ORGANIC LETTERS

2011
Vol. 13, No. 2
248−251

Synthesis of the Cyclohexane Core of Phomactins and a New Route to the Bicyclo[9.3.1]pentadecane Diterpenoid Skeleton

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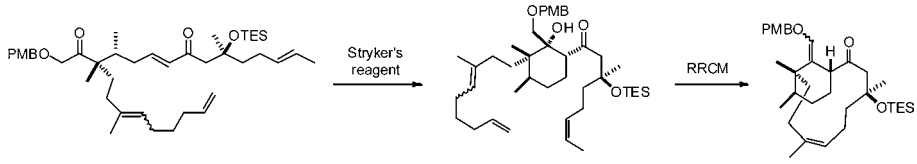
Received November 4, 2010

ABSTRACT



Conjugate reduction of an enone accompanied by in situ intramolecular aldol condensation was used to construct the tetrasubstituted cyclohexane nucleus of phomactins. Subsequent relay ring-closing metathesis completed the nine-membered ansa bridge of the diterpenoid framework.

The phomactins comprise a family of diterpenoids containing the unusual bicyclo[9.3.1]pentadecane skeleton,[1] phomactins A (**1**,[2] D (**2**)[3] and G (**3**)[4] being representative of the class (Figure 1). The core unit of these structures is a substituted cyclohexane or cyclohexene that is bridged by an unsaturated ansa chain. The intriguing structures of phomactins together with their activity as platelet activating factor (PAF) antagonists[5] have drawn intense synthetic activity toward these molecules with the result that there are now completed syntheses of **1**,[6] **2**,[7] and **3**.[6b] In addition, Wulff has published an elegant synthesis of phomactin B2,[8] and there are numerous reports of partially completed routes to these and other phomactins.[9]

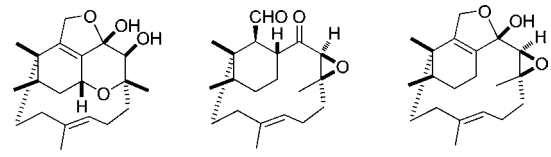


Figure 1. Representative members of the phomactin family of diterpenoids.

Our plan for building the cyclohexane core of phomactins is shown in Scheme 1 and envisioned construction of **4** from an acyclic precursor **5** containing all of the carbons needed

(1) Goldring, W. P. D.; Pattenden, G. *Acc. Chem. Res.* **2006**, *39*, 354–361. The bicyclo[9.3.1]pentadecane skeleton is found only in one other class of diterpenoids, the verticillanes, although the Taxane framework can be viewed as a tricyclic relative of this family.

(2) Sugano, M.; Sato, A.; Iijima, Y.; Oshima, T.; Furuya, K.; Kuwano, H.; Hata, T.; Hanzaw, H. *J. Am. Chem. Soc.* **1991**, *113*, 5463–5464.

(3) Sugano, M.; Sato, A.; Iijima, Y.; Furuya, K.; Haruyama, H.; Yoda, K.; Hata, T. *J. Org. Chem.* **1994**, *59*, 564–569.

(4) Sugano, M.; Sato, A.; Iijima, Y.; Furuya, K.; Kuwano, H.; Hata, T. *J. Antibiot.* **1995**, *48*, 1188–1190.

(5) Braquet, P.; Touqui, L.; Shen, T. Y.; Vargaftig, B. B. *Pharmacol. Rev.* **1987**, *39*, 97–145. Phomactin D (**2**), with an IC_{50} of 0.12 μM in PAF receptors, is the most biologically active member of the group. (Sugano, M.; Sato, A.; Saito, K.; Takaishi, S.; Matsushita, Y.; Iijima, Y. *J. Med. Chem.* **1996**, *39*, 5281–5284)

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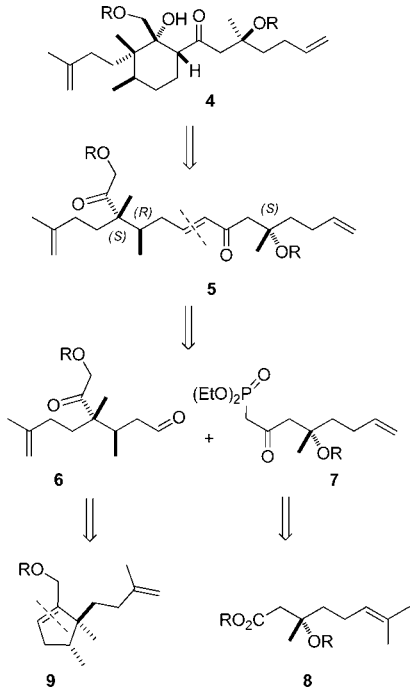
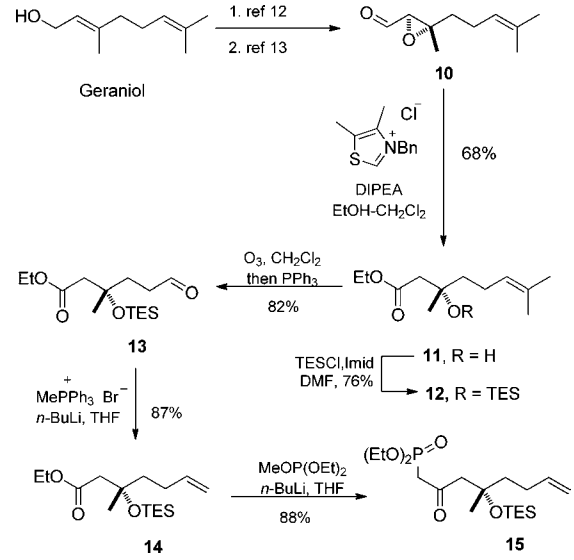
10.1021/ol1026816
Published on Web 12/16/2010

Scheme 1. Retrosynthetic Analysis of the Phomactin Core



Scheme 2. Synthesis of Ketophosphonate **7**



for the phomactin framework as well as three key stereocenters.[10] The configuration of **5** was considered crucial for the final stage of a phomactin synthesis that would close the nine-membered bridge across a preformed cyclohexane. Assembly of 1,8,15-hexadecatriene **5** was projected from coupling of aldehyde **6** with ketophosphonate **7**, the latter being derived from octenoate **8** which is accessible from geraniol. Oxidative cleavage of cyclopentene **9** was programmed as the means for acquiring **6**.

Bode's clever synthesis of β-hydroxy esters from α,β-epoxyaldehydes provided a convenient entry to (*S*)-**11** from aldehyde **10** (Scheme 2).[11] This aldehyde was prepared from geraniol via Sharpless asymmetric epoxidation[12] followed by Parikh−Doering oxidation.[13] Because our projected closure of the phomactin ansa bridge was to employ ring-closing metathesis,[14] we decided to replace the trisubstituted alkene of **11** with a terminal vinyl group in the expectation that this change would facilitate complexation with the RCM catalyst. After protection of alcohol **11** as its TES ether **12**, ozonolysis furnished aldehyde **13** which underwent Wittig olefination to give heptenoate **14**. Treatment of **14** with the lithio anion of diethyl methylphosphonate gave β-ketophosphonate **15**.

Ketoaldehyde **6**, projected as the coupling partner for **15**, required placing a pair of methyl substituents at vicinal stereogenic carbons, one of which is quaternary. Cyclopentene **9**, as the precursor to **6**, must therefore have a (4*R*,5*S*) configuration in order for oxidative scission of the trisubstituted alkene to deliver **6**. The starting point for our route to **9** was (*R*)-pulegone which was converted via a known route involving Favorskii ring contraction and reductive ozonolysis to keto ester **16** (Scheme 3).[15] Michael addition of **16** to methyl vinyl ketone gave major isomer **17** accompanied by 11% of the diastereomeric diketo ester.[16] Selective ketalization of the methyl ketone of **17** under Noyori's conditions[17] afforded **18** which was converted to enol triflate **19**. Palladium-catalyzed methoxycarbonylation of **19** then afforded diester **20**.

Our goal with **20** was selective reduction of the methyl ester to a primary alcohol, to be followed by exhaustive reduction of the ethyl ester to a methyl group. This scenario proved to be impractical, and **20** was therefore reduced nonselectively to diol **21** with the prospect of differentiating the two primary alcohols. The latter operation was accomplished by converting **21** to mono-*p*-methoxybenzyl ether **22**. Various methods were examined for reducing the primary alcohol of **22** to a methyl substituent, but the only successful

(9) (a) Seth, P. P.; Totah, N. I. *Org. Lett.* **2000**, *2*, 2507–2509. (b) Teng, D.; Wang, B.; Augatis, A. J.; Totah, N. I. *Tetrahedron Lett.* **2007**, *48*, 4605–4607. (c) Chemler, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695–2698. (d) Chemler, S. R.; Iserloh, U.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2949–2951. (e) Houghton, T.; Choi, S.; Rawal, V. H. *Org. Lett.* **2001**, *3*, 3615–3617. (f) Mi, B.; Maleczka, R. *Org. Lett.* **2001**, *3*, 1491–1494. (g) Balnaves, A. S.; McGowan, G.; Shapland, P. D. P.; Thomas, E. J. *Tetrahedron Lett.* **2003**, *44*, 2713–2716.

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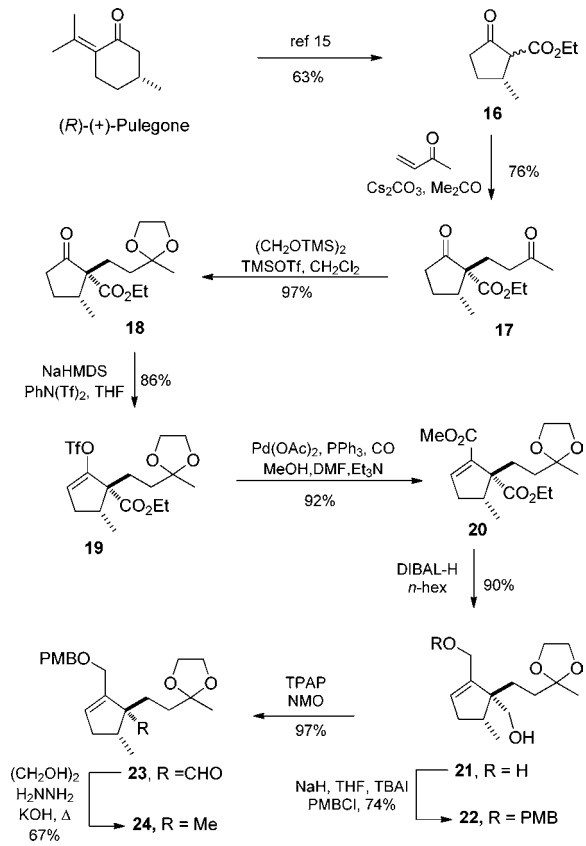
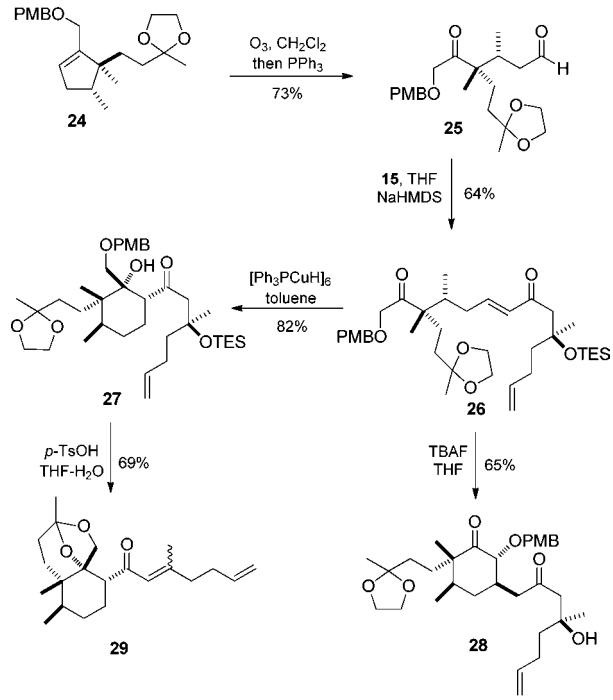
(17) Tsunoda, Y.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357–1358.

Scheme 3. Synthesis of Cyclopentene **24**



Scheme 4. Assembly of Enedione **26** and Its Cyclization via Conjugate Reduction and Aldol Condensation



route to **24** proved to be Wolff−Kishner reduction of aldehyde **23** obtained by oxidation of **22**.[18]

Ozonolytic ring cleavage of **24** cleanly furnished keto aldehyde **25** which underwent Horner−Wadsworth−Emmons (HWE) condensation with ketophosphonate **15** to give (*E*)-enone **26** as the sole isomer (Scheme 4). As we had anticipated, conjugate reduction of **26** resulted in spontaneous aldol cyclization of the intermediate enolate to produce hydroxy ketone **27**. The most effective reagent for this transformation was Stryker's copper hydride system.[19] An attempt was made to extend this useful ring construction by exposing **26** to tetra-*n*-butylammonium fluoride in the hope that the alkoxide generated from silyl ether cleavage would trigger a tandem sequence that would install the carbocyclic and tetrahydropyran rings of phomactin A concomitantly. Instead, the enolate generated from α-alkoxy ketone **26** under these conditions led to intramolecular Michael adduct **28**. A further surprise awaited us when ethylene ketal **27** was subjected to acidic hydrolysis. Expecting that Wittig methylenation of the resultant methyl ketone could lead to **4**, we found instead that internal ketal **29** was formed.

The flaw in our synthesis plan exposed by **29** was corrected by installing the exo methylene function needed for **5** within the side chain of cyclopentene **9**, i.e. prior to HWE condensation with **15**. Since ozonolytic cleavage of the cyclopentene would no longer be selective in this case, a modified sequence was introduced that first took **24** to cis diol **30** (Scheme 5). The diol was protected as cyclic carbonate **31** and acid hydrolysis then gave ketone **32**. Although Wittig methylenation of this ketone was straightforward and the product was advanced to **5** without incident, a decision was made at this juncture to invest **32** in an olefination that afforded diene **33**. This choice was motivated by the worrisome prospect that formation of the phomactin ansa bridge from a diene such as **4** by conventional ring-closing metathesis would be difficult. On the other hand, relay ring-closing metathesis (RRCM)[20] appeared to have a better chance of success.[21] To this end, cyclic carbonate **33** was hydrolyzed to diol **34** which underwent clean oxidative cleavage with lead tetraacetate to keto aldehyde **35**.

In order to ensure that the metathesis catalyst would deploy initially at the vinyl group of the sacrificial pentenyl unit rather than the distal olefin, the latter was replaced in **15** by a propenyl terminus. This modification simply required a different olefination of **13** to give **36**. Ester **36** was advanced to ketophosphonate **37** which upon HWE condensation with aldehyde **35** afforded diketone **38** (Scheme 6). As before, exposure of **38** to Stryker's copper hydride reagent resulted in conjugate reduction and in situ aldol cyclization to yield hydroxy ketone **39**.

(18) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.

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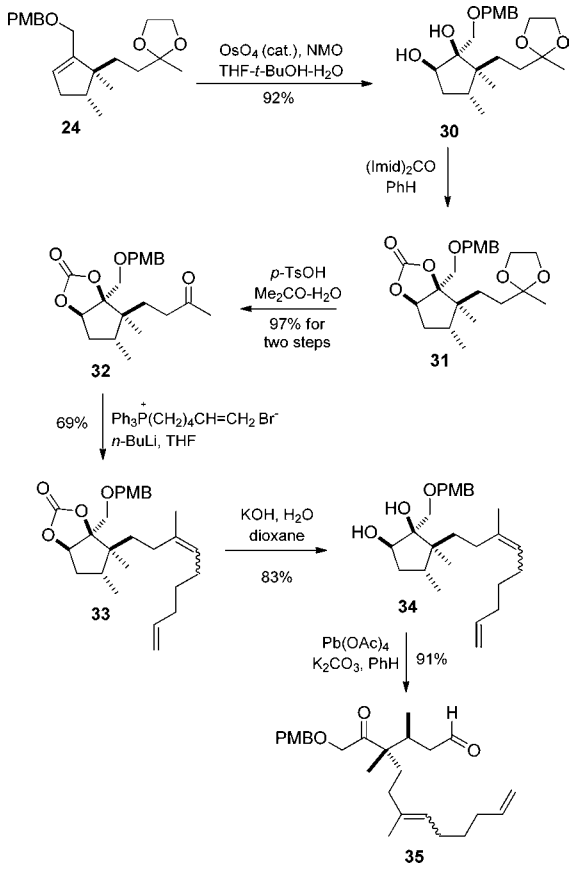
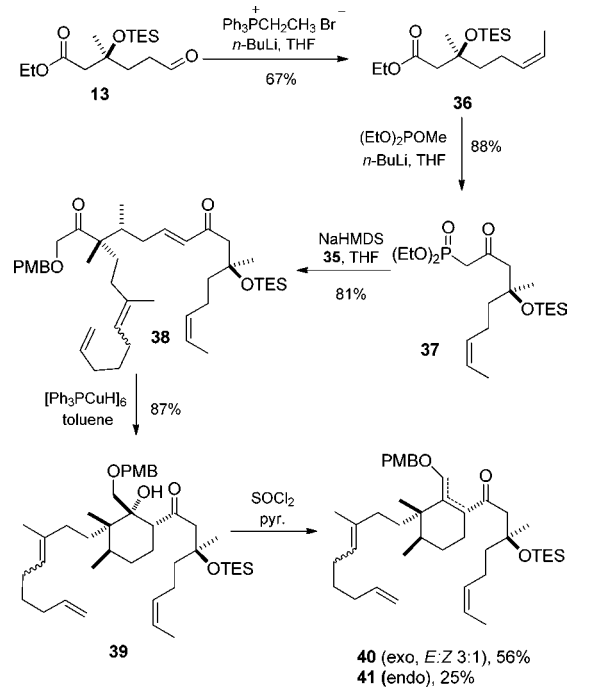
(20) Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912–1915.

(21) For an analogous RRCM, see: McGrath, N. A.; Lee, C. A.; Araki, H.; Brichacek, M.; Njardarson, J. T. *Angew. Chem., Int. Ed.* **2008**, *47*, 9450–9453.

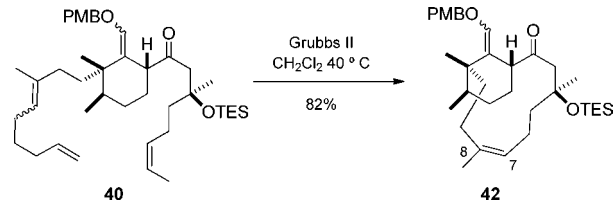
Scheme 5. Synthesis of Keto Aldehyde **35** for RRCM



Scheme 6. Synthesis of RRCM Precursors **40** and **41**



Scheme 7. RRCM of **40**



Initial attempts at RRCM of **39** were not encouraging, but after dehydration of **39** to separable exo and endo alkenes, **40** and **41**, a more favorable outcome resulted. In particular, RRCM of **40** (mixture of *E* and *Z* isomers) with Grubbs second generation catalyst gave **42** in high yield (Scheme 7). Although **42** was formed exclusively with the (*Z*) olefin configuration in the nine-membered bridge, protocols for olefin inversion to the C7−C8 (*E*) configuration of natural phomactins are available and are currently under study.[22]

In summary, we have described a new route to the tetrasubstituted cyclohexane core of phomactins from an acyclic precursor that incorporates all of the carbon atoms present in the diterpenoid skeleton. The key step is conjugate reduction of an enone accompanied by intramolecualr aldol condensation. The assembled core was shown to undergo efficient relay ring-closing metathesis to generate a bicyclo-[9.3.1]pentadecane system that is potentially a precursor to members of the phomactin family.

(22) Smith, A. B.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2006**, *128*, 5292–5299.

Acknowledgment. We are grateful to Dr. William Martin of this laboratory for helpful suggestions and to the National Science Foundation for financial support (0413994-CHE). Support for the Oregon State University NMR Facility from the Murdock Charitable Trust (Grant 2005265) and the National Science Foundation (CHE-0722319) is gratefully acknowledged.

Supporting Information Available: Experimental details, characterization data, and ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1026816