Effective, direct biomimetic synthesis of dibenzocyclooctene lignans by hypervalent iodine oxidation of phenolic dibenzylbutyrolactones

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Readily available *trans*-2,3-dibenzylbutyrolactones are converted in high yields *via* 4-hydroxycyclohexa-2,6-dienones into dibenzocyclooctene lignans by treatment with phenyliodonium diacetate in aqueous methanol followed by trifluoroacetic acid.

We have previously shown [1] that phenyliodonium bis(trifluoroacetate) (PIFA) reacts in trifluoroethanol (TFE) with readily available *trans*-2,3-dibenzylbutyrolactones **1a** and **1b**[2] to produce isosteganes **2a**, **2b** and steganes **3a** and **3b** (Scheme 1). The reactions proceed *via* spirodienones which subsequently rearrange to give the dibenzocyclooctene products **2** and **3**.

From **1a** the yield of **2a** was 48% and **3a** was 6%. From **1b** only 13% of a mixture of **2b** and **3b** was obtained. Thus, though the reaction was of great interest as providing a biomimetic model for the production of dibenzocyclooctene lignans, it was synthetically inefficient. However, as some of these lignans exhibit anti-cancer activity [3] it was of interest to explore further this novel oxidative approach to their synthesis.

By using a solvent consisting of methanol and water (9:1, v/v), compound **1a** was converted into the 4-hydroxycyclohexadienone **4a** in 91% isolated yield (Scheme 2). Moreover, **4a** on exposure to trifluoroacetic acid (TFA) gave a mixture (88:12) of **2a** and **3a** in 95% isolated yield.

The conversion of **4a** into **2a** and **3a** proceeds *via* **5a** which can rearrange by an aryl migration to either C-3 or C-5 (Scheme 3). The fixed conformation of ring B (as shown by NOE effects and X-ray structure)[4] makes C-3 the favoured terminus by path i. Thus, the aryl group preferentially migrates to the 'top' of the cyclohexadienone ring to yield isostegane **2a**.

Rather than isolate intermediates **4** and **5** we decided to try to proceed directly from **1** to **2** and **3**, using the same reagents as in Scheme 2, with the results shown in Table 1.

Table 1 demonstrates that we had achieved our initial objective of attaining a direct and efficient route from **1** to **2** and **3**. A striking fact that emerged was that the isostegane to stegane ratios of the products derived from **1a** and **1c** were very similar, but that the ratio altered considerably for the oxidation of **1b**.

Owing to the symmetrical 2,6-disposition of groups R^1 and R^2 on the phenolic rings of **1a** and **1c**, oxidation can in each case lead to only one spirodienone, **5a** and **5c**. Migration then preferentially follows path i for each compound to give dominance of isostegane products **2a** and **2c**. However **1b** is unsymmetrically substituted on the phenolic ring and can give rise to two spirodienones, **6** and **7** with the methoxy group on the cyclohexadienone ring positioned 'down' or 'up', respectively (Scheme 4).

Table 1 Yields of **2** + **3** and ratios of **2**:**3** produced directly from **1**

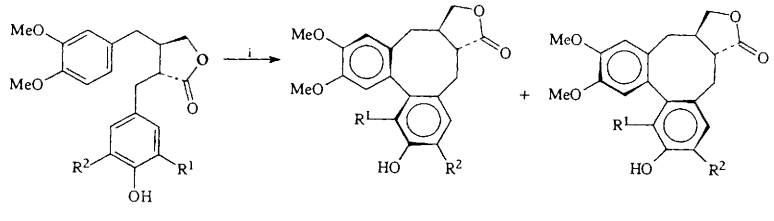
Phenol	Yield (%)[a]	Ratio of **2**:**3**
1a	87	88:12
1b	81	50:50
1c	75	87:13

[a] Isolated, purified products.

For **6** the aryl migration should proceed entirely by path i, as this process follows the sterically favoured trajectory onto a terminus without an α-methoxy substituent. The product would be isostegane **2b**.

However, for **7** aryl migration by path i would yield isostegane **8**, which could not be detected. This is in line with Taylor's observation [5] regarding the eupodienones in which there was neither an aryl nor alkyl migration to a terminus with an α-methoxy group. Kametani made a similar observation in the homoproaporphine series.[6] Therefore path ii would be favoured, an inference that was confirmed by treatment of pure, isolated **7** with a catalytic quantity of perchloric acid to give only the stegane **3b** in quantitative yield.[4] We were never able to isolate **6**, presumably because there are two favourable factors associated with aryl migration to C-3, and therefore the migration is particularly facile.

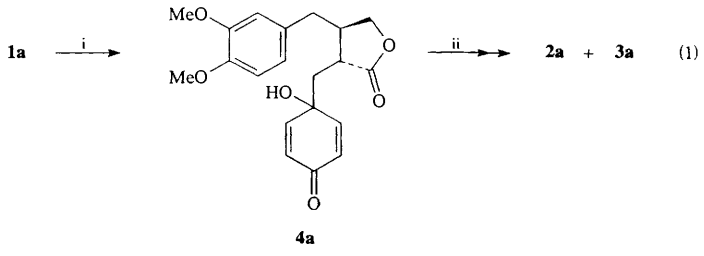
In summary, our hypothesis for the formation of a 1:1 mixture of **2b** and **3b** from **1b** is that the initially formed 4-



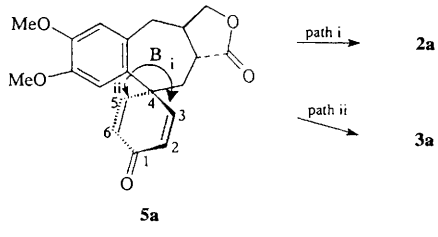
1 **a** $R^1 = R^2 = H$
b $R^1 = H$, $R^2 = OMe$
c $R^1 = R^2 = OMe$

2 **3**

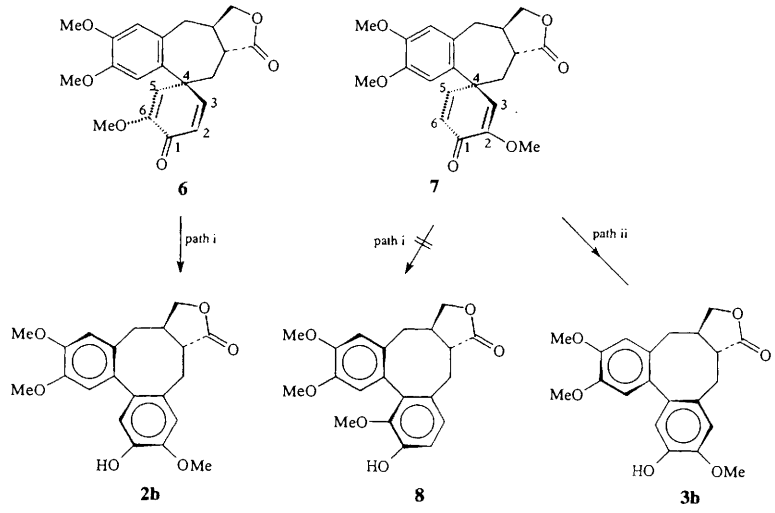
Scheme 1 *Reagent:* i, PIFA/TFE



Scheme 2 *Reagents:* i, PIFA/MeOH, H_2O (9:1); ii, TFA



Scheme 3



Scheme 4

hydroxycyclohexadienone **4b** undergoes cyclisation to a 1:1 mixture of **6** and **7**, each of which undergoes a specific aryl migration to give a 1:1 mixture of **2b** and **3b**.

It is important, for considerations of the generality of the sequence, that though aryl migration to a carbon α- to a carbon bearing a methoxy group is disfavoured, if there is no alternative, it can and does occur. This is shown by the rearrangement of the spiro dienone **5c** mainly by path i to give **2c** and **3c** in excellent yield.

The process outlined in this paper is a mild and efficient route from readily available precursors to complex dibenzocyclooctenes. It should be of utility for the production of a wide variety of these compounds in order to study their physiological properties.

Experimental

Procedure for the conversion of 1a into a mixture of 2a and 3a

A dry 100 cm^3 round-bottomed flask was fitted with a magnetic stirrer and charged with the starting phenol **1a** (0.5 g, 1.46 mmol). The phenol was then dissolved in a methanol–water mixture (9:1; 50 cm^3) and PIFA (3.14 g, 7.3 mmol), dissolved in the same solvent mixture (20 cm^3), was added slowly to the stirred solution of **1a**.

The resulting solution was stirred for 15 min after which the solvent was rapidly removed by evaporation using an oil pump, to yield a red gum (3.49 g). The gum was dissolved in EtOAc (20 cm^3) and the solution washed with water (3 × 30 cm^3), dried ($MgSO_4$) and filtered. Neutral silica (10 g) was added to the solution and the solvent removed by oil pump. The resulting silica was then placed on the top of a neutral silica column. Elution with light petroleum removed all of the iodobenzene formed during the reaction and elution with a mixture of light petroleum–EtOAc (3:7) gave a mixture of products **2a**, **3a**, **4a** and **5a** and left any unchanged PIFA on the column.

The fractions containing the mixture of products were combined and the solvent removed to yield an orange gum (0.48 g) which was dissolved in methanol (20 cm^3). TFA (20 cm^3) was added to the solution with constant stirring and the mixture left for 6 h. After this time the reaction had gone to completion and the solvents were removed by evaporation under reduced pressure. The residue was taken into EtOAc (30 cm^3) and the solution washed with water (3 × 30 ml), dried ($MgSO_4$), filtered and evaporated. The resulting residue contained only a mixture of the desired products **2a** and **3a** (0.44 g, 87%) and HPLC analysis showed a ratio of isomers of 88:12 for isostegane **2a** to stegane **3a**. Repeated crystallisations from EtOAc–light petroleum gave **2a** (0.365 g), mp 187–189 °C and **3a** (0.047 g), mp 184–186 °C, in a ratio of 89:11.

Acknowledgements

We thank the EPSRC and the Wellcome Foundation for financial backing for this work.

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Paper 5/04216J
Received 30*th June* 1995
Accepted 21*st July* 1995