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Determining a Synthetic Approach to Pierisformaside C

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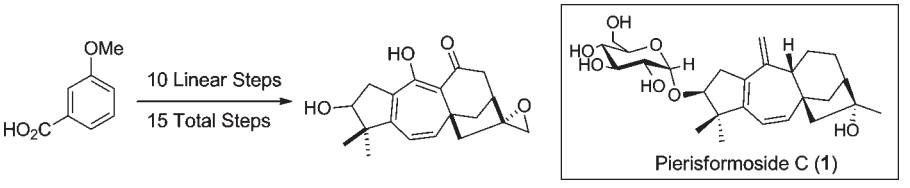
ABSTRACT



An efficient route detailing the construction of the central core of pierisformaside C, the first grayanane-type diterpene to possess three central double bonds, is reported.

Pieris formosa D. Don (Ericaceae) is a well-known poisonous evergreen shrub found in southwest China.[1] It has been reported that poultry fall into a coma after accidental consumption of the leaves, and even the traditional Chinese name "Mei-Li-Ma-Zui-Mu" described horse enebria after consumption.[1] The juice of the fresh leaves has been used in folk medicine as an insecticide or as a lotion for the treatment of tinea and scabies.[1]

To date, most grayanane-type diterpenes have been isolated from this species. However, in 2000, Qin isolated pierisformaside C (**1**),[2] which remains the only example possessing three double bonds in a grayanane skeleton.

It was to this latter feature that we were most attracted. We reasoned that if a route to **1** could be forged, access to closely related family members (**2**,[3] **3**,[4] **4**,[5] **5**[2,6]),[7] some of which display prominent biological activity,[6,8] might be possible via judicious implementation of hydration reactions (Figure 1).

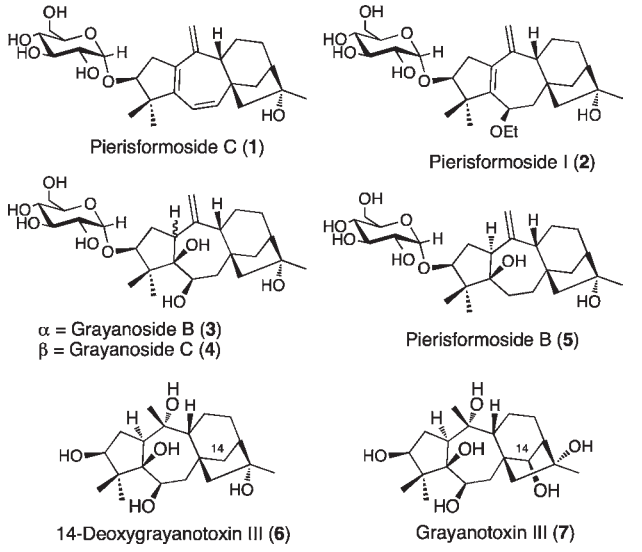


Figure 1. Diterpene glucosides **1**–**5** and grayanotoxins **6** and **7**.

(1) Chen, J. S.; Zheng, S. *Chinese Poisonous Plants*; Science Press: Beijing, 1987.

(2) Wang, L.-Q.; Chen, S.-N.; Cheng, K. F.; Li, C.-J.; Qin, G.-W. *Phytochemistry* **2000**, *54*, 847.

(3) Wang, L.-Q.; Qin, G.-W.; Chen, S.-N.; Li, C.-J. *Fitoterapia* **2001**, *72*, 779.

(4) Sakakibara, J.; Shirai, N.; Kaiya, T.; Nakata, H. *Phytochemistry* **1979**, *18*, 135.

(5) (a) Sakakibara, J.; Shirai, N.; Kaiya, T.; Iitaka, Y. *Phytochemistry* **1980**, *19*, 1495. (b) Wang, L.-Q.; Ding, B.-Y.; Wang, P.; Zhao, W.-M.; Qin, G.-W. *Nat. Prod. Sci.* **1998**, *4*, 68. (c) Wang, L.-Q.; Ding, B.-Y.; Zhao, W.-M.; Qin, G.-W. *Chin. Chem. Lett.* **1998**, *9*, 465.

(6) Zhang, H.-P.; Wang, L.-Q.; Qin, G.-W. *Bioorg. Med. Chem.* **2005**, *13*, 5289.

(7) For additional related family members, including aglycons not containing C14 hydroxylation, see: (a) Wang, L.-Q.; Chen, S.-N.; Qin, G.-W.; Cheng, K.-F. *J. Nat. Prod.* **1998**, *61*, 1473. (b) Sakakibara, J.; Kaiya, T.; Shirai, N. *Yakugaku Zasshi* **1980**, *100*, 540. (c) Kaiya, T.; Sakakibara, J. *Chem. Pharm. Bull.* **1985**, *33*, 4637. (d) Sakakibara, J.; Shirai, N. *Phytochemistry* **1980**, *19*, 2159. (e) Sakakibara, J.; Ikai, K.; Yasue, M. *Yakugaku Zasshi* **1974**, *94*, 1534.

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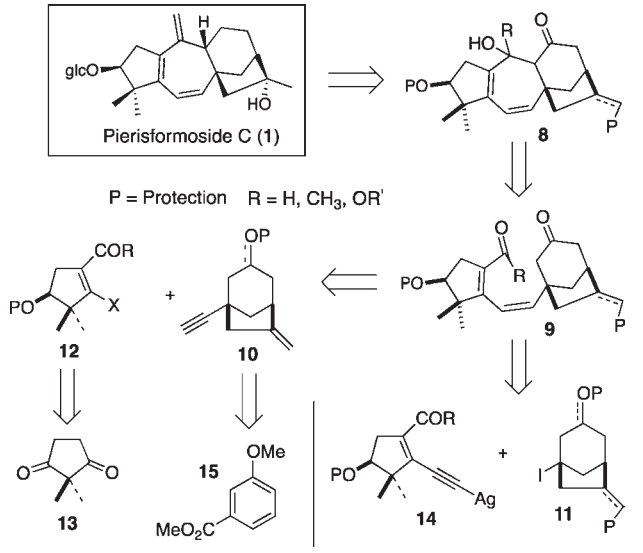
Surprisingly, these compounds and their aglycons have received only sparse synthetic attention. For example, there is only one article in the C-14 deoxy series (e.g., **1**–**6**) describing a partial synthesis of 14-deoxygrayanotoxin III (**6**).[7e] In the related C-14 oxy series, only four articles discussing the synthesis of three family members, grayanotoxin (partial synthesis),[9] grayanotoxin II (relay synthesis),[10] and (−)-grayanotoxin III (**7**)[11,12] (total synthesis), have been published.

Considering the biological activity, limited synthetic attention, and possibility of accessing a number of the pierisformaside family members, we devised and executed a plausible route to a common advanced intermediate, the results of which are reported herein.

Our retrosynthetic analysis of **1** was based on late-stage construction of the central seven-membered ring (**8**), obtained via an aldol or Claisen cyclization and controlled by the *cis*-double bond seen in **9** (Scheme 1). The key intermediate **9** arises from a five-membered ring left-hand fragment and a bicyclo[3.2.1]octane right-hand fragment.

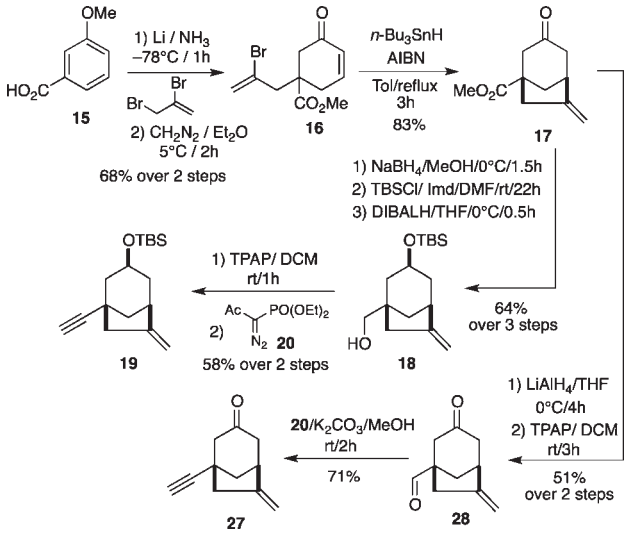
Scheme 1. Retrosynthetic Analysis for Pierisformaside C (1)



Two options are potentially available to construct **9**: (1) Sonogashira coupling of bicyclo[3.2.1]octane **10** to vinyl halide **12** followed by partial reduction or (2) bridgehead alkylation of bicyclo[3.2.1]octane **11** with a suitably functionalized silver(I) acetylide (**14**) again followed by partial reduction. Both five-membered ring systems, **12** and **14**, could conceivably be accessed via diketone **13**, whereas both bicyclo[3.2.1]octane systems (**10** and **11**) would be available from methyl 3-methoxybenzoate **15** (Scheme 1).

Of the two proposed avenues for arriving at intermediate **9**, we decided to pursue the Sonogashira route, as previous experience with bicyclo[3.2.1]octanes of type **11** and silver-(I) acetylide chemistry had not proven fruitful.[13] However, we found that construction of the bicyclo[3.2.1]octane **10**, in the first instance taking the form of a TBS-protected alcohol at position 3 (i.e., **19**), was readily achievable from **17** obtained via Birch reduction/alkylation of **15** and subsequent radical cyclization of **16** as reported[14] (Scheme 2). Treatment of **17** with sodium borohydride followed by TBS protection and reduction of the ester with diisobutylaluminium hydride afforded **18** [*endo*/*exo* (3:1)] in 64% yield over the three steps. Oxidation with TPAP[15] followed by treatment with the Seyferth–Gilbert reagent **20**[16] afforded **19** in 58% yield (Scheme 2).

Scheme 2. Synthesis of Bicyclo[3.2.1]octane Derivatives **19** and **27**

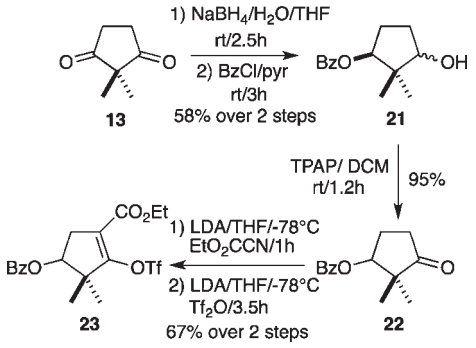


The synthesis of **23** started with diketone **13** (Scheme 3).[17] Sodium borohydride reduction of **13** in water/THF[18] followed by monobenzoylation gave **21**. Ketone **22** was then obtained via TPAP oxidation (Scheme 3). At this juncture, multiple options were available in terms of building in the carbonyl functionality required for the seven-membered ring closure. However, our choice was

(8) Shirai, N.; Sakakibara, J.; Kaiya, T.; Kobayashi, S.; Hotta, Y.; Takeya, K. *J. Med. Chem.* **1983**, *26*, 851.
(9) Hamanaka, N.; Matsumoto, T. *Tetrahedron Lett.* **1972**, 3087.
(10) Gasa, S.; Hamanaka, N.; Matsunaga, S.; Okuno, T.; Takeda, N.; Matsumoto, T. *Tetrahedron Lett.* **1976**, 553.
(11) Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5532.
(12) See also,Kan, T.; Matsuda, F.; Yanagiya, M.; Shirahama, H. *Synlett* **1991**, 391.
(13) (a) Pouwer, R. H.; Harper, J. B.; Vyakaranam, K.; Michl, J.; Williams, C. M.; Jessen, C. H.; Bernhardt, P. V. *Eur. J. Org. Chem.* **2007**, *2*, 241. (b) Pouwer, R. H.; Williams, C. M.; Raine, A. L.; Harper, J. B. *Org. Lett.* **2005**, *7*, 1323. (c) Pouwer, R. H.; Williams, C. M. In *Silver in Organic Chemistry*; Harmata, M., Ed.; Wiley: Hoboken, 2010; Chapter 1, p 1.
(14) Marinovic, N. N.; Ramanathan, H. *Tetrahedron Lett.* **1983**, *24*, 1871.
(15) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(16) For a short overview, see: Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59.
(17) Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 1485.
(18) Molander, G. A.; Huérou, Y. L.; Brown, G. A. *J. Org. Chem.* **2001**, *66*, 4511.

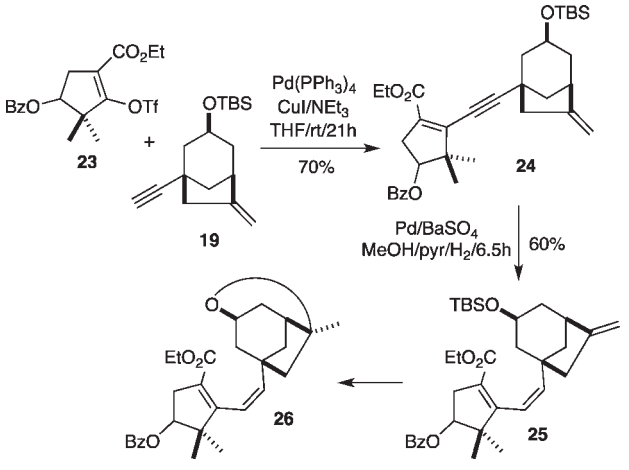
eventually determined by the chemistry performed. For example, PMB protection proved difficult, and installation of aldehyde functionality α to the ketone was not possible. Therefore, ketone **22** was converted, with ease, into triflate **23** via sequential treatment with LDA and Mander's reagent[19] and LDA/triflic anhydride (Scheme 3).

Scheme 3. Construction of the Left Hand Fragment **23**



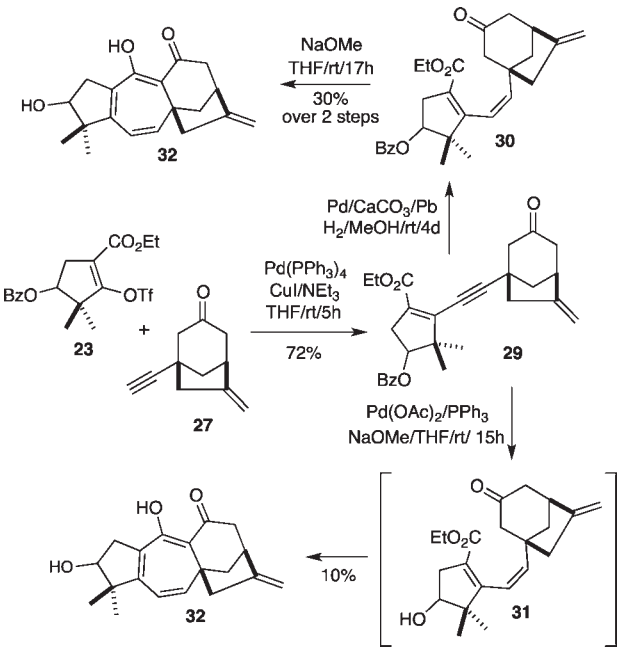
With both fragments in hand (i.e., **19** and **23**), the Sonogashira coupling[20] was performed using standard conditions giving the coupled product **24** in 70% yield. Lindlar reduction proceeded remarkably smoothly, most likely due to the steric congestion limiting over-reduction, which afforded the (*Z*)-diene (**25**) in 60% yield. Unfortunately, all attempts to remove the TBS protecting group[21] from **25** either returned starting material or gave material tentatively assigned as **26** (Scheme 4).

Scheme 4. Sonogashira Coupling of **23** and **19**: Exploring the Deprotection of **25**



Reflecting on the failure depicted in Scheme 4, we realized that a protecting group was probably not an absolute requirement, and therefore, we decided to investigate the use of bicyclo[3.2.1]octane **27**, also readily accessible from **17** via **28** (Scheme 2). Sonogashira coupling of **27** to **23** proceeded without adverse incident giving **29** in 72% yield. In light of previous difficulties in our laboratories with Lindlar reductions[22] (Scheme 4 being an exception), we decided to implement methodology described by Wei et al[23] utilizing palladium acetate and sodium methoxide (hydrogen source). In a fortuitous event, it was discovered that when using the conditions of Wei et al., the advanced intermediate **32** was obtained in a one-pot cascade. Although the timing of events is unclear, mechanistically, sodium methoxide removed the protecting group (i.e., **31**), partially reduced the triple bond (i.e., **31**), and facilitated the Claisen cyclization giving the seven-membered ring system (Scheme 5). Unfortunately, the one-pot cascade, which afforded only 10% yield of **32** along with over-reduction and isomerization side products, could not be further improved. If, however, a carefully controlled Lindlar reduction was performed and the crude material

Scheme 5. Construction of the Advanced Intermediate **32**

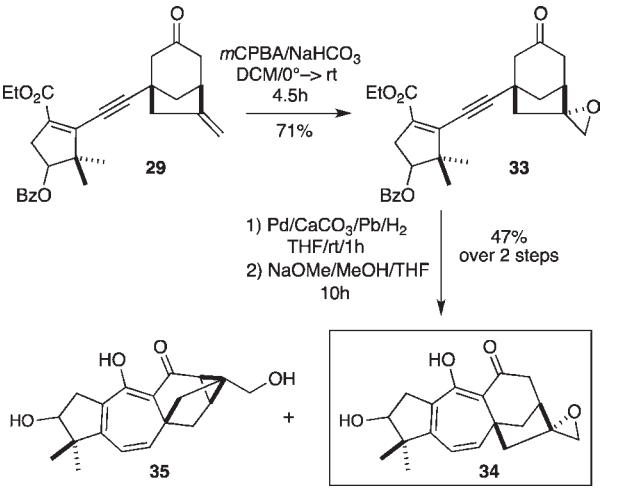


treated with sodium methoxide, the yield over two steps increased to 30%. Other Lindlar catalyst systems including P2−Ni[24] failed to offer any improvement.

Not satisfied with the above result (i.e., Scheme 5) and realizing that the bicyclic[3.2.1] exo methylene double

(19) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
(20) Negishi, E.-i.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.
(21) We have previously experienced difficulties with late-stage deprotection of TBS; see, for example: Schwartz, B. D.; Denton, J. R.; Bernhardt, P. V.; Davies, H. M. L.; Williams, C. M. *Synthesis* **2009**, 2840.
(22) Pouwer, R. H.; Schill, H.; Williams, C. M.; Bernhardt, P. V. *Eur. J. Org. Chem.* **2007**, 4699.
(23) Wei, L.-L.; Wei, L.-M.; Pan, W.-B.; Leou, S.-P.; Wu, M.-J. *Tetrahedron Lett.* **2003**, *44*, 1979.
(24) See, for example: Feutrill, J. T.; Lilly, M. J.; White, J. M.; Rizzacasa, M. A. *Tetrahedron* **2008**, *64*, 4880 and references therein.

Scheme 6. Optimized Reduction/Cyclization Giving Advanced Intermediate **34** toward a Total Synthesis of Pierisformaside C (**1**)



bond in **29** was surprisingly susceptible to reduction under Lindlar conditions, it was replaced with an epoxide ring. It was hoped that this tactical maneuver would avoid over-reduction products and bring the advanced intermediate closer to the target molecule (**1**, Figure 1). Treatment of **29** with *m*-chloroperbenzoic acid gave the desired material **33** as the major (6:1) product in 56% yield (71% brsm). Subjecting **33** to the two-step procedure of Lindlar reduction followed by exposure to sodium methoxide gave the deprotected cyclized advanced intermediate **34** in an acceptable yield of 47% (Scheme 6). If, however, treatment with methoxide was performed for an extended period, intramolecular epoxide ring-opening was observed (i.e., **35**) as the major product.

In conclusion, an advanced intermediate **34** en route to pierisformaside C (**1**) was forged in 10 linear steps (15 in total) laying the way for an asymmetric total synthesis and access to closely related family members (i.e., **2**–**6**).

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