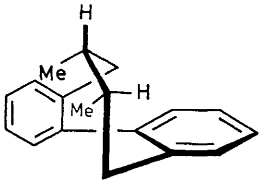
Synthesis of the Lignan (±)-Deoxyschizandrin

By Tesfaye Biftu, Braja G. Hazra, and Robert Stevenson*
(*Department of Chemistry, Brandeis University, Waltham, Massachusetts* 02154)

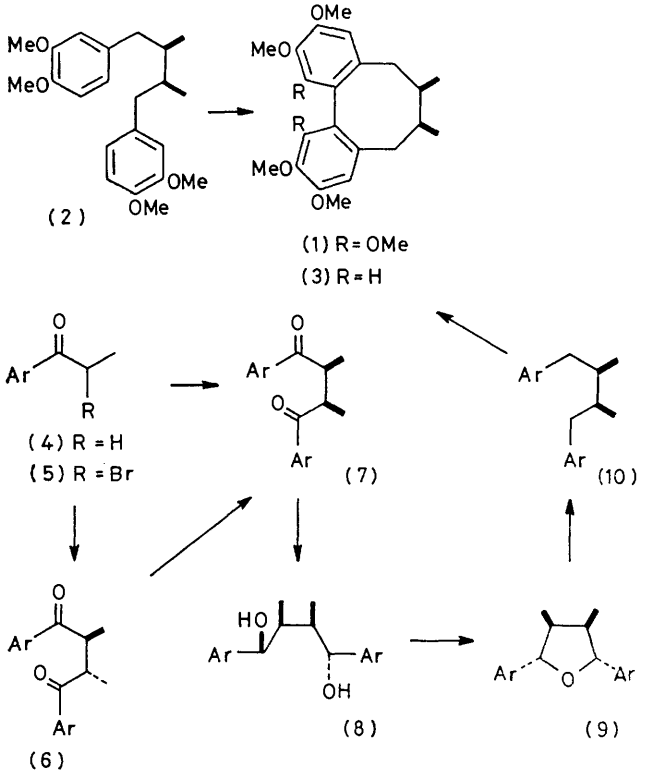
Summary A short synthesis of the bisbenzocyclo-octadiene lignan, (±)-deoxyschizandrin (**1**), based upon an intramolecular oxidation of 1,4-diarylbutane is described.

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 dibenzocyclooctadiene skeleton is formed from an *oo'*-dipropionyl biphenyl.

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

(*Received, 3rd March* 1978; *Com.* 220.)

---

[1] N. K. Kochetkov, A. Ya. Khorlin, and O. S. Chishov, *Izvest. Akad. Nauk S.S.R., Otdel. Khim. Nauk*, 1964, **1036** and earlier cited papers.

[2] H. Taguchi and Y. Ikeya, *Chem. Pharm. Bull.* (*Japan*), 1977, **25**, 364 and earlier cited papers.

[3] S. M. Kupchan, R. W. Britton, M. F. Ziegler, C. J. Gilmore, R. J. Restivo, and R. F. Bryan, *J. Amer. Chem. Soc.*, 1973, **95**, 1335.

[4] Y. Chen, R. Liu, H. Hsu, S. Yamamura, Y. Shizuvi, and Y. Hirata, *Bull. Chem. Soc. Japan*, 1977, **50**, 1824.

[5] A. S. Kende and L. S. Liebeskind, *J. Amer. Chem. Soc.*, 1976, **98**, 267; A. S. Kende, L. S. Liebeskind, C. Kubiak, and R. Eisenberg, *ibid.*, p. 6389; M. Mervič and E. Ghera, *ibid.*, 1977, **99**, 7673; F. E. Ziegler and J. A. Schwarz, *Tetrahedron Letters*, 1975, 4643; E. Brown and J.-P. Robin, *ibid.*, 1977, 2015; R. E. Damon, R. H. Schlessinger, and J. F. Blount, *J. Org. Chem.*, 1976, **41**, 3772; D. Becker, L. R. Hughes, and R. A. Raphael, *J.C.S. Perkin I*, 1977, 1674.

[6] E. Ghera, Y. Ben-David, and D. Becker, *Tetrahedron Letters*, 1977, 463.

[7] N. K. Kochetkov, A. Ya. Khorlin, and O. S. Chizhov, *Tetrahedron Letters*, 1962, 361; *Izvest. Akad. Nauk S.S.R., Otdel. Khim. Nauk.*, 1964, 963.

[8] S. M. Kupchan, A. J. Liepa, V. Kameswaran, and R. F. Bryan, *J. Amer. Chem. Soc.*, 1973, **95**, 6861.

[9] C. W. Perry, M. V. Kalnins, and K. Deitcher, *J. Org. Chem.*, 1972, **37**, 4371.

[10] Y. Kobayashi, T. Taguchi, and E. Tokuno, *Tetrahedron Letters*, 1977, 3741.

[11] K. V. Sarkanen and A. F. A. Wallis, *J.C.S. Perkin I*, 1973. 1869.