A Short Stereospecific Synthesis of a 2,6-Diarylmonoepoxylignanolide

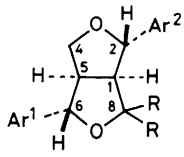
Clive P. Till and Donald A. Whiting*

Department of Chemistry, The University, Nottingham, NG7 2RD, U.K.

The 2-(*p*-methoxyphenyl)-6-phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (**6**), with natural stereochemistry, has been synthesised by a stereospecific route using an intramolecular aldol reaction [(**5**) → (**6**)].

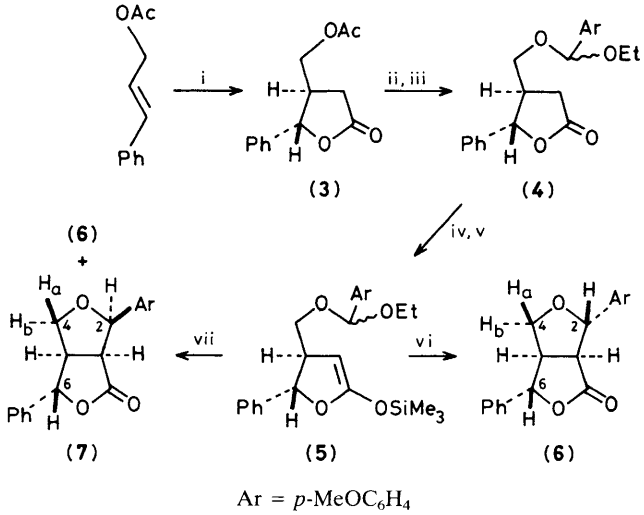
The 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane lignans[1] comprise a large group of natural products exhibiting a wide range of biological activity, and there is considerable interest in their synthesis.[2] The group includes a few lactones (**1**), 2,6-diarylmonoepoxylignanolides in Weinges' terminology,[3] showing *e.g.* antitumour action[4] and plant growth inhibition.[5] One lactone of type (**1**) has been prepared, by oxidation of a natural product,[6] and also by an oxidative coupling approach[5] which, although biomimetically interesting, is low yielding and not general.

We considered such compounds to be worthwhile targets both in their own right and as potential precursors, *via* reduction, to unsymmetrical compounds (**2**; $Ar^1 \neq Ar^2$). Various ingenious approaches to the symmetrical compounds (**2**; $Ar^1 = Ar^2$) have been described[7] but only one route reported[8] for the important unsymmetrical compounds. We set out here a short and stereospecific route, which should prove general, to the 2-(*p*-methoxyphenyl)-6-phenylmonoepoxyliganolide (**6**) with the geometry of the natural series (Scheme 1).



(**1**) $R_2 = O$

(**2**) R = H



Ar = *p*-$MeOC_6H_4$

Scheme 1. *Reagents:* i, $Mn(OAc)_3$, AcOH; ii, H_3O^+; iii, ArCH(Cl)(OEt); iv, LDA, −70 °C; v, Me_3SiCl; vi, $TiCl_4$, −78 °C; vii, $CF_3SO_3SiMe_3$.

The manganese(III) induced radical addition of acetic acid to olefins[9] was applied to *trans*-cinnamyl acetate to afford a single *trans*-lactone (**3**), (49%). The primary alcohol function was revealed on acid hydrolysis (78%) and reacted with 1-ethoxy-1-(*p*-methoxyphenyl)chloromethane at 0 °C, with triethylamine, to provide the mixed acetal (**4**), (53%). The lactone enol trimethylsilyl ether (**5**) was generated (92%) by successive treatments with lithium di-isopropylamide (LDA) and trimethylsilyl chloride.

Treatment of (**5**) with titanium tetrachloride at −78 °C gave the desired compound (**6**), (40%), as a single stereoisomer. This intramolecular aldol reaction impresses a *cis*-ring fusion, and the stereochemistry at the fourth chiral centre is controlled by transition-state conformation, possibly the chair-like arrangement of an enol titanium intermediate,[10] with the C-2 aryl equatorial. We know of only one related application of the intramolecular aldol reaction to prepare cyclic ethers in this way.[11] A competing scission of the acetal to anisaldehyde was also observed; it is planned to reduce this side reaction by direction of the site of co-ordination.

Ring closure of (**5**) using trimethylsilyl trifluoromethanesulphonate gave a mixture of (**6**) and its 2-epimer (**7**). In this case a cyclic transition state cannot be envisaged. The stereochemistry of lactones (**6**) and (**7**) was determined by comparison of ^1H and ^{13}C n.m.r. spectroscopic measurements with the substantial literature data,[1,4–7] and by examination of proton nuclear Overhauser enhancement effects. Thus in lactone (**6**), irradiation of 4-H_a led to signal enhancements (measured by Fourier transform difference methods) at 2-H (5%), 6-H (5%), and 4-H_b (17%), while in lactone (**7**) irradiation of 4-H_b produced enhancements at 2-H (6%), 5-H (9%), and 4-H_a (23%).

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