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A convenient synthesis of unsymmetrically substituted terphenyls of biologically active stilbenes via a double Suzuki cross-coupling protocol

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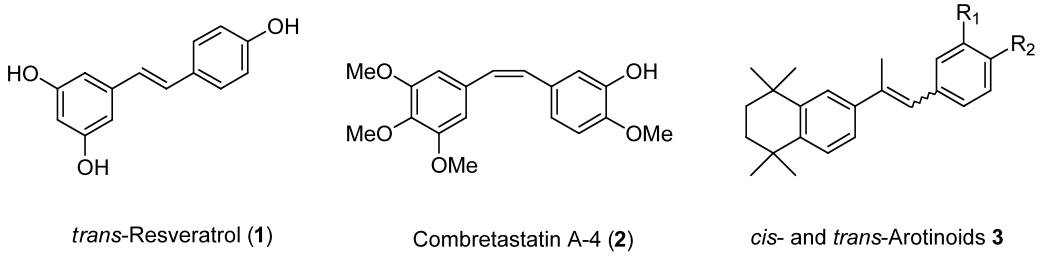
Abstract—A double Suzuki cross-coupling protocol has been devised as a practical route to a variety of terphenyls. Good chemoselectivity was observed. Unsymmetrically substituted triphenylenes were also easily prepared. © 2003 Published by Elsevier Science Ltd.

Stilbene-based compounds are widely represented in nature and have become of particular interest to chemists and biologists because of their wide range of biological activities.[1] Stilbene itself does not occur in nature, but hydroxylated stilbenes are abundantly represented; some of these, such as *trans*-resveratrol (**1**),[2] the *cis*-stilbene combretastatin A-4 (CA-4, **2**),[3] and the stilbene-based vitamin A analogues **3**[4] have shown unique potentialities for treatment of cancer and for cancer chemoprevention (Fig. 1).

Not unexpectedly, the ability of natural and synthetic stilbenes to elicit a wide range of physiological effects often stems from changes in olefin configuration. It is also well known that the natural products themselves, at least in many cases, can not be used directly, because of insufficient levels of activity and bad distribution properties, which are sometimes associated with a certain degree of instability. As a result, the search on the synthetic analogs has become of major importance and the synthesis of double bond-locked compounds appears particularly promising.[5]



trans-Resveratrol (**1**) Combretastatin A-4 (**2**) *cis*- and *trans*-Arotinoids **3**

Figure 1. Natural and synthetic stilbenoids.

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In this context, our attention was recently drawn to the idea that terphenyl-based architectures, which incorporate a phenyl ring as bioisosteric substitution of the alkenyl bridge, could constitute interesting carbon frameworks in obtaining conformationally restricted stilbene mimetics. With these criteria in mind we set out to search for a general synthetic approach to terphenyl analogues of CA-4 (**2**) (compounds **4a** and **13a**,**b**) as well as of the stilbene-based arotinoids **3** (compounds **4b**) (Fig. 2).

As palladium-catalyzed cross-coupling reactions between arylboronic acids and aryl halides or triflates (Suzuki coupling reaction) have become a common method for the synthesis of biaryls,[6,7] we envisaged the possibility that a highly convergent and flexible double Suzuki coupling approach could be used to prepare a variety of unsymmetrically substituted terphenyls. It is worth noting that such a procedure has been used only sporadically and has not yet received full recognition as a general route to terphenyls.[8]

The value of our approach is exemplified in a four-step synthetic route to terphenyls **4a** of CA-4. Additionally, the easy access to the combretastatin's *ortho*-terphenyl derivative **4a**, also allowed an easy entry to the more restricted triphenylene **5**. We speculated that a double Suzuki cross-coupling between **6** and intermediates **7** and **9** could accomplish the desired terphenyls **4a** (Scheme 1). A subsequent rational route to the triphenylene **5** could involve iron(III) chloride oxidative cyclotrimerisation of the newly synthesized *ortho*-terphenyl derivative **4a**.[9,10] Practically, the Suzuki coupling between **6** and the iodo-derivative **7** afforded in 65/81/73% yields (*ortho*-, *meta*- and *para*-isomers, respectively) and with chemoselectivity the bromobiphenyl derivatives **8**, in toluene/ethanol as solvent and tetrakis(triphenylphosphine)-palladium(0) as catalyst for the reaction, whereas aqueous Na_2CO_3 provided the basic environment required. The reaction was completed in 2 h at reflux. Flash column chromatography, followed by recrystallization afforded the desired product. The subsequent Suzuki cross-coupling between **8** and the boronic acid **9** gave, after removal of the benzyl protecting group, the desired **4a** in 52/85/64% yields (*ortho*-, *meta*- and *para*-isomers, respectively). As expected, treatment of the benzylated *ortho*-terphenyl derivative **4a** with iron(III) chloride in dichloromethane in the presence of traces of sulphuric acid easily gave the triphenylene **5** (70% yield). *O*-Debenzylation occurred just during the cyclization, thus avoiding a further hydrogenation reaction.

In the next step, commercially available **6** and **10a** were envisaged to be easily incorporated as the B- and C-rings of the terphenyl architectures **4b**, whereas **10b** the residual A-ring (Fig. 3). Somewhat surprisingly, Suzuki coupling between **6** and **10b** allowed only in very low yields the desired **11a**, because of the concomitant dimerization of **6**. Assuming that the relatively high steric hindrance given by the adamantane group could be responsible for the low yields of the coupling procedure, allowing a preferential self-condensation of the bromophenyl boronic acids, we opted to examine a different approach, where the iodo-bromo intermediates **12a** could be incorporated as the B-ring of the terphenyl system, while intermediates **10c** and **10a** as the A- and C-rings, respectively.

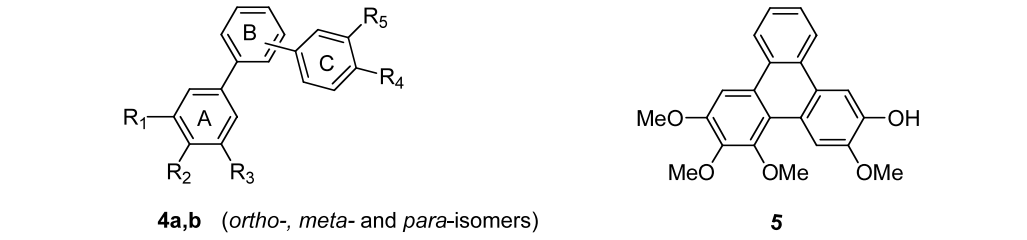
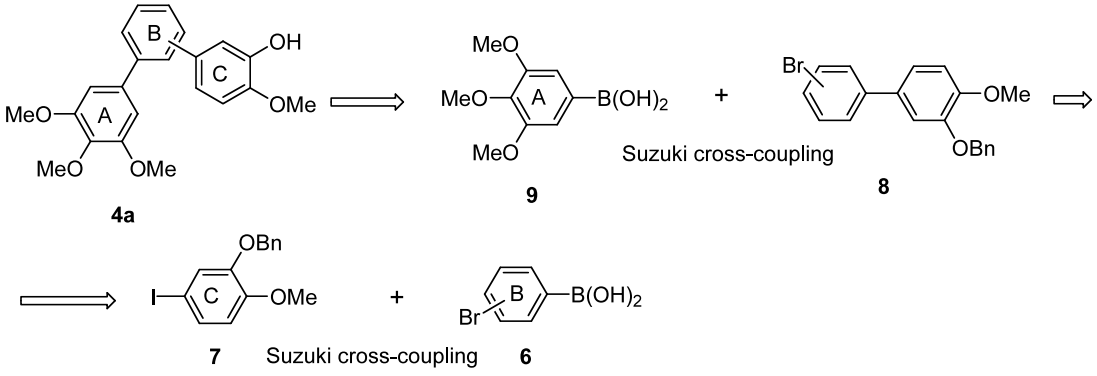


Figure 2. Terphenyl and triphenylene analogues of natural and synthetic stilbenoids.



Scheme 1.

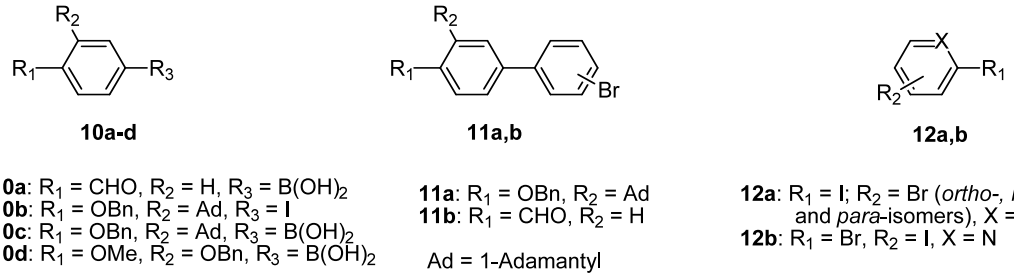


Figure 3. Synthetic intermediates.

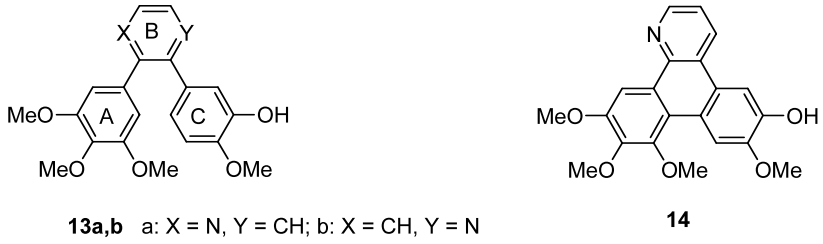


Figure 4. Terphenyl and triphenylene analogues of natural combretastatin A-4.

As a matter of fact, couplings between **10a** and **12a** were simply accomplished by the standard Suzuki procedure used above and completed in appreciable yields (52/85/64% for the *ortho*-, *meta*- and *para*-isomer, respectively) allowing **11b** within a few hours with chemoselectivity for the aryl iodide. The aldehydes **11b** were in turn oxidized by means of MnO_2 to the corresponding carboxylic acids and the subsequent Suzuki cross-coupling with the boronic acid **10c** were performed under the conditions used above for **11b**, allowing the benzylated **4b** (33/45/67% yields, respectively, for the *ortho*-, *meta*- and *para*-isomer) in turn subjected to standard *O*-debenzylation procedure (Pd/C catalyzed hydrogenation, 66% yield).

Finally, it is worth noting that the pyridine derivatives **13a** and **13b** were also prepared by means of the synthetic scheme described for **4b** employing the 2-bromo-3-iodo pyridine (**12b**) as the B-ring and intermediates **9** and **10d** for the other rings. Pd/C-catalyzed hydrogenation of the benzylated **13a**,**b** furnished the desired terphenyls in 86% yields (Fig. 4). The cyclocoupling procedure performed on the benzylated **13a**,**b** with iron(III) chloride gave principally the *O*-debenzylation. The triphenylene derivative **14** was obtained in only 10% yield.

In summary, the purpose of this study was to investigate methods for the preparation of terphenyl architectures as bioisosters of natural and synthetic stilbenes. In this context we have demonstrated the utility of a double Suzuki cross-coupling protocol to obtain a facile entry to terphenyls and triphenylenes. We have found that halogenated boronic acids or, alternatively, bromo-iodo aryls, could be utilized as the B ring of the terphenyl system, being the double cross-coupling procedure endowed with good chemoselectivity. The devised double Suzuki protocol works in many cases in a superior manner thus providing an easy preparation of a variety of terphenyls. The oxidative cyclization of the benzylated *ortho*-terphenyl derivative of combretastatin A-4, using ferric chloride, allowed the preparation of its triphenylene derivative. Finally, the simplicity of the reaction could suggest a possible application of this methodology for generation of combinatorial terphenyl or triphenylene libraries. The antiproliferative and apoptosis-inducing effects on HL60 cell line demonstrated an interesting activity for the terphenyl derivative **13a**.[11]

Acknowledgements

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11. The most effective compound was the terphenyl derivative **13a** that showed an activity (in HL60 cell line, antiproliferative activity $IC_{50}=0.3\pm0.07$ μM; apoptosis inducing activity $AC_{50}=0.7\pm0.03$ μM) similar to other chemotherapeutic drugs usually used in the clinical practice (*cis*-platinum: $IC_{50}=0.6\pm0.08$ μM, $AC_{50}=1.2\pm0.1$ μM; Etoposide: $IC_{50}=0.12\pm0.07$ μM, $AC_{50}=0.45\pm0.08$ μM; Citarabine: $IC_{50}=0.08\pm0.01$ μM, $AC_{50}=0.15\pm0.02$ μM; 5-Fluorouracil $IC_{50}=1.6\pm0.3$ μM, $AC_{50}=6.5\pm0.6$ μM).