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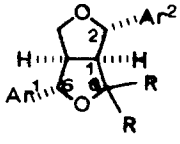
Synthetic Methods for (Exo,Exo)- and (Exo-,Endo)-2,6-Diarylbicyclo[3:3:0]octane Lignans: Syntheses of (±)-Aptosimon, (±)- Styraxin, (±)-Asarinin, and (±)-Pluviatilol

David R. Stevens and Donald A. Whiting*

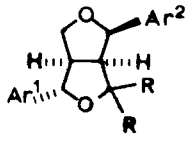
(Chemistry Department, The University, Nottingham, NG7 2RD).

Short practical syntheses are reported of the title lignans (9a), (9c), (13a), and (13b).

2,6-Diaryl-3,7-dioxabicyclooctanes, e.g. (1), (2), in which the aryl units are shikimate-derived, comprise a major sub-group of the natural lignans[1] whose members show a wide range of biological activities[1c], e.g. insect growth inhibition and both stimulant and depressant effects on the central nervous system. The group also includes several lactones (3), i.e. 8-oxo, showing e.g. antitumour activity[2] and plant growth inhibition[3].



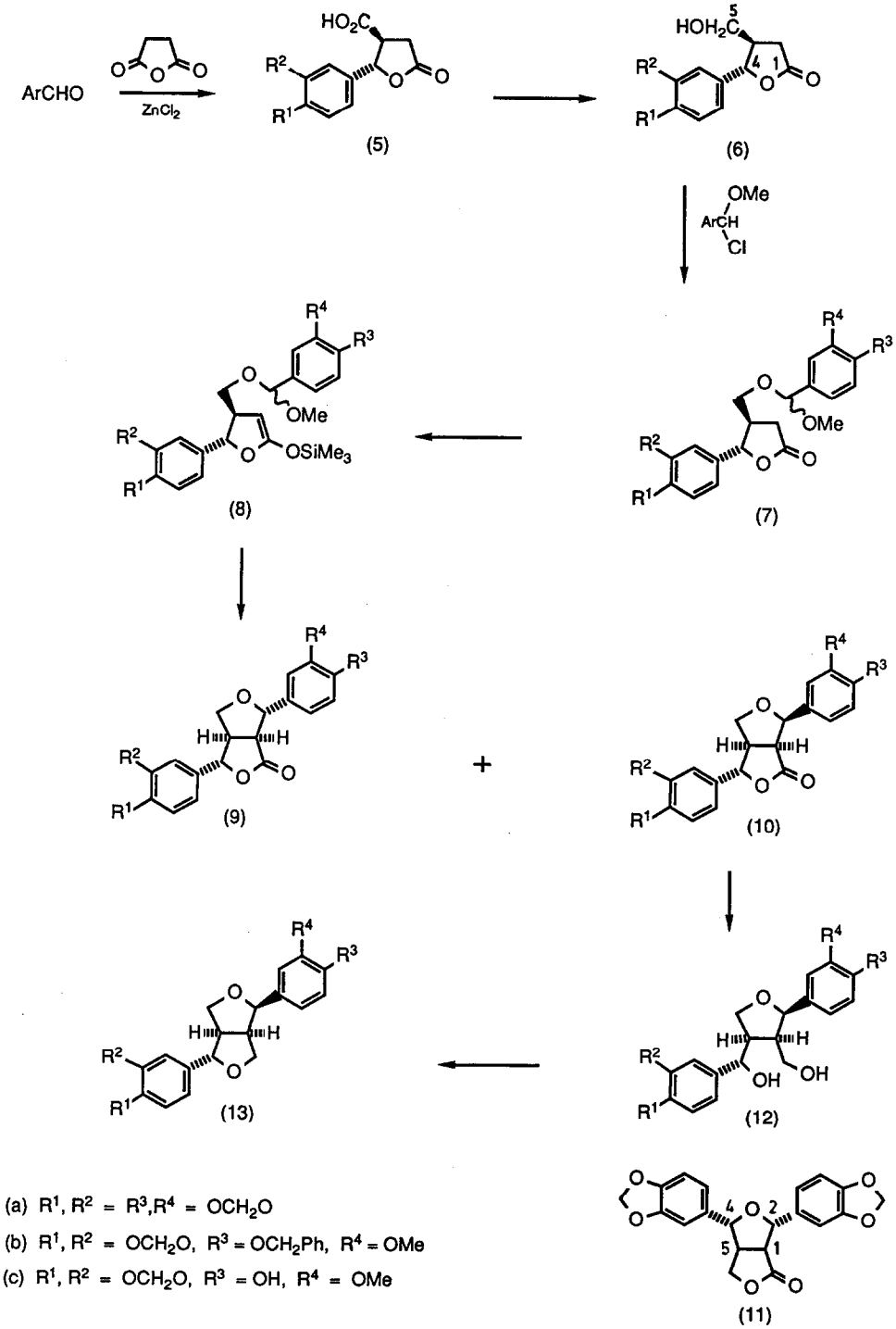
(1, R = H)
(3, R_2 = O)



(2, R = H)
(4, R_2 = O)

There is considerable interest in the synthesis of lignan types (1-4)[4]. A satisfactory synthesis must allow $Ar^1 \neq Ar^2$, a condition fulfilled by only one approach:[5] access through oxidative coupling[4] is unsatisfactory in this respect. In addition both stereochemistries (1), exo-exo, and (2), exo-endo, must be attainable. We present here a new and general solution to these problems and illustrate the methods by syntheses of (±)-styraxin[2] (antitumour), (±)-asarinin[1], (±)-pluviatilol[6], and (±)-aptosimon.[7] The synthesis of the last confirms that its structure must be revised from a 2,4-diarylmonoepoxy-lignanolide to a 2,6-diaryl structure.

The starting material for each of these compounds was the lactone acid (5a), prepared (70%) by the method of Lawlor and McNamee.[8] Reduction of this acid using borane-dimethyl sulphide proceeded efficiently (85%) to afford the lactone alcohol (6a). The <u>trans</u> stereochemistry of (6a), and hence of (5a), was demonstrated by the nOe effect (3.2%) observed at 5-H_2 on irradiation of



(a) $R^1, R^2 = R^3, R^4 = OCH_2O$

(b) $R^1, R^2 = OCH_2O$, $R^3 = OCH_2Ph$, $R^4 = OMe$

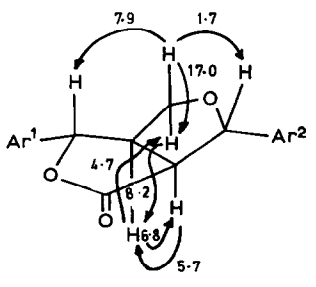
(c) $R^1, R^2 = OCH_2O$, $R^3 = OH$, $R^4 = OMe$

the 4-proton. α-Chloropiperonyl methyl ether was prepared, essentially quantitatively, from piperonal dimethylacetal by reaction with acetyl chloride and a trace of thionyl chloride, and was allowed to react with alcohol (6a) in the presence of triethylamine to provide the mixed acetal (7a), (58%), as a pair of diastereoisomers. Treatment of the acetal (7a) with trimethylsilyl-trifluoromethane sulphonate at 0°, in the presence of triethylamine, initially generated the silyl ketene acetal (8a) and catalysed its cyclisation to the lactones (9a) and (10a) (47%, 1:1.4). This intramolecular aldol reaction[9] impresses the required cis ring fusion. It is not yet apparent whether formation of two C-2 epimers derived from the presence of two diastereoisomers in the acetal (7a), or from other mechanistic factors: the lability of (7a) renders separation of its isomers difficult.

The ^{1}H n.m.r. and m.s. of our sample of the exo,exo-lactone (9a) were indistinguishable from those of natural aptosimon, kindly supplied by Professor Brieskorn. Aptosimon was originally assigned[7] structure (11) i.e. a 2,4-diarylmonoepoxylignanolide structure, chiefly on the basis of a m.s. fragment ion M-85 arising from 1-2, 4-5 cleavage (11). However this evidence has been shown to be inconclusive.[10] The present synthesis shows clearly that aptosimon has the 2,6-diaryl structure (9a). No 2,4-diaryl lactones of type (11) are thus known, although the structure contains the well-known framework of the bisbenzylbutyrolactone lignans.

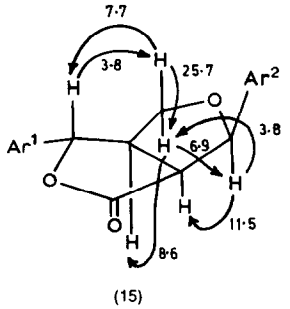
The major lactone (10a), m.p. 158 - 159°, was reduced with lithium aluminium hydride to the diol (12a) which cyclised very readily on exposure to acid to the dioxabicyclooctane (13a) (62% from 10a). This product was demonstrated to be (±)-asarinin, m.p. 132 - 133°, with exo-endo stereochemistry, by spectroscopic comparisons with authentic (-)-asarinin (we thank Professor L. Crombie for a sample of this compound).

The reactions used in this short sequence are compatible with protected phenolic hydroxyl groups. Thus the lactone alcohol (6a) was reacted with α-chloro (benzylvanillyl) methyl ether to provide the mixed acetal (7b), (59%). Cyclisation of this acetal with trimethylsilyl trifluoromethanesulphonate



(14)

nOe data for benzyl styraxin



(15)

nOe data for epiaptosimon

gave the furolactones (9b) and (10b) (34%, 1:1.9). Hydrogenolysis of the exo,exo-isomer (9b) gave (±)-styraxin[2] (9c), m.p. 108°. The ^{1}H n.m.r. spectrum of the synthetic sample was indistinguishable from that of natural styraxin, kindly supplied by Professor Ulubelen, which is a tumour-inhibitory lignan from Styrax officinalis. Reduction of benzyl 2-epistyraxin (10b) with lithium aluminium hydride afforded the diol (12b), cyclised without isolation to (±)-benzylpluviatilol (13b), (47%). Hydrogenolysis (81%) of this ether then gave (±)-pluviatilol[6] (13c), m.p. 142-145°, with ^{1}H and ^{13}C n.m.r. m.s. and i.r. data parallel to that of the natural product.

The stereochemistry of the key lactones (9) and (10) can be directly demonstrated, without reference to natural products, by homonuclear nOe spectra. Thus in the exo-exo group such measurements, as illustrated in (14), clearly show 2-H, 4-H_{ax}, and 6-H to be on one face, with 1-H, 4-H_{eq}, and 5-H occupying the other, while in the 2-epi series, as in (15), 4-H_{ax} and 5-H are adjacent, with 1-H, 2-H, 4-H_{eq}, and 5-H opposed.

It was noted that in the sequence (10)→(12)→(13), the configuration at C-6 was retained. This suggest that a C-6 carbocation is formed, which cyclises under steric control from the axial 2-aryl group. None of the endo-endo isomers were observed.

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