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ASYMMETRIC SYNTHESIS OF LIGNANS

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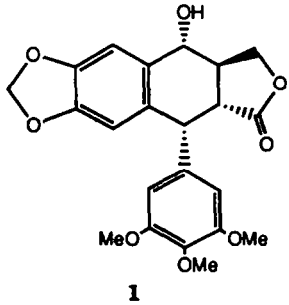
1. INTRODUCTION

Lignans (e.g. **1**–**4**) have long been recognised as challenging targets for organic synthesis[1] due to the varied structures which they possess[2] and the important biological properties exhibited by some



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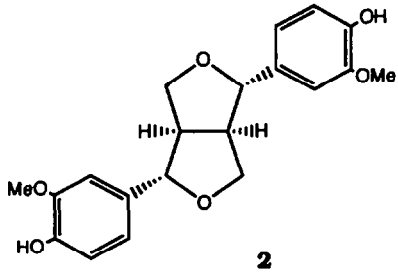

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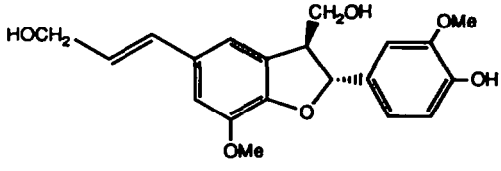

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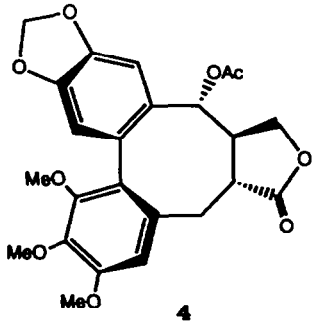

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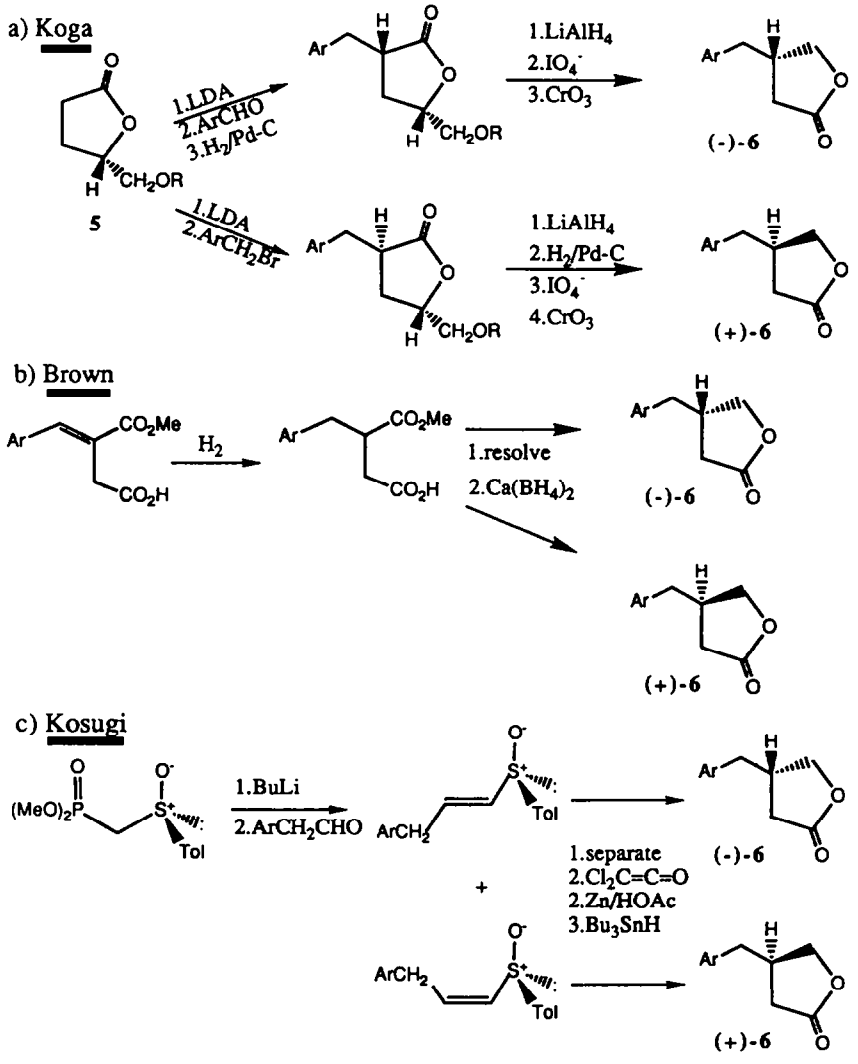
members of this class.[3] They also represent valuable target molecules for asymmetric synthesis due to the close juxtaposition and clearly defined relative configuration of the chiral centres present. In addition, they provide a framework for developing asymmetric synthetic methods applicable to substituted aromatic and saturated heterocyclic compounds, in contrast to the numerous methods which have been developed leading to aldol derived products.

The methods which have been used for the asymmetric synthesis of lignans are of four general types. This review will outline the main features of each approach and describe the currently reported examples of each type.

2. DIASTEREOSELECTIVE ALKYLATION OF CHIRAL BUTYROLACTONES

This represents one of the earliest approaches to the asymmetric synthesis of lignans and has been pioneered in particular by the groups of Koga (in Japan) and Brown (in France). The required monosubstituted butyrolactones **6** can be prepared from L-glutamic acid, via a multistep sequence involving diastereoselective alkylation of the benzyl and trityl ethers of 4-hydroxymethyl butyrolactone **5** (R = H), followed by carbonyl transposition, as shown in Scheme 1a.[4] The diastereo-

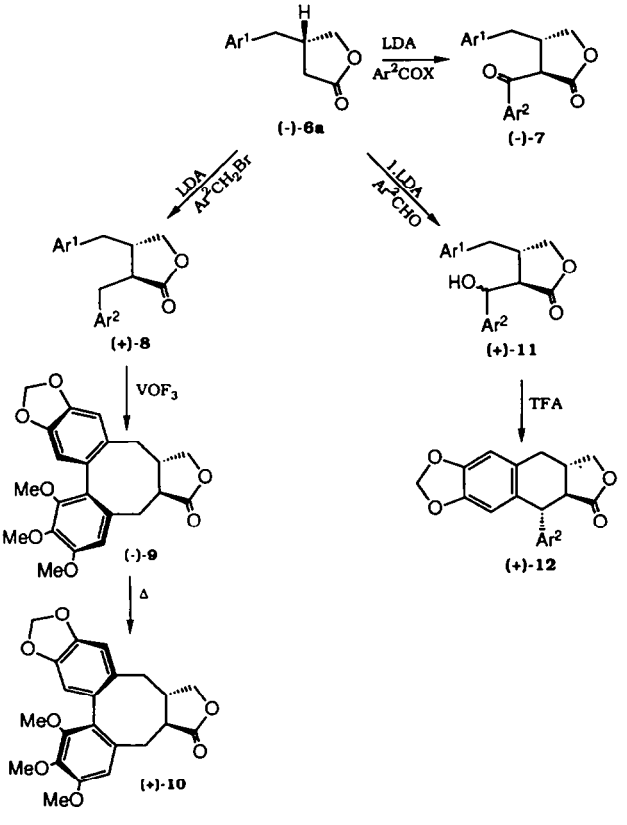


Scheme 1.

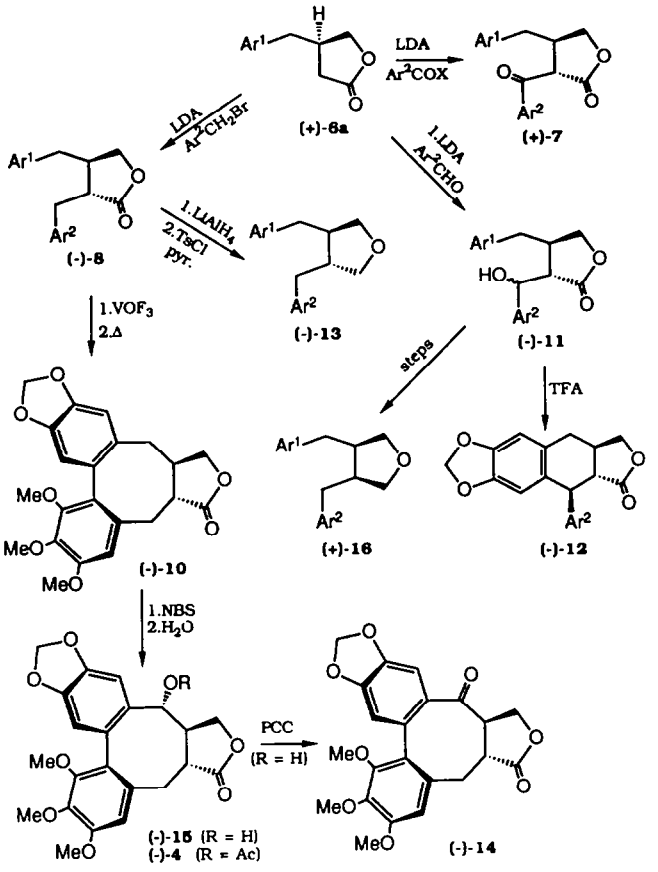
selectivities achieved were 64% and 57% leading to (−)- and (+)-**6** respectively. Alternatively, the monobenzyl butyrolactones **6** can be prepared by hydrogenation followed by resolution[5,6] (or indeed by asymmetric hydrogenation[7]) of appropriate Stobbe condensation products as shown in Scheme 1b. They can also be prepared by conjugate addition of a benzyl Grignard reagent to a chiral butenolide (see next section),[8] and more recently it has been shown that the same precursors can be obtained in high enantiomeric excess (94% and 96%) by stereospecific cyclisation (additive Pummerer rearrangement) of alkenyl sulphoxides with dichloroketene (Scheme 1c).[9] In addition, (+)-3-(3-methoxybenzyl)butyrolactone has been prepared by two different multistep procedures.[10,11]

Acylation of the lactone (−)-**6a** (Ar^1 = piperonyl) affords (−)-podorhizon (−)-**7b**[4,9] while alkylation affords (+)-deoxypodorhizon (+)-**8b** (see Scheme 2).[4] The latter product undergoes intramolecular oxidative coupling to yield (−)-isostegane (−)-**9**, which on heating isomerises to give (+)-stegane (+)-**10**.[12] Reaction of the lactone (−)-**6a** with 3,4,5-trimethoxybenzaldehyde affords a mixture of (+)-podorhizol and (+)-epipodorhizol (+)-**11b** which cyclise on treatment with trifluoroacetic acid to give (+)-deoxyisopodophyllotoxin (+)-**12b**; analogues (+)-**12c** and (+)-**12d** can also be prepared in a similar way.[5]

Similar acylation and alkylation of the lactone (+)-**6a** (Ar^1 = piperonyl) affords (+)-podorhizon (+)-**7b**,[4,9] (−)-hinokinin (−)-**8a** and (−)-deoxypodorhizon (−)-**8b** (see Scheme 3).[4] Compound (−)-**8b** has been converted into (−)-*trans*-burseran (−)-**13b**[13] and into (−)-stegane (−)-**10**,[12,14] which in turn yields (−)-steganol (−)-**15**, (−)-steganone (−)-**14** and (−)-steganacin



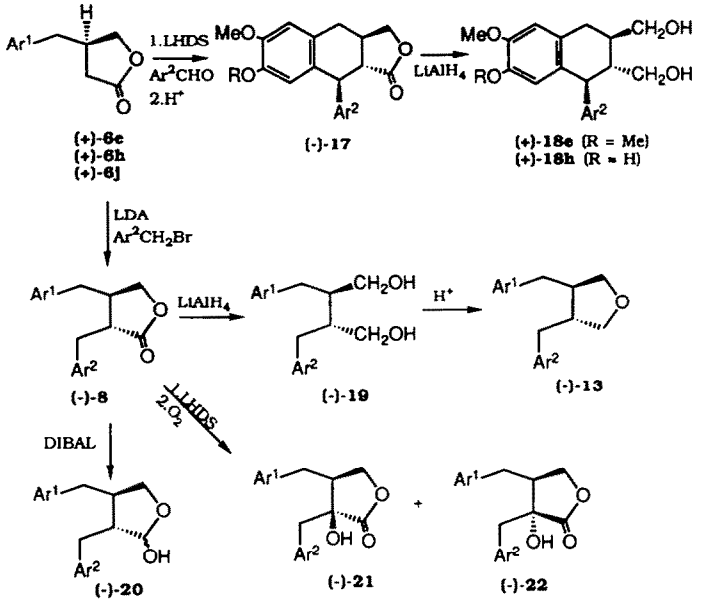
Scheme 2. Key to aryl groups: **a** Ar^1 (= Ar^2) = piperonyl; **b** Ar^1 = piperonyl, Ar^2 = 3,4,5-trimethoxyphenyl; **c** Ar^1 = piperonyl, Ar^2 = guaiacyl; **d** Ar^1 = piperonyl, Ar^2 = syringyl.



Scheme 3. Ar^1 and Ar^2 as defined in Scheme 2.

(−)-**4**.[14] Reaction of the lactone (+)-**6a** with 3,4,5-trimethoxybenzaldehyde affords a mixture of the epimeric alcohols (−)-**11b**,[5] which cyclise on treatment with acid to afford (−)-deoxy-isopodophyllotoxin (−)-**12b**,[5] and can also be converted into (+)-*cis*-burseran (+)-**16b**.[13] The aryltetralin lactones (−)-**12c** and (−)-**12d** can also be prepared by using appropriate aromatic aldehydes in the earlier condensation step.[5]

The use of this approach has been further exploited by the conversion of (+)-**6e** (Ar^1 = veratryl) into (+)-dimethyl isolariciresinol (+)-**18e**, (−)-dimethyl matairesinol (−)-**8e**, (−)-kusunokinin (−)-**8f**, (−)-arctigenin (−)-**8g**, (−)-dimethyl secoisolariciresinol (−)-**19e**, and related compounds (−)-**13e**, (−)-**20e** and (−)-**20f** as shown in Scheme 4.[5] Similarly, the lactone (+)-**6h** (Ar^1 = guaiacyl) has been converted into (+)-isolariciresinol (+)-**18h**, (−)-matairesinol (−)-**8h**, (−)-thujaplicatin methyl ether (−)-**8i**, (−)-secoisolariciresinol (−)-**19h**, and its anhydro-derivative (−)-**13h**.[5] The same approach has also been used to synthesise (−)-enterolactone (−)-**8k**, a compound isolated from human urine, by starting from (+)-3-(3-methoxybenzyl)butyrolactone (+)-**6j**.[10,11] More recently, Brown *et al.*[15] have shown that reaction of the anion derived from the dibenzyl ether of (−)-matairesinol (−)-**8h** with oxygen gave a mixture of epimeric alcohols which after debenzylation afforded (−)-nortrachelogenin (−)-**21h** and (−)-8′-epi-nortrachelogenin (−)-**22h**. Similarly, the benzyl ether of (−)-arctigenin (−)-**8g** was converted into (−)-trachelogenin (−)-**21g**. The enantiomers (+)-nortrachelogenin ((+)-wikstromol) (+)-**21h** and (+)-8′-epi-



Scheme 4. **e** Ar^1 (= Ar^2) = veratryl; **f** Ar^1 = veratryl, Ar^2 = piperonyl; **g** Ar^1 = veratryl, Ar^2 = guaiacyl; **h** Ar^1 (= Ar^2) = guaiacyl; **i** Ar^1 = guaiacyl, Ar^2 = syringyl; **j** Ar^1 (= Ar^2) = m-methoxyphenyl; **k** Ar^1 (= Ar^2) = m-hydroxyphenyl.

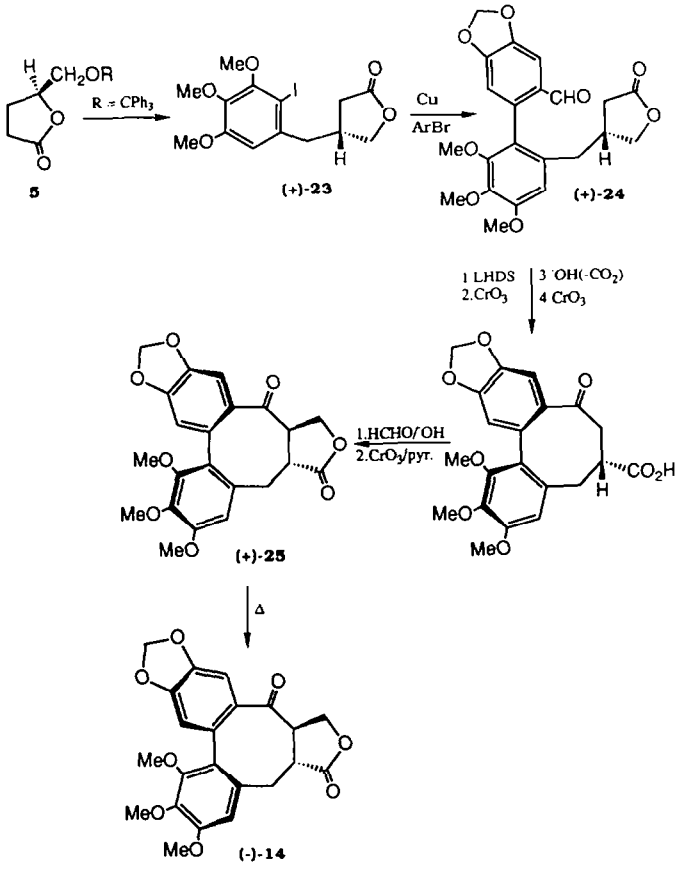
nortrachelogenin (+)-**22h** (not shown) have also been prepared in a similar way. By further modification of the same strategy (−)-α-conidendrin has also been prepared.[16]

In an elegant variation of this approach (see Scheme 5) Brown *et al.* have converted the chiral monolactone (+)-**23** into a biphenyl derivative (+)-**24** before carrying out an intramolecular condensation and a 1,4-carbonyl transposition leading to (+)-isosteganone (+)-**25** and (−)-steganone (−)-**14**.[17] This strategy demonstrates that the two aryl groups (Ar^1 and Ar^2) can be introduced in any order, and that the axially dissymmetric biphenyl linkage can either be formed prior to construction of the lactone moiety or at a later stage in the synthesis (cf. Scheme 3).

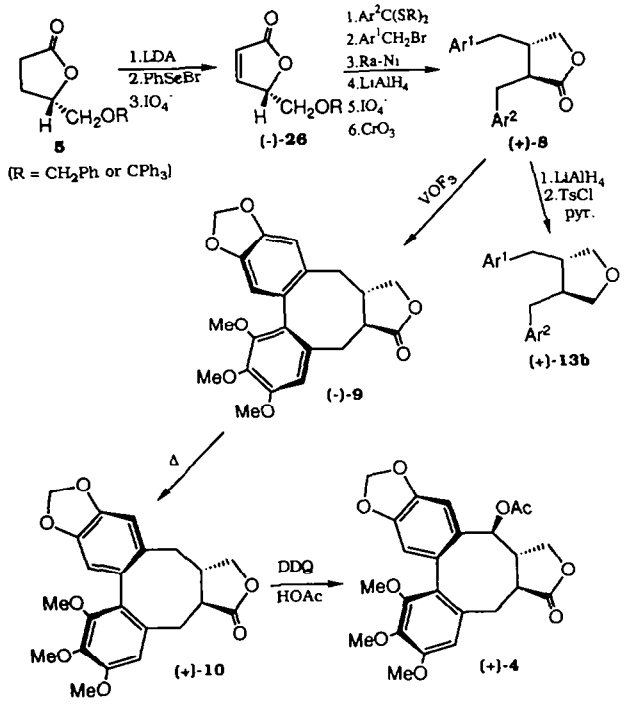
3. DIASTEREOSELECTIVE CONJUGATE ADDITION TO CHIRAL 2(5H)-FURANONES AND DIHYDROFURANS

As an alternative to the alkylation procedure outlined above, Koga *et al.* have converted the butyrolactone **5** into the corresponding butenolide (−)-**26** (see Scheme 6).[14] This undergoes nucleophilic addition by a sulphur stabilised carbanion followed by alkylation of the enolate so formed to give the disubstituted butyrolactone (+)-**8b** which is a useful precursor for the synthesis (+)-*trans*-burseran (+)-**13b** and (−)-isostegane (−)-**9**. On heating, (−)-isostegane yields (+)-stegane (+)-**10** which in turn can be converted into (+)-steganacin (+)-**4**,[14] although the latter compound is only obtained in low yield by this method (11% from (+)-**10**).

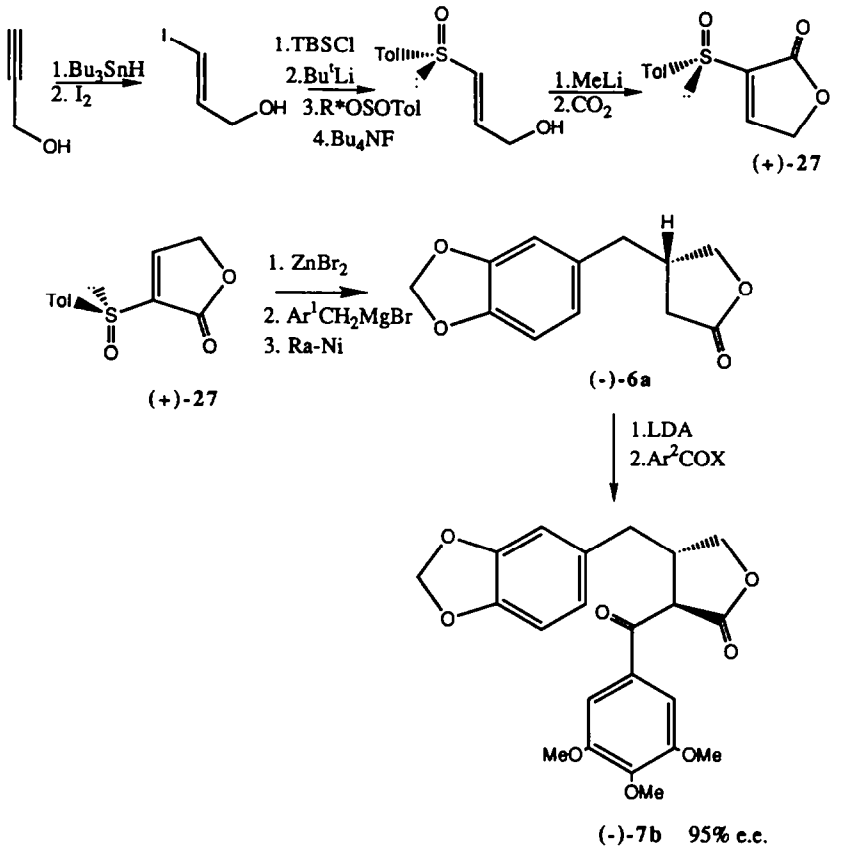
Posner *et al.* have prepared the *p*-toluenesulphinylbutenolide (+)-**27** from propargyl alcohol in seven steps and in >98% e.e.[8] The key step involves the reaction of a vinyl lithium reagent with



Scheme 5.



Scheme 6. Ar^1 = piperonyl, Ar^2 = 3,4,5-trimethoxyphenyl.



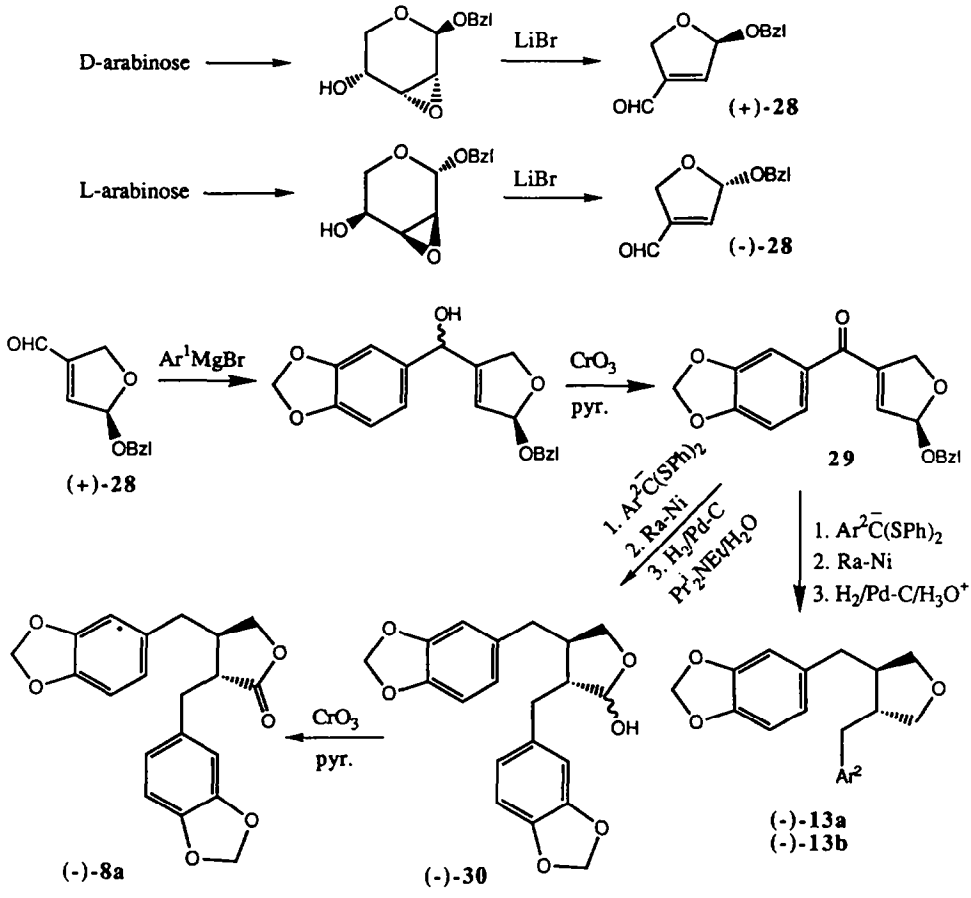
Scheme 7. R* = (−)-menthyl.

(−)-menthyl *p*-toluenesulphinate to give an unsaturated chiral sulphoxide which is then converted into the 2(5H)-furanone (see Scheme 7). Treatment of (+)-**27** with a benzyl Grignard reagent in the presence of zinc bromide affords the lactone (−)-**6a** which was converted into (−)-podorhizon (−)-**7b** in 95% e.e. using the method reported earlier by Koga *et al.* Since both (+)- and (−)-menthol are available both enantiomeric series of lignans can be prepared in this way.

Magnusson *et al.* have prepared the chiral dihydrofurans (+)- and (−)-**28** by lithium bromide induced ring contraction of benzyl 2,3-anhydro-D- and L-ribopyranosides (see Scheme 8).[18] 1,2-Addition of an aryl Grignard reagent to (+)-**28** followed by oxidation gives the unsaturated ketone **29**. 1,4-Addition of an appropriate sulphur stabilised carbanion followed by treatment with Raney nickel and hydrogenolysis gave (−)-*trans*-burseran (−)-**13b** (>98% e.e.), (−)-dehydroxycubebin (−)-**13a**, and (−)-cubebin (−)-**30**, which on oxidation gave (−)-hinokinin (−)-**8a**.[18] The enantiomeric series of compounds can also be prepared in the same way starting from (−)-**28**.

4. ROUTES INVOLVING CYCLOADDITION REACTIONS

Although asymmetric Diels–Alder reactions have been much used in other areas of asymmetric synthesis this approach has been used to only a limited extent for the asymmetric synthesis of lignans. However, Charlton *et al.* have synthesised (+)-isolariciresinol dimethyl ether (+)-**18e** (83% optical purity) using this methodology (Scheme 9).[19] The key step involves elimination of sulphur dioxide from the dihydrobenzothiophen derivative **31** to yield the *ortho*-quinone-methide



Scheme 8. **a** Ar^2 = piperonyl; **b** Ar^2 = 3,4,5-trimethoxyphenyl.

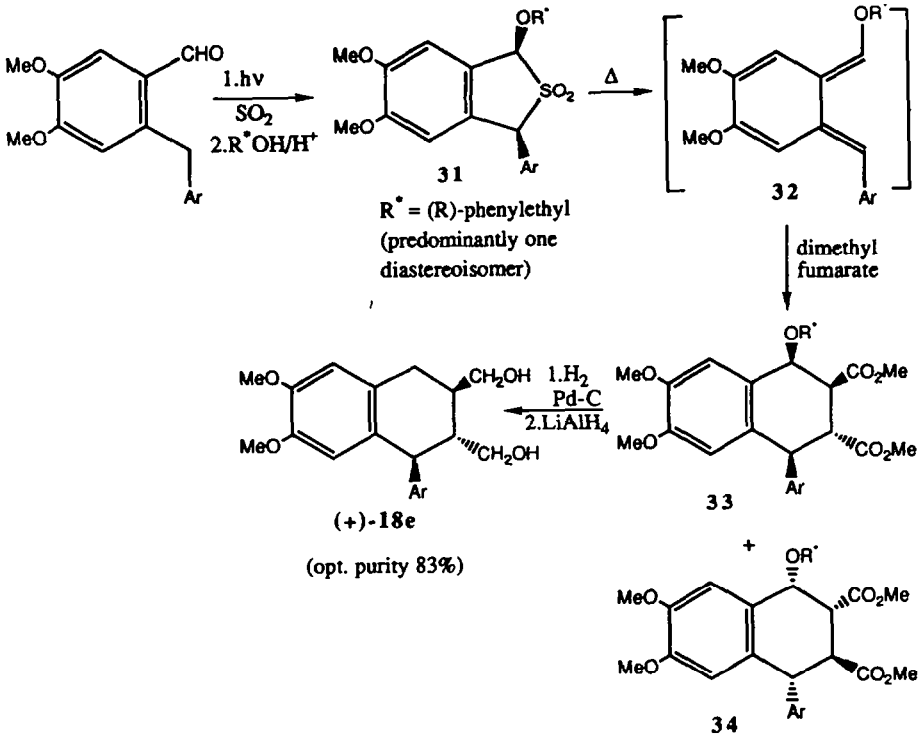
32 which undergoes cycloaddition with dimethyl fumarate to give a 70:30 mixture of the adducts **33** and **34**. The major diastereoisomer is then converted into (+)-**18e**.

Raphael *et al.* have used a (2+2) cycloaddition reaction followed by ring expansion to generate the dibenzocyclooctadiene skeleton of the steganacin series.[20] Resolution of the intermediate keto-acid **35** followed by lactone formation yields (+)-isosteganone (+)-**25**, which on heating can be converted into (−)-steganone (−)-**14**.

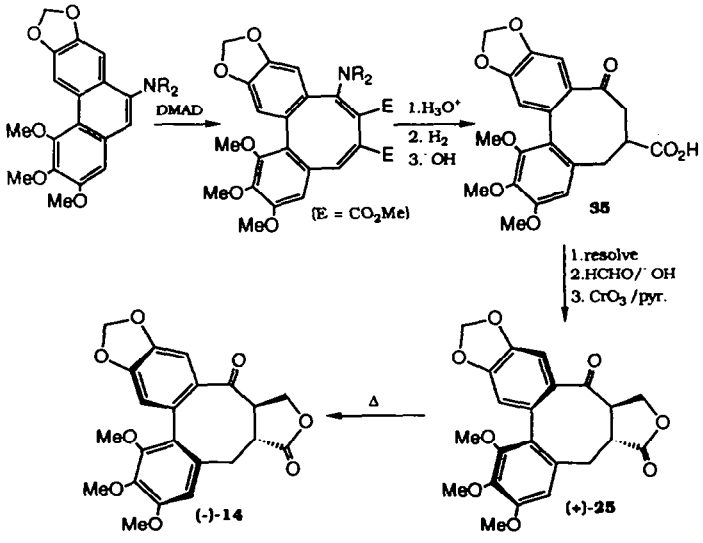
Takano *et al.* have devised a lengthy enantio-controlled synthesis of 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane lignans involving an intramolecular hetero-Diels–Alder reaction (Scheme 11).[21] The key step involves cycloaddition of the unsaturated ketone **36** derived from(+)-diethyl tartrate. This intramolecular Diels–Alder reaction establishes the vital β–β bond characteristic of these compounds and provides the basic six carbon skeleton of the 3,7-dioxabicyclo[3.3.0]octane nucleus. Subsequent transformations afford (−)-sesamin (−)-**37**, (−)-sesamolin (−)-**38**, and (−)-acuminatolide (−)-**39**.[21]

5. ROUTES INVOLVING THE USE OF CHIRAL OXAZOLINES

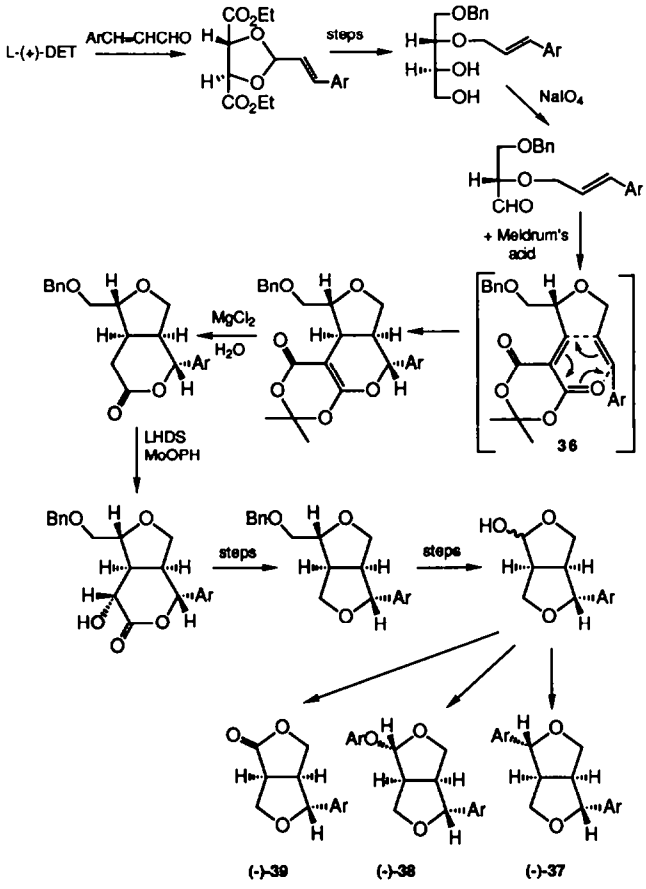
Meyers has pioneered the use of chiral oxazolines to synthesise enantiomerically enriched lignans belonging to both the dibenzocyclooctadiene and aryltetralin series.[22,23] In the first case (Scheme



Scheme 9. Ar = veratryl.



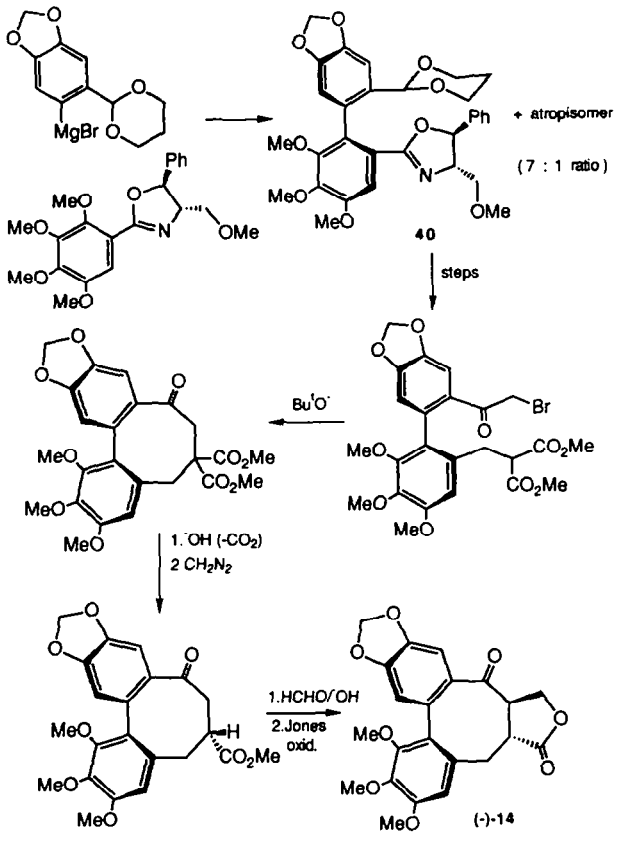
Scheme 10.



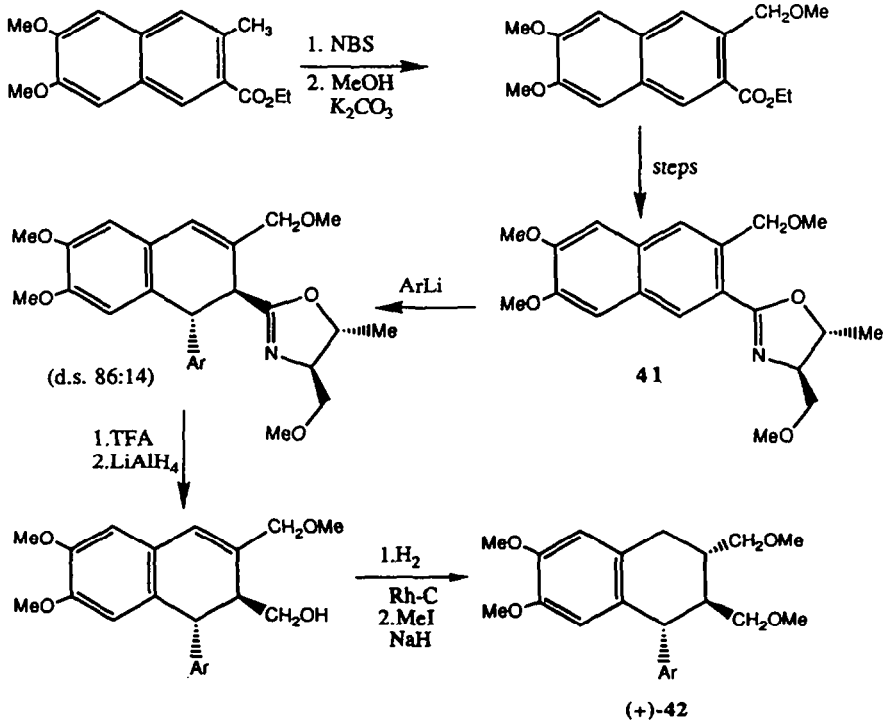
Scheme 11. Ar = piperonyl.

12) the chirality of the oxazoline moiety is used to induce diastereoselective coupling of the two aryl units furnishing an axially dissymmetric biphenyl derivative **40**. The two diastereoisomeric biphenyls are obtained in a 7:1 ratio and these can be separated before carrying through the major diastereoisomer **40** as shown in Scheme 12. The optical purity of the final product (−)-**14** is 80–84%. In contrast to most other asymmetric syntheses of steganone which rely either on the resolution of a chiral acid,[20] or the formation of a chiral non-racemic lactone prior to biaryl coupling,[14] in the present approach the axially dissymmetric biphenyl linkage is formed first and controls the eventual configuration of the lactone group.

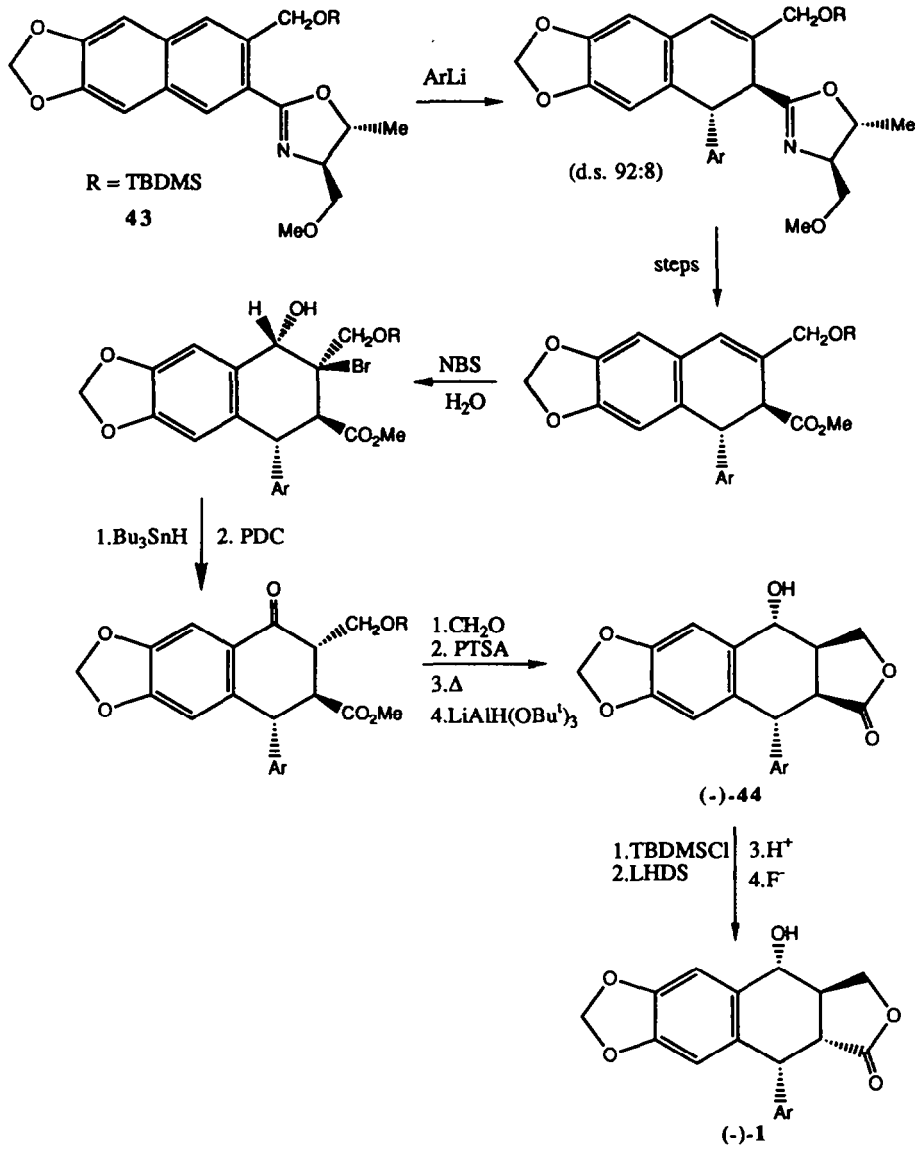
The second use of chiral oxazolines involves the asymmetric tandem addition of aryllithium reagents to chiral non-racemic naphthalene derivatives (**41** and **43**).[23] This approach has been used to synthesise (+)-phyltetralin (+)-**42** (Scheme 13) and (−)-podophyllotoxin (−)-**1** (Scheme 14). The tandem addition in each case gives an approximately 9:1 ratio of the diastereoisomeric products and these are carried through leading to a 68% e.e. of (+)-**42** and an 81% e.e. of (−)-**1**. The enantiomeric excess of the latter product was raised to 93% by recrystallisation. This approach is clearly ideally suited to compounds such as phyltetralin (+)-**42** which possess *trans*-stereochemistry at C-1 and C-2 of the tetralin moiety. It is less satisfactory for compounds such as podophyllotoxin (−)-**1** which have the *cis*-stereochemistry at C-1 and C-2. Indeed, the latter synthesis (Scheme 14) is clearly hampered by the lengthy sequence of reactions required to set up the correct relative stereochemistry at C-2, C-3 and C-4.



Scheme 12.



Scheme 13. Ar = veratryl.



Scheme 14. Ar = 3,4,5-trimethoxyphenyl.

6. CONCLUSION

While the schemes included in this review clearly show the high degree of ingenuity which has been used to introduce stereochemical control into lignan synthesis, it is equally apparent that there is a need for improved methods to be developed for the asymmetric synthesis of some types of compounds.

Thus, while several alternative methods are available for the asymmetric synthesis of compounds of the steganone type, the currently available methods for the asymmetric synthesis of the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes (Scheme 11) and the podophyllotoxin type (Scheme 14) are very lengthy and leave much room for improvement. Furthermore, there are several other classes of

lignans including the so-called neolignans for which no methods for asymmetric synthesis have so far been reported. Many new developments in this area can therefore be expected in the years ahead.

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