Synthesis of the Lignan (±)-Deoxyschizandrin

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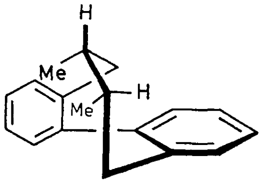
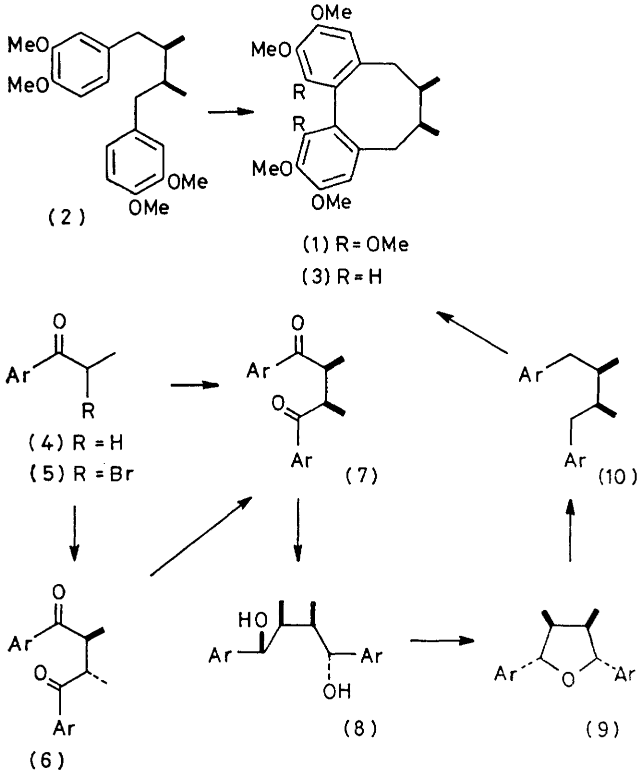
Summary A short synthesis of the bisbenzocyclo-octadiene lignan, (±)-deoxyschizandrin (**1**), based upon an intramolecular oxidation of 1,4-diarylbutane is described.

Naturally occurring bisbenzocyclo-octadienes of which the schizandrins,[1] the gomisins,[2] the steganes,[3] and the kadsurins[4] are representative, are now a well recognized subgroup of the lignan class. The broad range of therapeutic (notably anti-leukaemic[3]) activity reported for these compounds has led to recent interest in their synthesis.[5,6]

We report here a short synthesis of (±)-deoxyschizandrin[7] (**1**), a constituent of the seed oil of *Schizandra chinensis* Baill. (Magnoliaceae). To determine the feasibility of the key step, which involves the intramolecular oxidation of a



(A)



Ar = 3,4,5-Trimethoxyphenyl

1,4-diarylbutane, *meso*-dihydroguaiaretic acid dimethyl ether (**2**), a diarylbutane of established configuration, was oxidized with vanadium trifluoride oxide[8] and gave the *cis*-dimethyldibenzocyclo-octadiene (**3**), $C_{22}H_{28}O_4$, m.p. 175—177 °C. The chemical shifts of the non-equivalent secondary methyl groups of (**3**) (doublets, *J* 6 Hz, at δ 0·80 and 1·05), explicable by a restricted-rotation conformation such as (A) in which one methyl group is shielded by an aryl ring, agree with those reported for (+)-deoxyschizandrin. It thus appeared that the isomeric structure in which the methyl groups had a *trans* configuration, originally assigned to this lignan and supported by an unequivocal synthesis,[7] must be invalid; this conclusion is supported by recent related independent evidence.[6] The synthesis of (±)-deoxyschizandrin accordingly required the intermediate *meso*-diarylbutane (**10**), which was prepared as follows. Alkylation ($NaNH_2$, liquid NH_3)[9] of 3,4,5-trimethoxypropiophenone (**4**) with the α-bromo derivative (**5**) yielded the (±)-diaryl diketone (**6**), $C_{24}H_{30}O_8$, m.p. 165—166 °C (δ 1·32, d, *J* 7 Hz, sec. Me), in 93% yield. Treatment of a solution of (**6**) in tetrahydrofuran–ether–methanol (2 : 5 : 1) with sodium methoxide caused isomerisation to the *meso*-diketone (**7**), m.p. 194—196 °C (δ 1·17, d, *J* 7 Hz, sec. Me), which was precipitated in 91% conversion. Alternatively, the *meso*-diketone was obtained directly from (**4**) by oxidative dimerisation [LiNPr$^i_2$; $(CF_3SO_3)_2Cu$[10]]. Under these conditions, a readily separable mixture (90% yield) of the ether-insoluble (**7**) and ether-soluble (**6**) diketones was obtained in *ca.* 2 : 3 ratio. The chemical shifts of the secondary methyl groups in each diketone agree with the assigned configuration.[9]

Reduction of the *meso*-diketone (**7**) with lithium aluminium hydride in tetrahydrofuran yielded in 73% yield the racemic unsymmetric diol (**8**), $C_{24}H_{34}O_8$, amorphous solid (δ 0·66, d, and 0·92 d, both *J* 7 Hz, sec. Me), which on treatment with methanesulphonyl chloride or triphenylphosphine dibromide gave the *meso-trans*-tetrahydrofuran (**9**), $C_{24}H_{32}O_7$, m.p. 90—92 °C.[11] Reduction of (**9**) with sodium in liquid ammonia and 1,2-dimethoxyethane gave a mixture from which the required *meso*-diarylbutane (**10**), $C_{24}H_{34}O_6$, m.p. 87—89 °C, was separated chromatographically [overall yield 50% from (**8**)]. Oxidation of (**10**) with vanadium trifluoride oxide gave in 54% yield (±)-deoxyschizandrin (**1**), m.p. 114—115 °C, with n.m.r. data in agreement with those reported.[6] This five-step synthesis [(**4**) → (**7**) → (**8**) → (**9**) → (**10**) → (**1**)], which we believe should be of general applicability, is much simpler than the reported fifteen-step synthesis,[6] in which the dibenzocyclo-octadiene skeleton is formed from an *oo'*-dipropionyl biphenyl.

Concordant elemental analyses and ^1H n.m.r. spectra were obtained for all new compounds.

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