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# Multicomponent Coupling Approach to (±)-Frondosin B and a Ring-Expanded Analogue

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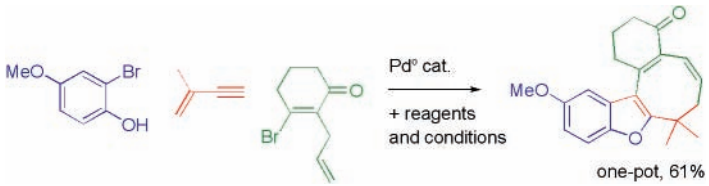
## ABSTRACT

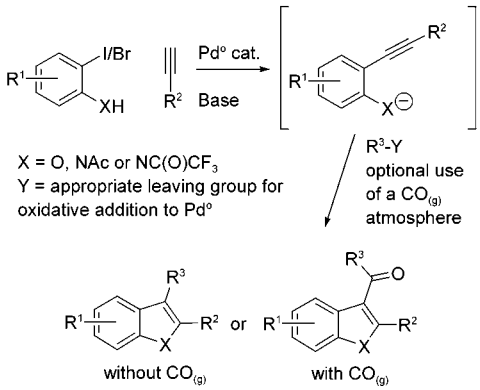



**A recently discovered multicomponent coupling reaction is used to give direct access to a late intermediate in the synthesis of frondosin B. This intermediate can also be efficiently converted to a ring-expanded analogue of frondosin B by sustained heating of the reaction mixture. An unprecedented tandem 1,7-hydrogen shift, 8$\pi$-electrocyclization is proposed to explain the formation of this ring-expanded species.**

Multicomponent reactions (MCRs) are, by definition, both convergent and multibond forming and, as such, are capable of synthetically addressing structural complexity in a manner that is both intellectually satisfying and practical.[1] Recently, we reported a palladium-catalyzed multicomponent coupling (MCC) approach to indoles and benzofurans (Scheme 1), which we have subsequently applied to a one-step synthesis of some potent analogues of the anticancer agent combretastatin A-4.[2,3] Herein, we report the application of this reaction to the concise synthesis of (±)-frondosin B and a ring-expanded analogue through a remarkable reaction cascade.

(+)-Frondosin B (**2**) belongs to a family of related marine sesquiterpenoids, the frondosins **1**−**5**, isolated from a marine sponge *Dysidea frondosa* (Figure 2).[4] The activity of (+)-frondosin B (**2**) as an interleukin-8 (IL-8) receptor antagonist and its novel molecular architecture have inspired the groups of Danishefsky and Trauner to pursue its total synthesis.[5,6] Danishefsky and co-workers prepared **2** in 18 steps in overall 0.8% yield and 88% ee.[5] Hughes and Trauner prepared **2** in

**Scheme 1.** Multicomponent Coupling (MCC) Approach to Benzofurans and Indoles

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(1) (a) Domling, D.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (b) Lee, D.; Sello, J. K.; Schreiber; S. L. *Org. Lett.* **2000**, *2*, 709. (c) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471. (d) Weber, L. *Curr. Med. Chem.* **2002**, *9*, 2085. (e) Weber, L. *Curr. Opin. Chem. Biol.* **2000**, *4*, 295. (f) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (g) Hughes, B.; Hulme, C.; Oddon G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321. (h) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101.

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(3) This MCC was based on some earlier studies performed by the group of Cacchi and Arcadi: Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280

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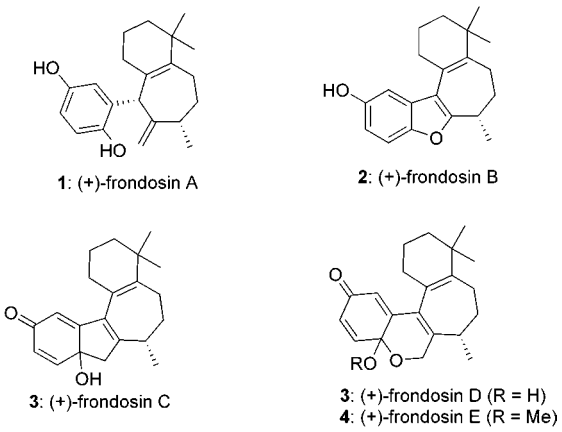


**Figure 1.** Frondosins. The stereochemistry of frondosins A and C−E (**1** and **3**−**5**, respectively) is based on that determined for B (**2**) and has not been independently determined.

20 steps in an overall 7.3% yield and 91% ee from commercially available substrates.[6] While these syntheses provide enantioselective access to the natural product, they are somewhat lengthy, so we sought to utilize our MCC protocol to provide a more concise, convergent access to this system and its analogues in order to aid structure−activity relationship (SAR) studies.

Commercially available 4-methoxyphenol (**6**) and 2-allyl-1,3-cyclohexandione (**7**) were converted to the bromides **8** and **10**, respectively, in excellent yields following standard procedures (Scheme 2).[7,8] These two bromides and the commercially available 3-methylbutenyne (**9**) were subjected to our MCC protocol. This involved deprotonating **8** and **9** with MeMgBr and coupling the resultant *o*-bromophenolate and acetylide (not shown) using palladium to give the *o*-alkynylphenolate **11**, which undergoes heteroannulative coupling with **10** at 80 °C giving the desired product **12** in an acceptable yield (48%). Other products resulting from the MCC included the protocyclized material **13** the nucleophilic addition−elimination product **14** and an unusual polycyclic product **15**. It was demonstrated that the latter product, **15**, could be selectively formed by extended heating of the reaction mixture at 100 °C for 48 h (61%), the structure of this material was determined by spectral methods and confirmed using X-ray crystallography (Figure 2).[9]

The desired MCC product **12** was efficiently cyclized using catalyst **16** in a ring-closing metathesis (RCM) reaction,

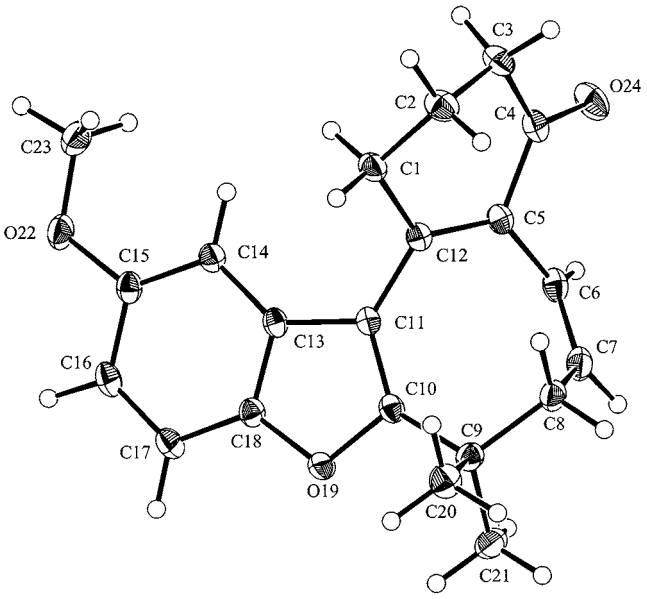


**Figure 2.** ORTEP representation of a molecule of **15** derived from a crystallographic study (arbitrary numbering).

providing a three-step (longest linear sequence) access to the basic core of frondosin B, **17**, from commercially available substrates.

Reetz and co-workers have described a method for converting ketones to *gem*-dimethyl groups using 2 equiv of $Me_2TiCl_2$.[10] In our attempts to convert **17** to **18** using the Reetz method, we observed very rapid reaction of **17** with $Me_2TiCl_2$ to give **18** at 0 °C but only to the point of approximately 50% conversion (41% **17** and 40% **18**, isolated), without any observable improvement after standing at room temperature for several hours (Scheme 3).[11] Interestingly, direct TLC analysis of the supernatant of the reaction mixture revealed almost complete consumption of the starting material **17** after 1 h but after hydrolytic workup, TLC analysis of the organic (EtOAc) extract revealed considerable starting material. This situation remained the same even in the presence of large excesses of Reetz reagent. Further experimentation revealed that considerable increases in yield could be obtained when the reaction was left to stir at room temperature for several days and that heating the reaction mixture to 85 °C (1,2-dichloroethane used in place of dichloromethane) for 24 h would give the product **18** in high

(4) (a) Patil, A. D.; Freyer, A. J.; Killmer, L.; Offen, P.; Carte, B.; Jurwicz, A. J.; Johnson, R. K. *Tetrahedron* **1997**, *57*, 5047. (b) Hallock, Y. F.; Cerdenellina. J. H.; Boyd, M. R. *Nat. Prod. Lett.* **1998**, *11*, 153.

(5) (a) Danishefsky, S. J.; Inoue, M.; Frontier, A. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 761−764. (b) Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1878.

(6) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569−1572. (Erratum: *Angew. Chem., Int. Ed.* **2002**, *41*, 2227).

(7) (a) Kajigaeshi, S.; Kakinami, T.; Okamoto, T.; Nakamura, H.; Fujikawa, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4187. (b) Dodsworth D. J.; Calcagno, M. P.; Ehrmann, E. U.; Devadas, B.; Sammes, P. G. *J. Chem Soc., Perkin Trans. 1* **1981**, 2120.

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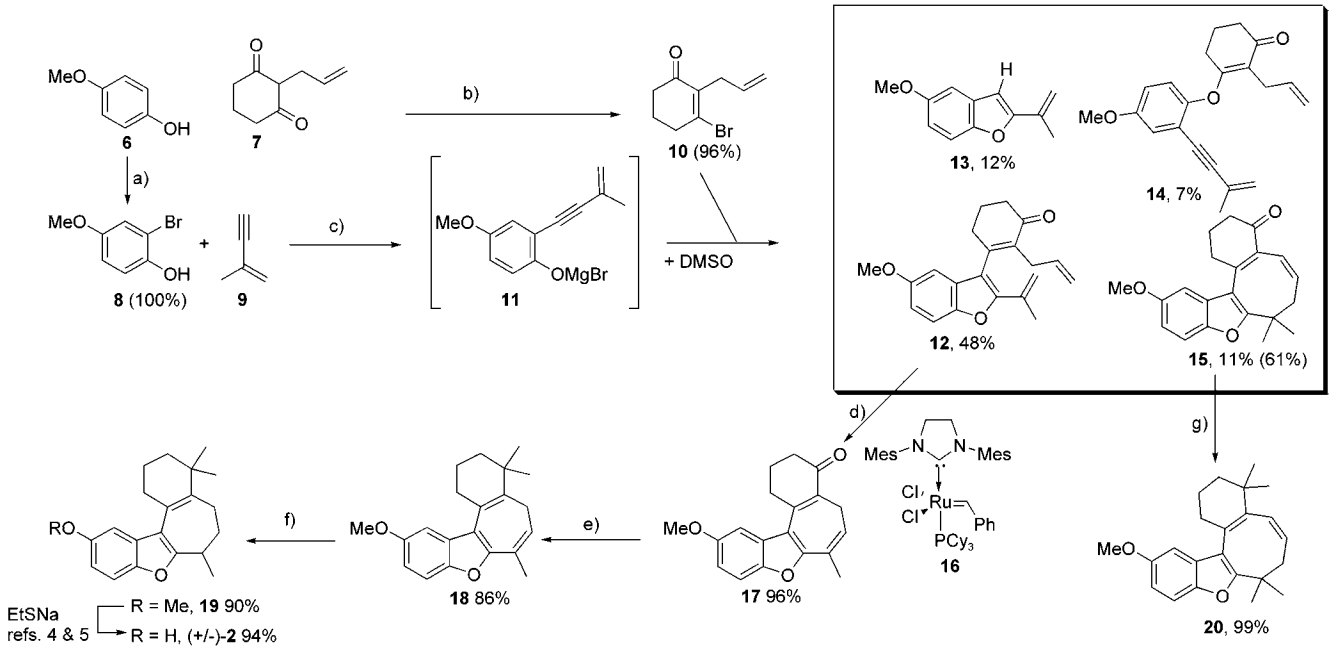
(9) Crystal data: $C_{21}H_{22}O_3$, $M = 322.40$, monoclinic, $a = 10.5169(2)$, $b = 9.5041(2)$, $c = 16.8671(3)$ Å, $\beta = 100.0201(7)$ °, $U = 1660.21(6)$ Å$^3$, $T = 200$ K, space group $P2_1/a$ (no. 14), $Z = 4$, $\mu$(Mo K$\alpha$) = 0.085 mm$^{-1}$, 37 199 reflections measured, 3811 unique ($R_{int} = 0.050$), 1811 with $I > 3\sigma(I)$ used in refinement. The final $R = 0.029$ and w$R = 0.034$ for the reflections used in the refinement. X-ray diffraction data were collected on a Nonius Kappa CCD diffractometer (graphite monochromator, $\lambda = 0.71073$ Å). Structure solution was by direct methods and refinement completed by full-matrix least-squares on *F*. Non-hydrogen atoms were refined with anisotropic displacement parameters, and hydrogen atoms were included at calculated positions and ride on the atoms to which they are bonded. The crystallographic data have been deposited with the Cambridge Crystallographic Data Center (CCDC 227359).

(10) Reetz, M. T.; Westermann, J.; Kyung, S. *Chem. Ber.* **1985**, *118*, 1050.

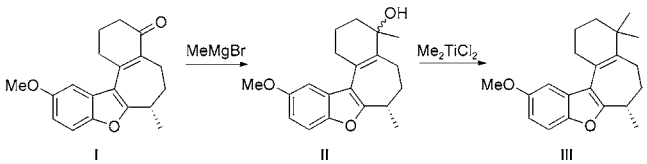
**Scheme 2** [a]




[a] Reagents and conditions: (a) $Br_2$, $CH_2Cl_2$. (b) $PPh_3.Br_2$, $Et_3N$, $CH_2Cl_2$. (c) **8** and **9**, 2.1 x MeMgBr, THF 0 °C then 5 mol % $Pd(PPh_3)_2Cl_2$, 65 °C for 24 h and then **10** and DMSO, 80 °C for 9 h (for selective formation of **12**) or 100 °C for 48 h (for selective formation of **15**). (d) Grubbs' catalyst **16**, 1,2-dichloroethane 55 °C for 1 h. (e) 3 x $Me_2TiCl_2$ (formed in situ from $Me_2Zn$ and $TiCl_4$), 1,2-dichloroethane, −30 to 18°C over 2 h, 83 °C for 20 h. (f) 10 mol % 10% Pd/C, MeOH, $H_2$ 1 atm, 9 h. (g) as for e in $CH_2Cl_2$, 0−18°C over 2 h, and then 40 °C for 19 h.

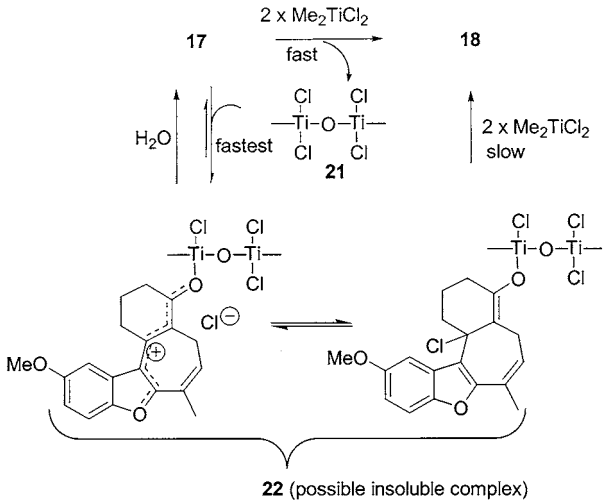
yield (Scheme 3). In short, the *gem*-dimethylation reaction appeared to proceed in two stages, a rapid initial stage to the point of approximately 50% conversion, with the remainder of substrate **17** evidently tied up as a hydrolytically labile species, which converts to **18** in a slow second stage. We have tentatively explained these observations as resulting from an initial reaction of **17** with the requisite 2 equiv of $Me_2TiCl_2$, giving **18** and a byproduct complex **21** (Scheme 3). As this byproduct **21** is formed, it reacts with the starting material **17** at faster a rate than $Me_2TiCl_2$ to give an insoluble complex of unknown structure (possibly of the structure **22**) that hydrolyses upon aqueous workup to return **17**. This complex **22** may react directly but slowly with the $Me_2TiCl_2$ to give **18** or through reversible formation of **17** where the overall reaction rate is reduced by virtue of the low equilibrium concentration of **17** present.

(11) During the course of our work in this area, Hughes and Trauner reported their synthesis of frondosin B (ref 5), in which they attempted to use the Reetz reaction to convert a ketone very similar to **17**, **I**, to the *gem*-dimethyl product **III**. They reported that "the low electrophilicity of the vinylogous aryl ketone (**I**)" was responsible for the initial failure of the Reetz reaction, which they then conducted in two steps, first converting the ketone **I** to the alcohol **II** with MeMgBr and then reacting **III** with $Me_2TiCl_2$ to give **III**. Based on the results of this study, such a modification of the Reetz protocol may not be necessary.




A similar two-stage reaction profile was also observed in the *gem*-dimethylation of **15** to give **20**, but again, a good

**Scheme 3** [a]




| conditions | **17** (%) | **18** (%) |
|---|---|---|
| 18°C, < 1h[a] | 41 | 40 |
| 18°C, 18h[a] | 35 | 57 |
| 18°C, < 172h[a] | 14 | 70 |
| 83°C, 20h[b] | 0 | 86 |

[a] In $CH_2Cl_2$ with 2 equiv of $Me_2TiCl_2$. [b] In 1,2-dichloroethane with 2 equiv of $Me_2TiCl_2$.

yield of product could be achieved upon overnight heating (Scheme 2).

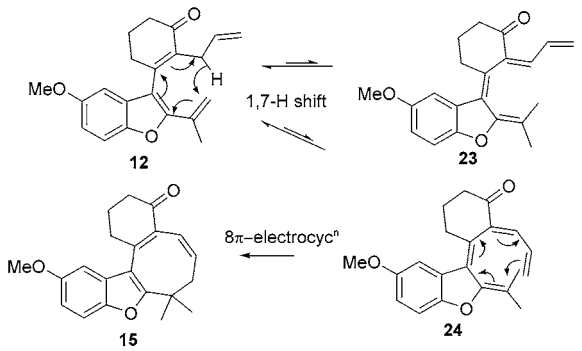
Selective hydrogenation of the sterically least congested C8−C9 double bond in **18** was achieved in excellent yield with a palladium on charcoal catalyst giving **19** (90%). Attempts to hydrogenate **18** enantioselectively using Pfaltz-type catalysts have thus far proven unsuccessful.[12]

Cleavage of the methyl ether in racemic **19** to give (±)-frondosin B (**2**) has been accomplished by others using sodium methylthiolate.[5,6]

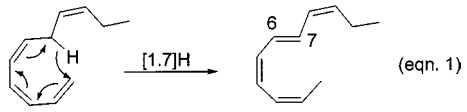
Albeit racemic, this approach to (±)-frondosin B does nonetheless provide ready access to analogues of this material for SAR studies. Further, studies into the enantioselective hydrogenation of **18** are ongoing.

Most remarkable is the single-step formation of **15**. This step brings three substrates together, forming four new bonds and two new rings. The most likely mechanism of formation of this product seems to be through a tandem 1,7-hydrogen shift, 8$\pi$-electrocyclization process, converting **12** into **15** (Scheme 4). That **15** results from simple thermal rearrangement of **12** and is not mediated by any other reagent or catalyst used in the MCC was evidenced by the fact that heating isolated **12** in toluene at 100 °C for 48 h gave **15** in high yield (95%). To the best of the authors knowledge, such tandem 1,7-hydrogen shift, 8$\pi$-electrocyclization processes are unprecedented. While the biosynthetic pathway leading to giffordene **26** has been shown to involve a similar 1,7-hydrogen shift from precursor **25**, this reaction is selective for the (6*E*)- arrangement of giffordene **26**, preventing what would otherwise be a very rapid 8$\pi$-electrocyclization from occurring (eq 1).[13] We propose that unlike **25**, which undergoes complete rearrangement through to the lower energy (more fully conjugated) tetraene system of giffordene **26**, the 1,7-hydrogen shift of **12** to **23** or **24** is reversible with the equilibrium lying to the left, in favor of the aromatized benzofuran. Even though **24** may be the highest energy arrangement of the three interconvertible species, **12**, **23**, and **24**, the fact that it can be rapidly and irreversibly converted to **15** through 8$\pi$-electrocyclization provides the necessary driving force for directing the total reaction flux through this intermediate. 8$\pi$-Electrocyclizations are generally quite facile,[13] and the cyclization of **24** to give **15** is expected to be particularly rapid since the benzofuran and cyclohexyl rings in **24** reduce the degrees of freedom of the molecule and because it restores aromaticity to the furan ring.

**Scheme 4.** Proposed Mechanism for the Thermal Rearrangement of **12** to **15**




In summary, we have provided a concise (six-step), protection−groupless access to (±)-frondosin B **2** from commercially available substrates **6**, **7**, and **9** in an overall 32% yield. The two key steps, MCC and RCM, are all that are required to convert any given set of 2-bromophenols, butenynes, and 1-bromo-2-allyl-1-cyclohexenes to a variety of frondosin B analogues, assisting SAR studies on these systems as IL-8 inhibitors. Furthermore, the MCC can be placed in tandem with a pericyclic cascade to provide direct access to a series of eight-membered ring analogues of the type **15**. Such concise, divergent access to complex polycyclic cores may have broader implications for the diversity-orientated synthesis of natural product-like compounds in other chemical biology studies.

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**Supporting Information Available:** Full experimental and spectroscopic details on all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035822Q

(12) Menges, F.; Pfaltz, A. *Adv. Synth. Catal.* **2002**, *344*, 40. A sample of a chiral N,P-chelated iridium catalyst was kindly supplied to us by this group. However, this catayst appeared to be inhibited by **18** since even known substrates were not able to be hydrogenated in the presence of a small amount of **18**.

(13) Pohnert, G.; Boland, W. *Tetrahedron* **1994**, *50*, 10235.