Synthesis and Configurational Analysis of a Dimer of Oxyresveratrol Tetramethyl Ether

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The diasteroisomers of 2-(3,5-dimethoxybenzyl)-1,2-di(2,4-dimethoxyphenyl)-5,7-dimethoxyindane are prepared and stereochemically characterized.

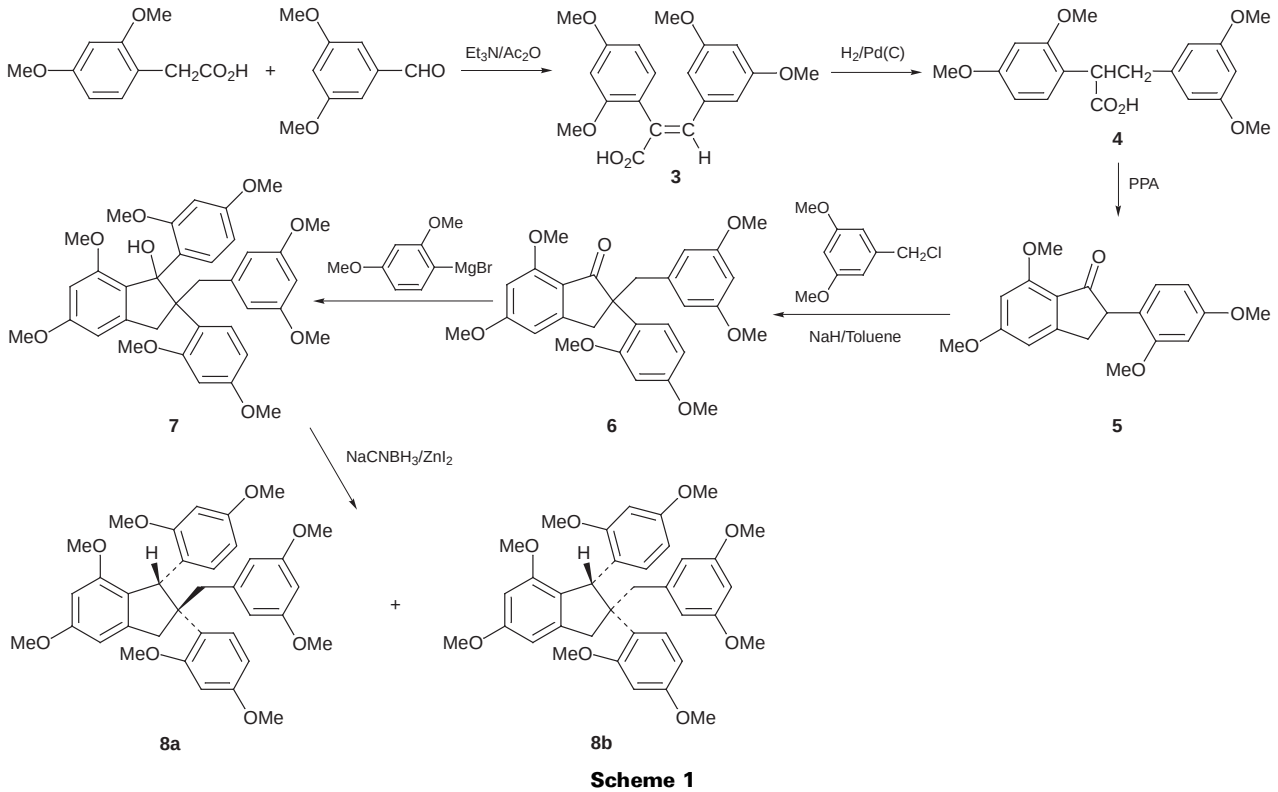
The indanes are of practical and theoretical interest due to their presence in plants and the biological activity of some of their derivatives. A set of natural indanes are produced by biopolymerization of oxystilbenes.[1]

Taking into account that many synthetic compounds possessing the dihydro[1*H*]indene skeleton have shown significant biological activity,[4] and considering our recently obtained results in the stereoselective synthesis of diastereoisomers of 2-benzyl-1,2-diphenylindane,[5] we were interested in exploring the synthesis of diasteroisomers **8a** and **8b** dimers of the tetramethylether of oxyresveratrol. In accordance with the importance of these compounds, there has been a large number of synthetic studies related with this ring system, but with a few exceptions,[6] there is lack of general stereoselective methods.

Initially, α-2,4-dimethoxyphenyl-3,5-dimethoxycinnamic acid (**3**) was obtained by the Perkin reaction.[7] (Scheme 1). It was assigned the *cis* configuration on the basis of the chemical shifts of its ^{1}H NMR spectrum *versus* calculated values.[8] Furthermore, this configuration was consistent with that of 2,3-diphenylpropenoic acid obtained by the same reaction.[9] Hydrogenation of **3** yielded the saturated acid **4** Intramolecular acylation of **4** with polyphosphoric acid (PPA) yielded indanone **5** which was then alkylated with 3,5-dimethoxy-1-chloromethylbenzene to render **6**.

The Grignard derivative from 1-bromo-2,4-dimethoxybenzene could not be obtained by the classic technique. Compounds containing oxy-groups tend to form an insoluble coating on the magnesium surface in their Grignard preparations, perhaps due to their propensity to form associated polymeric Grignard reagents,[10] thus they appear inert towards magnesium. Activated magnesium, especially the magnesium-1,2-dibromoethane system which provides continuous surface activation, is then generally used,[10] and the bromide of 2,4-dimethoxyphenyl magnesium was successfully prepared with this system. Treatment of indanone **6** with the above Grignard reagent afforded a single indanol **7**.

To assign a configuration to alcohol **7**, the main product of the reaction of BrMgPh on 2-benzyl-2-phenylindanone was first considered (compound **9**, Fig. 2). In that specific case, the alcohol was formed by the attack of the Grignard reagent on the indanone from the same side as the substituted phenyl group at the 2-position atom (*syn* attack).[5] This preference is attributable to the coordination effect of the phenyl group



Scheme 1

* To receive any correspondence.

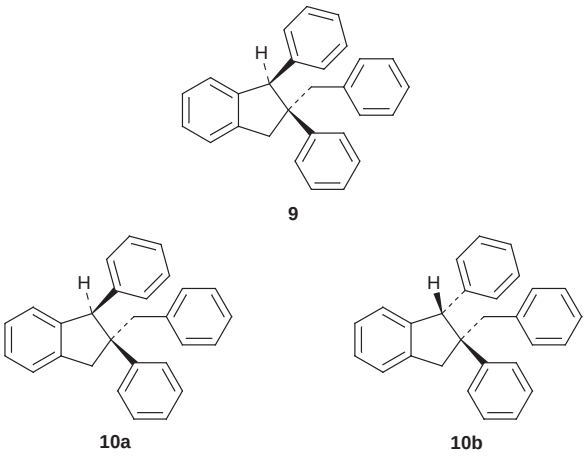


Fig. 2

with the magnesium for presenting an attractive orbital interaction with the phenyl π system. It may be expected that this coordination effect should be even stronger with the 2,4-dimethoxyphenyl group at the 2 position,[5] so that the configuration of **7** would correspond to a *cis* arrangement of two 2,4-dimethoxyphenyl groups.

Hydrogenolysis of **7** with $ZnI_2-NaCNBH_3$ yielded a racemic mixture of **8a** and **8b** (2:3). Mass spectra of **8** disclosed a signal at $M^+ = 600$ for each compound. Chemical shifts in the NMR spectra of these two compounds were in accord with those of the diastereoisomers of 2-benzyl-1,2-diphenylindane[5] (Table 1) (Fig. 2).

Comparison of the chemical shifts in the ^{13}C NMR spectrum of the substituent benzylic methylene groups (CH_2Ar) on the C-2 atom, between both epimers, shows for one a marked displacement to higher fields (**8b**) ($\Delta\delta = 8.5$ ppm) implying that this benzylic methylene group is subjected to a γ gauche effect in *cis* position to the aryl group linked to the C-1 atom. By contrast, the effect presented by the benzylic methylene group of compound **8a** is minor because it corresponds to a γ-*gauche* effect in *trans* position to the aryl group linked to the C-1 atom. These spectroscopic data allowed the assignment of the configuration of diastereoisomer compounds **8**: 2-(3,5-dimethoxybenzyl)-*r*-1, *c*-2-di(2,4-dimethoxyphenyl)-5,7-dimethoxyindane (**8a**) and 2-(3,5-dimethoxybenzyl)-*r*-*l*,*t*-2-di(2,4-dimethoxyphenyl)-5,7-dimethoxyindane (**8b**).

Table 1 Selected ^1H NMR chemical shifts (δ) of methyne and methylene groups

	10a	**8a**	**10b**	**8b**
CH_2 (*J*/Hz)	3.05 (13.3)	3.07 (12.8)	2.26 (13.3)	2.62 (12.8)
	3.21 (15.7)	3.39 (15.0)	2.97 (13.3)	3.02 (12.8)
	3.32 (13.3)	—[a]	3.20 (15.7)	3.20 (15.5)
	3.56 (15.7)	—[a]	3.33 (15.7)	3.36 (15.5)
H-1	4.60	4.94	4.57	4.93

[a] Overlapped with methoxy groups.

Techniques used: ^1H and ^{13}C NMR, MS, TLC.

Figures: 2

Schemes: 2

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