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The Total Synthesis of Frondosin B**

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Interleukin-8 (IL-8), a chemoattractant for neutrophils, is produced by macrophages and endothelial cells.[1] IL-8 promotes the accumulation and activation of neutrophils and has been implicated in a wide range of acute and chronic inflammatory disorders. Accordingly, blockade of IL-8-mediated chemotaxis represents a possible opportunity for the development of novel pharmacological agents. Frondosins A-E were recently isolated from the sponge *Dysidea frondosa* (Scheme 1). These compounds, which bear a casual relationship to one another, inhibit the binding of IL-8 to its receptor in the low micromolar range.[2a] The structures and relative stereochemistries of the frondosins were determined primarily by NMR spectroscopy. Their unifying feature is the presence of a bicyclo[5.4.0] ring system attached to variously permuted hydroquinione moieties.[3] A team from the National Cancer Institute (NCI) also isolated frondosins A and D from the HIV-inhibitory organic extract of the marine sponge.[2b, 4] It is worth noting that these compounds have optical rotations with different but opposite absolute values. Thus, the frondosins may occur as scalemic mixtures. Further biological studies of the frondosins could spur fruitful

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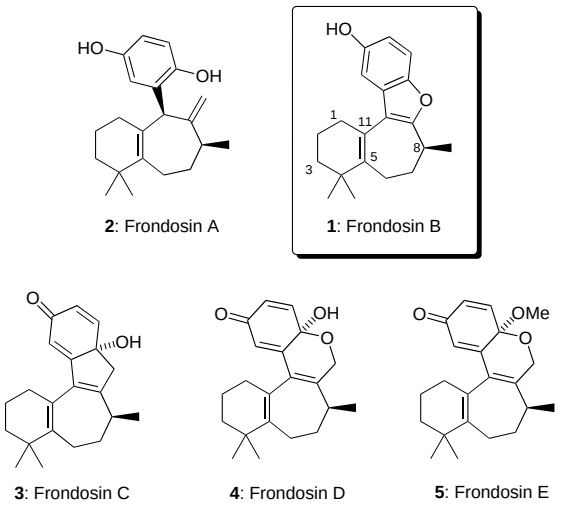
[**] This work was supported by the National Institutes of Health (Grant Numbers: AI16943 and CA08748). M.I. gratefully acknowledges the Uehara Memorial Foudation for a postdoctoral fellowship. A.J.F. gratefully acknowledges the American Chemical Society Organic Division and Merck & Co. for Graduate Fellowship support. We thank Dr. George Sukenick of the MSKCC NMR Core Facility and Vinka Parmakovic of the Columbia University Mass Spectral Facility for mass spectral analyses.

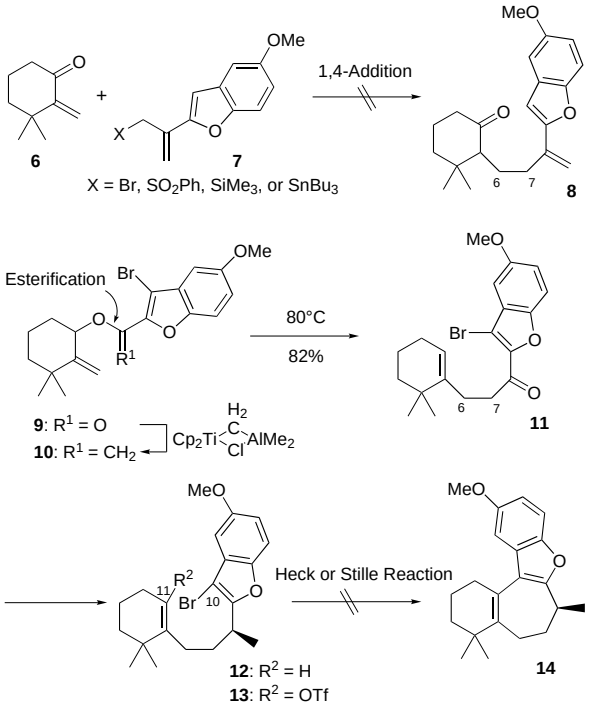


Scheme 1.

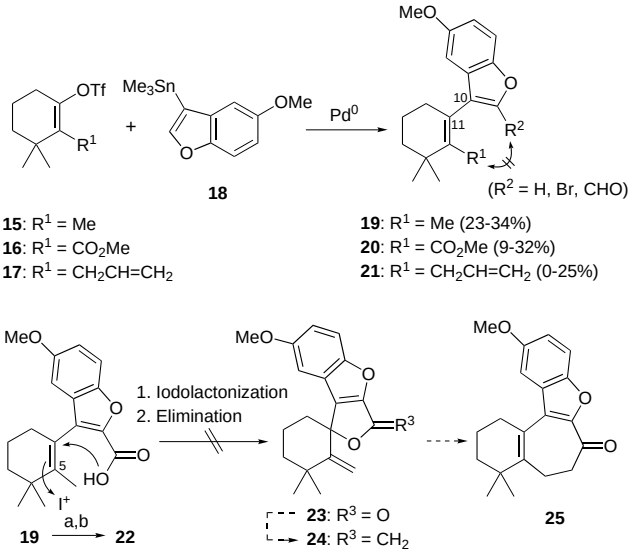
investigations into IL-8 inhibitory activity and thereby offer new opportunities for the development of novel anti-inflammatory agents. These considerations prompted a synthetic venture directed toward the frondosins. In the opening phase of the inquiry we focused on frondosin B (**1**),[2a] which contains an intriguing benzofuran ring system fused to a norsesquiterpenoid (14 carbon) framework. The other frondosins exhibit a 15 carbon atom framework. Herein we describe a highly efficient total synthesis of (+)-frondosin B.

We considered and evaluated a variety of strategies that seemed to hold promise for particularly concise total syntheses of frondosin B. In reality, many seemingly straightforward programs could not be implemented. Of course we emphasize that our failures with many attractive routes to frondosin B do not necessarily rule out possibilities for success by others who pursue these or related approaches.[5] In our case, there was much learned from these forays. Indeed, the plan by which the total synthesis of frondosin B was achieved evolved from appraisal of earlier setbacks described below and more fully elsewhere. Our first generation strategy was based on achieving a preliminary union of the C6-C7 bond, which would pave the way for ring formation by connecting C10 and C11 (Scheme 2). Early indications of the difficulties, presumably steric in nature, associated with bond formation in the region of the geminal methyl groups were seen in our inability to couple a variety of agents of the type **6** and **7** to reach **8**. Eventually, successful solution to the C6-C7 union was accomplished by intramolecular means (**9** → **11**). However numerous attempts to achieve transition metal induced closure of the C10-C11 bond (compare inter alia substrates **11** – **13**) by intramolecular Heck or Stille reactions were to no avail.[6]

Our second generation strategy contemplated the reverse order of steps, that is, initial union between C10 and C11 followed by cyclization through merger of C6 and C7. This plan was undercut by a series of unanticipated difficulties, which attended the proposed transition metal mediated coupling reactions en route to seco compounds of the type **19** – **21** (Scheme 3).[7] The few cases in which small-scale reactions produced these products in low yields could not be



Scheme 2. First generation strategy.



Scheme 3. Second generation strategy. a) $POCl_3$, DMF, $(CH_2Cl)_2$, reflux, 36% (65% based on recovered starting material), b) $AgNO_3$, aq NaOH, 75%.

scaled up to practical levels. Furthermore, no subsequent closures in which R^2 on benzofuran could be joined with R^1 on the dimethylcyclohexane ring could be achieved, despite testing several permutions.

One such C10-C11 coupling that could marginally be conducted on small scale was that of **15** + **18** → **19**. The latter was converted, as shown, into **22**. The thought was to reach **25** via **23** and **24**. Unfortunately, this program failed at the stage of the projected iodolactonization (**22** ↛ **23**), once again reflecting the difficulties of attack by a viable iodonium equivalent at C5, even in the presence of a proximal, and presumably participating carboxylate function.

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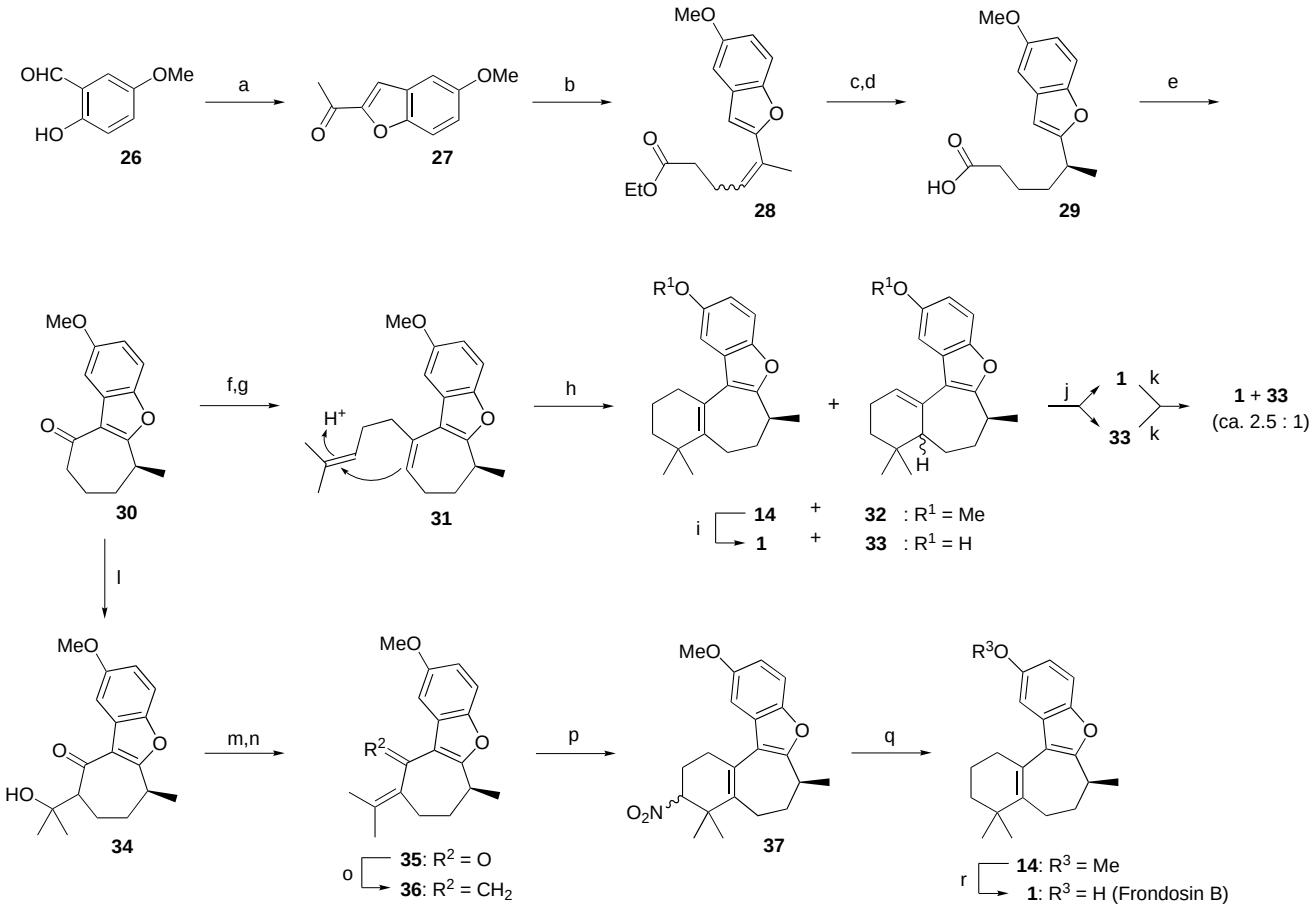
As a consequence of these difficulties, it was decided to target an intermediate structure of the type **30** and defer construction of the A ring corresponding to the 4,4-dimethylcyclohexene moiety until the last phase of the effort. Commercially available 5-methoxysalicylaldehyde (**26**) was converted into **30** by way of **27**[8] – **29** (Scheme 4). Homoprenylation of **30**,[9] gave rise to a labile adduct that underwent dehydration to afford **31**. Finally, treatment of **31** with formic acid gave an 81 % yield of a mixture of isomers.[10] The major product (56 %) was in fact *O*-methylfrondosin B (**14**). However, this compound was accompanied (ca. 24 %) by a 1:1 mixture of the stereoisomers corresponding to **32**. The ratio of **14**:**32** and the ratio of the stereoisomers **32** seemed to be virtually independent of the acidic conditions employed to bring about cyclization of **31**. Demethylation of the anisole moiety was accomplished on the mixture of **14** and **32** with BBr_3. After considerable efforts it proved possible to achieve separation of the products by preparative HPLC to afford fully synthetic and homogeneous frondosin B (**1**) as well as diasteromers **33**.

It was then found that the treatment of either of these materials with *p*-TsOH in benzene created the same 2.5:1 mixture of **1**:**33**. These data seem to confirm that the mixture of double bond isomers (**14** and **32** or **1** and **33**) that we obtain reflects thermodynamic equilibration and that this equilibration is quite rapid under strongly acidic conditions. Accordingly, to achieve control in our synthesis, it would be necessary to construct the dimethylcyclohexene from **30** without recourse to acidic catalysis in the critical steps leading to or following formation of the fully mature A ring.

Given these constraints, which were now properly recognized, we proceeded as follows. Condensation of **30** (via its zinc enolate) with acetone led to **34**[11] and thence, following dehydration, to **35**. Upon methylenation by the Tebbe method,[12] **36** was in hand. Remarkably, a Diels – Alder reaction with nitroethylene occurred at 80 °C to afford **37** as a mixture of nitro stereoisomers.[13] Reductive de-nitration[14] of **37** produced the previously mentioned **14** with no contamination from double bond isomers. Finally, de-methylation of **14** was carried out with sodium ethyl sulfide.[15] Frondosin B (**1**) was produced free of double bond isomers under these basic conditions. Although a trace specimen sample of the natural product that we received had entirely decomposed, we could still unambiguously establish the nature of our synthetic endpoint by independent spectrosopic analysis and comparisons with published data.



Scheme 4. Third and fourth generation strategies. a) Chloroacetone, K_2CO_3, 2-butanone, 80 °C, 72 %; b) $Br^-Ph_3P^+(CH_2)_3CO_2Et$, $NaN(SiMe_3)_2$, THF, 0 °C → RT, 87 %; c) H_2, Pd/C, EtOH, RT; d) LiOH, THF/MeOH/H_2O, 100 % (over 2 steps); e) $(COCl)_2$, CH_2Cl_2, reflux, then $SnCl_4$, −78 → −10 °C, 67 %; f) 4-methyl-3-pentenylmagnesium bromide, $CeCl_3$, THF, −78 °C; g) $CDCl_3$, 93 % (over 2 steps, endo:exo = 6:1); h) HCOOH, RT, 81 %, (**14**:**32** = ca. 2.5:1); i) BBr_3, CH_2Cl_2, −78 °C → RT, 98 %, (**1**:**33** = ca. 2.5:1); j) HPLC separation (silica gel, 5 % ethyl acetate/hexane); k) *p*-TsOH, benzene, 80 °C; l) $LiN(SiMe_3)_2$, $ZnCl_2$, acetone, THF, −78 °C → −40 °C, 81 % (96 % based on recovered starting material); m) MsCl, Et_3N, CH_2Cl_2, 0 °C, 88 %; n) NaOMe, MeOH, 0 °C, 96 %; o) Tebbe reagent, pyridine, THF, −40 °C, 97 %; p) excess nitroethylene, di-*tert*-butyl pyridine, 79 %; q) tri-*n*-butyltin hydride, AIBN, toluene, 110 °C, 58 %; r) NaSEt, DMF, reflux, 94 %. AIBN = azobisisobutyronitrile.

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In future studies we shall study other frondosins with a view to total synthesis, determination of absolute configuration, and biological evaluation.

Received: November 22, 1999 [Z14306]

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Self-Assembled Porphyrin Polymers**

Ulrike Michelsen and Christopher A. Hunter*

Supramolecular chemistry offers an attractive strategy for the construction of functional and responsive polymeric architectures.[1] Thermodynamically reversible noncovalent interactions such as hydrogen bonds and metal-ion coordination can be used to induce the self-assembly of suitably functionalized monomers into polymeric structures.[2, 3] However, the degree of polymerisation in such systems, N, depends critically on the stability constant of the monomer–monomer interaction, K:[3, 4]

$$N \approx (K\,[\text{monomer}])^{1/2} \quad (1)$$

Most studies of supramolecular polymer systems have been limited to the solid or liquid-crystalline states, where the value of [monomer] is maximized and the requirement for a strong monomer–monomer interaction is relaxed.[2] However, if K is sufficiently large, it is possible to generate very high molecular weight polymers in solution.[3] These systems have all the physical properties of covalently bound polymers, but in addition are sensitive to both changes in environmental conditions and the presence of small molecules which alter the stability of the monomer–monomer interactions, and hence the degree of polymerisation may be changed in a reversible manner.[1]

We have previously used the coordination of zinc porphyrins by pyridine ligands to assemble small cyclic oligomers.[5] Thus, zinc porphyrins, covalently linked to an appropriate pyridine side arm, form macrocyclic dimers with stability constants in the range $K = 10^6 - 10^8\,\text{M}^{-1}$ in chloroform (Figure 1a). These systems represent ideal building blocks for the formation of supramolecular polymers: Equation (1) predicts a degree of polymerisation of the order of $N = 10$ to 100 at millimolar monomer concentrations. Here, we show that this self-assembly strategy can indeed be used to generate soluble, high molecular weight porphyrin polymers. The rich photo- and electrochemical properties of the monomeric units make such polymers interesting from the point of view of charge storage and transport, solar energy conversion, and nonlinear optics.[6]

Figure 1 illustrates the approach. Changing the metal from zinc, which is five coordinate in a porphyrin, to cobalt, which is six coordinate, increases the number of vacant ligand binding sites from one to two,[7] and attachment of a second pyridine side arm yields a monomer with two identical

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[**] The authors thank Dr. J. P. Waltho and Dr. M. Conroy, Department of Molecular Biology and Biotechnology, University of Sheffield, for PGSE NMR spectra, and the EPSRC (U.M.) and the Lister Institute (C.A.H.) for funding.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

  0044-8249/00/11204-0780 $ 17.50+.50/0