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A new synthetic strategy for the synthesis of bioactive stilbene dimers. A direct synthesis of amurensin H

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ABSTRACT

2,3-Diarylbenzofurans are efficiently generated by the cyclization of ortho-benzyloxybenzophenones using the hindered phosphazene base P_4-*t*-Bu.

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Stilbene dimers are a class of natural products that are broadly distributed and exhibit diverse biological activity.[1] Representative examples are shown in Figure 1. Amurensin H (**1**), isolated from *Vitus amurensis*, shows significant anti-inflammatory activity in mice models. Compound **1** may have therapeutic potential for the treatment of allergic airway inflammation.[2] It has also been reported to treat chronic obstructive pulmonary disease.[2] It has been synthesized by an oxidative coupling reaction according to a biosynthetic pathway.[3] Gnetuhainin B (**2**) was isolated from *Gnetum hainanense* which grows only in the People's Republic of China.[4] Gnetuhainin G (**3**) is a novel furobenzofuran from *G. hainanense* and is an antioxidant.[5] α-Viniferin, structurally related to **1**, has been reported to be a potent MRP1 transport inhibitor.[6]

Several synthetic routes to benzofurans such as **1** are known.[7] The majority of these syntheses take place via disconnection A (Fig. 2). This includes the reaction of *ortho*-halophenols with acetylenes,[8] and the oxidative cyclization[9] of hydroxy stilbenes. A related pathway is the palladium-mediated arylation of benzofurans.[10] In contrast, disconnection B has rarely been utilized to prepare diarylbenzofurans. A notable example is a photocyclization that takes place via an intramolecular hydrogen atom abstraction of the benzylic hydrogen atom followed by radical recombination and dehydration.[11]

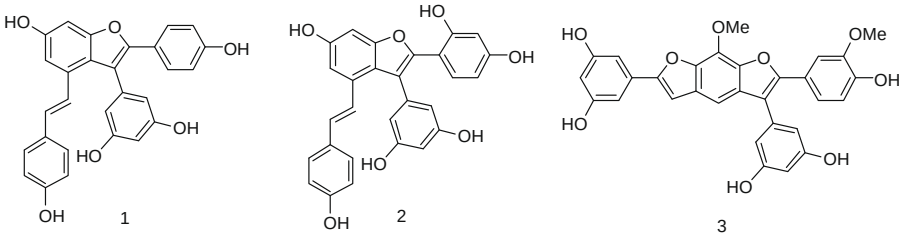

Figure 1. Structures of diarylbenzofurans.

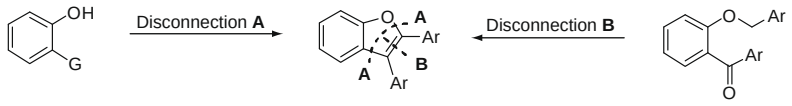

Figure 2. Synthetic strategies for benzofurans.

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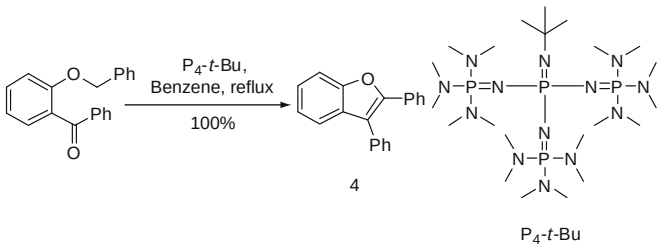
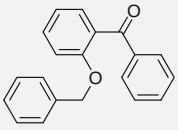
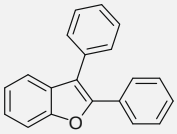
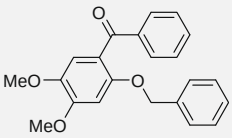
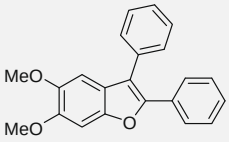
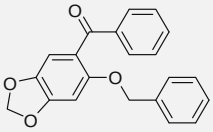
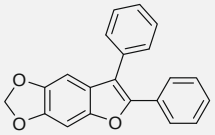
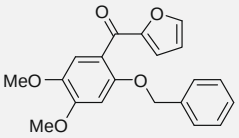
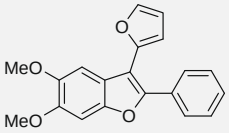
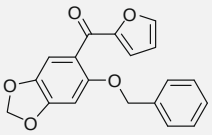
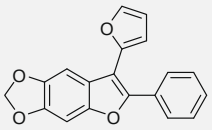
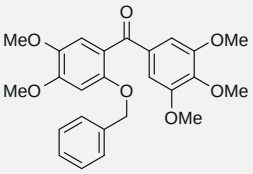
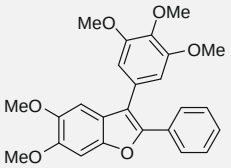
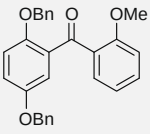
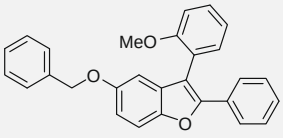


Scheme 1. Synthesis of Benzofuran **4**.

In connection with our studies of the synthetic potential of the hindered base P_4-*t*-Bu,[12] we reacted 2-benzyloxybenzophenone with P_4-*t*-Bu and isolated **4** in 100% yield (Scheme 1). We then evaluated an array of benzophenones. Our results are depicted in Table 1.

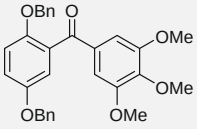
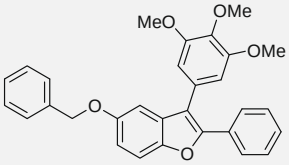
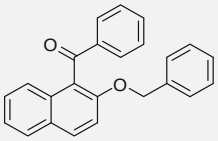
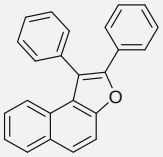
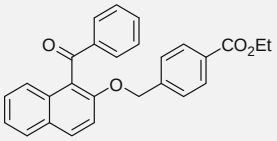
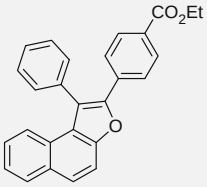
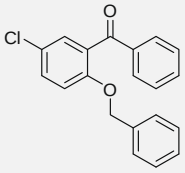
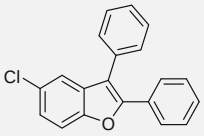
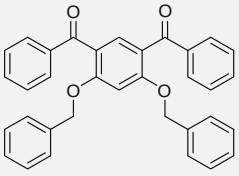
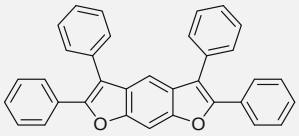
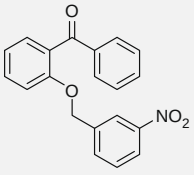
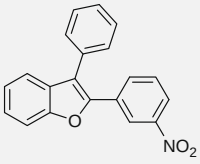
As the results in Table 1 illustrate, this cyclization is compatible with a variety of functional groups and represents a convenient entry to aryl substituted benzofurans.[13] As entry 12 indicates, this chemistry is extendable to the benzo[1,2-*b*:5,4-*b*′]difuran ring system in **3**. Interestingly, this cyclization proceeds in good yield de-

Table 1
Synthesis of benzofurans from benzophenones

S. No	Reactant	Time (h)	Product	Yield (%)
1		3		100
2		6		75
3		6		78
4		6.5		70
5		6		72
6		8		76
7		7.5		60

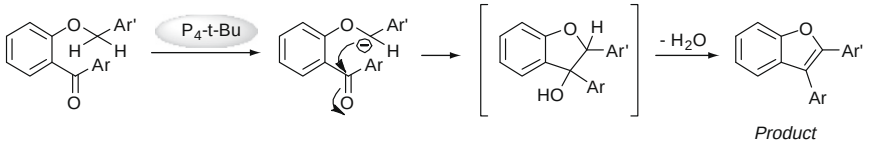
(*continued on next page*)

Table 1 (*continued*)

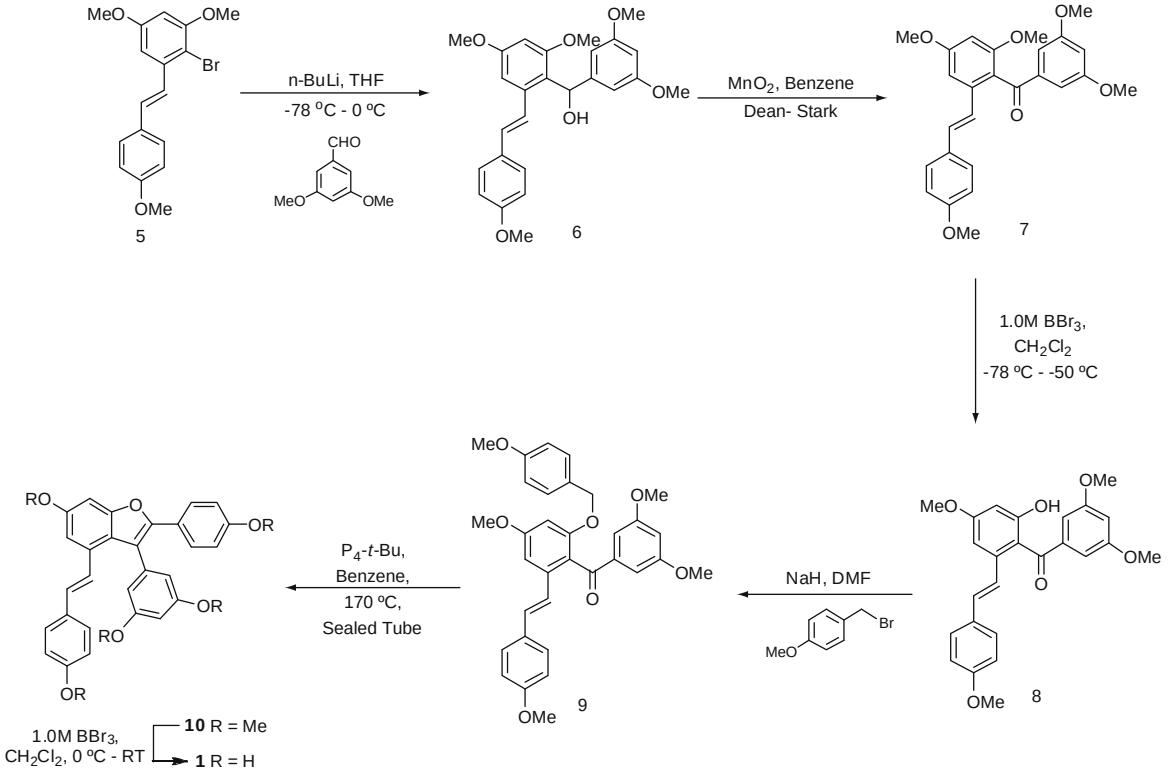
S. No	Reactant	Time (h)	Product	Yield (%)
8		7		59
9		6.5		66
10		7		67
11		8		72
12		12		61
13		4.5		65

spite the presence of two different benzyl groups in the benzophenone (entries 7 and 8).

The possible mechanism for these reactions is depicted in Scheme 2. It is based on the assumption that P_4-*t*-Bu successfully deprotonate the benzylic position which bears the most acidic hydrogen. The anion thus generated attacks the carbonyl carbon giving rise to the alcohol which undergoes dehydration at elevated temperature to give 2,3-diarylbenzofuran.



Scheme 2. Possible mechanistic pathway for the formation of 2,3-diarylbenzofurans.



Scheme 3. Synthesis of **1**.

This methodology can be used in a direct total synthesis of amurensin H **1** (Scheme 3). Starting from stilbene **5** (readily available from 3,5-dimethoxybenzaldehyde),[14] metal–halogen exchange followed by reaction with 3,5-dimethoxybenzaldehyde gave **6** and oxidation of **6** with activated manganese dioxide affords a benzophenone **7** in 77% yield from **5**. This benzophenone **7** can be selectively demethylated in 88% yield to give **8** using BBr_3 solution (1.0 M in CH_2Cl_2) at −50 °C. The resulting phenol **8** is converted into benzyl ether **9** in 86% yield.

Cyclization of **9** using P_4-*t*-Bu in dry benzene at 170 °C (sealed tube conditions) provided **10** in 42% yield. The higher temperature needed to effect the cyclization is likely a result of steric factors. Finally, the total synthesis of amurensin H **1** was achieved by exhaustive demethylation of benzofuran **10** using solution (1.0 M in CH_2Cl_2) at room temperature in 67% yield. The analytical data for **1** matched with the previously reported data.[3,15]

Acknowledgment

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References and notes

1. Cheng, K.-W.; Wang, M.; Chen, F.; Ho, C.-T. *ACS Symp. Ser.* **2008**, *987*, 36–58.
2. Li, Y.; Yao, C.; Bai, J.; Lin, M.; Cheng, G. *Acta Pharmacol. Sinica* **2006**, *27*(6), 735–740; Li, Y.; Cheng, G.; Lin, M.; Yao, C.; Huang, K.; Liu, B.; Bai, J.; Li, N. Faming Zhuanli Shenqing Gongkai Shuomingshu Application: CN 2006-10076299 20060421.
3. Huang, K.-S.; Lin, M.; Wang, Y.-H. *Chin. Chem. Lett.* **1999**, *10*, 817–820.
4. Huang, K.-S.; Wang, Y.-H.; Li, R.-L.; Lin, M. *J. Nat. Prod.* **2000**, *63*, 86–89.
5. Huang, K.-S.; Wang, Y.-H.; Li, R.-L.; Lin, M. *Phytochemistry* **2000**, *8*, 875–881.
6. Bobrowska-Hagerstrand, M.; Lillas, M.; Mrowczynska, L.; Wrobel, A.; Shirataki, Y.; Motohashi, N.; Hagerstrand, H. *Anticancer Res.* **2006**, *3A*, 2081–2084.
7. Hou, X.-L.; Yang, Z.; Yeung, K.-S.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2008**, *19*, 176–207; Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Curr. Org. Chem.* **2006**, *10*(12), 1423–1455.
8. Cho, C.-H.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *J. Comb. Chem.* **2008**, *6*, 941–947.
9. Bernini, R.; Cacchi, S.; De Salve, I.; Fabrizi, G. *Synthesis* **2007**, 873–882; Pan, C.; Yu, J.; Zhou, Y.; Wang, Z.; Zhou, M.-M. *Synlett* **2006**, 1657–1662; Colobert, F.; Castanet, A.-S.; Abillard, O. *Eur. J. Org. Chem.* **2005**, 3334–3341.
10. Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449–1451.
11. Abdul-Aziz, M.; Auping, J. V.; Meador, M. A. *J. Org. Chem.* **1995**, *60*, 1303–1308; Lappin, G. R.; Zannucci, J. S. *J. Chem. Soc. D: Chem. Commun.* **1969**, 1113.
12. Kraus, G. A.; Zhang, N.; Hoover, K. *Tetrahedron Lett.* **2002**, *43*, 5319.
13. *Representative procedure for the preparation of 2,3-diarylbenzofuran*: To a solution of 2-benzyloxybenzophenone (0.20 g, 0.69 mmol) in freshly distilled dry benzene (10 mL), P_4-*t*-Bu solution (0.77 mL, 0.76 mmol) was added at rt and the reaction mixture was heated to reflux. After the completion of reaction (3 h), benzene was partially evaporated and reaction mixture was purified by column chromatography using 10% ethyl acetate: petroleum ether to obtain pure product (100% yield).*2,3-Diphenylbenzo[b]furan* (**4**)**:** Mp 123–124.5 °C; ^{1}HNMR (400 MHz) δ 7.23 (t, J = 7.3 Hz, 1H), 7.28–7.35 (m, 4H), 7.38–7.52 (m, 6H), 7.55 (d, J = 8.3 Hz, 1H), 7.65–7.67 (m, 2H); ^{13}CNMR (100 MHz) δ 111.1, 117.5, 120.0, 122.9, 124.7, 127.0, 127.6, 128.3, 128.4, 129.0, 129.8, 130.2, 130.7, 132.8, 150.5, 154.0; MS *m/z* 270 (M^+).
14. Snyder, S. A.; Zografos, A. L.; Lin, Y. *Angew. Chem., Int. Ed.* **2007**, *43*, 8186–8191.
15. Ito, J.; Takaya, Y.; Oshima, Y.; Niwa, M. *Tetrahedron* **1999**, *55*, 2529–2544.