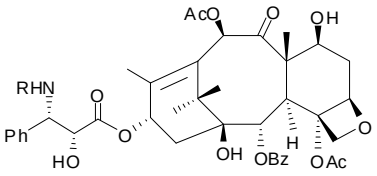
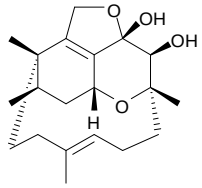
4. Verticillene, the Taxanes and the Phomactins

Most of us who were researching in natural product synthesis during the 1980s will remember how the discovery of the potent anticancer properties of Taxol **1a** seduced many synthetic chemists into designing and developing synthetic routes to this challenging target. In 1994 the teams led by Holton and by Nicolaou were the first to publish total syntheses of Taxol, to be followed later by the research groups of Sam Danishefsky, Paul Wender, T. Mukaiyama, and I. Kuwajima. Many of us will also remember the development of the analogue of taxol **1b**, known as Taxotere, by Pierre Poitier and Gueritte-Voegeliin at Gif-sur-Yvette, which remains one of the most highly successful drugs for the treatment of metastatic breast cancer. The "phomactins" are a family of platelet activating factor antagonists found in the marine fungus *Phoma*. The first of their member to be described was phomactin A (**2**) in 1991. Although not so well known as the taxanes, the two families of natural products show a striking structural and biosynthetic relationship.

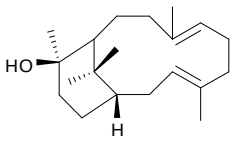


1

a, R = Bz; Taxol
b, R = $CO_2{}^tBu$; Taxotere



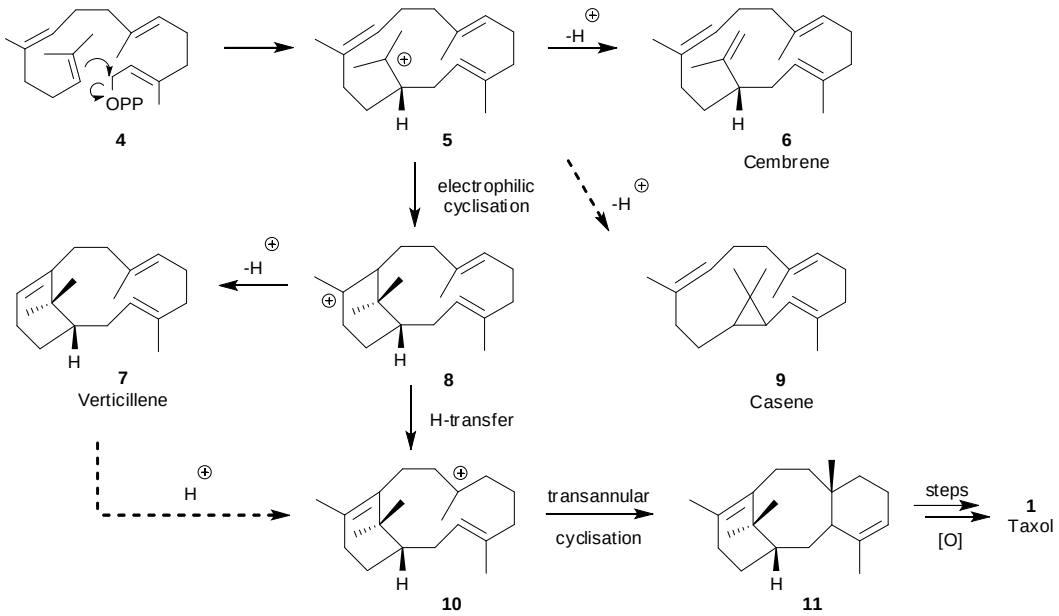
2
Phomactin A



3
Verticillol

We first became interested in the taxane ring system, *i.e.* **11,** following the publication, in 1978, of the structure of verticillol **3,** found in the conifer *Sciadopitys verticillata*. The hydrocarbon corresponding to **3** is verticillene **7** which has its origins in macrocyclisation of geranylgeranyl diphosphate **4 (**to **5)**, followed by an electrophilic transannulation reaction from **5** *via* the carbocation **8** (Scheme 1). Verticillene **7** is also related to the structures cembrene **6** and casbene **9** shown earlier (see Chapter 1), both of which are produced *in vivo* from the same carbocation intermediate **5**. The taxane ring system **11** was therefore thought to be derived from veticillene **7**, or the carbocation **8,** by a second tranannulation reaction.

In 1981 we took up the challenge of synthesising verticillene **7** and determining whether or not we could effect a biomimetic transannulation reaction across its 12-membered ring to produce the taxane ring system **11**. Thus, we rapidly assembled the verticillane ring system by first synthesizing the *bis*-aldehhde **12** starting from cyclohexane-1,3-dione and geranyl bromide. In one of the first demonstrations of the scope for the McMurray reductive coupling procedure at the time, when **12** was treated with a slurry of $TiCl_4$ and Zn-Cu couple, it gave the macrocyclic tetraene **14** as the major product (Scheme 2). The product **14** was derived from **12** by 1,5-H sigmatropic rearrangement in the initially formed macrocyclic tetraene **13**. Much to our satisfaction, treatment of **14** with Na in NH_3 resulted in smooth



Scheme 1. Proposed origin of the taxane ring system **11** from geranylgeranyl diphosphate **4** *via* the carbocations **5**, **8** and **10**; relationships with cembrene **6**, verticillene 7, and to casbene **9**.

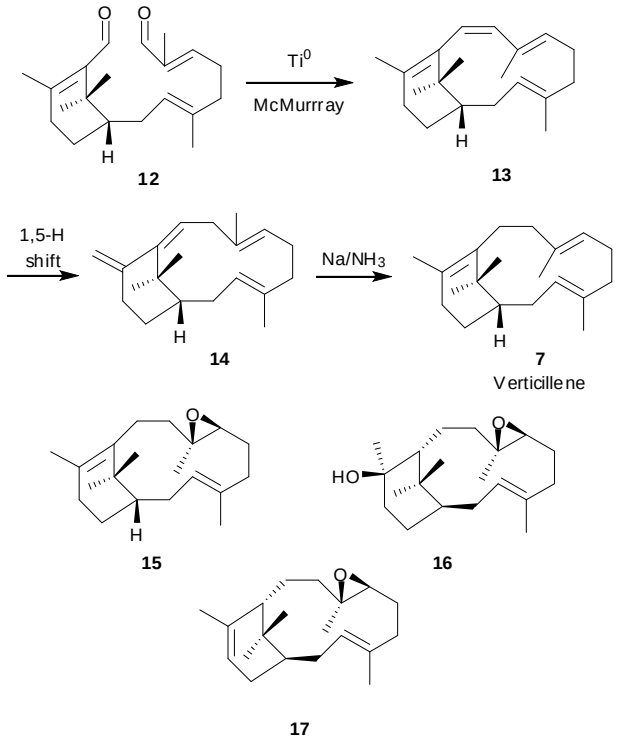
Taxus baccata (English yew tree)

Taxus brevifolia (pacific coast yew tree and bark); source of taxol **1a**

Images from https://www.flickr.com/photos/yourpalbill/1836145348 and http://www.theguardian.com/environment/2011/nov/10/iucn-red-list-tree-chemotherapy

Chinoecetes opilio (crab) on which fungus *Phom*a grows; source of phomactin A (**2**)

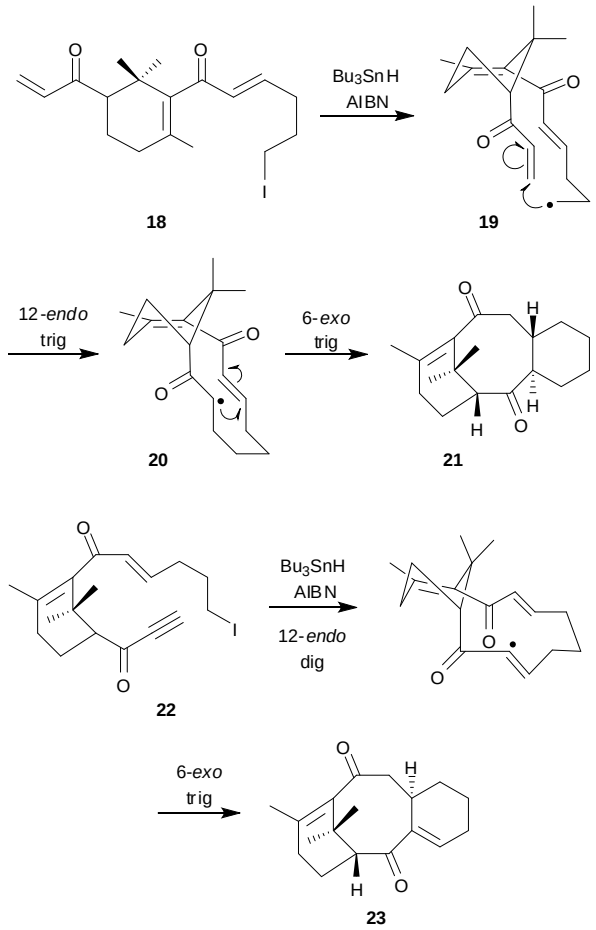
1,4-reduction of the conjugated diene unit in **14**, and led to verticillene **7**; we published this synthesis in 1985.[1] We then spent several months attempting to effect transanannular cyclisation reactions with verticillene **7** and also with the epoxide derivatives **15, 16,** and **17** in the presence of a number of Lewis acids. Alas, all of this was to no avail and, instead the only products we ever isolated were those corresponding to ring-opening and rearrangement of the epoxide rings in the substrates **15-17**.[2] In passing, these outcomes should be compared and contrasted with the successful electrophilic transannular cyclisations we achieved in our contemporaneous syntheses of the triquinane-based sesqiterpenes capnellene and pentalenene, which are described later (see Chapter 2).



Scheme 2. Total synthesis of verticillene **7**; attempts to effect transannular cyclisations in **7,** and in the epoxide derivatives **15-17**, leading to taxanoids.

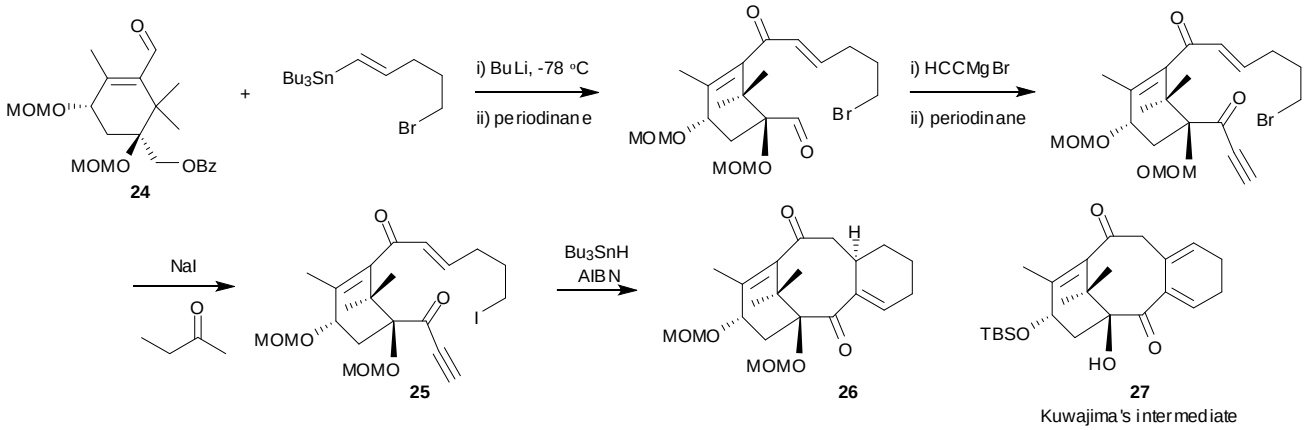
Several years later, and at the beginning of our studies in the early 1990s when we were examining the scope for radical-mediated macrocyclisation reactions in tandem with radical transannulation cyclisation processes in synthesis (Chapter 9), we discovered a concise route to the 6,8,6-ring fused tricyclic sytem in taxol.

Thus, in 1992 my PhD student Steve Hitchcock showed that when the iodo-trienone **18** containing an intact cyclohexenone (A-ring related to the taxanes) was treated with Bu_3SnH-AIBN it led to the taxane **21** (~ 30%) in one step *via* a tandem radical macrocyclisation (*i.e.* **19** → **20**)-transannulation (*i.e.* **20** → **21**) sequence (Scheme 3).[3] This particular tandem radical approach was investigated over the ensuing few years, using a variety of different substituted precursors and, apart from the acetylene-substituted compound **22** which led to the taxadiene **23** on treatment with Bu_3SnH-AIBN, with mixed success.[4] Ultimately we synthesized the fully oxygen-functionalised A-ring **24** of taxol,[5] and next elaborated this compound to the enynedione **25**. A tandem radical cyclisation from **25** then gave the tetraoxy-*bis*-nortaxadiene **26** in 44% yield (Scheme 4).[6] Our synthetic approach to the taxane ring system was distinct from other published routes, in that the B and C rings in the structure **26** were produced in a single step from an A-ring precursor. Although our approach to taxol itself was eventually thwarted by the lack of sufficient quantities of **26** to continue with, it was some consolation that the 6,8,6-ring fused tricycle **26** was at the same oxidation level, and of similar constitution, to the advanced intermediate **27** used by I. Kuwajima *et al.* in their total synthesis of taxol.

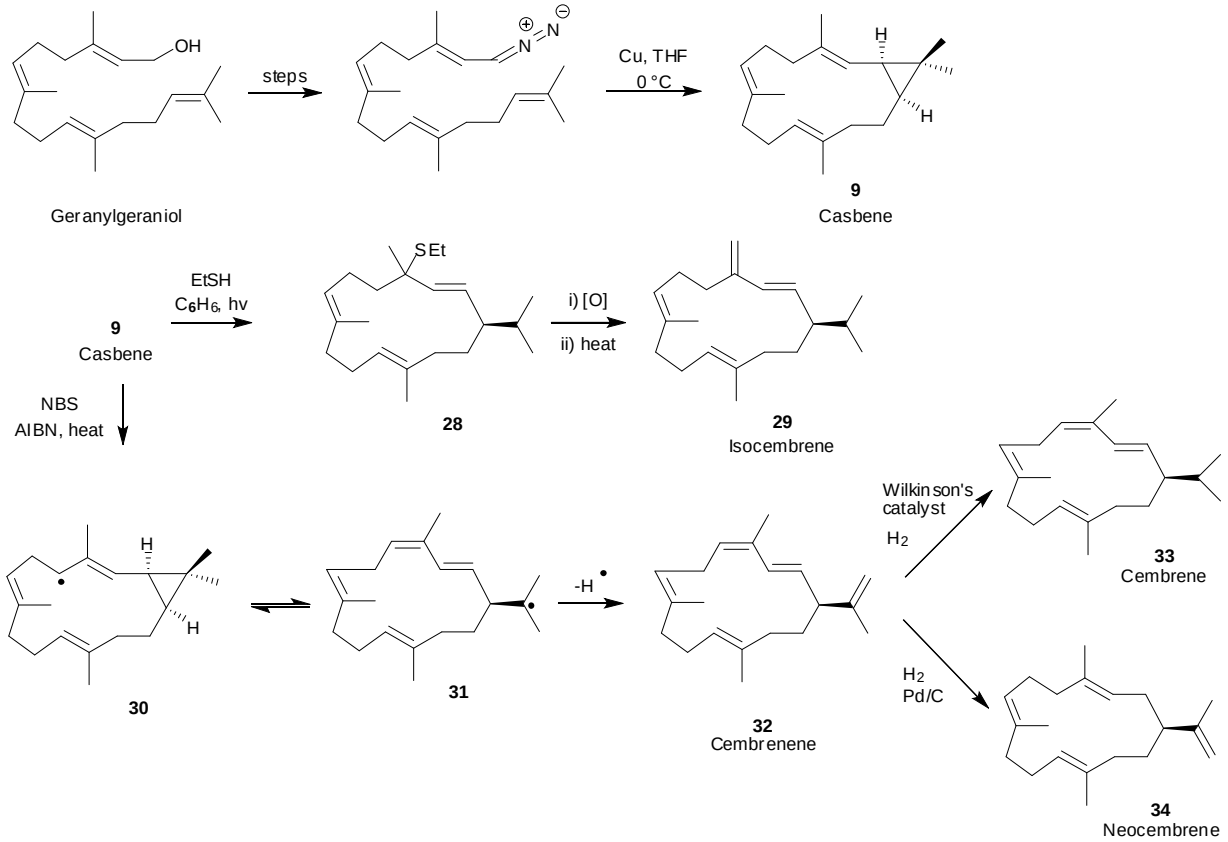


Scheme 3. Tandem radical macrocyclisation-transannulation sequences leading to the taxane ring system, *i.e.* **18→19→20→21,** and **22→23**.

Having achieved a radical–mediated transannulation reaction within a 12-membered ring in producing the 6,8-fused ring system in the taxanes, *i.e.* **20→21**, we ventured to return to an earlier interest and examine transannular reactions across the 14-membered ring in the diterpene hydrocarbon casbene **9** we had synthesized some fifteen years earlier, in the presence of radical initiators. A bonus for us was that in the intervening years T. Takahashi *et al.* had published a short biosynthetic-type synthesis of casbene starting from geranylgeraniol and we, ourselves, had secured an excellent source of large quantities of this precious alcohol from seeds of *Bixa orenalla* (see Chapter 5). Hence we were able to prepare relatively large amounts of casbene for



Scheme 4. Total synthesis of the tetraoxy-*bis*-nortaxadiene **26**, based on a tandem radical cyclisation from the enynedione **25;** *cf*. Kuwaijima's intermediate **27** to taxol **1.**



Scheme 5. Radical reactions with casbene **9** leading to the synthesis of the isomeric cembrenes **29, 32**, **33** and **34**.

studies of its chemistry using the procedure of T. Takahashi *et al*. Thus, when Alison Smithies, in 1992, heated casbene **9** with ethanethiol in benzene we observed 1,4-addition of ethanethiol radical to the vinylcyclopropane ring in casbene, with the formation of the cembrene sulfide **28** in approximately 70 % yield. Oxidation of the sulfide **28**, followed by thermolysis of the resulting sulfoxide then gave isocembrene **29**, which is found in *Pinus sibircia* (Scheme 5). Likewise, when casbene was heated with NBS in carbon tetrachloride it underwent oxidative rearreangement, *via* the radical intermediates **30** and **31**, leading to cembrenene **32**, which had been isolated from the soft coral *Sinularia maji*. Finally, hydrogenation of the isopropylidene double bond in cembrenene **32,** using Wilkinson's catalyst gave cembrene **33**, whereas hydrogenation of **32** in the presence of Pd/C led to neocembrene **34** (Scheme 5).[7] Disappointingly, we did not observe the formation of any polycyclic products, resulting from transannular radical reactions in casbene during these studies.

As we mentioned earlier, the structure of phomactin A (**2**) with its plethora of quaternary centres and unusual functionality, was

published in 1991 and we began working towards a synthesis of this secondary metabolite almost straightaway. After nearly a decade, working with a sequence of able students,[8] we ultimately achieved the first total synthesis of this challenging target, and published the details in 2002.[9] The success of our synthesis rested on a Cr(II)/Ni(II) [Nozaki-Hiyami-Kishi (NHK)] macrocyclisation from the advanced aldehyde vinyl iodide precursor **35**, which led firstly to the ring-fused macrocyclic secondary alcohol **36** (Scheme 6). The synthesis from this point was based on biosynthesis speculation, where we planned to produce the substituted epoxide **38** corresponding to **36**, and then elaborate the pyran ring in the natural product from **38** *via* the corresponding epoxy-ketone **39**. Thus, inversion of the stereochemistry of the secondary OH group in **36** and treatment of the resulting alcohol **37** with $VO(acac)_2$-t-BuO_2H led to the β-epoxide **38**. Oxidation of **38**, using periodinane, next gave the epoxy-ketone **39** which, gratifyingly, on treatment with DDQ in dichloromethane underwent deprotection and spontaneous pyran-cyclic hemiacetal ring formation, leading to phomactin A (**2**).

During the course of our synthetic studies with phomactins, we also achieved a synthesis of phomactin G (**40**), which is a likely biosynthetic precursor to phomactin A (**2**), by way of allylic oxidation to **41**, followed by spontaneous pyran-ring formation.[10] The interesting epoxy cyclic hemiketal structure **41** had been proposed for a co-metabolite of phomactin A, and was known as Sch 49028. However, syntheses of the isomeric structures **42** and **43** gave no credibility to this proposal.[11] Instead, our study showed that Sch 49028 does not exist and was never isolated. Unfortunately its NMR spectroscopic data were confused with those of phomactin A itself recorded in a different solvent! We later examined the relative PAF antagonistic activities of the natural and non-natural phomactins we had synthesised in these studies.[12]

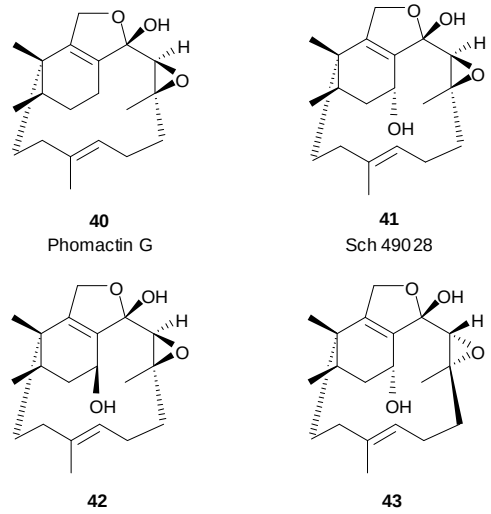
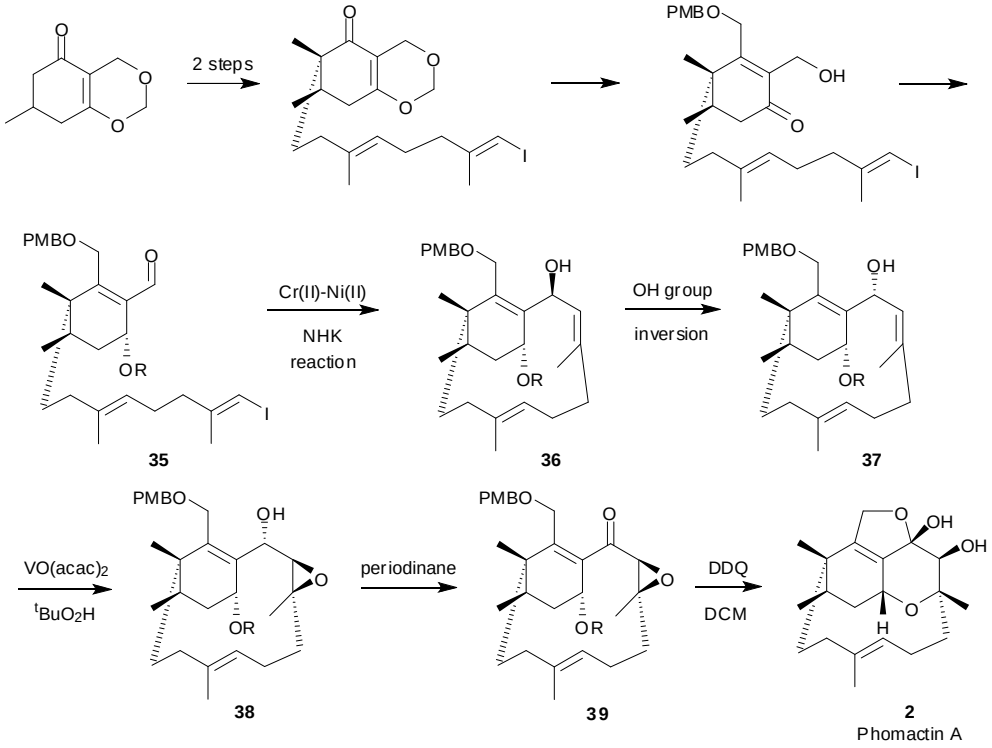


Figure 1. Syntheses of phomactin G (**23**) and the epoxy cyclic hemiketal structures **25** and **26**, related to the purported natural product Sch 49028 (**24**).

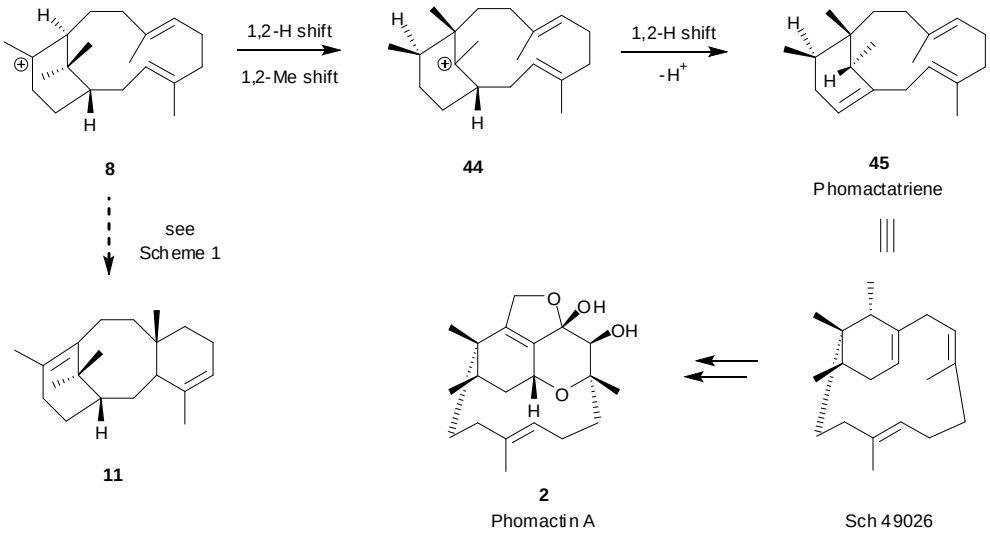
Lastly, in a Review I published with Bill Goldring in 2006,[13] we discussed the unique relationship between the phomactins and the taxanes, and at the same time presented a cogent picture of plausible biosynthetic interrelationships within the entire family



Scheme 6. The first total synthesis of phomactin A(**2**).

of phomactins. Thus, in the proposed origin of the phomactin ring system, a sequence of 1,2-hydrogen and 1,2-methyl group shifts in the verticillyl carbocation **8** (*cf.* Scheme 1) first leads to the new carbocation intermediate **44** (Scheme 6). A further 1,2-hydrogen shift in **44** followed by elimination of a proton, next produces the known metabolite phomactatriene **45** (also known as Sch 49026). A series of specific enzymatic oxidations on **45** then lead to the various phomactins, and ultimately to phomactin A(**2)** itself.

Over the past two and more decades a number of research groups , particularly those led by R. M Williams and Rodney Croteau, have made inroads into elucidating some details of the myriad of biological oxidations used to convert taxadiene **11** into taxols, *eg.* **1a** *in vivo*. Chris Hayes, who was the first PhD student in my group to work towards our synthesis of phomactin A (**2**) has also recently contributed some exciting research in this area.



Scheme 7. Divergent biosynthetic pathways to the phomactane and the taxane ring systems, **45** and **11** respectively,*via* the key verticillyl carbocation intermediate **8**.

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