

## Simple Synthesis of Furanoid and Dioxabicyclo[3.3.0]octane Lignans

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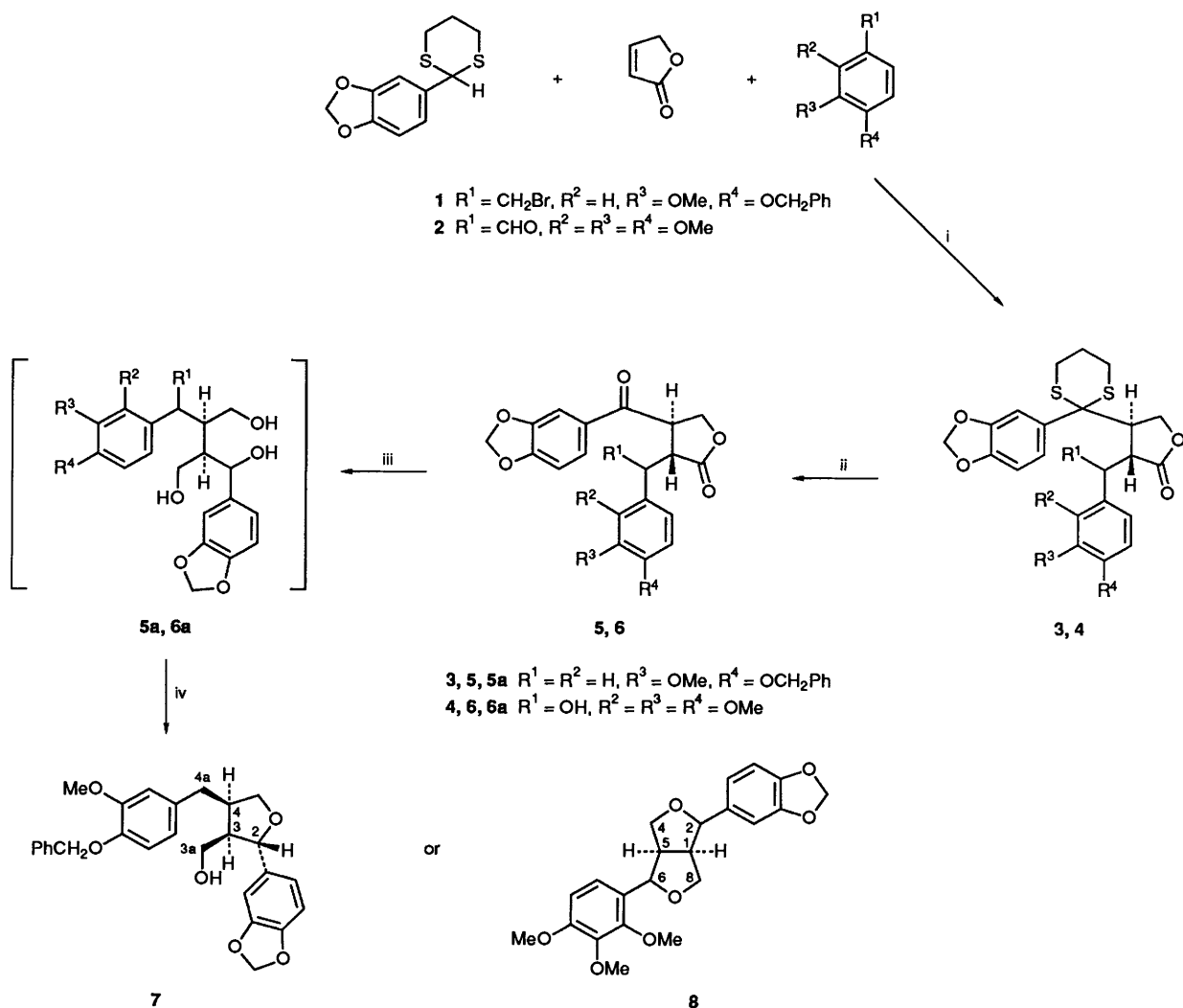
The key intermediates, the keto lactones **5**, **6** obtained by convergent synthesis, were transformed into furanoid and dioxabicyclo[3.3.0]octane lignan analogues **7**, **8** by means of sodium borohydride reduction and subsequent acid-catalysed cyclisation.

Furanoid and 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane lignans, isolated from natural sources, have diverse biological properties. Here we report a simple general route for the synthesis of such lignans and their analogues by initially utilising a tandem Michael addition.

The tandem conjugate addition<sup>1</sup> of the carbanion of piperonal trimethylenedithioacetal to but-2-en-4-olide and 4-benzyloxy-3-methoxybenzyl bromide **1** at  $-78^\circ\text{C}$  under an argon atmosphere gave the *trans*-dithiane lactone adduct **3** (70%). This adduct upon dethioacetalisation<sup>2</sup> in the presence of red mercuric oxide and  $\text{BF}_3\cdot\text{Et}_2\text{O}$  gave the keto lactone **5** (80%) presumably having the *trans* configuration. Reduction of **5** with an excess of sodium borohydride in methanol and subsequent cyclisation in the presence of dilute sulfuric acid furnished the tetrahydrofuran **7** (55%) as the sole product. NMR evidence

$[\delta_{\text{H}} 4.70$  (d,  $J$  6.3, 2-H), 2.63 (m, 4-H) and 2.28 (m, 3-H); and  $\delta_{\text{C}} 82.8$  (C-2), 52.7 (C-3), 42.3 (C-4), 72.9 (C-5) and 60.7 (C-3 $\alpha$ )] confirm the presence of a furanoid moiety having a hydroxymethylene side chain. The NMR spectral data of **7** are in close agreement with those of naturally occurring furanoid lignans.<sup>3</sup> Comparison of the chemical shift ( $\delta$  4.70) and the coupling constant value ( $J$  6.3) of 2-H with those of naturally occurring furanoid lignans reveals that the 2-H and 3-H in **7** are *trans* orientated. The formation of the furanoid compound **7** conceivably takes place through an intermediate triol resulting from the reduction of the ketonic as well as lactonic functions of **5**. Cyclisation occurs in the preferred conformer **5a** having a primary and a secondary alcoholic group on the same side so that the relative stereochemistry of 3-H and 4-H is *cis* in **7**.

The furanoid compound having been synthesized it was



Scheme 1 Reagents and conditions: i, BuLi,  $-78^\circ\text{C}$ ; Ar; ii, HgO,  $\text{BF}_3\cdot\text{Et}_2\text{O}$ ; iii,  $\text{NaBH}_4$ , MeOH; iv,  $2 \text{ mol dm}^{-3} \text{H}_2\text{SO}_4$

presumed that the dioxabicyclo[3.3.0]octane lignan skeleton could be built up from an intermediate **6**, containing a hydroxy group at C-6 position. The tandem addition was, therefore, carried out with an aromatic aldehyde. Here piperonal trimethylenedithioacetal, but-2-en-4-olide and 2,3,4-trimethoxybenzaldehyde **2** reacted in the presence of BuLi at  $-78^{\circ}\text{C}$  under an argon atmosphere to furnish the adduct **4** (68%). Tandem addition gave only one diastereoisomer **4**, although the formation of two diastereoisomeric alcohols (*erythro* and *threo*) is possible. Dethioketalisation of the ketonic compound **6** (62% yield) followed by sodium borohydride reduction and acid-catalysed cyclisation, presumably *via* the intermediate **6a**, afforded the furofuranoid lignan analogue **8** (52%). The structure of **8** was established from its  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectral data (three pairs of chemical shifts at  $\delta_{\text{C}}$  54.0 and 54.7 (C-1, C-5), 82.2 and 85.4 (C-2, C-6) and 71.3 and 73.0 (C-4, C-8). It has been reported<sup>4</sup> that the benzylic carbon (C-2 or C-6) bearing an equatorial aryl group appears at a lower field ( $\delta$  85.6–87.7) than the corresponding benzylic carbon bearing an axial aryl group ( $\delta$  81.1–83.9). In the light of the above observation, the appearance of two signals at  $\delta$  82.2 and  $\delta$  85.4 for two benzylic methine carbons in the  $^{13}\text{C}$  NMR spectrum of **8** indicate the axial-equatorial orientation of the two aryl groups in the compound.

### Experimental

**Synthesis of Compounds 7 and 8.**—To a solution of **5** (46 mg, 0.1 mmol) or **6** (43 mg, 0.1 mmol) in methanol ( $15\text{ cm}^3$ ) was added sodium borohydride (0.5 mmol) and the mixture was stirred for 4 h at  $4^{\circ}\text{C}$ . It was then diluted with water ( $30\text{ cm}^3$ ) and neutralized by  $2\text{ mol dm}^{-3}$  hydrochloric acid and extracted with ether ( $3 \times 20\text{ cm}^3$ ). Evaporation of the extract gave a

residue which was treated with  $2\text{ mol dm}^{-3}$  sulfuric acid ( $5\text{ cm}^3$ ) and warmed at  $80^{\circ}\text{C}$  for 30 min. It was then cooled, diluted with water ( $20\text{ cm}^3$ ) and extracted with ether ( $3 \times 20\text{ cm}^3$ ). The combined extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure. Chromatographic purification of the residue over silica gel furnished **7** [ $\text{CHCl}_3$ –MeOH (100:1, v/v) as eluent] (24.6 mg, 55%) or **8** ( $\text{CHCl}_3$ ) (20.8 mg, 52%).

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