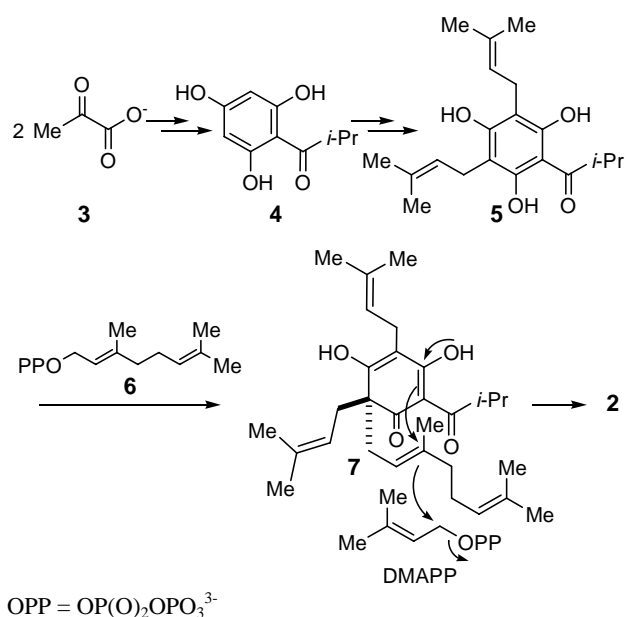


Hyperforin (**2**, Figure 1) is a structurally similar natural product to that of **1**, which is isolated from St.-John's wort and used as a herbal treatment for mild depression. The relative stereochemistry was established in 1975 by degradation experiments.⁵ In addition, recent ¹³C labelling experiments have been performed to determine the biosynthesis of this compound.⁶ The natural product is believed to be derived from acyl phloroglucinol **4**, which is synthesized from 2 equivalents of pyruvate (**3**, Scheme 1). The absolute sequence of steps to convert **4** into Hyperforin is still unknown, but it is postulated^{5, 6} that double electrophilic aromatic substitution of **4** with two prenyl groups derived from dimethylallyl diphosphate (DMAPP) would give **5**. Next, addition of a geranyl pyrophosphate (**6**) would produce **7**, which upon subsequent intramolecular ring closing and attack on another equivalent of DMAPP would afford **2**.

Scheme 1. Proposed Biosynthesis of **2**.

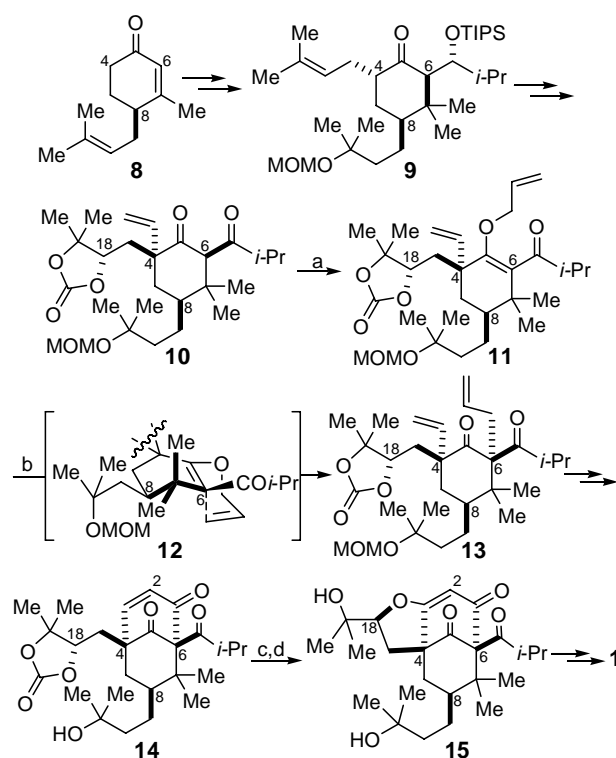


Shibasaki's successful total synthesis of Garsubellin A (Scheme 2), involved formation of the **C** ring of **1** by an intramolecular Wacker oxidative cyclization of an appendant 2° alcohol on to the enone of the **B** ring. The **B** ring was formed by a RCM, where the required diene was formed using a Claisen rearrangement. The allyl ether Claisen precursor would ultimately come from the substituted cyclic enone **8**.

To initiate his synthesis, enone **8** was treated with methyl cuprate followed by trapping with isobutyraldehyde to give the aldol product in a >50:1 three:erythro ratio and a 4:1 mixture with respect to C-6

and C-8. The alkene of the prenyl group from **8** was then hydrated followed by protection of the resultant alcohol as a MOM ether. A second prenyl group was then installed at C-4 in >30:1 diastereoselectivity to afford **9** by deprotonation followed by trapping with prenyl bromide. The requisite allyl ether (**11**) for the Claisen rearrangement was derived from **9** using standard functional group manipulations, including an aldol condensation with acetaldehyde to install the alkene at C-4, and a Sharpless asymmetric dihydroxylation of the prenyl group, with AD-mix- α , to install the diol. Surprisingly, a 1:1 mixture of epimers at C-18 was obtained in the dihydroxylation. With **11** in hand, the Claisen rearrangement, through the proposed transition structure **12**, successfully gave the desired diene (**13**) as one diastereomer. RCM of **13** followed by allylic oxidation installed the **B** ring of **1** to give **14**. Finally, the **C** ring was closed by deprotection of the diol, followed by Wacker oxidative cyclization. Shibasaki completed the molecule by addition of the final prenyl group at C-2 using a Stille coupling after installing an iodide at C-2 of **15**. The route employed by Shibasaki provides **1** as a racemic mixture, but he does show that enone **8** can be formed in 95% *ee* using an enantioselective alkylation developed by Koga.⁷

Scheme 2. Shibasaki's Total Synthesis of **1**



(a) NaHMDS, 4 Å MS, ethylene carbonate; allyl iodide, 82%;
 (b) NaOAc, 200 °C, 96%; (c) LiOH; (d) Na₂PdCl₄, TBHP, 71% (two steps).

(5) Bystrov, N. S.; Chernov, B. K.; Dobrynin, V. N.; Kolosov, M. N. *Tetrahedron Lett.* **1975**, 32, 2791.

(6) Adam, P.; Arigoni, D.; Bacher, A.; Eisenreich, W. *J. Med. Chem.* **2002**, 45, 4786.

(7) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, 116, 8829.

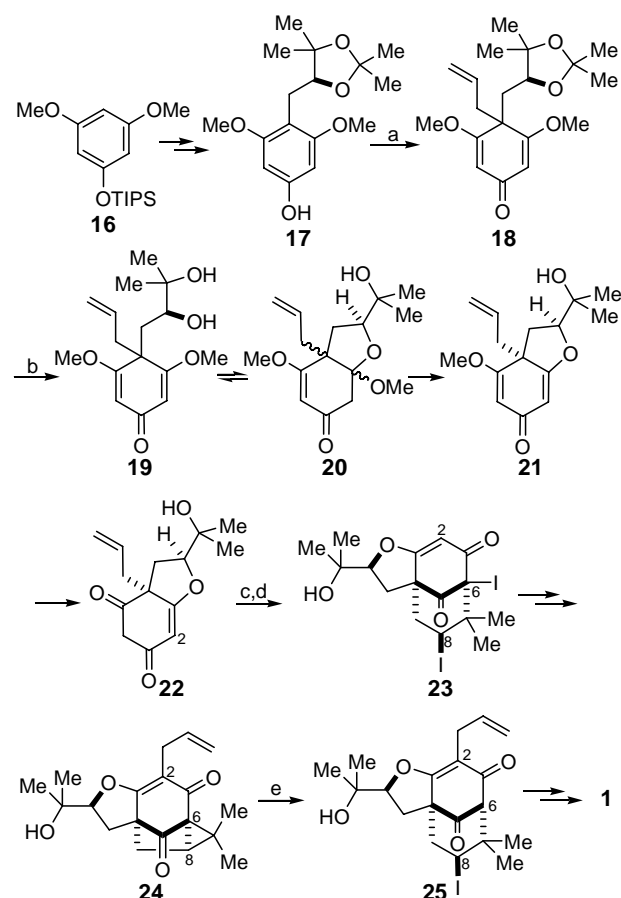
In addition to the synthesis of natural **1**, Shibasaki has previously reported a model synthesis of the core of **1**, where the prenyl group at C-8 was missing.⁸ He was able to construct the **B** ring using an intramolecular aldol reaction; however, when he applied this approach to the analogous compound with the prenyl group at C-8, the aldol reaction would not proceed.

Unlike Shibasaki who started his synthesis with the **A** ring intact and subsequently installed the **B** followed by the **C** rings, Danishefsky's approach utilized arene **16**, which would become the **B** ring of **1** (Scheme 3). He next installed the **C** ring by an acid promoted cyclization, and lastly formed the **A** ring by an iodocarbocyclization. Interestingly, **16** is similar to intermediate **4** in the proposed biosynthesis; however, Danishefsky states that it was not their intention to create a biomimetic synthesis, but that the dearomatization of **16** could prove to be a very efficient way to construct the core of **1**.

In order to implement this dearomatization strategy, phenol **17** was synthesized from **16** by prenylation of the aromatic ring, followed by dihydroxylation and protection of the resultant diol. Dearomatization of **17** was achieved by a Pd-catalyzed allyl addition at the *para* position of the phenol to give **18** in a moderate 62% yield. Interestingly, treatment of **18** with perchloric acid at 80 °C initially cleaved the acetonide to give **19**; however, **19** was not observed in the reaction, instead **20** was observed at short reaction times as a mixture of 4 diastereomers. If the reaction time was extended, **20** converted to **21** as a single diastereomer, and after prolonged reaction times, the vinylogous ester moiety of **21** hydrolyzed to yield diketone **22**. This remarkable one-pot sequence appends the **C** ring in a 71% overall yield. Finally, to install the **A** ring of **1**, the allyl moiety of **22** was converted to the prenyl group using cross metathesis, and the resultant product was treated with I₂ to promote the carbocyclization reaction between the prenyl group and the diketone to give bisiodide **23**. At this point the prenyl group at C-2 needed to be installed and was done so by an interesting protocol. First, iodination was performed at C-2 to give the trisiodide, which was subsequently treated with isopropylmagnesium chloride at low temperature. A transannular Wurtz cyclopropanation occurred between C-6 and C-8 at low temperature followed by formation of the vinyl Grignard at C-2 upon warming. The Grignard was trapped with allyl bromide to give cyclopropane **24** in 67% yield. Finally, the cyclopropane was opened with TMSI to reinstall the iodo functionality at C-8 in **25**. This compound was carried on to **1** by first installing an allyl group at C-8 using a radical coupling between **25** and allyltributyltin. Both allyl groups were then converted to prenyl moieties using cross metathesis as before. Finally, iodination of C-6 followed by Barbier coupling with isobutyraldehyde installed the sidechain at C-6. Simple oxidation of the resultant alcohol afforded **1**.

In addition to these two total syntheses, many research groups have devised routes to the core of **1**, as alluded to earlier. Nicolaou^{4a} published the first synthesis of the functionalized core of **1** in 1999 (Scheme 4). Nicolaou used a Se-promoted cyclization in the presence of a stoichiometric amount of SnCl₄ to produce bicycle **27** from **26**. The reaction proceeds in remarkable yield and adds molecular complexity very efficiently. Unfortunately, a stoichiometric amount of Sn and Se, which are very toxic and bear an unpleasant odor, are required. Compound **27** was further converted to **28** through several steps, and the enone moiety was subjected to a [2 + 2] photocycloaddition reaction followed by acid hydrolysis to give cyclobutanone **29**. This cyclobutanone was later expanded to the 5-membered lactone using a Bayer-Villiger oxidation.

Scheme 3. Danishefsky's Synthesis of **1**



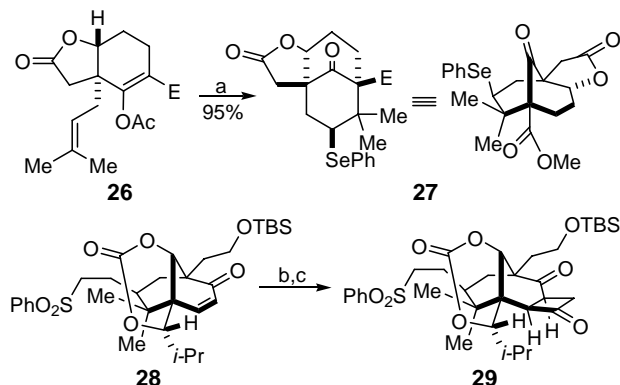
(a) Pd(OAc)₂, PPh₃, Ti(*i*-PrO)₄, allyl methyl carbonate, C₆H₆, 80 °C, 62%; (b) HClO₄, H₂O/dioxane, 60 °C, 71%; (c) Grubb's 2nd generation catalyst, CH₂Cl₂/2-methyl-2-butene, 40 °C, 68%; (d) I₂, KI, KHCO₃, THF/H₂O, 85%; (e) TMSI then 1 N HCl, 0 °C, CH₂Cl₂, 98%.

Stoltz^{4d} put forth a synthesis of the bicyclo[3.3.1]nonane core in 2002 utilizing an annulation strategy (Scheme 5) between prenylated silyl enol ether, **30**, and malonyl dichloride (**31**). While only low yields of

(8) (a) Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 3621. (b) Usuda, H.; Kanai, M. Shibasaki, M. *Org. Lett.* **2002**, *4*, 859.

the desired product were obtained, the reaction generates an incredible amount of complexity in a simple straight forward manner. The major byproduct from the reaction was ketone **33**, produced from hydrolysis of the silyl enol ether. Due to the fact that **30** could be readily converted into **32** in 98% yield, the problem of poor reaction yield was circumvented by recovery of **32** and conversion into **30**, followed by resubjection to the annulation. This sequence enabled them to isolate **33** in an overall yield of 55%.

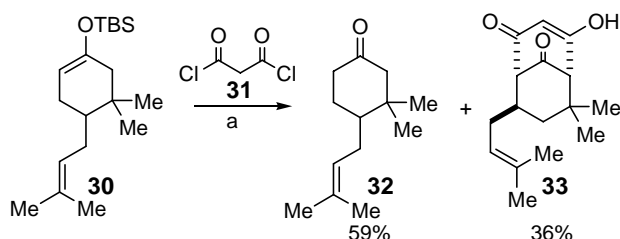
Scheme 4. Nicolaou's Efforts



E = CO₂Me. (a) *N*-(phenylseleno)phthalimide, SnCl₄, CH₂Cl₂, -23 °C, 15 min, 95%; (b) 20 eq (MeO)₂=CH₂, hv, C₆H₆, rt, 8 h, 44%; (c) H₂SO₄, Et₂O, rt, 12 h, 82%.

Similarly, Grossman^{4e} and Kraus^{4f} have synthesized the core using annulation strategies (Scheme 6) starting from the 6-membered dicarbonyl **34**. From **34a**, Kraus introduced an allyl group at C-2 using standard techniques, followed by a Mn(OAc)₃ promoted radical cyclization to give the bicyclo[3.3.1]nonane framework (**35**) in 76% yield. He was then able to install the vinylogous acid functionality using several transformations, including bromination and a Claisen rearrangement, to arrive at **36**. Grossman installed an α -silylacrolein moiety at C-2 of **34b** to give **37** and then closed the ring with an acid catalyzed aldol in 72% yield to arrive at **38** as a 1:1 mixture of epimers at C-7.

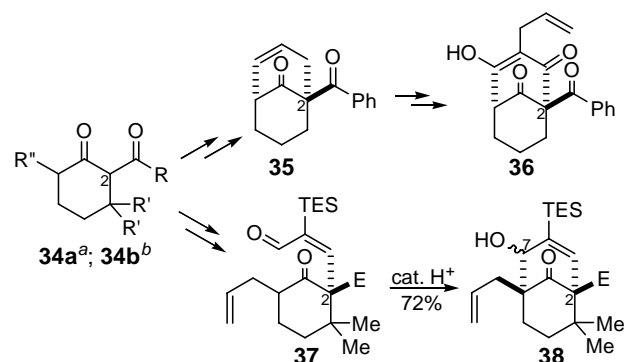
Scheme 5. Stoltz's Efforts



(a) 2 eq **31**, CH₂Cl₂, -10 °C, 11h; KOH, BnEt₃NCl, H₂O, -10 °C to rt.

Finally, Mehta has constructed the bicyclo[3.3.1]nonane core using the chiral pool approach⁹ starting from α -pinene (Scheme 7). α -Pinene was converted into ketone **39** using a variety of known functional group manipulations. Next, using the Kende¹⁰ cyclization to complete the nonane, **39** was first converted into the requisite silyl enol ether followed by treatment with Pd(OAc)₂ to close the ring and complete the bicycle.

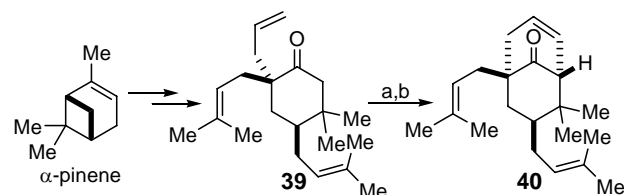
Scheme 6. Kraus' and Grossman's Efforts



^aR = Ph, R' = H, R'' = H. ^bR = CO₂Me, R' = Me, R'' = allyl

In summary, the complexity of **1** has generated considerable explorations into the design of novel approaches to its molecular framework in both a rapid and efficient manner. These efforts have showcased valuable transformations that may be useful in other areas of organic synthesis. In addition, the remarkable ability of chemists to synthesize such complex organic molecules in ingenious ways, as to avoid lengthy linear approaches, has been illustrated by the research efforts described above. Finally, no synthesis of enantiopure **1** has been completed; however, formally both Shibasaki's and Danishefsky's routes are amenable to an enantioselective synthesis.

Scheme 7. Mehta's Efforts



(a) LDA, TMSCl, THF, -78 °C, 1h; (b) Pd(OAc)₂, MeCN/CH₂Cl₂, rt, 12 h, 30% (two steps).

(9) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 5th ed.; John Wiley & Sons, Inc.: New York, New York, 2001; pp 147.

(10) Kende, A. S.; Roth, B.; Sanfilippo, P. J. *J. Am. Chem. Soc.* **1982**, *104*, 1784.