Synthesis of the Lignan (±)-Dihydrosesamin: Problems of Stereocontrol in the Formation of 2,3,4-Trisubstituted Tetrahydrofurans and Tetrahydrofuranones

David R. Stevens and Donald A. Whiting*
Chemistry Department, The University, Nottingham NG7 2RD

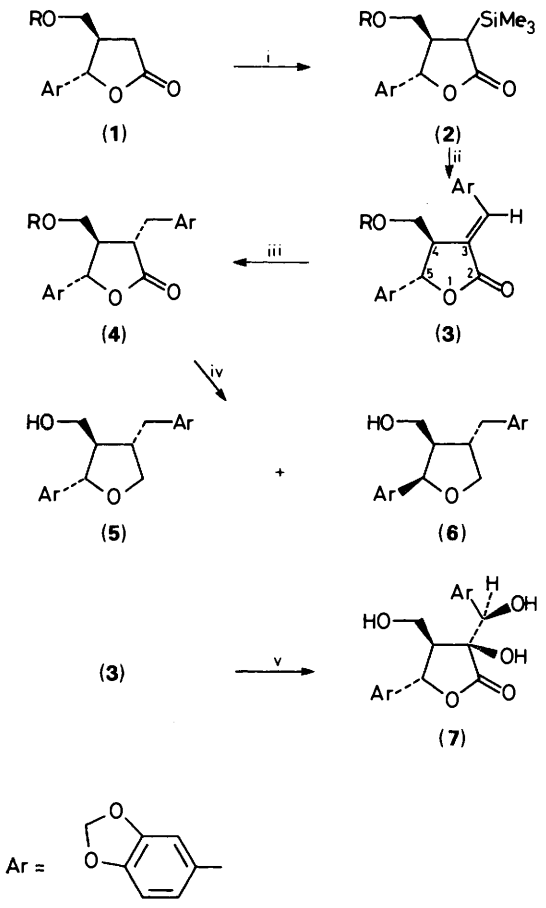
It is shown that the stereochemistry of addition reactions to 3-arylidene lactones (**3**) and (**9**) is controlled by the 5- rather than the 4-substituent: synthesis of the 2,3-*trans* 3,4-*cis* lignan dihydrosesamin (**11**) thus requires use of the 4,5-*cis* lactone (**8**), with epimerisation at C-2 following establishment of 3,4-*cis* geometry.

Tri- and tetra-substituted tetrahydrofurans comprise a major sub-group of the natural lignans, and a number of members show varied biological activities.[1] The synthesis of this type of compound poses interesting questions of stereochemical control, and following recent work on the synthesis of 3,7-dioxabicyclo lignans,[2] we turned our attention to (−)-dihydrosesamin (**11**). This lignan was isolated from *Daphne tangutica* Maxim., the Chinese drug 'Ai tuotuo' used in the treatment of rheumatism; *etc.*[3] Dihydrosesamin has been obtained only by hydrogenation of natural sesamin.[4] Related natural products are lariciresinol, from a variety of conifers, and sanshodiol (ex *Xanthoxylum piperitum* DC).[5]

In this paper, we report a total synthesis of racemic dihydrosesamin, employing the paraconic acids (**1**) and (**8**), readily available through the procedure of Lawlor and McNamee.[6] Thus, the (±)-*trans*-lactone (**1**; R = TBDMS) was treated with trimethylsilyl triflate[7] to yield the *C*-trimethylsilyl lactone (**2**; R = TBDMS) (38% when purified chromatographically), which was then converted by lithium di-isopropylamide and piperonal into the unsaturated lactone (**3**; R = TBDMS) (54%) with the spectroscopic characteristics of an *E*-cinnamate. Hydrogenation then afforded a single saturated lactone (**4**; R = TBDMS). It was expected this product would have the 3,4-*cis*, 4,5-*trans* stereochemistry with the direction of hydrogenation controlled by the adjacent 2-substituent. However, subsequent chemistry demonstrated 3,4-*trans*, 4,5-*trans* geometry. Thus, reduction of the lactone with lithium aluminium hydride followed by cyclisation in the acidic work up gave two 2,3,4-trisubstituted tetrahydrofuran alcohols (1:1), neither of which had spectroscopic data matching that of dihydrosesamin, and assigned structures (**5**) and (**6**) (Scheme 1). Also, treatment of (**3**; R = H) with *N*-methylmorpholine *N*-oxide with catalytic osmium tetroxide gave a single crystalline triol (**7**) which was stable to acidic conditions expected to induce ring closure in a 3,4-*cis* compound. The hydrogenation of the unsaturated lactone as its trimethylisopropylsilyl derivative (**3**; R = TIPS) gave the same stereochemical result, despite the bulkier silyl group.

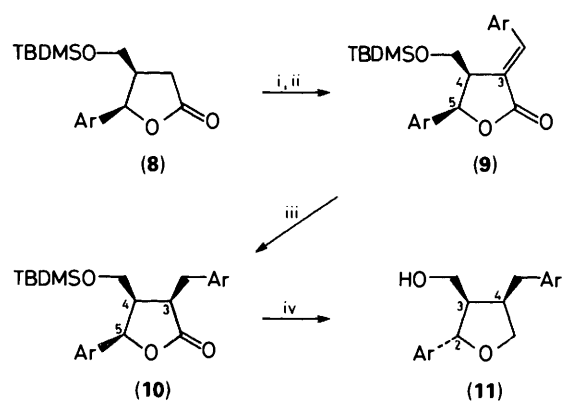
However, the C-1 epimerisation observed in the conversion of (**4**) ⟶ (**6**) suggested that a successful sequence could be initiated from the *cis*-lactone (**8**).[6] The α-arylidene lactone was formed by the Peterson procedure as above, and hydrogenation proceeded smoothly (74%) to yield the 3,4-*cis*-4,5-*cis*-tetrahydrofuranone (**10**). Lithium aluminium hydride reduction of this lactone gave a diol which cyclised and deprotected in work-up with aqueous acid and ethyl acetate, to afford (±)-dihydrosesamin (**11**) and its acetate (34%) (Scheme 2). The ^{1}H NMR data of the alcohol and of the acetate agreed well with those reported in the literature.[3] No 2,3-*cis* products were isolated.

In an effort to exploit this chemistry to form 3,7-dioxabicyclo[3.3.0]oxctane lignans, requiring *cis* tetrahydrofuran fusion, we effected hydroxylation of the arylidene lactone (**9**) to the diol (**12**). However, desilylation using tetrabutylammonium fluoride gave a triol which was clearly from NMR spectroscopy a 3,4-disubstituted tetrahydrofuranone rather than a 3,4,5-trisubstituted one; rearrangement as in (**15**) is envisaged to lead to the 3,4-*trans*-triol (**13**) (Scheme 3). In accord with this geometry, treatment of (**13**) with acidic methanol did not induce

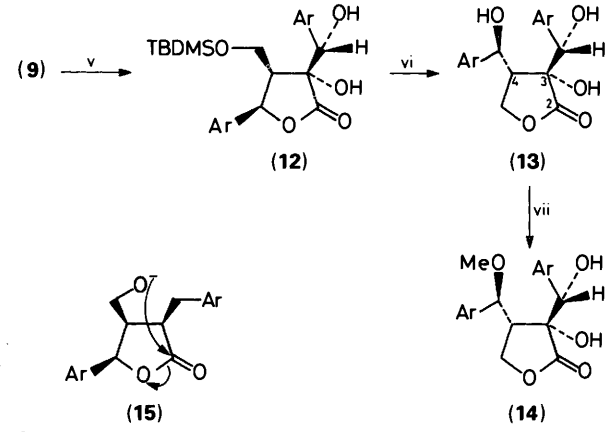


Scheme 1. *Reagents and conditions*: i, TMSOTf, Et_3N, THF, 0 °C, 2 h; ii, LDA, THF, −78 °C; ArCHO, 2 h, −78 °C, 1 h, room temp.; iii, H_2 EtOAc, 10% Pd/C; iv, $LiAlH_4$, THF, reflux, 1 h; 2M HCl; v, OsO_4, NMMNO, Bu^tOH–THF–H_2O; vi, TBAF, THF, room temp; vii, MeOH–0.5% HCl, reflux, 1 h.

ring closure but gave only the monomethyl ether (**14**). Anchimeric assistance to methanolysis by the 3-hydroxyl group, at the further benzylic site, is envisaged.



Scheme 2. For *Reagents and conditions*, see **Scheme 1.**



Scheme 3. For *Reagents and conditions*, see **Scheme 1.**

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