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Cyclopropene Cycloadditions with Annulated Furans: Total Synthesis of (+)- and (−)-Frondosin B and (+)-Frondosin A

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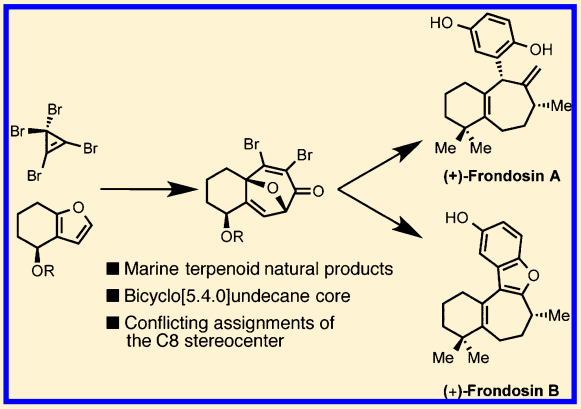
Supporting Information

ABSTRACT: The asymmetric total syntheses of the natural products (+)- and (−)-frondosin B and (+)-frondosin A are reported based on a diastereoselective cycloaddition between tetrabromocyclopropene and an annulated furan to provide a highly functionalized common building block. The bridged bicyclic intermediate could be stereo- and chemoselectively manipulated to produce the two structurally distinct members of the frondosins. Both syntheses feature regioselective palladium-coupling reactions and an unprecedented phosphine-mediated ether bridge cleavage. Surprisingly, the planned enantioselective synthesis of frondosin B led to the opposite epimer of the natural product, suggesting an unusual late stage stereoinversion at C8. Frondosin A, but not frondosin B, was shown to have selective antiproliferative activity against several B-cell lines.



The frondosin family[1] of marine-derived meroterpenoid natural products (Figure 1) represent an intriguing array of compounds

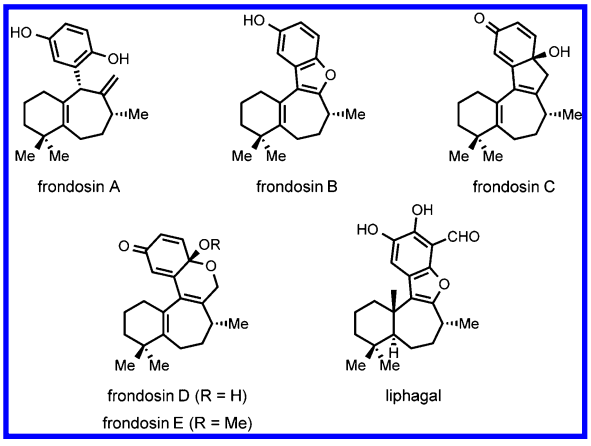


Figure 1. Meroterpenoid natural products.

possessing a bicyclo[5.4.0] undecene core with significant structural diversity introduced through alternative annulations with an appended hydroquinone moiety.[2] The structure of frondosin B[3] is also reminiscent of the marine natural product liphagal[4] as both incorporate an appended arene system in the form of a fused benzofuran motif. Frondosin B has been a popular target for total synthesis which ultimately led to assignment of the absolute stereochemistry. The first two syntheses of (+)-frondosin B by Danishefsky[3a,b] and Trauner[3c,d] produced conflicting assignments for the single stereogenic center at C8. A subsequent asymmetric synthesis by Ovaska[3g] provided further confirmation for the *R*-configuration at this center. The initial discrepancy in assignments was later explained by MacMillan[3j] who established that an inversion of the C8-center had occurred during the Trauner synthesis. It was suggested that an unusual stereochemical relay process had occurred during a key palladium-catalyzed cyclization of the B-ring to ultimately deliver the *S*-configuration at C8. Frondosin A has also been the subject of synthetic studies[2] including one asymmetric[2a] synthesis, which established that the related C8-center also naturally occurs as the *R*-configuration.

Several of the frondosins were noted for their potential to act as antagonists toward the interleukin-8 receptor (IL-8), and frondosin B has also been reported to be a modest inhibitor of the serine/threonine kinase protein kinase C (PKC). The related terpene liphagal was shown to be a relatively potent and isozyme-selective inhibitor of the lipid kinase phosphatidylinositol-3-kinase (PI-3K). However, there have been few subsequent investigations into the biological activity of the frondosins or their analogs.[1a] Herein, we present an asymmetric total synthesis of both enantiomers of frondosin B and the natural enantiomer of frondosin A through a unified strategy featuring a complexity building cycloaddition between an annulated furan and a perhalocyclopropene. The syntheses also feature a new protocol for opening of a pivotal oxa-bridged intermediate. Central to the ultimate design was a flexible dibromoenone intermediate derived from a [4 + 3] cylcoaddition reaction with an annulated furan. Interestingly, we observed the same stereochemical inversion during our frondosin B synthesis as noted in the Trauner system. This appears to involve a highly unusual stereochemical inversion of

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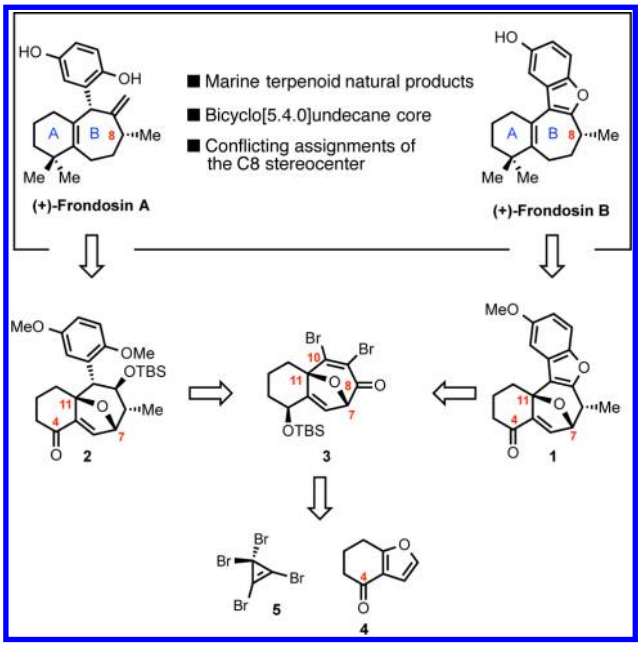
a carbocation intermediate. We also report the second asymmetric total synthesis of frondosin A which proceeds directly without the observed inversion process. Frondosin A was also shown to have selective antiproliferative action toward B-cell lines.

The retrosynthetic analyses for both natural products targeted late stage oxabridged intermediates **1** and **2** that contained the intact carbocyclic framework of the respective natural products with a temporary bridging ether spanning C7−C11 of the B-ring (Scheme 1). These intermediates were

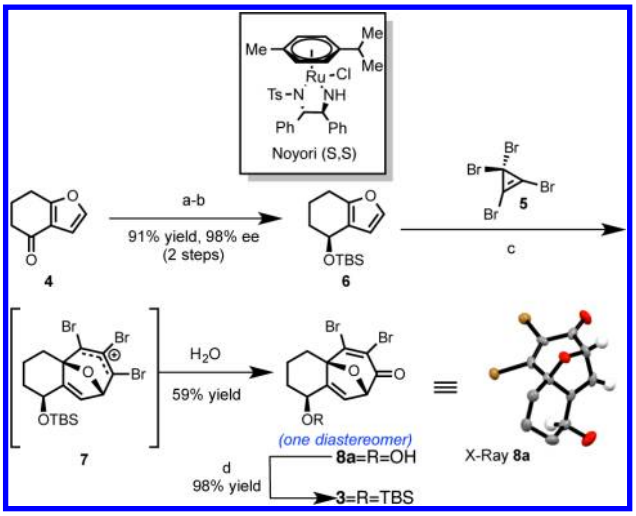
Scheme 1. Retrosynthesis of (+)-Frondosin A and (+)-Frondosin B



envisioned to arise from a common precursor, dibromoenone **3**, the product of a diastereoselective cycloaddition between tetrabromocyclopropene (TBCP, **5**) and an annulated furan derivative such as **4**. TBCP is readily available in a one step transformation from the commercially available tetrachlorocyclopropene, by reaction with boron tribromide. We have worked considerably with the TBCP adducts of simple substituted furans[5] but had not previously attempted to extend this formal [4 + 3] cycloaddition to annulated furans such as **4**. Although the analogous reaction between annulated furans and oxyallyl cations is known to be difficult, with simple electrophilic substitution products arising,[6] it was hoped that high reactivity of TBCP toward direct cycloaddition with furans would compensate for the increased steric demands.[7] Moreover, we were attracted to the notion that an asymmetric center at C4 of the A-ring could control the diastereoselectivity of the cycloaddition and that this information could be used to establish the other stereogenic centers located on the seven-membered B-rings. The commercially available ketone **4** seemed an ideal starting point, and in fact, asymmetric reduction of **4** to the *R*-alcohol has been previously reported by Noyori.[8]

We required the *S*-alcohol and found that it could be prepared with excellent selectivity through reduction of ketone **4** with the (*S*,*S*)-Noyori transfer hydrogenation catalyst (Scheme 2).[8b] The alcohol was converted to the silyl ether **6** and condensed with TBCP to give a mixture of regioisomeric

Scheme 2. TBCP Cycloaddition with Chiral Annulated Furan[a]



[a]Reagents and conditions: (a) (*S*,*S*)-Noyori (0.01 equiv), HCO_2H:Et_3N, rt, 7 days; (b) TBSCl (1.1 equiv), imidazole (1.5 equiv), DMAP (0.10 equiv), DCM, rt, 5 h, 91% (2 steps), 98% ee; (c) (i) **5** (1.0 equiv), 1,4-dioxane, rt to 90 °C, 5 h; (ii) $AgNO_3$ (2.0 equiv), 2:1 acetone:H_2O, rt, 8 h, 77% (1 step); (d) TBSOTf (1.0 equiv), 2,6-lutidine (1.5 equiv), DCM, −78 °C, 1 h, 98%.

tetrabromides in excellent overall yield. Pleasingly, the facial selectivity was high with the C4-silyloxy exerting a strong directing effect on the initial Diels−Alder reaction leading to a *syn*-relationship between the protected alcohol and the oxa bridge. The resulting crude tetrabromides could be directly treated with aqueous silver nitrate, proceeding through a pseudosymmetrical tribromoallyl cation **7** that can lead to the regioisomeric enones **8a** and **8b** (**8b** shown in Supporting Information only), depending upon which terminus of the cation water attacks. The bridgehead substitution at C11 provided a reasonable directing effect which favored the formation of **8a** as the major regioisomer (r.r.=3.3:1). This one-step conversion of furan **6** to bridged intermediate **8a** was highly efficient and was amenable to a gram-scale production of the dibromoenone.

The two vinylic bromides in these systems display substantially different levels of reactivity that allows for the controlled, stepwise introduction of functionality. We were able to take advantage of this versatile array to easily annulate the CD-ring benzofuran substructure (Scheme 3). Suzuki cross-coupling of **3** with the aryl trifluoroborate salt **9**[9] occurred exclusively at the *β*-bromide to deliver the phenols **10** as a (∼1:1) mixture of noninterconverting atropisomers. The use of the trifluoroborate salt was critical in the cross-coupling to this somewhat hindered bromide. Application of more traditional borates derived from the electron-rich phenol led to the formation of deborinated byproducts, producing only 55% yield of the coupled product. Exposure of the crude mixture of phenols to stoichiometric copper(I)iodide led to a smooth coupling of the phenolic hydroxyl group to the remaining bromide, thus giving the annulated benzofuran **11** in excellent overall yield.[10] Frondosin B contains a single stereogenic center at C8, typically a challenging type of center to set on a seven-membered ring. However, the temporary ether bridge induces rigidity into this otherwise flexible cycloheptyl ring and effectively differentiates the two faces of the carbocycle. This

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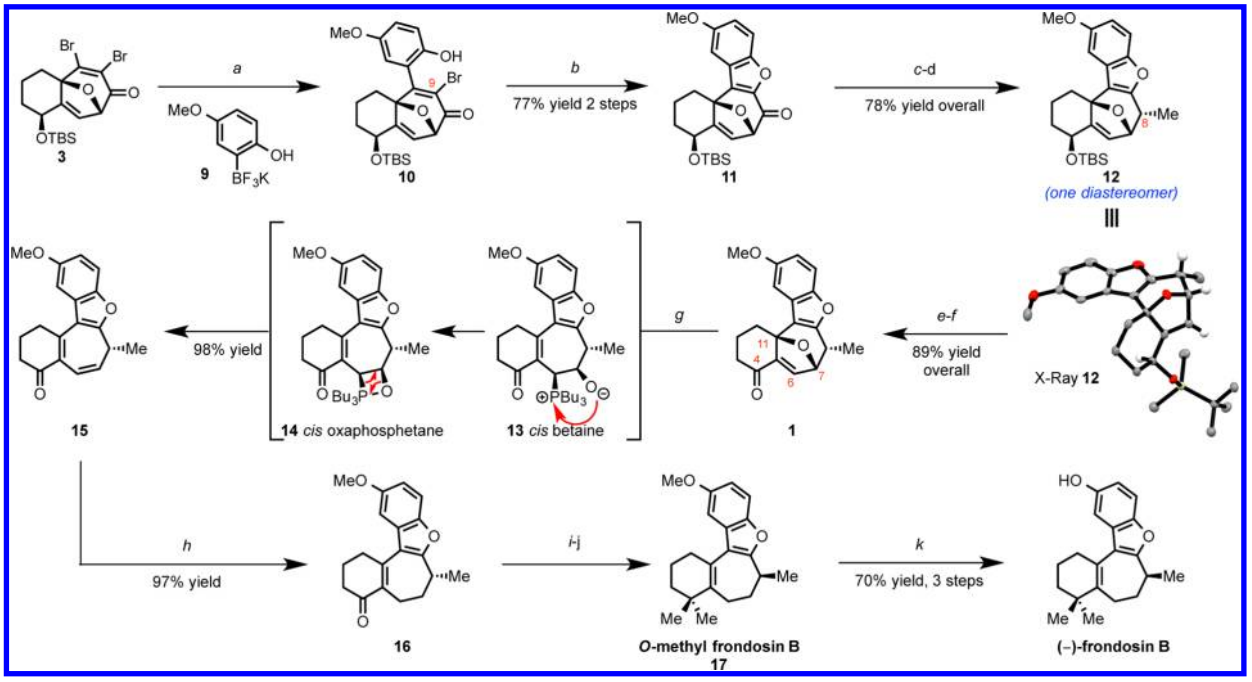
Scheme 3. Total Synthesis of (−)-Frondosin B[a]



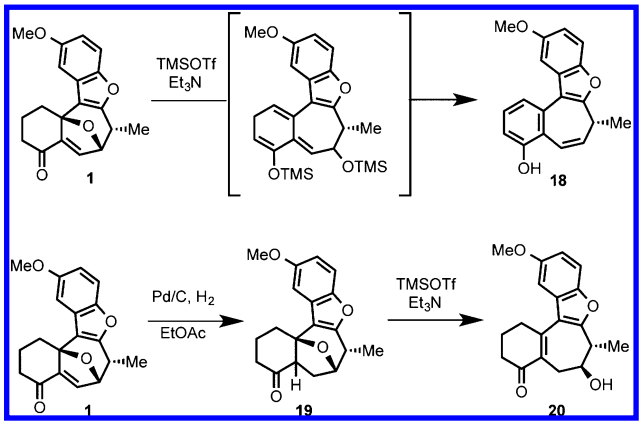
[a]Reagents and conditions: (a) **9** (1.25 equiv), $Pd(PPh_3)_4$ (0.10 equiv), Cs_2CO_3 (1.25 equiv), 10:1 THF:H_2O, 70 °C, 4 h; (b) CuI (1.5 equiv), 1:1 MeCN:Et_3N, 80 °C, 18 h, 77% (2 steps); (c) Ph_3PCH_3Br (3.0 equiv), *n*-BuLi (3.0 equiv), THF, 0 °C, 1.5 h 82%; (d) PtO_2 (0.20 equiv), H_2 (1 atm), PhH, 3 h, 95%; (e) HF·pyridine (20 equiv), THF, 0 °C to rt, 10 h; (f) Dess-Martin periodinane (2.0 equiv), $NaHCO_3$ (10 equiv), DCM, rt, 1.5 h, 89% (2 steps); (g) Bu_3P (1.5 equiv), DCE, rt, 5 min, 98%; (h) Pd/C (0.10 equiv), H_2 (1 atm), EtOAc, 2 h, 97%; (i) MeMgBr (3.2 equiv), $CeCl_3$ (3.2 equiv), THF, 0 °C, 15 min; (j) $TiCl_4$ (1.0 equiv), Me_2Zn (2.0 equiv), DCM, 0 °C, 15 min, 74% (2 steps); (k) NaSEt (20 equiv), DMF, 140 °C, 5 h, 95%.

facial bias was exploited by initial Wittig condensation to give the *exo*-methylene derivative that was stereoselectively hydrogenated from the *exo*-face to produce **12** as a single diastereomer, which was confirmed though a single crystal X-ray structure determination. Deprotection of the silyl ether preceded oxidation of the resulting allylic alcohol to give enone **1**.

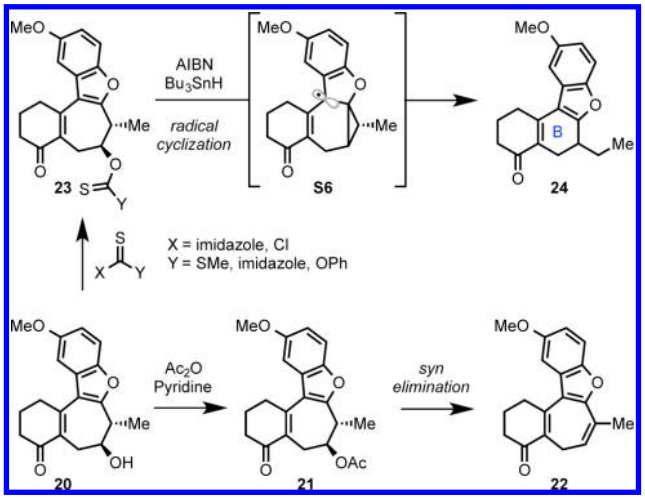
With completion of the carbocyclic core of frondosin B, attention turned to opening of the ether bridge and completion of the synthesis. The first productive ring-opening was realized with a combination of TMSOTf and Et_3N (Scheme 4). This Lewis acid-assisted opening did produce a ring opened product, however the reaction proceeded to give phenol **18**. In an attempt to impede the rapid aromatization of the A-ring, we first reduced the enone olefin and then treated the saturated ketone **19** with TMSOTf/Et_3N. To our delight, a productive ring-opening had occurred and generated alcohol **20**.

Initial attempts to effect removal of the secondary alcohol of **20** with pyridine and Ac_2O were hampered by a preference for elimination reactions to yield a C8-olefin **22**, thus destroying the stereogenicity of this center (Scheme 5). Upon converting **20** to its corresponding assorted thioxoesters **23**, radical deoxygenation failed to deliver the desired product as a ring contracted compound **24** formed preferentially, independent of the various esters examined. The contraction is proposed to occur though an intermediate cyclopropylcarbinyl radical **S6**

Scheme 4. Initial Ring-Opening Attempts



Scheme 5. Attempts to Deoxygenate 20



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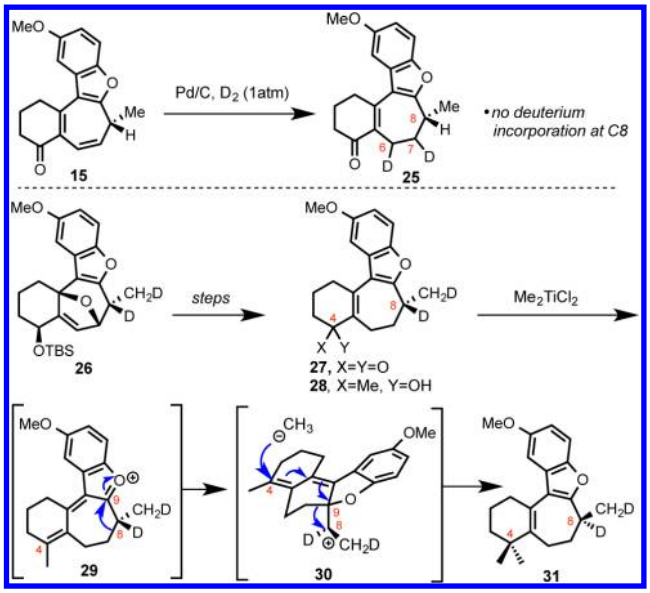
produced by a transannular addition to the furan olefin. It is likely that the driving force for this radical rearrangement is the formation of the more stable six-membered B-ring.

These difficulties prompted us to develop an interesting phosphine-mediated deoxygenation protocol that provided complete regiocontrol over the final elimination reaction. Addition of tributylphosphine to the enone **1** led to direct conversion to the triene **15** in high yield. A probable mechanism for this deoxygentation, akin to the phosphine-induced reduction of epoxides to olefins, involves an initial conjugate addition of the phosphine to the more accessible *exo*-face to produce an initial enolate followed by ejection of the *β*-disposed ether.[11] The elimination yields a transient betaine **13** that collapses through the intermediacy of the oxaphosphatane **14** to deliver the desired olefin.

Regioselective hydrogenation of the disubstituted alkene produced enone **16**, a late stage intermediate in the Trauner synthesis.[4c,d] Although we were pleased that **16** matched the reported spectral data, it was surprising that our intermediate also matched Trauner's reported optical rotation, as that compound was later shown to possess the incorrect S-configuration at C8, ultimately leading to the antipode of the natural product. Compound **16** was advanced to frondosin B according to Trauner's protocol and, as reported, possessed the opposite rotation as that reported for (+)-frondosin B. Our initial concern was that the assignment of silyl alcohol **6** was incorrect as it was based on NMR shift analysis of the corresponding Mosher esters. Fortunately, a single crystal structure determination of dibromoenone **8a** allowed for the unambiguous assignment of the absolute stereochemistry through analysis of the Flack parameter (Scheme 2).[12] The structure confirmed that the original assignment of **8a,** which in consideration of the X-ray structure of **12** (Scheme 3), unambiguosly established that the C8 center possessed the correct *R*-configuration in **12** and was somehow inverted to the incorrect *S*-configuration during the final steps of the synthesis. We first set out to determine if the configuration at C8 had somehow been inverted in the processing of **12** to the Trauner intermediate **16**, perhaps through equilibration of the methyl group to the more stable *exo*-orientation in one of the bridged intermediates. Strong NOE enhancements between the C8 methyl group and the C6-vinylic protons in the intermediates leading to **1** confirmed that the methyl group had remained in the *endo*-position.

To further probe the configuration of this center during the final stages of the synthesis, a series of deuterium labeling experiments were conducted (Scheme 6). Reduction of the dieneone **15** under a deuterium atmosphere only showed incorporation at C6−7 and no incorporation at the C8 position of **25**. Likewise, reduction of the exomethylene derived from **11** with deuterium gas gave labeled intermediate **26** that was converted to the Trauner-like intermediate **27** without exchange of the methine deuterium for hydrogen. As this surprising inversion of configuration occurred in both our synthesis and Trauner's, it seems most likely that it is related to a common process, namely the conversion of the C4 ketone **16** to *O*-methyl frondosin B through an intermediate carbonium ion. Interestingly, there is precedent for an inversion of the analogous C8-center in liphigal under cationic reaction conditions.[13] Our working hypothesis centers around the initial, highly delocalized carbocation **29** that may undergo a stereoselective, reversible alkyl shift producing an intermediate ring contracted cation **30** (which could be reversibly

Scheme 6. Isotopic Labeling Studies and a Working Model for Stereochemical Inversion



intercepted by chloride). The strong propensity to contract the B-ring as seen during the attempted deoxygenation of **20** to **24** provides support for this pathway. Critically, this migration generates a new stereogenic center at C9 and acts to preserve the stereochemical information in the molecule. In compound **30**, the planarized C8 carbon should adopt a conformation that orients the methyl group outside the ring system such that when the final nucleophilic attack at C4 triggers reformation of the C7−C8 bond, the migration is stereoselective. In this manner, the initial C8 configuration controls the stereochemistry produced at C9 of **30**, which in turn dictates the configuration when the C8 center is re-established. The intermediacy of a C8 cation allows for the process to occur with overall stereochemical inversion. Based on this hypothesis, it appeared straightforward to prepare the natural configuration using the antipode of silyoxy **6.** Utilizing the (*R*,*R*)-Noyori catalyst for the reduction of ketone **4** produced the enantiomeric compound (+)-**6** (after protection as its silyl ether) which could be taken through the same sequence to deliver (+)-frondosin B.

With a successful synthesis of frondosin B complete, our attention turned to the total synthesis of the related frondosin A from the common intermediate **3**. This synthesis would also provide an opportunity to probe the hypothesis that the extended conjugation from the benzofuran allows a C4 cationic center to invert stereochemistry at C8. The saturation of the C9−C10 olefin of frondosin A should effectively eliminate this pathway.

Again taking advantage of the differential reactivity of the two vinylic bromides of **3**, the 2,5-dimethoxy arene moiety was introduced at the *β*-position of the enone **3** through Suzuki−Miyaura cross-coupling reaction (Scheme 7). With the protected *o*-phenol, it was not necessary to utilize the trifluoroborate derivative in the coupling as was necessary in the synthesis of frondosin B. Exploiting the curvature embedded in the oxabicyclo[3.2.1]octadiene core, exposure of the resulting crude material to catalytic hydrogenation conditions, in the presence of triethylamine, produced the saturated ketone **32** in 76% yield over the two steps and with

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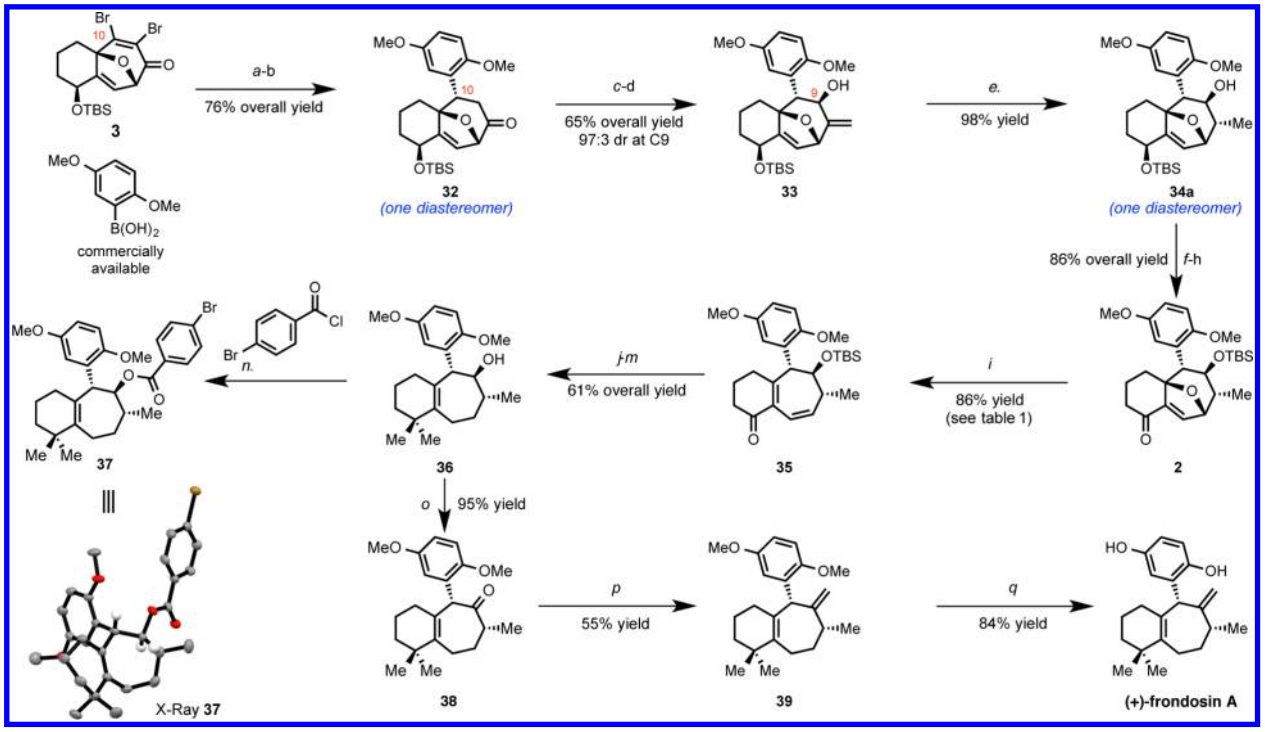
Scheme 7. Total Synthesis of (+)-Frondosin A[a]



[a]Reagents and conditions: (a) 2,5-dimethoxyphenyl boronic acid (1.25 equiv), $Pd(PPh_3)_4$ (0.10 equiv), Cs_2CO_3 (1.25 equiv), 10:1 THF:H_2O, 70 °C, 4 h; (b) Pd/C (0.10 equiv), Et_3N (7.0 equiv), H_2 (1 atm), THF, 24 h, 76% (2 steps); (c) Ph_3PCH_3Br (3.0 equiv), *n*-BuLi (3.0 equiv), THF, 0 °C, 1.5 h, 80%; (d) SeO_2 (0.50 equiv), *t*-BuOOH (3.0 equiv), DCM, rt, 16 h, 81%; (e) [Rh(nbd)(diphos-4)]BF_4 (0.20 equiv), THF (0.025 M), H_2 (600 PSI), rt, 2 h, 98%; (f) TBSOTf (1.0 equiv), 2,6-lutidine (1.5 equiv), DCM, −78 °C, 1 h; (g) TBAF (1.2 equiv), THF, 0 °C to rt, 6 h; (h) Dess-Martin periodinane (2.0 equiv), $NaHCO_3$ (10 equiv), DCM, 0 °C to rt, 1.5 h, 86% (3 steps); (i) Ti(*i*-OPr)$_4$ (3.0 equiv), Me_3P (3.0 equiv), THF, 70 °C, 3 h, 86%; (j) MeMgBr (6.4 equiv), $CeCl_3$ (3.2 equiv), THF, 0 °C, 15 min; (k) $TiCl_4$ (1.0 equiv), Me_2Zn (2.0 equiv), DCM, 0 °C, 15 min; (l) TBAF (8.0 equiv), 65 °C, 36 h; (m) Pd/C (0.10 equiv), H_2 (1 atm), MeOH, rt, 5 h, 61% (4 steps); (n) *p*-bromobenzoyl chloride (3.0 equiv), Et_3N (3.0 equiv), DMAP (1.0 equiv), DCM, 45 °C, 3 h, 80%; (o) Dess-Martin periodinane (2.0 equiv), $NaHCO_3$ (10 equiv), DCM, 0 °C to rt, 1.5 h, 95%; (p) Mg (16 equiv), $TiCl_4$ (4 equiv), DCM, 60 °C, 6 h, 55%; (q) (i) AgO (2.0 equiv), 6N HNO_3 (3.0 equiv), 1,4-dioxane, rt, 15 min; (ii) Pd/C (0.05 equiv), H_2 (1 atm), DCM, 15 min, 84%.

complete diastereoselectivity.[14] A subsequent Wittig condensation gave the corresponding exocyclic methylene derivative. Further reliance on the facial bias that the temporary ether bridge provides was illustrated when the alkene was subjected to allylic oxidation conditions with SeO_2 to provide the key alcohol **33** with high diastereoselectivity, producing 97:3 mixture of *exo*:*endo* allylic alcohols.[15]

The *exo*-alcohol installed at C9 of intermediate **33** would not only serve as a precursor for the exocyclic olefin in the natural product but also employed to reinforce the expected *exo*-mode reduction of the methylene group to produce the *endo*-methyl group at C8. To probe the natural preference for hydrogenation, alcohol **33** was subjected to hydrogenation in the presence of Pd/C and PtO_2. In both cases, a high-yielding reduction occurred to give a 4:1 mixture of diastereomers **34a:34b**.

To evaluate a hydroxyl-directed hydrogenation, **33** was exposed to [Rh(nbd)(diphos-4)]BF_4 catalyst at 600 psi of H_2 pressure.[16] Interestingly, it was found that at a higher catalyst load (20 mol %), a 10:1 mixture of diastereomers was produced. Further optimization revealed that the concentration of the reaction had a dramatic effect on the diastereomeric ratio. Reduction at 0.025 M in THF led to a completely diastereoselective hydrogenation to give **34a** exclusively.

With the appropriate stereocenters of frondosin A intact, the stage was set for cleavage of the bridging ether. Prior results from the total synthesis of frondosin B suggested that ether bridge cleavage could be effectively accomplished on late stage intermediate **2** using trialkylphosphine reagents. In efforts to advance **34a** to **2**, a selective deprotection scheme was utilized to exploit the difference in reactivity between the C4 allylic alcohol and the C9 secondary alcohol. Protection with TBSOTf followed by selective removal of the allylic silyl ether with TBAF provided the requisite alcohol that oxidized with Dess-Martin periodinane (DMP) to give the α,β-unsaturated enone **2**.[17]

Initial attempts at ether bridge cleavage of **2** revealed that this system was significantly less reactive toward phosphine nucleophiles, compared to a corresponding frondosin B intermediate. As Lewis acids have often been employed to facilitate the opening of oxabicyclic intermediates, we investigated whether compatible additives would catalyze the desired transformation (Table 1).[18] Pleasingly, when enone **2** was exposed to a mixture of In(III)Cl and *n*-Bu_3P (entry 4), a productive ring-opening/elimination reaction occurred, however the isolated yield was only 25% along with 10% of an unidentified phosphine-containing adduct. Increasing the nucleophilicity of the phosphine reagent greatly impacted the isolated yield of ring-opened diene **35**. A combination of Me_3P with Ti(*i*OPr)$_4$ proved particularly effective (entries 8,9), producing the formal deoxygenation product **35** in an isolated yield of 86%.

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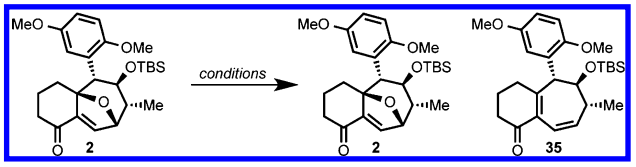
Table 1. Trends in Lewis-Acid Assisted Ether Cleavage



entry	Lewis acid[a]	phosphine[b]	solvent/temp	yield 2[c]	yield 35[c]
1	–	n-Bu_3P	DCE/23 °C	94%	–
2	–	n-Bu_3P	DCE/80 °C	56%	–
3	$InCl_3$	n-Bu_3P	DCE/23 °C	70%	–
4	$InCl_3$	n-Bu_3P	THF/70 °C	–	25%
5	$InCl_3$	Me_3P	THF/70 °C	–	55%
6	$Ti(OiPr)_4$	n-Bu_3P	THF/70 °C	–	62%
7	$Ti(OiPr)_4$	t-Bu_3P	THF/70 °C	–	70%
8	$Ti(OiPr)_4$	Me_3P	THF/70 °C	–	77%
9	$Ti(OiPr)_4$[d]	Me_3P	THF/70 °C	–	86%

[a]6 equiv of Lewis acid used unless otherwise stated. [b]3 equiv of trialkylphosphines used in all reactions. [c]Isolated yield. [d]Performed with 3 equiv of Lewis acid.

Prior conversion of the C4 carbonyl of **35** to the geminal dimethyl group was crucial to eliminate the cross-conjugated dienone and allow for a selective saturation of the C6–C7 alkene. The dimethyl intermediate was difficult to isolate given the nonpolar nature, and thus the crude material was immediately deprotected in the presence of TBAF, at elevated temperature, followed by traditional hydrogenation conditions (Pd/C, MeOH, 1 atm H_2) to produce intermediate **36**.

The intermediacy of alcohol **36** provided an ideal opportunity to confirm the absolute stereochemistry. Alcohol **36** was reacted with 4-bromobenzoyl chloride to generate highly crystalline benzoate **37** that yielded thin plate crystals. X-ray crystallographic analysis of **37** allowed for the unambiguous conformation of the absolute stereochemistry.[19]

To complete the synthesis of frondosin A, alcohol **36** was oxidized with DMP to late stage intermediate **38** matching the spectral data reported by the Ovaska group.[2b] Conversion of the C9 carbonyl to the required *exo*-methylene group was attempted with a variety of standard olefination procedures (Wittig, Petasis) but only returned unreacted starting material. The desired olefination of the hindered B ring carbonyl carbon was ultimately accomplished by applying the bimetallic $TiCl_4$-Mg promoted methylene transfer reaction to deliver known dimethoxy-frondosin A **39**.[20]

Initial attempts at final deprotection of the dimethoxy-arene **39** with CAN/$Na_2S_2O_4$, as disclosed in previous total syntheses of frondosin A, resulted in a less than effective deprotection with only around 35% recovered product. Reports of deprotection of dimethoxy frondosin A with BBr_3 are known to result in decomposition, while reports of deprotection with sodium ethanethiolate only yielded monodeprotected products. A significant improvement was made through a two-step oxidative (AgO, HNO_3)/reductive (Pd/C, H_2) procedure to provide the enantiomerically pure frondosin A in a 84% yield over the two steps and possessing optical rotation reflective of the natural product $[\alpha]_D^{22}$ = +29.8 (c = 0.25, MeOH); lit. $[\alpha]_D$ = +31.5 (c = 0.25, MeOH).[21] Importantly, no inversion at C8 was observed, supporting the role of extended conjugation in the unusual results obtained in the frondosin B synthesis.

As the frondosins were suggested to exhibit inhibitory action on signaling through IL-8 receptor in blood cells, we evaluated both (+)-frondosin A and (+)-frondosin B for effects on proliferation of a panel of leukocytes (Table 1).[22] (+)-Frondosin A, but not frondosin B, inhibited proliferation of lymphocytic cell lines suggesting the necessity of the free hydroquinone moiety for activity. This was further supported by the finding that the dimethyl ether analog of frondosin A (**39**) was also inactive toward the cell lines. The potency of (+)-frondosin A was an order of magnitude higher for B cell lines compared to the T-cell lines that were tested. Surprisingly, (+)-frondosin A inhibited Ba/F3 cells[23] that express oncogenic IL-7 receptor mutations more potently than the IL-3-dependent wild-type Ba/F3 cells. Taken together, these data suggest that in addition to IL-8 in neutrophils, frondosins may have inhibitory activity against other leukocyte cytokine receptors. Further evaluations of the biological activity are currently underway.

Table 2. Inhibition of Cell Growth[a]

72 h (GI_{50} values in μM)				
cell type	cell line	(+)-Fro A	(+)-Fro B	*O*-methyl-(+)-Fro A
B-cell	Daudi	2.62	N/A	N/A
	CH12	2.05	N/A	N/A
	Ba/F3 WT	4.49	N/A	N/A
	Ba/F3 WT mut IL7R (88i)	0.87	N/A	N/A
	Ba/F3 WT mut IL7R (GCins)	1.58	N/A	N/A
T-cell	HuT 78	17.23	N/A	N/A
	Jurkat	23.73	N/A	N/A
	Molt-4	25.65	N/A	N/A
myeloid	K562	N/A	N/A	N/A

[a]N/A - not active at 33 μM.

Overall, we have developed a synthesis of both the natural and unnatural enantiomers of frondosin B and the natural enantiomer of frondosin A utilizing a highly selective perhalocyclopropene/furan cycloaddition reaction to access the central core of the natural product. The versatile common intermediate could be converted to two structurally distinct members of this class of marine natural product. The synthesis has also suggested the possibility of a very unusual inversion of configuration in a carbocationic intermediate that will warrant further investigation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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