. Merino, S. Martín, and A. San Feliciano, *Tetrahedron*, 1995, **51**, 6343.

84. J. L. López, E. del Olmo, B. Pascual-Teresa, M. Merino, and A. San Feliciano, *Tetrahedron*, 1996, **52**, 4903.
85. E. ter Haar, H. S. Rosenkranz, E. Hamel, and B. W. Day, *Bioorg. Med. Chem.*, 1996, **4**, 1659.
86. H. L. Pearce, N. J. Bach, T. L. Cramer, M. K. Danks, G. B. Grindey, C. J. Kalterjohn, S. M. Linzel, and W. T. Beck, *Proc. Am. Can. Res.*, 1990, **31**, 441.
87. Y. L. Zhang, Y. G. Shen, and Z. Q. Wang, *J. Nat. Prod.*, 1992, **55**, 1100.
88. Z. Q. Wang, H. Hu, H. X. Chen, Y. C. Cheng, and K. H. Lee, *J. Med. Chem.*, 1992, **35**, 871.
89. E. K. Lehnert, K. E. Miller, J. S. Madelengoitia, T. J. Guzi, and T. L. Macdonald, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 2411.
90. Y. Ducharme, C. Bridean, D. Dubé, C. C. Chan, J. P. Falgueyret, J. W. Gillard, J. Guay, J. H. Hutchison, C. S. McFarlane, D. Liendeau, J. Cheigetz, and Y. Girard, *J. Med. Chem.*, 1994, **37**, 512.
91. J. P. Falgueyret, D. Denis, D. Macdonald, J. H. Hutchinson, and D. Riendeau, *Biochemistry*, 1995, **34**, 13603.
92. D. C. Untherwood, R. R. Osborn, L. B. Novak, J. K. Matthews, S. J. Newsholme, B. J. Undem, J. M. Hand, and T. J. Turphy, *J. Pharmacol. Exp. Ther.*, 1993, **266**, 306.

Received, 17th November, 1998