



High-yielding TfOH-catalyzed condensation of phenols with aromatic aldehydes at high pressure. A model synthesis of the benzylidene biphenol key skeleton of blepharismins[†]

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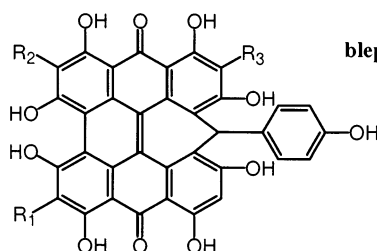
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Abstract—An approach to the benzylidene biphenol key component of blepharismins, photoreceptor pigments isolated from *Blepharisma japonicum*, is reported. This method relies on an efficient TfOH-catalyzed condensation of phenols with aromatic aldehydes in EtOH as a solvent at 3 kbar pressure. © 2001 Elsevier Science Ltd. All rights reserved.

Blepharismins 1–5 (**1–5**), which have recently been isolated from the protozoan *Blepharisma japonicum*, are pink-colored pigments that represent a new structural class of natural products.² Not only do blepharismins act as photosensors responsible for the photobehavior of that unicellular organism, they also exhibit a variety of biological activities including anti-retroviral activity.³ Over the past few years we have been very interested in discovering their mode of action at a molecular level. However, the limited quantities of blepharismins available from natural sources prompted us to try to synthesize these molecules.⁴

Structurally, blepharismins can be classified into naturally occurring polycyclic quinones, like hypericin and stentorin,⁵ and can be divided into three discrete com-

ponents: a perylenequinone structure, an anthraquinone segment, and a benzylidene biphenol moiety. The latter of these gives blepharismins the ability to generate considerable intramolecular distortion, and is a challenging issue for synthetic chemists. The most explicit answer to this problem must be the condensation of phenols with benzaldehydes. Although several methods to achieve this type of transformation have been reported in the literature, most are unsatisfactory with respect to their generality, selectivity, productivity and efficiency.⁶ We expected that the application of a high-pressure technique would provide a new general alternative to more classical methods, since it is well known that organic reactions with a large molecular contraction are highly favorable under high pressure.⁷ We describe here the realization of this expectation.



blepharismin-1 (1): $R_1 = R_2 = \text{Et}$, $R_3 = \text{H}$

-2 (2): $R_1 = \text{Et}$, $R_2 = i\text{-Pr}$, $R_3 = \text{H}$

-3 (3): $R_1 = R_2 = i\text{-Pr}$, $R_3 = \text{H}$

-4 (4): $R_1 = \text{Et}$, $R_2 = i\text{-Pr}$, $R_3 = \text{Me}$

or $R_1 = i\text{-Pr}$, $R_2 = \text{Et}$, $R_3 = \text{Me}$

-5 (5): $R_1 = R_2 = i\text{-Pr}$, $R_3 = \text{Me}$

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To establish the optimum conditions, the reaction between 4-*t*-butylphenol (**6**) and *p*-anisaldehyde (**7**) was examined under a variety of conditions (Table 1).⁸ Of several acids tested, the best results were obtained using a catalytic amount of trifluoromethanesulfonic acid (TfOH) as a very strong acid,⁹ and at 3 kbar pressure the reaction was dramatically accelerated to give the adduct **8** in 87% yield (run 4). However, no significant increase in the product yield was observed at higher pressures (runs 5 and 6).

The general feasibility of this method is shown in Scheme 1.^{10–14} Thus, several reactions with a series of phenols and aldehydes gave the desired adducts **9–18** in good yields. For the less-reactive substrates such as 2,4-dimethylphenol, *p*-chlorobenzaldehyde and *p*-nitrobenzaldehyde, rather drastic conditions were necessary to prepare sufficient amounts of the products **10**, **14** and **15**. We also examined the reaction using propanal as an aliphatic aldehyde, and in this case a fairly low yield of the adduct **19** (10%) was observed, accompanied by a xanthene-type compound **20** (31%).¹⁵ Terephthalaldehyde also reacted smoothly with 6.0 equiv. of 2-naphthol to produce tetranaphthol **18** in 85% yield.

With these results in hand, we were able to construct a key skeleton of blepharismins (Scheme 2). Thus, treatment of naphthol **21** with **7** according to the standard procedure produced the adduct **22** in 83% yield. Methylation of the two phenol groups followed by debenzoylation under catalytic hydrogenation conditions gave bisnaphthol **23** in 85% yield. Intramolecular oxidative biaryl coupling of this sample took place by Koga's copper-catalyzed reaction¹⁶ to furnish the benzylidene biphenol derivative **24**, which is a key component of blepharismins, in 73% yield. Interestingly, the spectral data show that **24** exists mostly as a cyclized hemiacetal form of **25**, implying the spatial proximity of two phenol functions.¹⁷

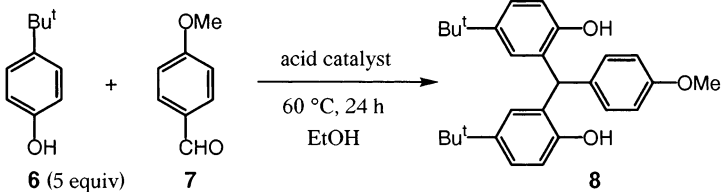
In conclusion, we have developed a simple and efficient synthetic method for the high-pressure-promoted condensation of phenols with aromatic aldehydes using TfOH as a strong acid catalyst. Furthermore, the successful construction of **24**, a key skeleton of blepharismins, demonstrates the potential utility of this technique to derive blepharismins themselves. Further studies along these lines are now in progress.

Typical experimental procedure for the preparation of **8:** A mixture of 4-*t*-butylphenol (**3b**; 750 mg, 5.0 mmol), *p*-anisaldehyde (**7**, 136 mg, 1 mmol), and TfOH (25 mg, 0.16 mmol) in EtOH (1.5 ml) was placed in a Teflon reaction vessel at 3 kbar and 60°C for 24 h. After evaporation of the solvent, the crude product was purified by preparative TLC (hexane/AcOEt=2:1) to give **8** (362 mg, 87%) as a colorless solid: mp 125.5–127.0°C (from hexane–CH₂Cl₂); FTIR (KBr) 3352, 1510 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.18 (18H, s), 3.81 (3H, s), 4.89 (2H, br s), 5.82 (1H, s), 6.76 (2H, d, *J*=8.5 Hz), 6.86 (2H, d, *J*=8.6 Hz), 6.96 (2H, d, *J*=2.4 Hz), 7.09 (2H, d, *J*=8.6 Hz), 7.15 (2H, dd, *J*=8.5, 2.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 31.4 (×6), 34.1 (×2), 44.3, 55.2, 114.0 (×2), 115.7 (×2), 124.7 (×2), 127.2 (×2), 128.3 (×2), 130.2 (×2), 133.4, 143.7 (×2), 151.2 (×2), 158.4.

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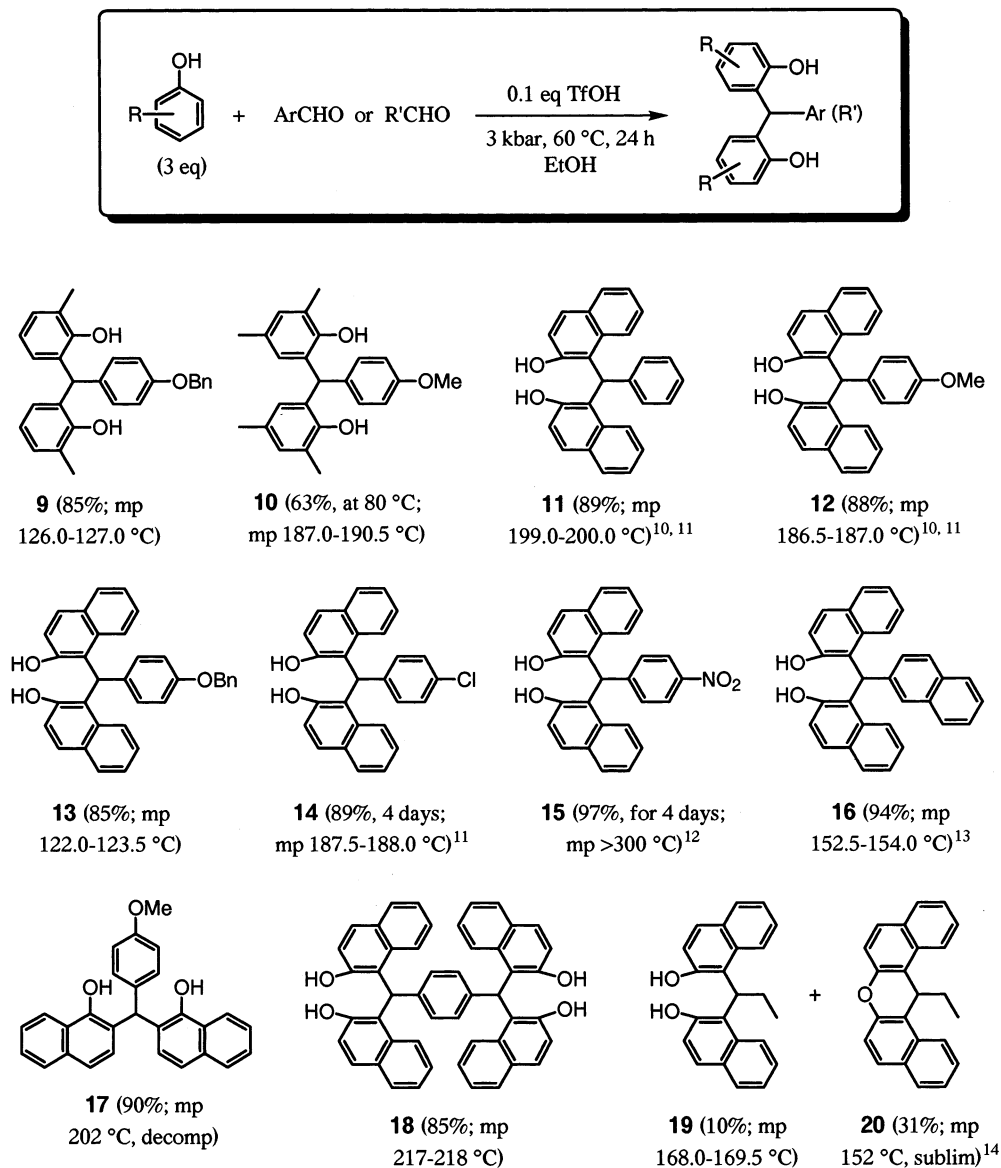
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Table 1. Acid-catalyzed condensation of **6** with **7** under various conditions

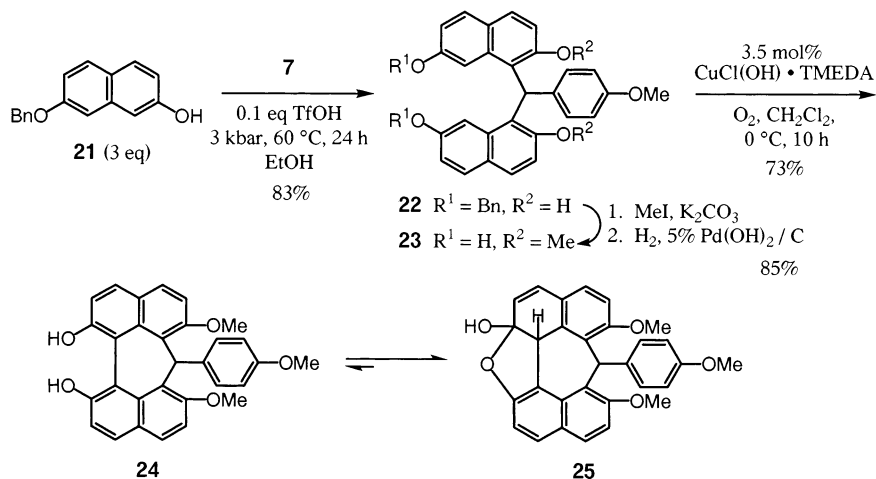
			
Run	Catalyst (0.1 equiv.)	Pressure (kbar)	Yield of 8 (%) ^a
1	CH ₃ COOH	0.001	No reaction
2	Conc. HCl	0.001	29 ^b
3	TfOH	0.001	46
4	TfOH	3	87
5	TfOH	5	87
6	TfOH	7	86

^a Isolated yield.

^b 3 equiv. of **6** was used.



Scheme 1.



Scheme 2.

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17. Data for **25**: Mp 86.5–88.0°C (amorphous solid); FTIR (KBr) 3436, 1626, 1508, 1263 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.25 (1H, br s), 3.70, 3.89, 3.95 (each 3H, s), 4.77 (1H, s), 5.82 (1H, d, *J*=9.9 Hz), 6.46 (1H, d, *J*=9.9 Hz), 6.72 (2H, d, *J*=8.8 Hz), 6.80 (1H, d, *J*=8.3 Hz), 6.83 (2H, d, *J*=8.8 Hz), 6.93 (1H, d, *J*=8.8 Hz), 7.02 (1H, d, *J*=8.3 Hz), 7.16 (1H, d, *J*=9.0 Hz), 7.18 (1H, s), 7.59 (1H, d, *J*=8.8 Hz), 7.72 (1H, d, *J*=9.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 34.7, 50.5, 55.2, 56.3, 57.6, 107.4, 109.5, 109.9, 112.0, 113.9 (×2), 117.0, 118.4, 120.9, 122.2, 126.2, 127.5, 127.8 (×2), 129.0, 129.6, 129.8, 130.1, 131.4, 134.9, 135.6, 153.2, 156.1, 157.7, 158.0; HRMS, calcd for C₃₀H₂₄O₅+H⁺ 465.1702, found 465.1683. Supportive evidence was also obtained by X-ray analysis.