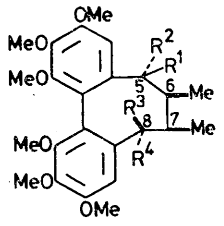
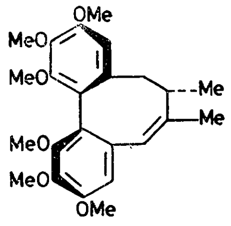
Total Synthesis of the Lignan (±)-Schizandrin

By Eugene Ghera* and Yehoshua Ben-David
(*Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel*)

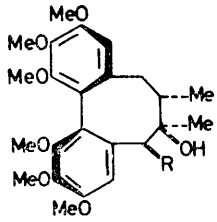
Summary A total synthesis of (±)-schizandrin (**1**), a bis-benzocyclo-octadiene lignan of biological interest, has been completed starting from the diketone (**2**).



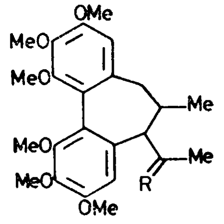
(2) $R^1,R^2=O, R^3,R^4=O$
(3) $R^1=OH; R^2=H; R^3,R^4=O$
(4) $R^1=OMs; R^2=H; R^3,R^4=O$
(5) $R^1=R^2=H; R^3,R^4=O$
(6) $R^1=R^2=H; R^3=OH; R^4=H$



(7)



(8) R = OH
(1) R = H



(9) R = H, OH
(10) R = O

Schizandrin (**1**) is the main biologically active lignan component of the fruits of *Schizandra chinensis* Baill.[1] and the parent compound of the Schizandraceae family of bisbenzocyclo-octadiene lignans.[2] Its stereostructure and absolute configuration have been recently determined.[2b,d] We describe herein the first total synthesis of racemic (**1**) by a regio- and stereo-specific pathway from the intermediate (**2**),[3] in which we found previously that only one of the two ketone groups could attain coplanarity with the adjacent aromatic ring. Attempted introduction of a tertiary hydroxy group at C-6 or C-7 was precluded by the reluctance of either ketone group in (**2**) to enolize or to form enol esters. Accordingly the ketone which is coplanar with the adjacent aromatic ring was selectively reduced *via*: (i) hydrogenation (Pd–C, AcOH, 50 lb in^{-2}) to the hydroxy-ketone (**3**), m.p. 208—210 °C,† ν_{max} ($CHCl_3$) 1702 cm^{-1}, (ii) mesylation ($MeSO_2Cl$, pyridine, 10 °C, 3 h) to (**4**), m.p. 136—138 °C, and (iii) hydrogenation in the presence of a base (Pd–C, MeONa, MeOH), affording in 68% overall yield the ketone (**5**) m.p. 177—178 °C, δ ($CDCl_3$), *inter alia*, 6·45, 6·41 (each 1H, s). Reduction ($LiAlH_4$) converted the ketone (**5**) stereospecifically into the alcohol (**6**) m.p. 153—154 °C (91%) which upon dehydration (anhydrous $KHSO_4$, 150 °C, 30 min) gave the olefin (**7**) in 79% yield, δ ($CDCl_3$) 6·44 and 6·42 (each 1H, s), 6·19 (1H br s), 1·64 (3H, s), and 1·05 (3H, d, J 7 Hz). The stereochemical assignments for the chiral axis and the chiral centre were made on the basis of hydrogenation of the double bond in (**7**) which affords exclusively deoxyschizandrin of known[3] (*cis*-dimethyl) configuration.‡ The hindered double bond of (**7**) could not be epoxidized by peracids but reacted with OsO_4 in pyridine affording the diol (**8**), m.p. 189—191 °C (62%), by attack from the less hindered site. Treatment of (**8**) with $MeSO_2Cl$ in pyridine (10 °C, 5 h), followed by the reduction of the mesylate with $NaBH_4$ in dimethylformamide (80 °C, 2 h) afforded (±)-schizandrin, m.p. 129—131 °C (55% yield in two steps), δ ($CDCl_3$) 6·62, 6·55 (each 1H, s), 1·25 (3H, s), and 0·82 (3H, d, J 7 Hz), identical by t.l.c., ^1H n.m.r., i.r., and u.v. spectral data with the naturally

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† Satisfactory elemental analysis or exact mass spectral data have been obtained for all new compounds.

‡ Inspection of molecular models showed that different results would be expected if hydrogenation of the biaryl rotamer of (7) were performed.

occurring schizandrin. This result confirms the stereostructure assigned to (**1**).[2b]

It is noteworthy that the attempted reduction of the mesylate of (**8**) with $LiEt_3BH$[4] or $LiAlH_4$ in tetrahydrofuran gave exclusively the Wagner–Meerwein rearrangement product (**9**), characterized by oxidation to the ketone (**10**).

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[2] For other schizandrin type lignans from *Schizandra* see: (a) H. Taguchi and Y. Ikeya, *Chem. and Pharm. Bull* (*Japan*), 1975, **23**, 3296; 1977, **25**, 364; (b) Y. Ikeya, H. Taguchi, and I. Yosioka, *ibid.*, 1978, **26**, 328; (c) Y. Ikeya, H. Taguchi, and Y. Iitaka, *Tetrahedron Letters*, 1976, 1359; (d) Chen Yan-Yong, Shu Zeng-Bao, and Li Lian-Niang, *Scientia Sinica* (*Peking*), 1976, **19**, 276.

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[4] S. Krishnamurty and H. C. Brown, *J. Org. Chem.*, 1976, **41**, 3064.