Preparation of Dibenzocyclooctadiene Lignans and Spirodienones by Hypervalent Iodine Oxidation of Phenolic Dibenzylbutyrolactones

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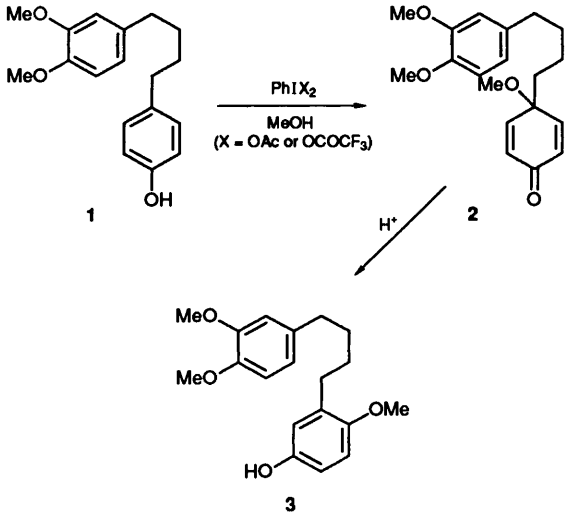
Treatment of the dibenzylbutyrolactone **4** with $PhI(OCOCF_3)_2$ in trifluoroethanol gives as the major product either the dibenzocyclooctadiene **7a** or the spirodienone **8**, depending upon the time allowed for the reaction. The structures and stereochemistry of **7a** and **8** have been determined by NMR methods and by X-ray crystallography. Reaction of a second dibenzylbutyrolactone **5** under the same conditions gives the products **10**–**12**. These reactions provide the first syntheses of spirodienones such as **8** and **10** which have been postulated as intermediates in the biosynthesis of dibenzocyclooctadiene lignans.

We have previously shown[1] that bis(acetoxy)iodobenzene in methanol reacts with phenols to give cyclohexadienones and quinone ketals which are valuable intermediates in organic synthesis.[2] Oxidation of phenols in less nucleophilic solvents (*e.g.* CH_3CN, CF_3CH_2OH) allows intramolecular reactions to proceed leading to cyclisation.[3,4] Of particular interest are examples in which carbon–carbon bond formation is achieved.[5–7] We have attempted to make use of this reaction to imitate the oxidatively induced cyclisations involved in the biosynthesis of various classes of lignans.[8]

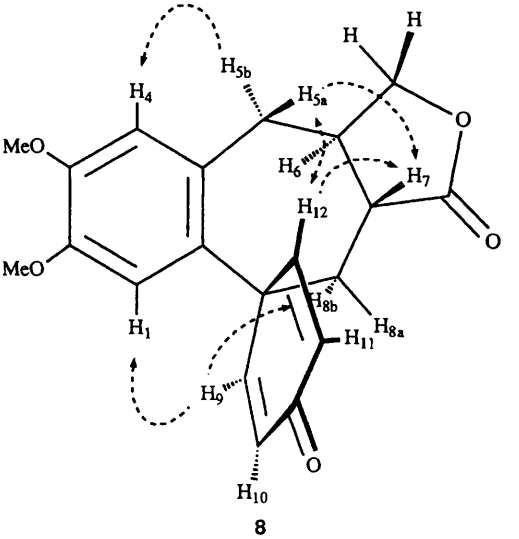
Reaction of the diarylbutane **1** with either $PhI(OAc)_2$ or bis(trifluoroacetoxy)iodobenzene in methanol gave the 4-methoxycyclohexadienone **2** in 30% isolated yield (Scheme 1). However, treatment of **2** with acid gave only the rearranged



Scheme 1

compound **3** with no hint of cyclisation. We therefore turned our attention to the phenolic dibenzylbutyrolactones **4** and **5** in which the two benzyl groups are held in a more rigid orientation. They are also more closely analogous to the lignan precursors than **1**. The dibenzylbutyrolactones **4** and **5** were prepared using the tandem conjugate additon methodology developed in these laboratories,[9] and will be described in a full paper.

Treatment of **4** with $PhI(OCOCF_3)_2$ in methanol gave a mixture of products, amongst which were the cyclohexadienones **6a** and **6b** as well as some cyclised material (Scheme 2). When the same reaction was carried out in the less nucleophilic solvent trifluoroethanol (TFE) the products were the isostegane derivative **7a** and the spirodienone **8**. When the reaction was left for 24 h the major product (48%) was the isostegane derivative **7a**, together with some of the corres-



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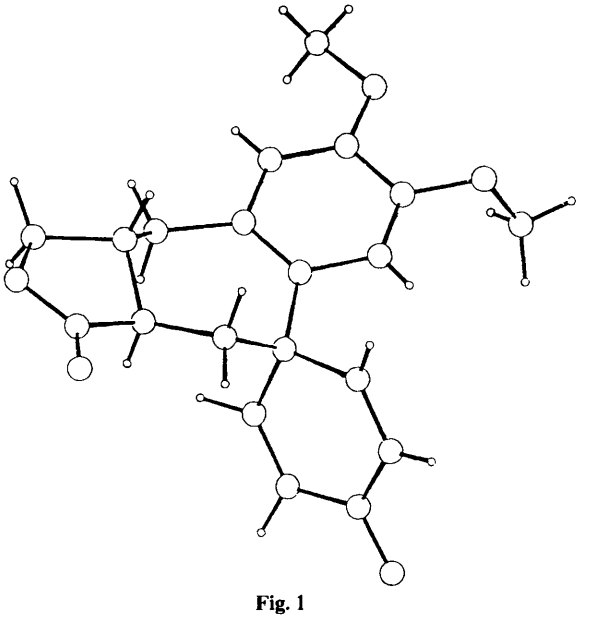
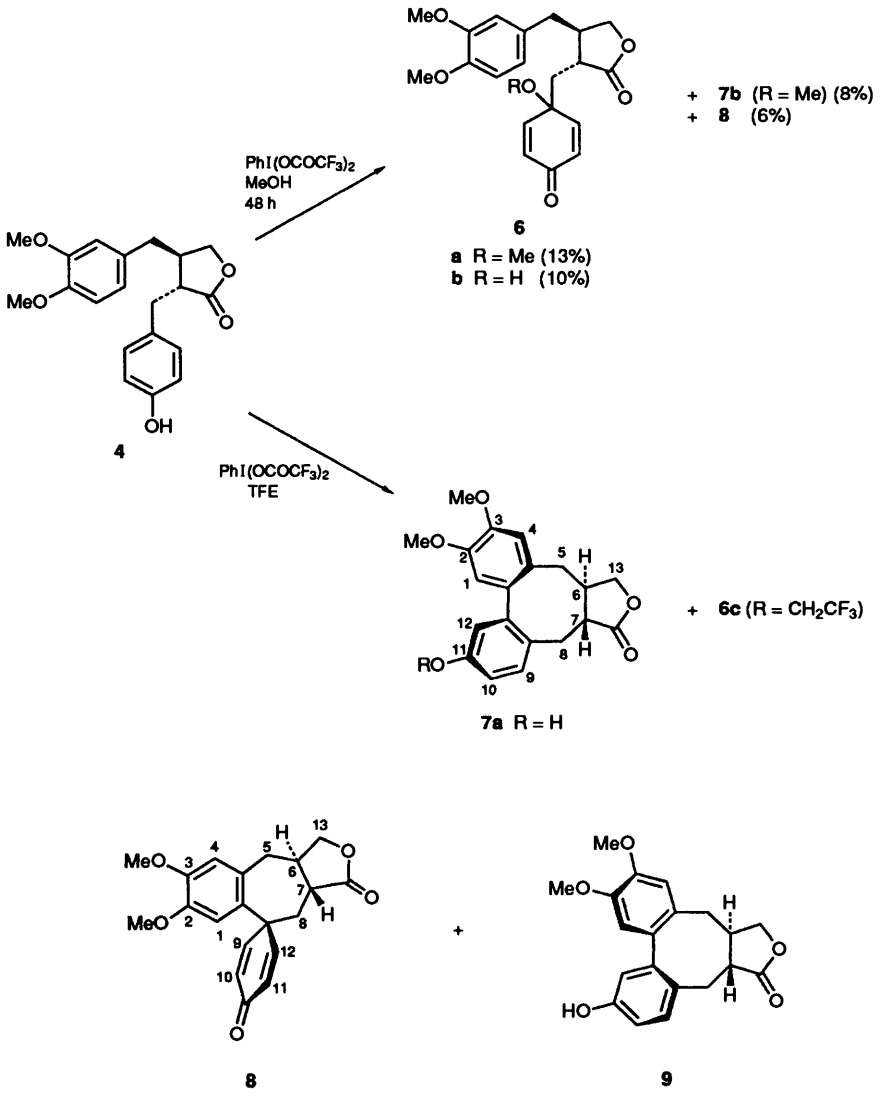
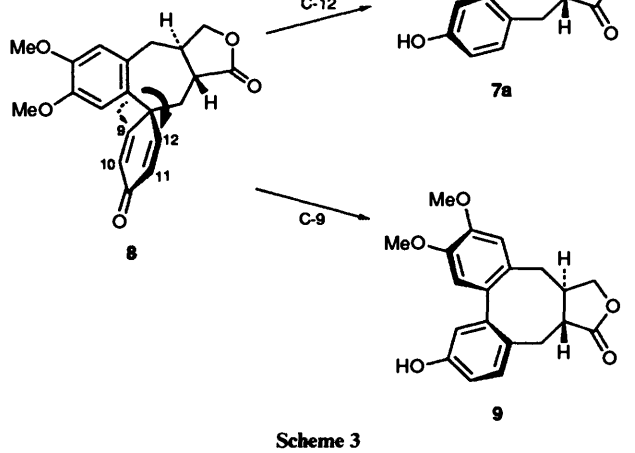


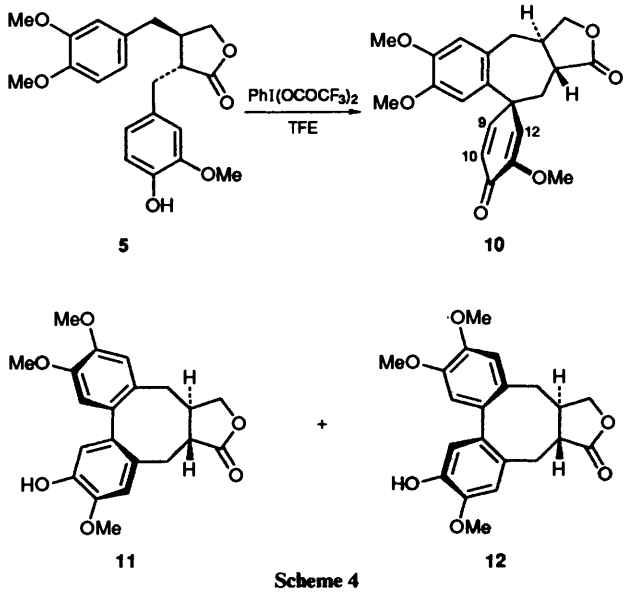
Fig. 1



Scheme 2

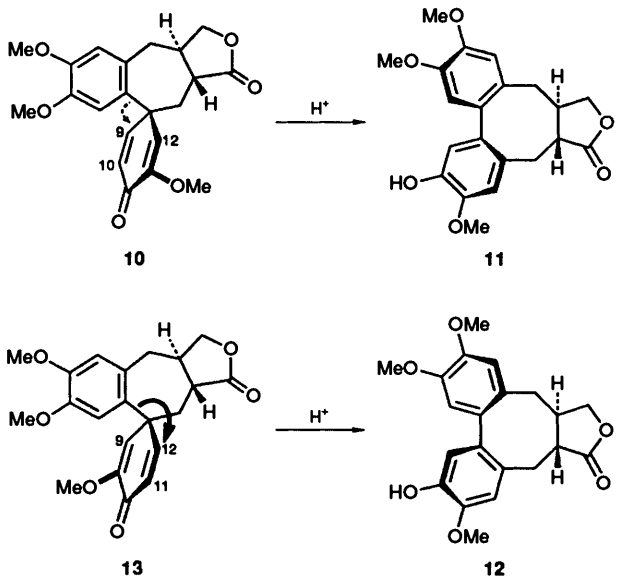


Scheme 3



Scheme 4

ponding stegane isomer **9** (6%). When the reaction was left for only 1 h the major product (47%) was the spirodienone **8**. A minor amount of the trifluoroethoxy compound **6c** was also obtained.



Scheme 5

That **7a** was formed by rearrangement of **8** was confirmed by treating **8** with trifluoroacetic acid in TFE which gave a nearly quantitiative yield of **7a**.

The structure of the dibenzocyclooctadienes **7a** and **9** were based upon a detailed analysis of their ^1H and ^{13}C NMR spectra and comparison with the spectral data of related compounds. In particular, the zero coupling between 5α-H and 6-H, and between 8β-H and 7-H, in **7a** is characteristic of the isosegane series, as is the chemical shift of C-6 and C-7 at *ca.* 47 and 50 ppm respectively.[10,11] The observation of the corresponding carbon signals at *ca.* 39 and 43 ppm in **9** indicated that it belonged to the stegane series.

Furthermore, the observation of a clear NOE between 9-H and the aliphatic protons at C-5 and C-8 showed that both compounds **7a** and **9** had the OH group located at C-11. The structure assigned to **7a** was subsequently confirmed by X-ray crystallography. Thus, **7a** must be formed by an aryl group migration from the spirodienone **8**. The structure assigned to **9** also suggests that if this compound is formed by the same pathway, then it too must be formed by an aryl migration. This contrasts with the results reported for eupodienones 1–9, of which only one, eupodienone-8, rearranges with aryl migration.[12]

The structure assigned to the spirodienone **8** was based upon a detailed analysis of its ^1H and ^{13}C NMR spectra, including NOE experiments, and was confirmed by X-ray analysis. Dreiding models indicate the possible existence of two distinct conformers of **8** differing in the relative orientation of the cyclohexadienone ring and the aryl group. The observed NOE effects and the X-ray structure indicate that the conformation shown in Fig. 1 is the preferred arrangement both in solution and in the solid state. Thus, the observed NOE effects between 1-H and 9-H, 5a-H and 12-H, 5a-H and 7-H and 7-H and 12-H are only consistent with this conformation.

Models indicate that aryl migration to C-9 would give the stegane isomer **9**, whereas aryl migration to C-12 would give the isostegane **7a** (Scheme 3).[13] Furthermore, the latter pathway in this case is considerably more favourable, leading to relief of strain.

Finally, treatment of the second dibenzylbutyrolactone **5** with $PhI(OCOCF_3)_2$ in TFE gave a low yield (13%) of the spirodienone **10** and a mixture (14%) of the two dibenzocyclooctadienes **11** and **12** (Scheme 4).

There are two possible isomeric structures for the isolated dienone **10**, depending upon whether the methoxy group is attached to C-10 or C-11. NOE experiments clearly indicate that the compound isolated has the structure **10** shown with the OMe group at C-11. Furthermore, ^1H and ^{13}C NMR spectra of **11** and **12** indicate that they belong to the stegane and isostegane series respectively, and that the phenolic OH group is at C-11 in **11**. Significantly, reaction of the spirodienone **10** with perchloric acid gave a quantitative yield of **11** only. This therefore indicates that **11** is formed by an aryl migration to C-9 (Scheme 5). Examination of molecular models suggests that **12** must be formed from the isomeric dienone **13**. These reactions provide the first synthesis of spirodienones such as **8** and **10** which have been proposed as intermediates in both the synthesis[13] and biosynthesis[8] of dibenzocyclooctadiene lignans. The reactions also provide a rapid biomimetic route to compounds of the dibenzocyclooctadiene series.

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