Total Synthesis and Determination of the Absolute Configuration of Frondosin B

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Received June 12, 2000. Revised Manuscript Received September 18, 2000

Abstract: Two concise syntheses of (±)-frondosin B (1), an interleukin-8 receptor antagonist, have been achieved from commercially available 5-methoxysalicylaldehyde. The seven-membered ring in ketone 33, the common intermediate for both syntheses, was built by a classical Friedel-Crafts reaction. The key step of the first route was facile cationic cyclization of the vinylogous benzo furan to the trisubstituted olefin (30 → 16 + 38) to construct a six-membered carbocycle. Although this route demonstrated the efficacy of the stepwise approach to the frondosin ring-system, it also resulted in olefinic isomers that were easily isomerized in acidic conditions. In the second route, we utilized a Diels-Alder reaction between sterically demanding diene 42 and nitroethy lene to fix the double bond in its required position in the resultant dimethylcyclohexane ring. A third total synthesis was devised for the purpose of determining the absolute configuration of frondosin B. It reached diene 42, this time in the enantiomerically defined form. From this point, naturally configured frondosin B was obtained in the enantiomerically enriched form. These studies establish the absolute configuration of the secondary methyl center in frondosin B to be R.

Introduction

Interleukin-8 (IL-8), a chemoattractant for neutrophils, is produced by macrophages and endothelial cells. IL-8 has been implicated in a wide range of acute and chronic inflammatory disorders, including psoriasis and rheumatoid arthritis. Furthermore, various animal models of inflammation have established IL-8 as a principal chemotactic factor directing neutrophil recruitment to the inflammatory focus. Therefore, an IL-8 receptor antagonist represents a promising target for the development of novel pharmacological agents against autoimmune hyperactivity.

Frondosins A-D were recently isolated from the sponge Dysidea frondosa. Each of them inhibited the binding of IL-8 to its receptor in the low micromolar range. The structures of these compounds, which bear a casual relationship to one another, were determined mainly by NMR spectroscopy. Their unifying architectural theme is the presence of bicyclo[5.4.0]-undecane ring systems in the context of permuted linkages to various hydroquinone-based moieties. A National Cancer Institute (NCI) team also obtained frondosins A and D from the HIV-inhibitory organic extract of the marine sponge Eury sp odina sp. It is worth noting that the frondosins, which were isolated at the NCI, exhibit opposite optical rotations with different absolute values in comparison to the previously isolated frondosins. Thus, the frondosins, except for frondosin B, are apparently fashioned by nature in both enantiomeric forms. It was anticipated that further biological studies of frondosins could spur fruitful investigations into IL-8 activity and present new possibilities for the development of novel antiinflammatory agents. These considerations, as well as the novel structure of the frondosins, prompted us to undertake a program directed toward their total synthesis.

In the opening phase of our inquiry we focused on frondosin B (1), which contains an intriguing benzo furan ring system fused to a nor sesquiterpenoid (14-carbon) framework. In this paper, we report an account of a highly efficient total synthesis of this compound by three different routes. The third reaches the naturally occurring enantiomer in 84% ee and establishes it to be of the R configuration. We first focused on frondosin B racemate as our goal. A number of "retrosynthetic disconnections" were employed in pursuing the racemate synthesis. Initially, we planned to couple two fragments by forming a bond between C6 and C7 then closing the seven-membered ring via a C10-C11 bond formation (Scheme 1). The union of the left and right domains can be envisioned as arising from the 1,4-addition of a suitably functionalized benzo furan 3 to the exocyclic enone, 2. We also took note of the possibility that

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sequential 1,2-addition and oxy-Cope rearrangements could provide an alternative to the 1,4-addition pathway.

Following preparation of the benzofuran derivative 3, the first difficulty we encountered, even after screening numerous reaction conditions, was that neither 1,4- or 1,2-addition could be accomplished. Presumably, these difficulties reflect the steric demand of the gem-dimethyl group. Apparently, the trajectory for nucleophilic attack at the exocyclic methylene group incurs serious hindrance from the proximal quarternary center.

Accordingly, we modified the coupling strategy to rely on an intramolecular delivery modality. It was hoped that Claisen rearrangement of compound 10 could serve to create the elusive C6-C7 linkage (Scheme 2). To test this strategy, alcohol 6 was prepared by 1,2-reduction of ketone 29 and compound 8 was synthesized by installation of bromine at C10 via the known carboxylic acid 7. The synthesis proceeded with the joining of the two domains by standard esterification of 8 with 6. The resultant ester 9 was smoothly transformed to diene 10 using the Tebbe reagent. Gratifyingly, subsequent heating gave, cleanly, the Claisen rearrangement product 11 in good yield.

The ketone in 11 was converted to the required C19 methyl function in two steps. Thus, addition of methylmagnesium bromide, followed by reduction of the resultant carbinol with sodium cyanoborohydride in the presence of anhydrous zinc iodide, provided compound 12 in good yield.

Having successfully constructed the desired functionality, we undertook a series of initiatives aimed at achieving ring closure. A Heck reaction was attempted first as we began to evaluate the applicability of palladium chemistry in this series. Experiments were conducted on bromides 11 and 12. No cyclization was observed under the various conditions we employed. We then focused our attention on Stille-type reactions. Installation of a ketone at C11 was achieved by hydroboration of 12 and (7) (a) White, J. D.; Skeean, G. L.; Trammell, G. L. J. Org. Chem. 1985, 50, 1939. (b) Adams, J.; Lepine-Frennette, C.; Spero, D. M. J. Org. Chem. 1991, 56, 4494.


When the coupling of 18 and 19 was conducted under ligandless conditions, as recommended for sterically demanding substrates, the adduct was isolated in modest yield. In this reaction, substantial amounts of 3-methoxybenzofuran were obtained. Installation of a carboxylic acid at C9 was achieved by a two-step procedure. Vilsmeier formylation successfully introduced the aldehyde. Following oxidation, compound 21 was in hand. Our plan included activation of the tetrasubstituted alkene in order to effect halolactonization. Unfortunately, the lactonization could not be achieved. We took this disappointing result to reflect the difficulties of attack by a viable iodonium equivalent at C5, even in the presence of a proximal, and presumably participating, carboxylate function. This negative outcome provided further testimony to the high risks in attempting to conduct chemistry proximal to the gem-dimethyl quarternary center.

Even as these unsuccessful efforts were in progress, efforts directed toward an alternative construction of the seven-membered ring were initiated (Scheme 4). The methyl ester vinyl triflate 24 and allyl-substituted vinyl triflate 25 were synthesized as shown. However, merger of 24 or 25 with activated benzofuran (19, 26, or 27) using palladium(0) as a catalyst was low-yielding and unreliable. The coupling yields deteriorated still further when the reaction was conducted on scales larger than a few milligrams. Because we were unable to solve this material availability problem, progress was severely hindered, and this initiative was also abandoned.

The series of negative results described above, augmented by many others, underscored several important points: First, bond formation in spatial proximity to the dimethyl quarternary center.


For a recent review of the Vilsmeier reaction, see: Jones G. Org. React. 1997, 49, 1.


hydrogenated using palladium on carbon. Subsequent saponification furnished carboxylic acid 34 in quantitative yield. In the hydrogenation step, extended reaction times resulted in formation of significant quantities of dihydrobenzofuran. Fortunately, the critical Friedel–Crafts reaction could be accomplished. Thus, reaction of 34 with oxalyl chloride and treatment of the resultant acid chloride with stannic chloride gave ketone 33 in good yield. 38

Nucleophilic attack of the cerium reagent, 29 prepared from 4-methyl-3-pentenylmagnesium bromide, led to an addition product. Dissolution of the resultant tertiary alcohol in chloroform afforded the diene 30 as a 5:1 mixture with its endo isomer in 93% yield. The remarkable susceptibility of the tertiary alcohol to dehydration presumably arises from participation of the benzofuran in stabilizing an intermediate bearing cationoid character. Fortunately, acid-induced cyclization of 30 proceeded under mild conditions in reasonable yield. Various acid combinations (BF3·OEt2, HCOOH, H3PO4) resulted in the formation of the six-membered ring in an approximately 2.5:1 mixture favoring the desired compound 16 and olefinic isomer mixture 38. Mercury trifluoroacetate-mediated reaction, 30 in which olefin isomerization after cyclization was expected to be minimal, also proceeded smoothly. Unfortunately, following reductive cleavage of the carbon–mercury bond, very similar isomeric ratios were obtained. The results of these reactions suggested that the product distribution might be reflecting the thermodynamic stability order of rapidly equilibrating isomers. However, there remains the possibility that the nonvariant ratio could arise from kinetic factors.

Although these isomers were inseparable by silica gel chromatography, we attempted to complete the total synthesis, hoping for a later-stage separation (Scheme 6). Deprotection of the methyl ether was effected with boron tribromide to afford (±)-frondosin B (1) and its olefinic isomers 39 in 87% yield. These isomers were separated with HPLC (silica gel, 5% ethyl acetate–hexane). The 1H, 13C NMR and IR spectra obtained from synthetic frondosin B were identical with those reported from the naturally occurring material. 31 Thus, the total synthesis of racemic frondosin B has been achieved in 9 steps from commercially available 2-hydroxy-5-methoxybenzaldehyde. Although this synthesis is highly concise and ensures quick access to reasonable amounts of material, the unsolved problem associated with control over the regiochemistry of olefin formation still remained irksome and prompted a fresh approach.

We noted that subjection of 1 and 39 separately to a variety of acidic conditions led to formation of a 2.5:1 mixture of the same products (Scheme 6). These data seemed to confirm that the mixture of double-bond isomers (16 and 38 or 1 and 39). Accordingly, to achieve control in our synthesis, it would be necessary to construct the dimethylcyclohexene from 33 without recourse to acidic catalysis in the formation of the fully mature A ring or after its construction.


(28) Friedel–Crafts cyclization to benzofuran is relatively rare. For an example leading to a six-membered ring, see: Bhide, G. V.; Tikotkar, N. L.; Tilak, B. D. Tetrahedron 1960, 10, 223–229.


(31) We note that direct comparison of synthetic racemate and material product was not possible because a specimen of natural frondosin furnished to us reached our lab in a totally decomposed and unrecognizable state.

Emerging as rather difficult and would be particularly risky with advanced intermediates. Furthermore, attachment of tetrasubstituted olefin derivatives to the β-position of the furan (corresponding to C10 of the target frondosin) by organometallic methods, appears to be highly problematic.

With these considerations in mind, we developed a totally revised approach to the problem. The new perception involved incorporation of the cyclohexene ring containing the gem-dimethyl group onto a preexisting matrix wherein the seven-membered ring was already in place (Scheme 5). More specifically, in this stepwise approach, the seven-membered ring diene 30 would be synthesized by addition of a homoprenyl group to a ketone such as 33. This bond formation would set the stage for subsequent acid-induced cyclization, exploiting the activated benzofuran ring to promote and guide the sense of electrophilic attack on the cycloheptenyl double bond (see 30 → 16). 24 We hoped that the tetra-substituted olefin between C5 and C11 would be markedly more stable than trisubstituted isomers and could accordingly be generated under equilibrating conditions. 25

The synthesis started from the acetyl benzofuran 35, which was prepared from 2-hydroxy-5-methoxy benzaldehyde by the known protocol, 26 shown in Scheme 6. Four-carbon extension of 35 by Wittig methodology proceeded smoothly to give olefin 37 (Z:E = 3:2) in 87% yield. 27 The olefin in 37 was rendered using palladium on carbon. Subsequent saponification furnished carboxylic acid 34 in quantitative yield. In the hydrogenation step, extended reaction times resulted in formation of significant quantities of dihydrobenzofuran. Fortunately, the critical Friedel–Crafts reaction could be accomplished. Thus, reaction of 34 with oxalyl chloride and treatment of the resultant acid chloride with stannic chloride gave ketone 33 in good yield. 38

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We noted that subjection of 1 and 39 separately to a variety of acidic conditions led to formation of a 2.5:1 mixture of the same products (Scheme 6). These data seemed to confirm that the mixture of double-bond isomers (16 and 38 or 1 and 39). Accordingly, to achieve control in our synthesis, it would be necessary to construct the dimethylcyclohexene from 33 without recourse to acidic catalysis in the formation of the fully mature A ring or after its construction.
Scheme 6. Cationic Cyclization Strategy

\[ \text{MeOCHO} \xrightarrow{a} \text{MeO} \xrightarrow{b} \text{MeO} \xrightarrow{c,d} \text{OH} \]

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“Reagents and conditions: (a) chloroacetone, K$_2$CO$_3$, 2-butanol, 80 °C, 72%; (b) Br$_3$Ph$_2$P(CH$_2$)$_2$COEt (36), NaNSiMe$_3$, THF, 0 °C to room temperature, 87% (Z:E = 3:2); (c) H$_2$, Pd/C, EtOH, room temperature; (d) LiOH, THF–MeOH–H$_2$O, 100% (2 steps); (e) (COCl)$_2$, CH$_2$Cl$_2$, reflux, then SnCl$_4$, −78 °C to −10 °C, 67%; (f) 4-methyl-3-pentene magnesium bromide, CeCl$_3$, THF, −78 °C; (g) CDCl$_3$, 93% (2 steps, endo:exo = 5:1); (h) BF$_3$-Et$_2$O, MeCN, room temperature, 81%, (16:38 = 2.5:1); (i) BBr$_3$, CH$_2$Cl$_2$, −78 °C to room temperature, 98%, (1:39 ≈ 2.5:1); (j) HPLC separation (silica gel, 5% ethyl acetate–hexane); (k) p-TsOH, PhH, 80 °C.

Given these constraints, which were by now well appreciated, we modified the synthetic route to attain a completely regiocontrolled outcome. To install the double bond at the proper C5–C11 position without the requirement for acidic conditions, we came to favor a Diels–Alder-inspired logic to form the C1–C2 and C3–C4 bonds. Accordingly, construction of the corresponding diene (see structure 42) was initiated via the aldol condensation of ketone 33 with acetone (Scheme 7). The zinc enolate of the ketone, prepared by transmetalation of the lithium enolate, reacted with acetone to furnish adduct 40 in 85% yield.33 Not surprisingly, this compound was prone to retro-aldolization, especially in acidic media. Indeed, treatment of 40 with p-toluenesulfonic acid produced ketone 33 in 77% yield along with a trace amount of olefin 41. After several experiments, dehydration of the tertiary alcohol was accomplished by treatment of 40 with mesyl chloride and triethylamine. This protocol gave rise to a mixture of olefinic isomers (~1:1) in 88% yield. Treatment of this mixture of sodium methoxide in methanol effected isomerization of the $\beta$–$\gamma$ unsaturated olefin tautomers to provide the desired compound 41 in 96% yield. Finally, diene 42 was prepared in 97% yield following exposure of 41 to the Tebbe reagent$^{11}$ buffered with pyridine.

As was noted in preliminary reconnaissance experiments, compound 42 is sensitive to acid. In addition, it is relatively unreactive. However, reaction of 42 with maleic anhydride at 110 °C for 2 days did give a Diels–Alder adduct, albeit in only 27% yield.$^{35}$ Considering the acid-sensitivity of 42 as well as the expected tendency toward olefin migration of the product, a Lewis acid-promoted Diels–Alder reaction would be problematic. Accordingly, we elected to use nitroethylene as a reactive ethylene equivalent under acid-free conditions.$^{36}$ It was expected that the nitro group could be easily removed through a free radical protocol. In addition, it was anticipated that the nitro group might actually be useful for synthesizing structural analogues for biological investigations.

Diels–Alder reaction of 42 with excess nitroethylene in the presence of di-tert-butyl pyridine at 80 °C afforded adduct 43 in 79% yield. The nitro group was removed by radical reduction to afford O-methyl frondosin B 16 in 58% yield. Finally, synthesis of geometrically pure frondosin B (1) was achieved by deprotection of the methyl group, this time with sodium ethanethiolate (94%).$^{38}$ In this alternative route, the total synthesis of (±)-frondosin B was realized in 12 steps. The method clearly has potential for the synthesis of numerous structural variants.

Having completed the synthesis of racemic frondosin B, we embarked on an enantio-defined preparation of the natural product. The goal was not only to gain access to the naturally occurring enantiomer but also to include determination of the absolute configuration of frondosin B. We would start with a chiral precursor of known absolute configuration and use it to

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(35) Side-reactions could involve acid-catalyzed 1,5-proton shift cycloadditions or one-reactions with maleic anhydride.

(37) Ono, N.; Kaji, A. Synthesis 1986, 693.
**Scheme 7.** Diels–Alder Strategy

![Diagram](image)

- Reagents and conditions: (a) LiN(SiMe₃)₂, ZnCl₂, acetone, THF, -78 °C to 40 °C, 81% (96% BORS; (b) MeCl, Et₂N, CH₂Cl₂, 0 °C, 88%; (c) NaOMe, MeOH, 0 °C, 96%; (d) Tebbe reagent, pyridine, THF, -40 °C, 97%; (e) excess nitroethylene, di-tert-butyl pyridine, 80 °C, 79% (5:1 mixture of diastereomers); (f) tri-n-butyltin hydride, AIBN, PhMe, 110 °C, 58%; (g) NaSeEt, DMF, reflux, 94%.

Reach either frondosin B or the enantiomer of frondosin B. In either case, we would have answered our question. Because the Diels–Alder route (Scheme 7) had provided racemic frondosin B in a regio-controlled fashion, benzofuran 34, an intermediate in the synthesis of the racemate, appeared to be a reasonable target (Scheme 8). The annulation between alkyne 44 and 4-methoxy-2-iodophenol (45) to afford an enantiomer-enriched 2-substituted benzofuran system would then serve as one of the key steps in synthesis.

With this program in mind, a method for enantioselectively installing the secondary methyl group was required. Prior work had shown that treatment of 2,3-epoxy alcohols with AlMe₃ results in the regioselective opening of epoxides to give 3-methyl-1,2-diols. Thus, we felt that the Sharpless asymmetric epoxidation of a prochiral alcohol followed by C-methylation of the epoxy alcohol via AlMe₃ would serve as a highly region-selective method for introducing the secondary methyl group and could ultimately lead to enanti-enriched alkynyl 44.

As shown in Scheme 9, the synthesis of (+) frondosin B (1) commenced with the epoxidation of the known methyl 7-hy-..
of (−)-51 proceeded smoothly to give (−)-50 in 62% yield under Kundu conditions at 50 °C (Scheme 11).

At this point, the asymmetric synthesis nominally intersected with the racemic synthesis of frondosin B when 2-substituted benzofuran (−)-50 was converted to carboxylic acid (−)-34 by saponification. Under identical conditions previously described (Scheme 6), ketone (−)-33 was furnished in good yield via the intramolecular Friedal-Crafts acylation of the acyl chloride that was derived from carboxylic acid (−)-34. Chiral stationary phase (CSP) HPLC analysis of the material revealed that (−)-33 had been prepared in 84% ee.

Because we were concerned with the possibility of racemization at the C8 chiral center, we were forced to proceed cautiously in our approach to the condensation of the enolate of ketone (−)-33 with acetone. As shown in Scheme 12, a control experiment revealed that the lithium enolate of (−)-33 could be formed almost quantitatively without racemization at C8. This was evidenced by the fact that the reaction of (−)-33 with 1 equiv of LiHMDS, followed by MeOD quench, gave recovered (−)-33 exclusively with 95% incorporation of deuterium at C5. Aldol condensation between the zinc enolate of (−)-33, prepared from the lithium enolate, and acetone gave alcohol 40 in 55% yield along with ketone 33 in 45% yield. However, recovered ketone (−)-33, most likely regenerated via a retro-aldol reaction, had a 24% ee (Scheme 12). Future studies would show that the C8 center in 41 was most likely racemized as well (vide infra). The racemization at the C8 center is probably due to the excess base remaining after the formation of the enolate of (−)-33. Deprotonation at C8 of the zinc chelate of 40 may serve as the racemization step. Unfortunately, the aldol product 40 was generated in low yields when only 1 equiv of LiHMDS was used. Gratifyingly, though, the problems of racemization and the retro aldol reaction were circumvented by generating the silyl enol ether of (−)-33 in situ. 49 As depicted in Scheme 12, (−)-52 was then smoothly transformed to tertiary alcohol 40 without epimerization at C8 (60% de) in 70% yield by the Mukaiyama reaction. 50

Unfortunately, the dehydration of 40 resulted in another setback. As in the synthesis of the racemate (Scheme 7), conversion of 40 to its mesyl ether, followed by elimination, provided ∼1:1 mixture of olefinic isomers (Scheme 13). However, treatment of the olefinic isomers with sodium methoxide in methanol delivered olefin 41 exclusively as its racemate. In a parallel experiment with MeOD as the solvent, 1H NMR analysis revealed that 40 was partially deuterated.

Table 1. Palladium (II)-Catalyzed Reactions between 4-Methoxy-2-iodophenol (45) and Methyl (−)-5(R)-6-heptynoate (44)

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<th>mol % Cul</th>
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<th>temp °C</th>
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<td>2.0 NEt₃</td>
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<td>24</td>
<td>(−)-51 74</td>
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Scheme 11a

Experimental Section

Preparation of Olefin 37. To a stirred solution of phosphonium salt 36, a solution of NaHMDS in THF was added at 0 °C. After 30 min at 0 °C, methyl ketone 35 was added to the ylide via cannula, and the resultant solution was stirred at 0 °C for 30 min and at room temperature for 1.5 h. The reaction mixture was quenched with saturated aqueous NH₄Cl and diluted with EtOAc (400 mL). The organic layer was washed with H₂O and brine, dried (Na₂SO₄), and concentrated. Flash column chromatography (10–20% EtOAc–hexane) gave olefin 37 as a 3:2 mixture of Z:E isomers (5.25 g, 86%): IR (film) 2980, 1731, 1728, 1584, 1574, 1559, 1558, 1495, 1494, 1297, 1296, 1289, 1265, 1258, 1253, 1129, 1125, 1114, 1111, 1048, 1033, 1031, 1017, 78, 60.3, 55.9, 34.5, 33.9, 25.0, 23.7, 21.8, 14.2, 13.3; HRMS (FAB) [M⁺] calcd for C₂₀H₂₀O₄, 328.1355; found, 328.1355.

Carboxylic Acid 34. A solution of olefin 37 (2.07 g, 7.19 mmol) and Pd/C (400 mg) in EtOAc (50 mL) was stirred at room temperature under hydrogen for 2 h. The mixture was filtered through Celite and concentrated to give the crude ester, which was used in the next reaction.
without further purification: IR (film) 2967, 1732, 1476, 1205, 1179 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) 7.28 (d, J = 8.9 Hz, 1H), 6.95 (d, J = 2.6 Hz, 1H), 6.79 (dd, J = 8.9 Hz, 2.6 Hz, 1H), 6.32 (s, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 2.89–2.94 (m, 1H), 2.29 (t, J = 7.2 Hz, 2H), 1.75–1.80 (m, 1H), 1.58–1.67 (m, 3H), 1.31 (t, J = 7.0 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 173.5, 164.0, 155.6, 149.4, 129.3, 111.4, 111.1, 103.1, 101.1, 60.3, 55.9, 34.7, 34.2, 33.4, 22.5, 18.9, 14.2. A solution of the above ester in THF–MeOH–H₂O (4:1:1, 60 mL) was treated with LiOH·H₂O (930 mg, 22.2 mmol), and the mixture was stirred at room temperature for 2 h. The solution was acidified with 1N HCl (45 mL) and extracted with CHCl₃ (100 mL). Drying (Na₂SO₄) concentration, and flash column chromatography (5–10% MeOH–CHCl₃) gave carboxylic acid 34 (1.88 g, 100%); IR (film) 3300–2500, 2935, 1707, 1476, 1205 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.29 (d, J = 8.9 Hz, 1H), 6.96 (d, J = 2.6 Hz, 1H), 6.80 (dd, J = 8.9 Hz, 2.6 Hz, 1H), 6.32 (s, 1H), 3.82 (s, 3H), 2.90–2.96 (m, 1H), 2.35 (t, J = 7.1 Hz, 2H), 1.79–1.85 (m, 1H), 1.60–1.70 (m, 3H), 1.32 (d, J = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 179.6, 163.9, 155.7, 149.5, 129.3, 111.5, 111.1, 103.2, 101.1, 55.9, 34.7, 33.9, 33.5, 22.3, 18.9; HRMS (FAB) [M]+ calcd for C₁₅H₁₈O₄, 262.1205; found, 262.1205.

A mixture of benzofuran (–)-50 (432 mg, 1.56 mmol) and LiOH·H₂O (197 mg, 4.69 mmol) in THF–MeOH–H₂O (4:1:1; 16.5 mL) was stirred at room temperature for 2 h before acidification with 5 mL of 1 N HCl. After typical workup as

Scheme 12

Reagents and conditions: (a) 1.1 equiv LiHMDS, THF, −40 °C, 0.5 h; MeOD, −40 °C; (b) 1.5 equivs LiHMDS, THF, −40 °C, 0.5 h; 1.5 equivs ZnCl₂, Et₂O, −40 °C, 10 min; 2.0 equivs Me₂CO, −40 °C, 0.5 h; (c) 3.0 equivs LiHMDS, 3.0 equivs TMSCl, THF, −40 °C, 1 h; (d) 1.1 equivs TiCl₄, 2.0 equivs Me₂CO, 0 °C, 1 h.

Scheme 13

Reagents and conditions: (a) MsCl, NEt₃, CH₂Cl₂, 0 °C; (b) MeONa, MeOD(H), 0 °C; (c) PdCl₂(MeCN)₂, PhH, reflux, 93%.

(-)-(R)-Carboxylic Acid 34. A mixture of benzofuran (–)-50 (432 mg, 1.56 mmol) and LiOH·H₂O (197 mg, 4.69 mmol) in THF–MeOH–H₂O (4:1:1; 16.5 mL) was stirred at room temperature for 2 h before acidification with 5 mL of 1 N HCl. After typical workup as
A solution of LiHMDS (1.0 M solution in THF) in THF (2.4 mL, 2.4 mmol) was cooled to −40 °C, and the mixture was stirred at −40 °C for 20 min at −40 °C for 30 min at 40 °C for 30 min. The solution was cooled to −78 °C and was treated with SnCl₂ (321 mg, 2.74 mmol). The mixture was stirred at −78 °C for 30 min and warmed to −10 °C, and the stirring was continued for 30 min. The reaction was then quench with 1N HCl, saturated aqueous NaHCO₃, and brine. Drying (Na₂SO₄), concentration, and flash column chromatography (10–30% EtOAc–hexane) gave tertiary alcohol 40 as a 1:2.5 mixture of isomers (504 mg, 85%), along with recovered starting material 33 (54.4 mg, 11%).

**Absolute Configuration of Frondosin B**


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**Scheme 14**

- Reagents and conditions: (a) Tebbe reagent, THF, −40 °C, 98%; (b) nitroethylene 2,6-di-tert-butylpyridine, PhH, 80 °C, 36 h, 65%; (c) Bu₃SnH, AIBN, PhMe, 110 °C, 4 h, 40%; (d) Et₂Sn, DMF, 140 °C, 4 h, 78%.

**Absolute Configuration of Frondosin B (II)** chloride. The benzene was removed under vacuum and the crude residue was purified via column chromatography (5% EtOAc-hexane) to give 6.9 mg (93%) of (+)-silyl enol ether 52. After being stirred at 0 °C for 4 h, the solution was acidified with Dowex 50-X8 and filtered. Concentration and flash column chromatography (10% EtOAc–hexane) gave 41 (43.9 mg, 96%).

**Tertiary Alcohol 40** from (+)-(R)-Silyl Enol Ether 52. A solution of 60.1 mg (0.190 mmol) of (+)-(R)-silyl enol ether 52 in 0.80 mL of CH₂Cl₂ was added dropwise to a solution of (0 °C) of 23.0 mL (0.227 mmol) of titanium (IV) chloride. The benzene was removed under vacuum and the crude residue was purified by column chromatography (10% EtOAc-hexane) of the crude residue afforded 39.6 mg (69%) of the titled compound as well as 5.7 mg (12%) of (+)-(R)-ketone 33. CSP HPLC analysis showed that the recovered ketone 33 had an ee of 84% (er, 92:8).

**Olefin 41**. A solution of tertiary alcohol 40 (55.5 mg, 0.183 mmol) and EtN₂ (260 µL, 1.86 mmol) was cooled to 0 °C and treated with methanesulfonyl chloride (71 µL, 0.92 mmol). After being stirred at 0 °C for 1 h, the mixture was diluted with EtOAc (20 mL) and washed with H₂O and brine. Drying (Na₂SO₄), concentration, and flash column chromatography (10% EtOAc–hexane) gave 41 (43.9 mg, 96%). IR (film) 2934, 1650, 1626, 1473, 1415, 1377 cm⁻¹; HRMS (FAB) [M⁺] calcd for C₁₈H₂₃O₄, 303.1596; found, 303.1589.

**Tertiary Alcohol 40**. A solution of LiHMDS (1.0 M solution in THF, 2.4 mL, 2.4 mmol) in THF (3 mL) was cooled to −78 °C, and ketone 33 (479 mg, 1.96 mmol) in THF (2 + 1 + 1 mL) was added to this solution. The mixture was stirred at −78 °C for 20 min and at −40 °C for 30 min. This solution was then diluted with 80 mL of EtOAc and washed with 15-mL portions of water; 1N HCl, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5% EtOAc–hexane) to give 42.0 mg (35%) of the desired (+)-(R)-olefin 41 and 47.7 mg (40%) of its olefinic isomer.

**Olefin 41**. A solution of 128 mg (0.423 mmol) of tertiary alcohol 40, prepared from (+)-52, and 0.185 mL (2.13 mmol) of methanesulfonyl chloride in 4.2 mL of CH₂Cl₂ was cooled to 0 °C and 0.590 mL (4.23 mmol) of triethylamine was added dropwise. The resulting yellow mixture was stirred at −30°C for 3 h. The mixture was then submitted to 80 mL of EtOAc and washed with 15-mL portions of water; 1N HCl, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5% EtOAc–hexane) to give 42.0 mg (35%) of the desired (+)-(R)-olefin 41 and 47.7 mg (40%) of its olefinic isomer.
(130 μL, 1.60 mmol) in THF (8 mL) was cooled to −40 °C and treated with Tebb reagent (0.5 M in toluene, 3.2 mL, 1.6 mmol). After being stirred at −40 °C for 1 h, the reaction mixture was diluted with Et₂O (12 mL), and 15% aqueous NaOH and solid Na₂SO₄ was added to this mixture. The resulting mixture was stirred at room temperature for 1.5 h and filtered through Celite. Concentration and flash column chromatography (10% EtOAc–hexane) gave diene 176 (147 mg, 97%): IR (film) 2930, 1614, 1474, 1200 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.32 (d, J = 8.9 Hz, 1H), 7.17 (d, J = 2.6 Hz, 1H), 6.81 (dd, J = 8.9 Hz, 2.6 Hz, 1H), 5.55 (d, J = 2.2 Hz, 1H), 5.11 (d, J = 2.2 Hz, 1H), 3.85 (s, 3H), 3.05–3.11 (m, 1H), 2.55–2.60 (m, 1H), 2.42–2.50 (m, 1H), 2.00–2.07 (m, 1H), 1.85–1.91 (m, 1H), 1.80 (s, 3H), 1.70–1.79 (s, 3H), 1.33 (d, J = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 137.5, 125.3, 119.7, 116.4, 115.6, 114.7, 112.1, 111.1, 103.0, 56.3, 31.9, 29.3, 22.3, 19.9, 18.6; HRMS (FAB) [M + H⁺]⁺ calcd for C₂₉H₄O₂: 283.1689; found, 283.1696.

(8) Dienes were prepared in a similar manner as racemate diene 2: [α]D = +22.0 (c 1.26, CHCl₃).

Diels–Alder Adduct 43. A solution of diene 42 (313.9 mg, 1.11 mmol), nitroethane (800 mg, 10.9 mmol) and 2,6-di-tert-butylpyridine (110 mg, 0.574 mmol) in benzene (7 mL) was placed in a sealed tube and heated at 80 °C for 36 h. After being cooled to room temperature, the solution was concentrated. Flash column chromatography (5–10% EtOAc–hexane) gave diene–Aldred Adduct 43 as a 51% mixture of isomers (311.6 mg, 79%): IR (film) 3072, 1588, 1543, 1473, 1369, 111.1, 103.0, 56.3, 31.9, 29.3, 22.3, 19.9, 18.6; HRMS (FAB) [M + H⁺]⁺ calcd for C₂₉H₄O₂: 283.1689; found, 283.1696.

O-Methyl Frondosin B 16. A solution of Diels–Alder adduct 43 (31.9 mg, 0.0890 mmol), AIBN (15.0 mg, 0.0910 mmol) and n-Bu₃SnH (500 μL, 1.85 mmol) in toluene (2 mL) was heated at 110 °C for 1.5 h. After being cooled to room temperature, the solution was concentrated and subjected to flash column chromatography (5% EtOAc–hexane) to afford O-methyl frondosin B 16 (16.3 mg, 58%): IR (film) 2927, 1591, 1473, 1204, 1035 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.28 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 2.5 Hz, 1H), 7.05 (d, J = 2.5 Hz, 1H), 6.82 (dd, J = 8.9 Hz, 2.5 Hz, 1H), 4.67 (dd, J = 10.4 Hz, 3.2 Hz, 4H), 4.63 (dd, J = 12.4 Hz, 2.9 Hz, 1H), 3.83 (s, 3H), 3.21 (m, 4H), 3.18 (m, 1H), 2.74–2.76 (m, 2H), 2.21–2.37 (m, 3H), 2.04–2.14 (m, 2H), 1.79–1.83 (m, 1H), 1.38 (d, J = 7.0 Hz, 3H), 1.36 (s, 3.5H), 1.34 (s, 12.5H), 1.14 (s, 12.5H), 1.11 (s, 3.5H); ¹³C NMR (CDCl₃, 125 MHz) of major isomer δ 157.5, 154.9, 140.9, 140.8, 128.6, 123.9, 115.5, 111.1, 111.0, 104.9, 92.6, 56.1, 39.7, 38.2, 33.4, 27.2, 26.1, 25.4, 23.9, 22.3, 20.1; HRMS (FAB) [M + H⁺]⁺ calcd for C₂₉H₄O₂: 315.1784; found, 355.1776. (+)-(R)-diene 42 was converted to 43 in the same manner as described above.

Methyl 6-oxohexanoate, which was immediately used in the next step.
dimethyl (diazomethyl)phosphonate in 10.0 mL of THF was added to a 0.90 M solution (~78 °C) of potassium t-butoxide (9.13 mmol) in THF. The yellow solution was stirred at ~78 °C for 5 min and a solution of crude methyl 5-(R)-methoxy-6-oxohexanoate in 1.5 mL of THF was added dropwise over a 30-min period. Gas evolution was observed within 5 min. The orange mixture was stirred overnight at ~50 °C. The orange mixture was concentrated to ~1 mL and then purified by column chromatography (5% EtOAc–hexane) to give 915 mg (71%) of the volatile alkyne: [α]D27 = −23.0 (c 0.160, CHCl3); IR (film) 3295, 2970, 2934, 2847, 1740, 1454, 1375, 1292, 1167 cm⁻¹; ¹H NMR (CDCl3, 400 MHz) δ 3.68 (s, 3H), 2.42–2.48 (m, 1H), 2.34 (t, J = 7.5 Hz, 2H), 2.05 (d, J = 2.3 Hz, 1H), 1.73–1.86 (m, 2H), 1.20–1.50 (m, 2H), 1.19 (d, J = 7.0 Hz, 3H); ¹3C NMR (CDCl3, 100 MHz) δ 173.91, 88.62, 68.54, 51.50, 35.98, 33.76, 25.46, 23.01, 18.87; MRMS (EI) m/z: calcd for C12H16O, 154.0994; found, 154.0984.

2-iodo-4-methoxyphenyl (45). A solution of 5.23 g (23.4 mmol) of diethyl carboxylic acid (4-methoxyphenyl ester) and 2.10 mL of a 1.20 M solution of diethyl carbamic acid (4-methoxyphenyl ester) 53 and 2.9 mL of tetramethylthelenediamine (25.7 mmol) in THF was added dropwise over a 30-min period. Gas evolution was observed within 5 min. The orange mixture was stirred at ~78 °C for 1.5 h to complete the directed ortho-lithiation and a saturated solution of iodine in THF was added dropwise until an orange color persisted in the reaction mixture. The orange mixture was stirred at ~50 °C for 1.5 h and then was quenched with 15 mL of H2O. The aqueous layer was extracted with EtOAc (3 × 30 mL) and 2 × 20 mL). The combined organic extracts were washed with H2O (5 × 25 mL) and brine (1 × 25 mL), dried (MgSO4), and concentrated under reduced pressure. Flash chromatography (5–10% EtOAc–hexanes gradient) yielded 843 mg (61%) of benzofuran 50 as well as 114 mg (8%) of recovered starting material 51: [α]D27 = −20.2 (c 0.104, CHCl3); ¹H NMR (CDCl3, 400 MHz) δ 7.30 (d, J = 8.9 Hz, 1H), 6.97 (d, J = 2.6 Hz, 1H), 6.81 (d, J = 8.9 Hz, 2.6 Hz, 1H), 6.33 (s, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 2.91–2.96 (m, 1H), 2.31–2.35 (m, 2H), 1.76–1.83 (m, 1H), 1.33 (d, J = 6.9 Hz, 3H), 1.61–1.70 (m, 3H); ¹3C NMR (CDCl3, 100 MHz) δ 173.93, 164.05, 155.70, 149.49, 129.30, 114.11, 117.00, 101.09, 55.94, 51.49, 34.79, 33.36, 33.47, 22.56, 18.95; MRMS (EI) m/z: calcd for C19H18O2, 276.1362; found, 276.1352.

2-iodo-4-(hydroxyphenyl) (46). A mixture of 69.0 mg (0.282 mmol) of (−)-4-ketone 33, 0.107 mL (0.843 mmol) of chlorotrimethylsilane, and 0.107 mL of crushed molecular sieves in 1.4 mL of THF was cooled to ~0 °C and 0.860 mL of a 0.98 M solution of LiHMDS (0.843 mmol) was added dropwise. The resulting dark yellow solution was stirred at ~0 °C for 1 h before quenching with 2.0 mL of saturated aqueous NaHCO3. The aqueous layer was separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with 2 mL of brine, dried, washed with 10 mL of Et2O, and concentrated under vacuum. The crude residue was purified by flash chromatography (20% EtOAc–hexane) to give 66.6 mg (75%) of the silen ester as well as 7.4 mg (11%) of recovered starting material: [α]D27 = +18.8 (c 1.13, CHCl3); ¹H NMR (CDCl3, 400 MHz) δ 7.47 (dd, J = 8.9 Hz, 2.7 Hz, 1H), 7.29 (d, J = 8.9, 1H), 6.85 (d, J = 2.7 Hz, 1H), 5.28 (t, 6.5 Hz, 1H), 3.86 (s, 3H), 3.32 (six-line pattern, J = 7.0 Hz, 1H), 2.24–2.33 (m, 1H), 2.02–2.06 (m, 1H), 1.61–1.80 (m, 1H), 1.40 (d, J = 7.0 Hz, 3H), 0.31 (s, 3H); ¹3C NMR (CDCl3, 100 MHz) δ 155.48, 148.58, 145.83, 128.34, 113.94, 113.09, 112.42, 111.05, 110.88, 110.68, 109.52, 104.94, 55.83, 35.17, 32.52, 22.38, 20.29, 0.23; MRMS (FAB) m/z: calcd for C18H20O3Si, 316.1495; found, 316.1485.

Acknowledgment. This work was supported by the National Institutes of Health (Grant No: AI16943). M.W.C. gratefully acknowledges the U.S. Army Breast Cancer Research Program (DAMD17-98-1-8154). M.I. gratefully acknowledges the U.S. Army Breast Cancer Research Program (DAMD17-98-1-8154). M.I. gratefully acknowledges the U.S. Army Breast Cancer Research Program (DAMD17-98-1-8154). M.I. gratefully acknowledges the U.S. Army Breast Cancer Research Program (DAMD17-98-1-8154).

Supporting Information Available: Experimental procedures and spectral character not involved in the most specific total synthesis (general method, 1, 6–9, 11–14, 18–21, 30, 39) and ¹H NMR spectral data for compounds (1, 16, 30, 33, 34, 37, 39–43). This material is available free of charge via the Internet at http://pubs.acs.org.