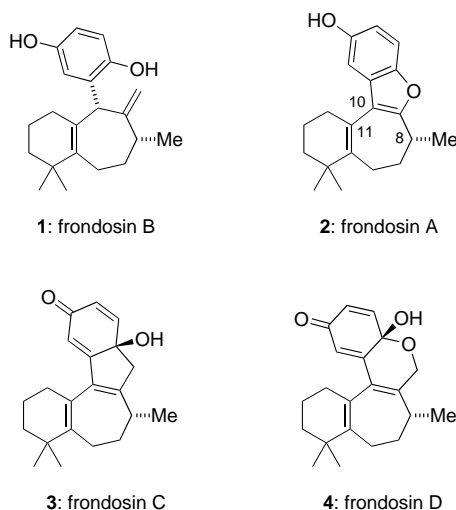


Concise Total Synthesis of (–)-Frondosin B Using a Novel Palladium-Catalyzed Cyclization**

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The frondosins (Scheme 1), a family of marine terpenoids isolated from the sponge *Dysidea frondosa*, have been found to inhibit the binding of interleukin-8 (IL-8) to its receptor in the low micromolar range.^[1a] IL-8, which is produced by macrophages and endothelial cells, recruits T-lymphocytes



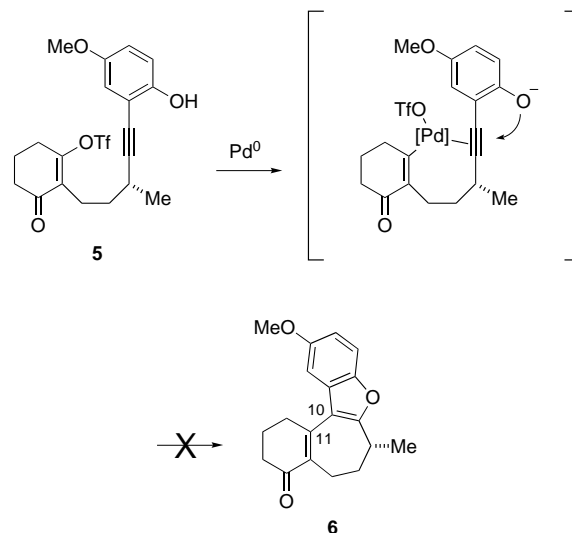
Scheme 1. The frondosins. The absolute stereochemistry shown is arbitrary.

and neutrophils to an inflammatory site and is implicated in a wide range of acute and chronic inflammatory disorders. IL-8 receptor antagonists like the frondosins, therefore, interfere with the inflammatory cascade and might ultimately be used to prevent autoimmune disorders such as rheumatoid arthritis and psoriasis. Equally important, members of the frondosin family have also been shown to exhibit HIV-inhibitory properties.^[1b]

Recently, (+)-frondosin B (**1**) has attracted much attention. The first total synthesis of this interesting norsesquiterpenoid by the Danishefsky group confirmed the structure and led to the assignment of an absolute configuration.^[2] Although **1** features only one stereocenter, it represents a considerable synthetic challenge because of its unusual tetracyclic skeleton, which incorporates a 2,3-disubstituted benzofuran moiety and a readily isomerized tetrasubstituted double bond.

A key connection, also noticed by others,^[2] is the formation of the bond between C10 and C11 to establish the central seven-membered ring of the target. Our original plan foresaw the implementation of the Arcadi–Cacchi reaction^[3] for the

construction of the tetracyclic core from an alkynyl phenol precursor of type **5** (Scheme 2). No intramolecular version of this palladium-catalyzed reaction has been reported to date. Despite efforts to convert **5** into **6** with a range of palladium reagents, however, we were unable to effect the desired cyclization. Instead, extensive decomposition of the starting material took place.



Scheme 2. Initial strategy for the key cyclization in the synthesis of frondosin B (**1**). Tf = trifluoromethanesulfonyl.

Attempting to gain more insight into the mechanism of the Arcadi–Cacchi reaction, we found that efficient, palladium-catalyzed bond formation could indeed be achieved provided the benzofuran moiety was already in place. This observation greatly simplified and streamlined our overall synthetic plan, as the formation of the free phenol **5**, unlike the corresponding benzofuran **15** (see below), could be realized only through difficult protective group manipulations.

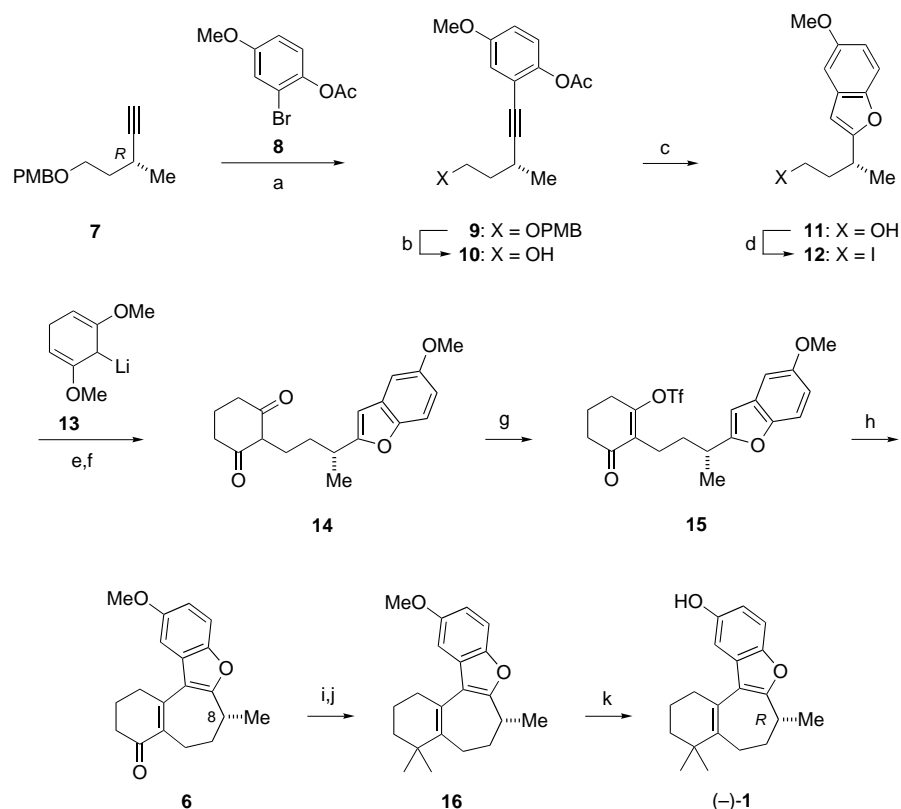
Our synthesis starts with the known *R*-configured alkyne **7**^[4] (obtained in 91 % *ee* by means of a Sharpless epoxidation) and the known aryl bromide **8**^[5] (Scheme 3). Sonogashira coupling^[6] of these two components followed by acidic deprotection^[7] gave the primary alcohol **10**. Subsequent saponification of the phenolic acetate with concomitant cyclization afforded benzofuran **11** in high yield. This material was then converted to the corresponding iodide **12**. Alkylation of dimethoxylithiocyclohexadiene **13** by using the Piers protocol^[8] followed by hydrolysis afforded cyclohexa-1,3-dione **14**.^[9] This surprisingly unstable diketone decomposed on standing and was therefore immediately converted into enol triflate **15** by which the stage for the key cyclization was set.

The key bond formation between C10 and C11 was achieved in good yield by heating **15** with a catalytic amount of [Pd(PPh₃)₄] in dimethyl acetamide (DMA) in the presence of Hünig's base.^[10] Importantly, no detectable racemization of the C8 stereocenter occurred under these conditions (see *Experimental Section*).^[11]

The conversion of the carbonyl group into a *gem*-dimethyl moiety was achieved by using a protocol developed by Reetz

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Scheme 3. Total synthesis of (–)-frondosin B (–)-**1**. a) $[\text{Pd}(\text{PPh}_3)_4]$, CuI , Et_3N , MeCN , reflux, 94 %; b) TFA , CH_2Cl_2 , RT, 83 %; c) K_2CO_3 , MeOH , reflux, 92 %; d) MsCl , Et_3N , THF , 0°C , then NaI , Me_2CO , reflux, 93 %; e) **13**, HMPA , THF , $-78^\circ\text{C} \rightarrow \text{RT}$, 85 %; f) ion-exchange resin, Me_2CO , H_2O , reflux; g) NaHMDS , PhNTf_2 , THF , Et_2O , RT, 75 % (2 steps); h) $[\text{Pd}(\text{PPh}_3)_4]$, DMA , $i\text{Pr}_2\text{NEt}$, 90°C , 70 %; i) MeMgBr , THF , $-78^\circ\text{C} \rightarrow \text{RT}$; j) Me_2Zn , TiCl_4 , CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{RT}$, 82 % from **6**; k) NaSEt , DMF , reflux, 90 %. PMB = *para*-methoxybenzyl, TFA = trifluoroacetic acid, Ms = methanesulfonyl, HMPA = hexamethylphosphoramide, NaHMDS = sodium bis(trimethylsilyl)amide, DMA = *N,N*-dimethylacetamide.

et al.^[12] As a result of the low electrophilicity of the vinyl-ogous aryl ketone, this procedure had to be carried out in two separate steps. Reaction of ketone **6** with MeMgBr gave the corresponding crude, highly acid-sensitive tertiary alcohol, which was subsequently subjected to the action of $[\text{Me}_2\text{TiCl}_2]$ (formed in situ from Me_2Zn and TiCl_4). This afforded *O*-methyl frondosin B (**16**) in good overall yield. Finally, *O*-demethylation following a previously reported procedure gave frondosin B (**1**) in high optical purity.^[2]

To our surprise, however, the optical rotation of the (*R*)-configured material thus obtained was opposite to that of the natural product ($[\alpha]_{\text{D}}^{25} = -16.8$ compared to $[\alpha]_{\text{D}} = +18.6$ ^[1a]). Though the natural product had been assigned the *R* configuration in the synthesis by Danishefsky et al., according to our work, (+)-frondosin B is *S*-configured. Having ruled out trivial mistakes, we were left with the puzzling possibility that either Danishefsky's or our material had undergone an unnoticed inversion of configuration at some stage (see below).

For the key cyclization **15** \rightarrow **6**, several mechanistic scenarios can be imagined. Control experiments with various Lewis acids (e.g. ZnCl_2 , MgBr_2 , $\text{BF}_3 \cdot \text{OEt}_2$) gave no product, which suggests that the reaction does not proceed by means of conjugate addition/elimination. Nucleophilic catalysis by

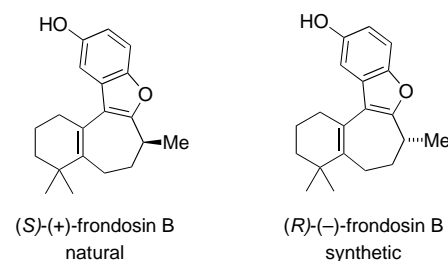
triphenylphosphane or amines was also excluded. Thus, it appears that oxidative addition of palladium to the carbon–oxygen bond of the triflate is essential and that this is a genuine palladium-catalyzed reaction.

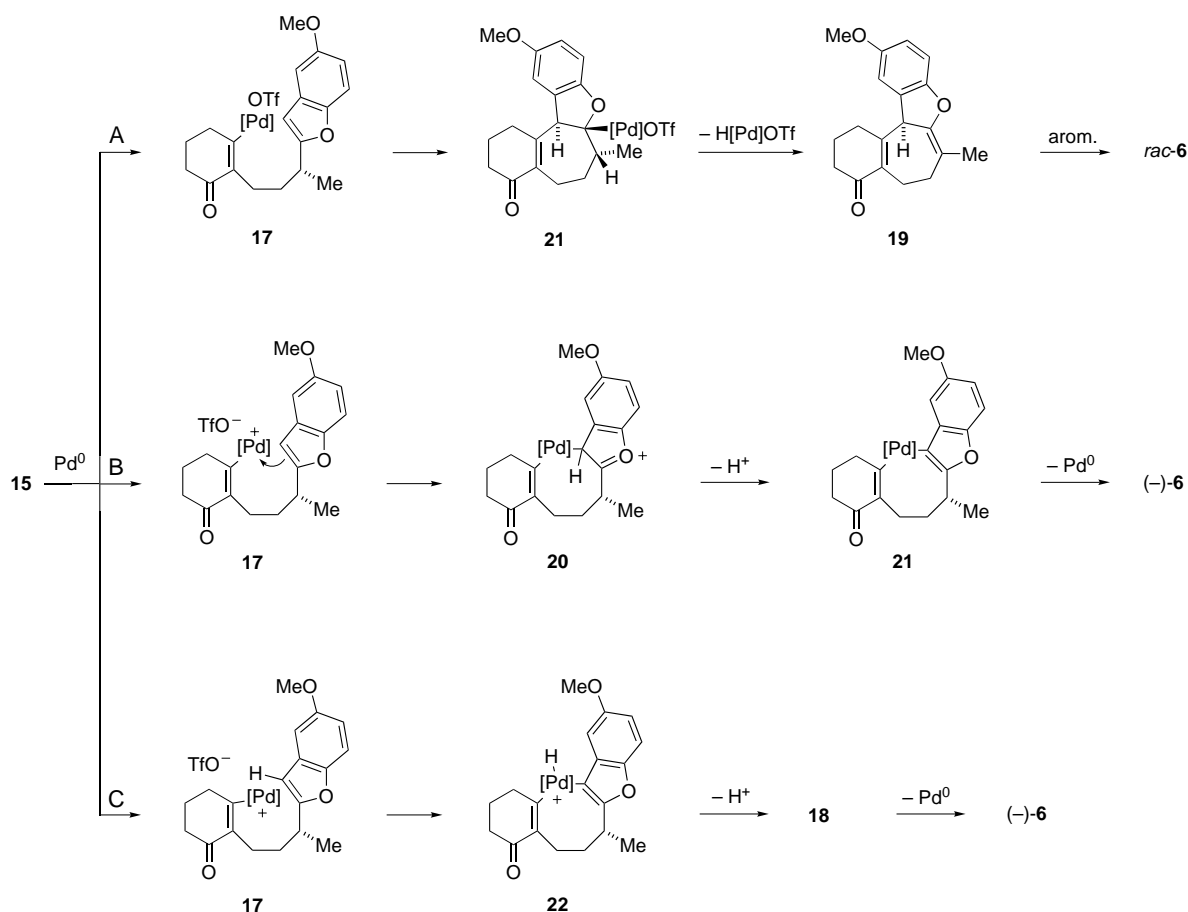
Although isolated examples of Heck reactions involving furans have been reported,^[13] none have been used in the total synthesis of a natural product.^[14] Moreover, no benzofurans have been employed as substrates. The fact that the stereocenter at C8 does not racemize under the reaction conditions raises the question whether a standard Heck mechanism involving oxidative addition (**15** \rightarrow **17**), migratory insertion (**17** \rightarrow **18**), and β -hydride elimination (**18** \rightarrow **19**) operates (Scheme 4, pathway A). Provided that the product of migratory insertion, **18**, undergoes *syn*-elimination of a hydridopalladium species, racemization would be expected upon rearomatization of the resulting enol ether **19**.

Since racemization does not occur, however, an alternative mechanism may be operating (Scheme 4, pathways B and C). In the first, oxidative addition is followed, instead, by nucleophilic attack of the electron-rich benzofuran onto the palladium(II) intermediate **17**, which is possibly cationic in nature. Deprotonation of the cationic intermediate **20** then affords

21, which reductively eliminates Pd^0 to yield the product (–)-**6** with the stereocenter at C8 left intact. In the second, the highly electrophilic, cationic palladium species **17** undergoes intramolecular C–H insertion^[15] to afford the palladium(IV) intermediate **22**, which upon loss of a proton and reductive elimination again gives (–)-**6**.

If mechanism A applies, the rearomatization of **19** may possibly occur in a completely stereoselective fashion and lead to inversion of the stereocenter at C8.^[16] It appears, however, that the absolute configuration was unintentionally switched as a result of neighboring group participation in an early stage of the previous synthesis.^[17, 2b] We therefore suggest that naturally occurring (+)-frondosin B (**1**) corresponds to the *S* isomer.^[18]





Scheme 4. Mechanism of the key cyclization.

In summary, we have achieved an expedient, asymmetric total synthesis of (–)-frondosin B (**1**) from simple starting materials (22% overall yield from the known alkyne **7**). The salient features of the synthesis include two palladium-catalyzed reactions: an efficient Sonogashira coupling with an aryl bromide and a novel cyclization onto a benzofuran. Furthermore, the usefulness of the Reetz protocol for installing a *gem*-dimethyl group in a natural product has been demonstrated. Studies toward the synthesis of other members of the frondosin family are underway and will be reported in due course.

Experimental Section

To a degassed solution of *i*Pr₂NEt (0.78 mL, 4.5 mmol) in dry DMA (110 mL) was added [Pd(PPh₃)₄] (65 mg, 0.056 mmol), and the mixture was heated under Ar to 90 °C. A solution of triflate **15** (500 mg, 1.12 mmol) in dry DMA (5 mL) was then added with a syringe pump over 3 h. The reaction mixture was stirred at 90 °C for an additional 36 h, cooled, diluted with saturated aqueous bicarbonate solution, and extracted four times with Et₂O (200 mL). The combined Et₂O extracts were washed twice with water (100 mL), once with brine (50 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (15% EtOAc in hexanes) to afford 234 mg (70%) of **6** as a viscous oil: $[\alpha]_D^{25} = -36.1$ ($c = 1.00$, CHCl₃); IR (film): $\tilde{\nu} = 2934, 1656, 1474$ cm⁻¹; ¹H NMR (400 MHz, CDCl₃, 25 °C): $\delta = 7.33$ (d, $J = 8.8$ Hz, 1H), 7.16 (d, $J = 2.4$ Hz, 1H), 6.87 (dd, $J = 8.8$ Hz, 2.4 Hz, 1H), 3.85 (s, 3H), 3.28 (m, 1H), 3.06–2.95 (m, 2H), 2.80 (m, 1H), 2.59–2.47 (m, 2H), 2.35 (m, 1H), 2.17–2.04 (m, 3H), 1.55 (m, 1H), 1.38 (d, $J = 6.8$ Hz, 3H); ¹³C NMR (75 MHz, CDCl₃, 25 °C): $\delta = 197.6, 164.5, 156.0, 149.3, 149.1, 137.2, 128.3,$

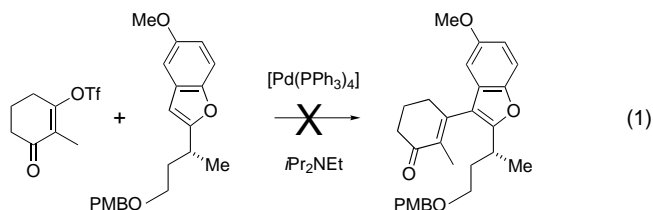
115.8, 111.7, 111.5, 105.9, 56.3, 37.9, 36.1, 35.1, 30.9, 23.7, 21.4, 20.6; HRMS (EI) m/z calcd. for C₁₉H₂₀O₃, 296.1412; found, 296.1414. The enantiomeric excess was determined by HPLC [Chiralpak ADTM column, 2% *i*PrOH in hexanes at 1.0 mL min⁻¹; t_R (major enantiomer) = 25.8 min, t_R (minor enantiomer) = 33.8 min] to be 91% (e.r. = 95.5:4.5).

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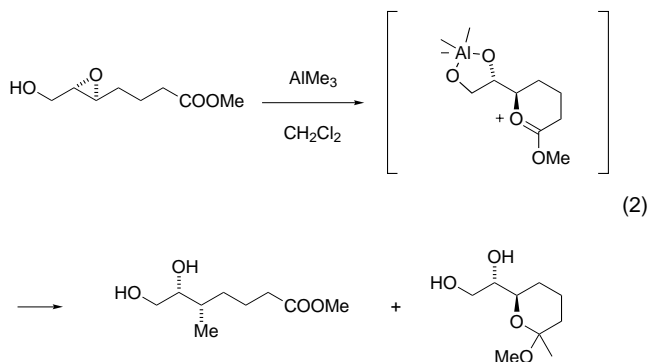
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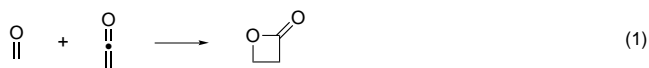
- [18] Attempts to assign the absolute configuration of frondosin B independently by X-ray crystallographic analysis of its bromobenzoate and camphanoyl ester have thus far been unsuccessful.

Mechanism and Origin of Stereoselectivity in Lewis Acid Catalyzed [2 + 2] Cycloadditions of Ketenes with Aldehydes**

Daniel A. Singleton,* Yingcai Wang, Hong Woon Yang, and Daniel Romo*

Stereoselectivity as a general phenomenon arises from differences in free energy associated with diastereomeric transition states or diastereomeric products. Free-energy differences between diastereomeric pathways are a requirement for stereoselectivity, but they are not sufficient in themselves. For example, high kinetic enantioselectivity may be compromised by product racemization. Another common situation is when stereoisomeric products are formed by differing mechanisms, so the inhibition of alternative mechanisms is often pivotal in the development of stereoselective methodology. A more complex possibility is that stereoisomeric pathways may have different rate-limiting steps.^[1] We describe here evidence for such an event in a cycloaddition in which diastereomeric products are formed, and we discuss the impact of divergent rate-limiting steps on selectivity.

β -Lactones are exceptionally versatile intermediates in organic synthesis,^[2] and there has been considerable interest in their direct synthesis from the [2 + 2] cycloaddition of ketenes with carbonyl compounds [Eq. (1)].^[3] A growing number of variants employ achiral^[4] or chiral^[5] Lewis acid catalysts to afford optically enriched β -lactones by substrate or reagent control, respectively.



The synthetic utility and fundamental allure of these formally forbidden cycloadditions make their mechanism of considerable interest. Experimental studies have been limited to substituent, solvent, and stereochemical effects in the uncatalyzed reaction,^[6] but several theoretical studies have

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