A Short, Diastereospecific Approach to Symmetrical and Unsymmetrical 2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octane Lignans

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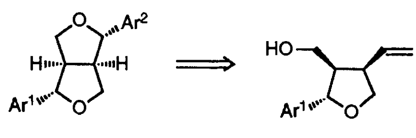
Enolate Claisen rearrangement of the lactone **7** leads to the tetrahydrofuran (THF) ester **9** as a single diastereoisomer, reduction of which gives the general bis-THF lignan precursor **2**.

The development of a viable and general synthetic approach to the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane class of lignans **1** (bis-THF lignans) must address a number of problems. Firstly, the two aryl groups must be introduced at the correct positions and with the correct stereochemistry both relative to each other and to the two ring junction protons. Secondly, it should be possible to incorporate different aryl groups as many such natural lignans are unsymmetrical (*i.e.* **1**; $Ar^1 \neq Ar^2$). Finally, a truly general approach would allow the preparation of optically pure material in a stereocontrolled fashion. The aryl substituents are typical shikimate residues such as 3,4-dimethoxyphenyl, 3,4-methylenedioxyphenyl and various *O*-methylated derivatives of 3,4,5-trihydroxyphenyl functions.[1] Only relatively recently have examples of such methods been reported; these include the Pelter route,[2] based upon homologations of butyrolactones, the Whiting methods[3]



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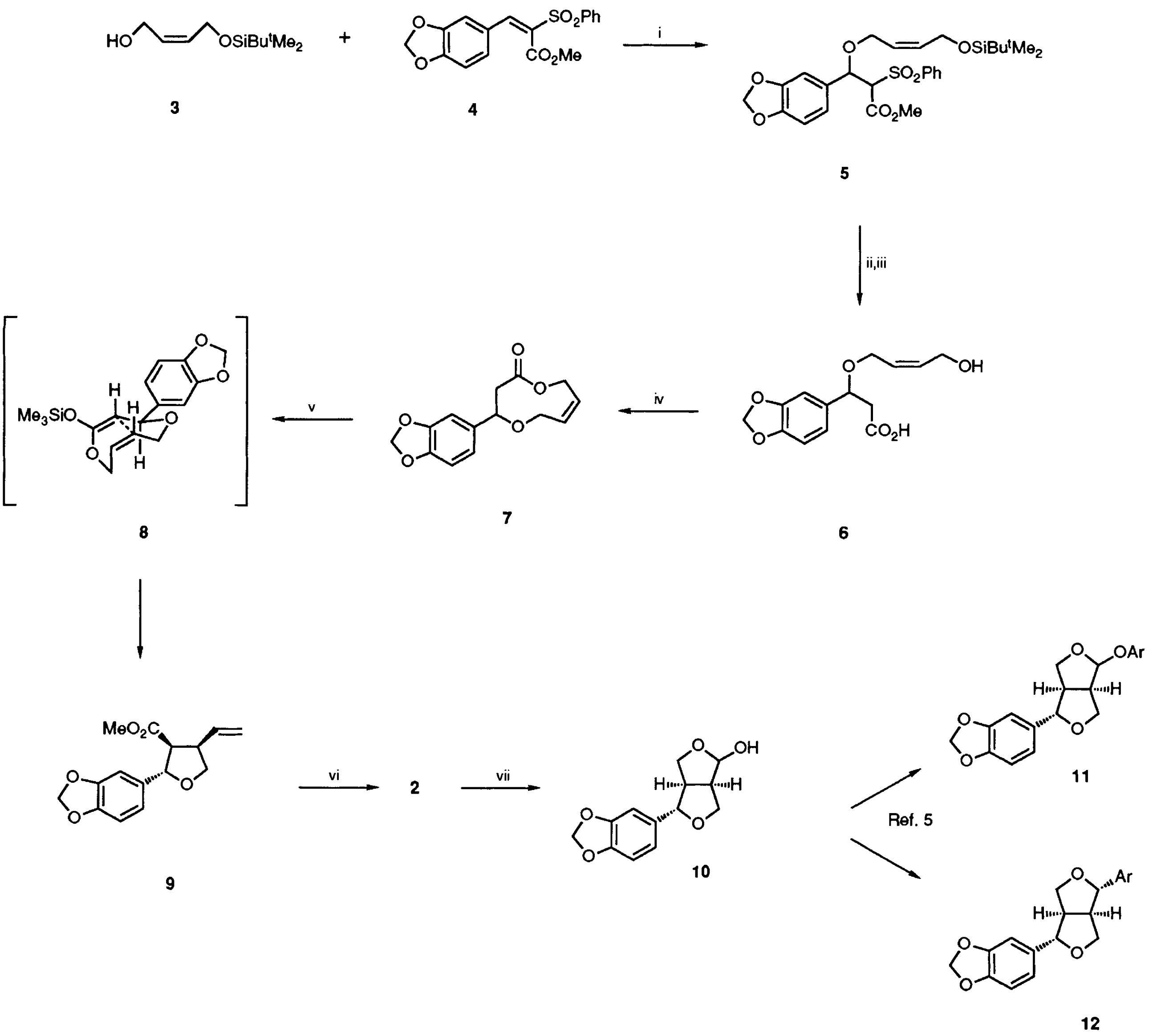

Scheme 1 *Reagents and conditions*: i, **3**, NaH, THF, 0–20 °C, 0.5 h, add **4**, 0.5 h, 20 °C (80%); ii, 1% Na–Hg, Na_2HPO_4, THF–MeOH, −50 to 0 °C, 1 h (70%); iii, 2 mol dm^{-3} KOH, MeOH, 20 °C, 24 h (89%); iv, 2-chloro-1-methylpyridinium iodide, Et_3N, MeCN (5 mmol dm^{-3} in **6**), 80 °C, 44 h (51%); v, a, 3 equiv. LDA, TMSCl, THF, −100 °C, add **7**, warm to −30 °C, 1 h, then 20 °C, 1 h; b, MeOH, 0.25 h; c, CH_2N_2, Et_2O (44%); vi, $LiAlH_4$, THF, 0 °C, 1 h (53%); vii, OsO_4, $NaIO_4$, (95%)

which also feature butyrolactones as intermediates and the Kraus photochemical method.[4] Only one enantiocontrolled and general route has so far been reported which is based on a rather neat application of an intramolecular Diels–Alder reaction but which requires a considerable number of synthetic operations to reach the desired goals.[5] A key intermediate in this latter approach was the 3-tetrahydrofuranmethanol **2** which we reasoned could be more readily accessed using the alicyclic version of the enolate Claisen rearrangement.[6] Herein, we report the successful outcome of this approach.

Our synthesis began (Scheme 1) with a Michael addition of the sodium salt of the monoprotected (*Z*)-but-2-ene-1,4-diol **3** to the α-sulphonylcinnamate **4**,[7] which smoothly led to the ether **5**.† Reductive desulphurization[8] using 1% sodium amalgam followed by base hydrolysis and simultaneous removal of the silyl protecting group then gave the hydroxy acid **6**† in good overall yield. Higher concentrations of sodium in the amalgam caused extensive decomposition of the substrate. The key lactone **7**† was then obtained in an isolated yield of 51% using Mukaiyama's procedure.[9] The central Claisen rearrangement was effected using a 'pre-mix' method[10] in which the base [lithium diisopropylamide (LDA)] and the trapping reagent [trimethylsilyl chloride (TMSCl)] were first mixed at low temperature prior to the addition of the lactone **7**. The intermediate lithio enolate was thus immediately trapped by *O*-silylation before decomposition could occur *via* a retro-Michael process. Rearrangement of the resulting (*E*)-*O*-silyl enolate then ensued upon warming to ambient temperature, presumably *via* the boat-like conformation **8**[6] and delivered only the desired THF diastereoisomer **9**,† following desilylation and esterification. Subsequent reduction using lithium aluminium hydride in cold THF then gave the corresponding alcohol **2**, which was identical to a sample prepared previously by the Diels–Alder route mentioned above.[5] No traces of any other diastereoisomers were detected. Finally, oxidative cleavage of the vinyl function led to (±)-samin **10**,[11]† which was also identical to a synthetic sample.[5] This compound has subsequently been converted into the lignans of type **11** and **12**.[5]

We have therefore established that this relatively short approach can be used to prepare both symmetrical and unsymmetrical lignans belonging to these classes. The one remaining problem, that of the incorporation of chirality into the sequence, is currently under investigation.

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† Satisfactory microanalytical and spectroscopic data have been obtained for all compounds reported.