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DESOXYSCHIZANDRIN, STEREOCHEMISTRY AND TOTAL SYNTHESIS

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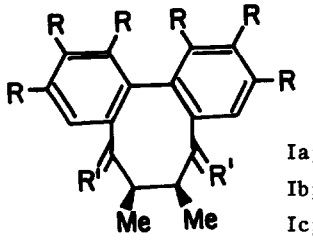
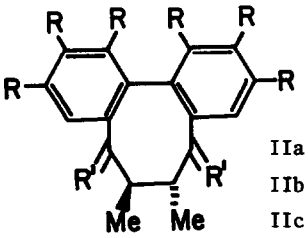
The extracts of fruits and seeds of Schizandra Chinensis Baill. contain several substances, members of a rare group of lignans,[1] characterized by a bisbenzocyclooctadiene skeletal structure and by a varied medicinal activity which includes, *inter alia*, a significant stimulant action on the central nervous system,[2] without apparent ill effects.[2b]

As part of a program concerned with the synthesis and biological evaluation of schizandrin type lignans, we report here the stereoselective total synthesis of (±) desoxyschizandrin (Ia). In the original structure determination[3] a *trans* stereochemistry (IIa) was assigned to the natural compound on the basis of the observed optical stability. However, this property should be inherent in both stereoisomers (Ia and IIa) in view of the well documented[4] restricted rotation about the biphenyl bond in *ortho*-disubstituted bridged biaryl systems. Moreover, the ^{1}H NMR spectrum of desoxyschizandrin[3] exhibits two distinct doublets for the two methyl groups and therefore is in agreement with a *cis* rather than *trans* orientation of these groups: in the *cis*-isomer the methyl groups are nonequivalent whereas in the *trans*-isomer these groups should be equivalent because of twofold symmetry.[5] The analogs Ib (bp 82°/1.5 mm) and IIb (mp 68°), devoid of methoxyl groups, have been now prepared from Ic and IIc[5,6] and their NMR spectra were indeed in agreement with this assumption ($CDCl_3$): δ 0.79 (d, J=7Hz, CH_3), 1.04 (d, J=7Hz, CH_3) for Ib and 1.07, d, J=6Hz (2xCH_3) for IIb.

While the previous synthesis[3] employed a route leading to IIa,[7] our approach was based on a stereoselective intramolecular coupling to an eight membered ring leading ultimately to Ia



Ia; R=OMe; R'=H_2
Ib; R=H; R'=H_2
Ic; R=H; R'=O



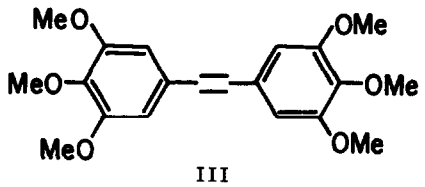
IIa; R=OMe; R'=H_2
IIb; R=H; R'=H_2
IIc; R=H; R'=O

by the following sequence. The Wittig reaction between 1,3,5-trimethoxybenzaldehyde and the ylide generated from 1,3,5-trimethoxybenzylbromide[8] (DMF, LiOMe, 90°) gave a mixture of *cis*- and *trans*-stilbene III (95% yield) which on irradiation[9] (cyclohexane, THF, I_2) afforded the phenantrene IV, mp 164° (82% yield). Osmylation (pyridine, 96 hr) produced the diol V, mp 178° (92%) which was oxidized, using pyridine-sulfur trioxide in DMSO[10] (30 min, r.t.), to the quinone VI, mp 154° (84%). Treatment with EtMgBr (reflux in benzene, 2 hr) afforded a single diol VII, mp 180° (78%), which was cleaved by lead tetraacetate (pyridine-benzene, 1 hr, r.t.) to VIII, mp 98° (86%). Bromination (Br_2 in dioxane-ether) produced a mixture of isomeric dibromides IX (95%) which was submitted to cyclization with Zn-Cu couple[11] yielding a single diketone X, mp 131° (60%). The *cis*-dimethyl stereochemistry in X was assigned by analogy with Ic[5]: NMR ($CDCl_3$) δ 0.95 (d, J=7Hz, CH_3), 1.21 (d, J=7Hz, CH_3), 2.51 (dq, CH), 3.31 (dq, CH), 3.48-3.93 (6xOCH_3), 6.50 (s, 1H), 7.19 (s, 1H), m/e 444 (M^+), IR ($CHCl_3$), 1700 and 1667 cm^{-1}.[12] The significant increase of free energy for biaryl rotation, as compared with Ic, was evidenced by NMR: no coalescence of methyl peaks occurs up to 190° (tc for Ic = 67°C).

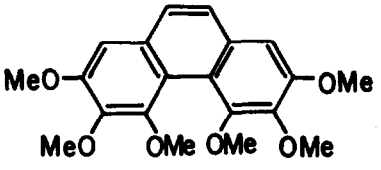
Although direct hydrogenolysis of X to Ia was unsuccessful, (±) desoxyschizandrin could be obtained in a two-step sequence. Treatment of X with LiAlH $(t\text{-BuO})_3$ in THF resulted in the selective reduction of the carbonyl group which is not coplanar with the adjacent aromatic ring[13] (at 1700 cm^{-1} in IR), yielding the hydroxyketone XI (79%), IR ($CHCl_3$) 1668 cm^{-1}, aromatic protons in NMR ($CDCl_3$) at δ 6.46 and 7.62. Hydrogenation of XI (Pd/C, AcOH + 1% $HClO_4$, 50 psi, 18 hr) affords Ia, mp 112°-113°, in 80% yield,[14] NMR ($CDCl_3$) 0.76 (d, J=7Hz, CH_3), 1.01 (d, J=7Hz, CH_3). 2.12 - 2.59 (m, 2xCH_2) 3.59-3.89 (6xOCH_3) and 6.55 (s, 2H), m/e 416 (M^+). The conservation of stereochemistry during hydrogenation[15] was ascertained by the use of an alternative reductive sequence: mesylation of hydroxyketone XI (CH_3SO_2Cl, pyridine) to XIII,

followed by reduction in nonenolizing conditions ($LiAlH_4$) yielded the carbinol XIV which was again submitted to mesylation and reduction affording finally Ia, though in lower yield.

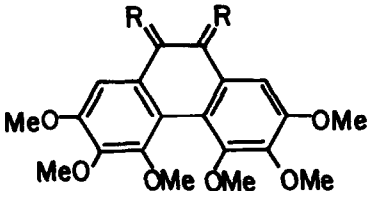
The identity between Ia and desoxyschizandrin has been sustained by the comparison of the IR and UV spectra[16] and by the synthesis of a *trans* isomer IIa which shows similar IR and UV spectra but, unlike the natural compound, exhibits in NMR a single doublet for both methyls (δ 0.87, J=7Hz). The compound IIa was obtained via dehydration of XIV ($KHSO_4$, 170°) and hydrogenation of the formed olefin (Pd/C, ethyl acetate).



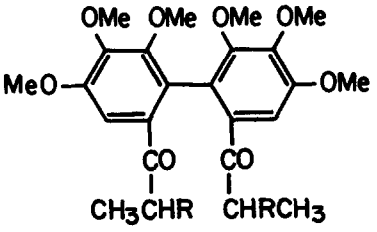
III



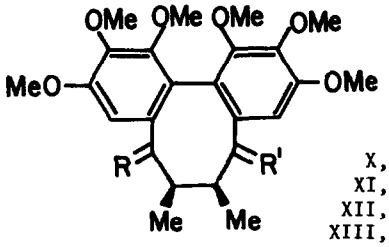
IV



V, R=H,OH
VI, R=O
VII, R=Et,OH



VIII, R=H
IX, R=Br



X, R,R'=O
XI, R=H,OH; R'=O
XII, R=H,OAc; R'=H_2
XIII, R=H,OMs; R'=O^2
XIV, R=H_2; R'=H,OH

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Note added in proof

Further evidence on the identity between Ia and authentic desoxyschizandrin has been provided by comparison of the NMR spectra of both compounds.

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2. For references on the medical literature dealing with the use of these plant extracts as a stimulant, in heart diseases and in psychiatry, see: a) N.K. Kochetkov, A. Khorlin and O.S. Chizhov, *Zh. Obshch. Khim., SSSR, 31,* 3554 (1961); b) L.I. Vigorov, G.N. Novoselova, *Doklady Akad. Nauk. SSSR, 219,* 1492 (1974).
3. a) N.K. Kochetkov, A. Khorlin and O.S. Chizhov, *Tetrahedron Lett.*, 361 (1962); b) N.K. Kochetkov, A. Khorlin and O.S. Chizhov, *Izv. Akad. Nauk. SSSR, Otd. Khim.*, 1036 (1964).
4. See e.g., K. Mislow, M. Glass, R.E. O'Brien, P. Rutkin, D. Steinberg, J. Weiss and C. Djerassi, *J. Am. Chem. Soc., 84,* 1455 (1962). See also the observations on the barrier of inversion of compound X.
5. See E. Ghera, Y. Gaoni and S. Shoua, *J. Am. Chem. Soc., 98,* 627 (1976).
6. Via hydrogenolytic reduction (Pd/C, $HClO_4$, 50 psi, 8 hr) of the diketones Ic and IIc, respectively.
7. The 6,7-dicarboxylate used in ref. 3 was prepared by the procedure of L.V. Dvorken, R.B. Smith and K. Mislow, *J. Am. Chem. Soc., 80,* 486 (1958) which leads to the *trans*-isomer exclusively.
8. A.S. Kende and L.S. Liebeskind, *J. Am. Chem. Soc., 98,* 267 (1976).
9. C.S. Wood and F.B. Mallory, *J. Org. Chem., 29,*3373 (1964).
10. L.F. Fieser "Experiments in Org. Chemistry" p. 337, D.C. Heath and Comp., Boston, 1957.
11. DME-DMSO 1:1 was used as solvent at 60°; for other experimental conditions see ref. 5.
12. Analogous IR carbonyl absorptions were observed also in Ic but not in IIc(unpublished data).
13. Stereochemical considerations in this series will be discussed in a separate report.
14. A mixture of Ia and XII is initially formed by hydrogenation. Our yield was obtained by treating the chromatographically separated XII with $LiAlH_4$ and resubjecting the product to the hydrogenation conditions.
15. In view of a remote possibility of acid-catalyzed dehydration and hydrogenation.
16. The spectra of the natural compound are reproduced in ref. 3b.
17. Spectral and analytical data were in good agreement with the structure of all new compounds.