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A Pauson–Khand Approach to the Hamigerans

Christian E. Madu and Carl J. Lovely*

Department of Chemistry and Biochemistry, The University of Texas at Arlington,
Arlington, Texas 76019

lovely@uta.edu

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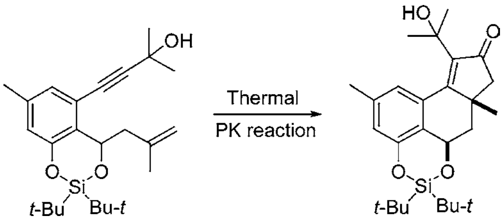
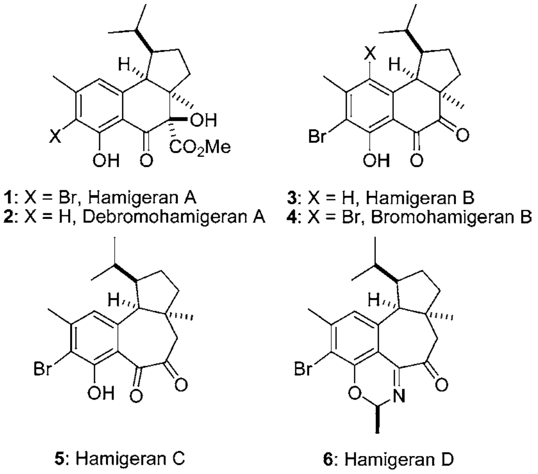
ABSTRACT



An intramolecular Pauson–Khand reaction has been used in the construction of the tricyclic core common to the hamigeran terpenes. For effective cyclization, it was necessary to tether the olefin-containing moiety to the aromatic framework to reduce its conformation mobility; this was accomplished using a silylene protecting group. Efficient construction of the aryl enyne from a salicylic acid derivative was accomplished via *ortho* lithiation and Sonogashira cross-coupling chemistry.



1: X = Br, Hamigeran A
2: X = H, Debromohamigeran A
3: X = H, Hamigeran B
4: X = Br, Bromohamigeran B
5: Hamigeran C
6: Hamigeran D

Figure 1. Hamigeran family of natural products.

The hamigerans (Figure 1) are a small class of brominated terpenes which were isolated by Cambie and co-workers from a marine sponge, *Hamigerans tarangaensis*, Bergquist and Fromont found off the Chicken and Egg Islands, near New Zealand.[1] These terpenes possess several unique structural features including the benzannulation of an indenyl (**1**−**4**) or an azulene fragment (**5** and **6**). In addition to these novel structural features, these natural products exhibited antiviral activity against several viruses, including polio.[1] As a result of both the structural and biological features, these natural products have attracted attention from several groups and have resulted in the completion of a number of total syntheses of **1**−**4** and several reports of construction of the core skeleton.[2,3] To date, no syntheses of the higher homologues **5** and **6** have appeared in the literature. Our own interest in

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[1] Wellington, K. D.; Cambie, R. C.; Rutledge, P. S.; Bergquist, P. R. *J. Nat. Prod.* **2000**, *63*, 79.

[2] (a) Nicolaou, K. C.; Gray, D.; Tae, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3675. (b) Nicolaou, K. C.; Gray, D.; Tae, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3679. (c) Clive, D. L. J.; Wang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 3406. (d) Mehta, G.; Shinde, H. M. *Tetrahedron Lett.* **2003**, *44*, 7049. (e) Clive, D. L. J.; Wang, J. *Tetrahedron Lett.* **2003**, *44*, 7731. (f) Nicolaou, K. C.; Gray, D. L. F.; Tae, J. *J. Am. Chem. Soc.* **2004**, *126*, 613. (g) Trost, B. M.; Pissot-Soldermann, C.; Chen, I.; Schroeder, G. M. *J. Am. Chem. Soc.* **2004**, *126*, 4480. (h) Clive, D. L. J.; Wang, J. *J. Org. Chem.* **2004**, *69*, 2773. (i) Sperry, J. B.; Wright, D. L. *Tetrahedron Lett.* **2005**, *46*, 411. (j) Trost, B. M.; Pissot-Soldermann, C.; Chen, I. *Chem.*—*Eur. J.* **2005**, *11*, 951.

[3] For a review of this area, see: Clive, D. L. J.; Wang, J. *Org. Prep. Proced. Int.* **2005**, *37*, 1.

10.1021/ol7018604 CCC: $37.00

developing approaches to these natural products grew out of experience with the Pauson−Khand (PK) reaction of aryl enynes,[4,5] which suggested that use of this particular disconnection might provide a concise approach into the core framework found in these molecules. In this report, we describe our investigation of the feasibility of this approach.

Our retrosynthetic analysis of this family of natural products is depicted in Figure 2. Initial adjustment of the oxidation state in the cyclopentyl moiety leads to the enone **7**, which we planned on constructing using an intramolecular PK reaction. The precursor would then be the corresponding enyne **8**, which in turn would be constructed by the addition of an organometallic reagent to install the allyl moiety and a Sonogashira reaction to install the alkyne,[6] leaving the iodobenzaldehyde derivative **9** as a precursor. This, in turn, would disconnect back to the salicylic acid derivative via a directed *ortho* metalation (DOM) sequence.[7] Of particular note here is that there is an element of divergency in this approach, in which simply choosing the appropriate organometallic reagent would allow access to either subfamily (**1**−**4** or **5**−**6**) from a common intermediate. Further, the use of a nonracemic methallyl organometallic reagent would permit an asymmetric synthesis.

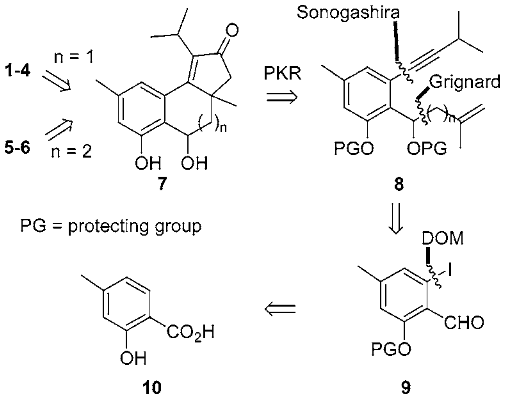
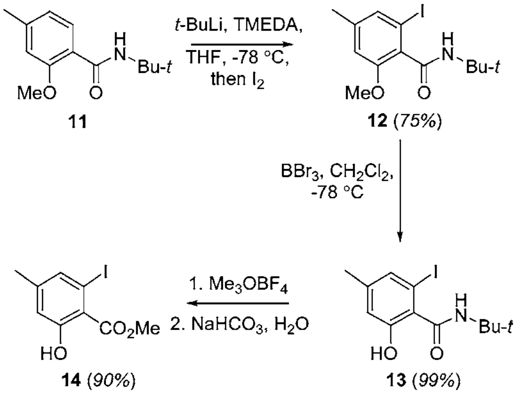


Figure 2. Retrosynthetic analysis of the hamigerans.

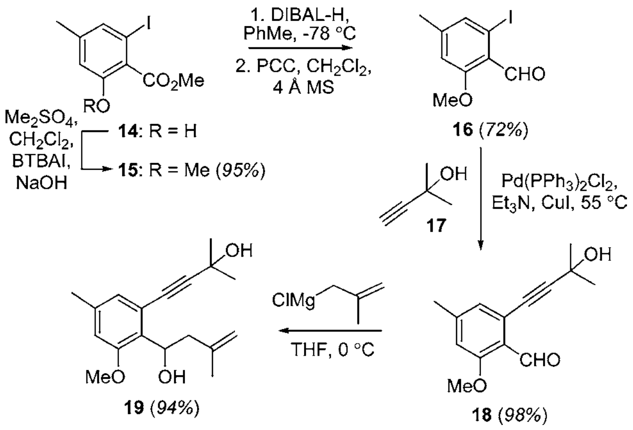
All of the proposed chemistry had solid precedents in the literature, with the exception of the PK reaction leading to highly substituted cyclopentenones of the type that we wished to prepare. As far as we are aware, only two reports exist describing PK cyclizations of substrates related to **8**;[5b,8] however, substrates which contained either a terminal TMS moiety on the acetylene or an internal methyl substituent on the olefin either gave low yields or failed to cyclize.[5b] Subsequent studies from our group have demonstrated that this reluctance can be overcome by the incorporation of steric buttressing elements (bulky *ortho* substituents), which in effect reduce the entropic penalty associated with cyclization and thus enhance both rates and yields of cyclization.[5a,c,d,9] Therefore, as we proceeded through our studies, this issue was at the forefront of our minds.

Our synthetic efforts began with the preparation of the iodobenzaldehyde derivative **16** (Scheme 2), which we planned on constructing via directed *ortho* metalation, in analogy with Nicolaou's approach to these natural products.

Scheme 1



Scheme 2



Accordingly the *tert*-butyl amide **11**[10] was prepared by standard acylation chemistry from the salicylic acid and then

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(4) (a) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (b) Schore, N. E. *Org. React.* **1991**, *40*, 1. (c) Schore, N. E. Transition Metal Alkyne Complexes: Pauson−Khand Reaction. In *Comprehensive Organometallic Chemistry-II*; Hegedus, L. S., Ed.; Pergamon: Oxford, 1995; Vol. 12, p 703. (d) Geis, O.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **1998**, *37*, 911. (e) Ingate, S. T.; Marco-Contelles, J. *Org. Prep. Proced. Int.* **1998**, *30*, 123. (f) Chung, Y. K. *Coord. Chem. Rev.* **1999**, *188*, 297. (g) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (h) Gibson, S. E.; Stevanazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800. (i) Blanco-Urgoiti, J.; Anorbe, L.; Perez-Serrano, L.; Dominguez, G.; Perez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32. (j) Gibson, S. E.; Mainolfi, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022. (k) Struebing, D.; Beller, M. *Top. Organomet. Chem.* **2006**, *18*, 165.

(5) (a) Lovely, C. J.; Seshadri, H.; Wayland, B. R.; Cordes, A. W. *Org. Lett.* **2001**, *3*, 2607. (b) Lovely, C. J.; Seshadri, H. *Synth. Commun.* **2001**, *31*, 2479. (c) Madu, C. E.; Seshadri, H.; Lovely, C. J. *Tetrahedron* **2007**, *63*, 5019. (d) Madu, C. E.; Lovely, C. J. *Synlett* **2007**, 2011.

(6) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.

(7) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(8) Blanco-Urgoiti, J.; Casarrubios, L.; Dominguez, G.; Perez-Castells, J. *Tetrahedron Lett.* **2001**, *42*, 3315.

(9) For a review of this general area, see: Sammes, P. G.; Weller, D. J. *Synthesis* **1995**, 1205.

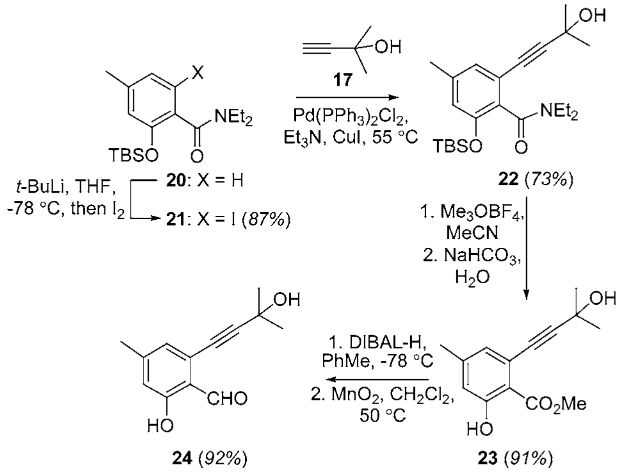
treated with *n*-BuLi and the resulting aryl lithium trapped with iodine affording **12** (Scheme 1). We planned on hydrolyzing the amide and then adjusting the oxidation state of the resulting acid. Unfortunately, we were unable to hydrolyze the amide under a variety of standard conditions.[11] During these experiments, we became aware of an investigation of the hydrolysis of related benzamide derivatives by the Keck group.[12] In this report, a series of benzamides were converted to the corresponding imidates by treatment with Meerwein's salt and hydrolyzed with aqueous $NaHCO_3$ to give the methyl ester. Among several observations, they noted that the presence of a substituted *o*-phenolic hydroxyl in systems related to **12** resulted in the complete shutdown of hydrolysis, but if the substituent were removed the hydrolysis proceeded uneventfully. Accordingly, we attempted this manoeuvre by first cleaving the methyl ether with excess BBr_3 (Scheme 1) and then treating the resulting amide **13** with Meerwein's salt and then aqueous base. In this way, we were able to obtain the methyl ester **14** in 89% yield for the three-step sequence. The phenolic OH was remethylated, providing **15**, and then the oxidation state of the ester was adjusted via reduction and oxidation to provide the key aldehyde **16** (Scheme 2).

Once efficient access to the iodobenzaldehyde derivative **16** was obtained, the introduction of the two unsaturated fragments required for the PK cyclization was investigated (Scheme 2). After some experimentation, it was found that the methylbutyne moiety could be incorporated via a Sonogashira reaction, provided that the butynol derivative **17** was employed, rather than the parent alkyne.[13] Presumably, the low boiling point of the parent alkyne contributes to this result. Subsequently, a simple Grignard reaction with methallylmagnesium chloride completed the sequence to give the PK precursor **19**. Unfortunately, when this substrate was converted into the corresponding $Co_2(CO)_6$ complex, it failed to undergo PK cyclization under a variety of thermal or oxidative conditions.

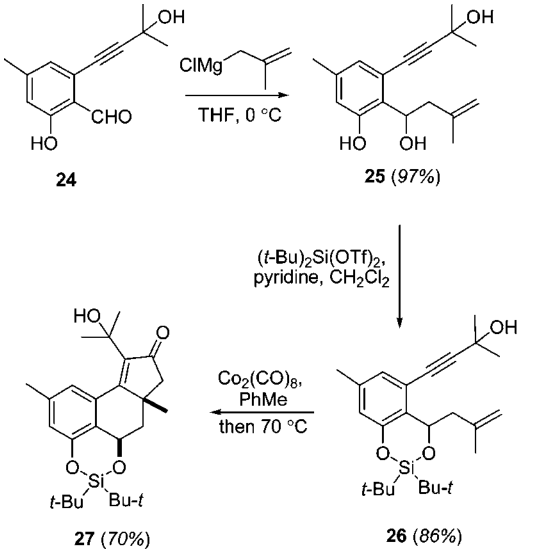
As indicated above, this outcome was not necessarily unexpected, as we had previously found that highly congested systems of this type were not readily accessible without the presence of bulky *ortho* substituents to facilitate the cyclization. Presumably in this case, the *O*-methyl group adopts a conformation to avoid steric interactions with the alkene-bearing substituent, resulting in a nonproductive decomplexation rather than desired cyclization. Therefore, we decided to investigate whether linking the phenolic moiety and the homoallylic alcohol might lead to improved efficiencies in the PK reaction.

Our initial attempt to access such cyclization substrates involved the deprotection of the methyl ether **19** with BBr_3; unfortunately, this proved unsuccessful, and so an alternative approach was sought, and this is outlined in Scheme 3. Rather than use **11**, however, the corresponding TBS derivative was used in the DOM chemistry,[14] providing the iodide in 87% yield.[15] Sonogashira cross-coupling with the 2-methyl-2-butynol and hydrolysis of the amide using the two-step procedure via the imidate provided **23**, which also underwent concomitant desilylation. Oxidation state adjustment through reduction with DIBAL-H to the benzyl alcohol and oxidation with MnO_2 gave the key aldehyde **24**. Reaction with methallylmagnesium chloride smoothly provided the diol **25**, which on treatment with $(t\text{-Bu})_2Si(OTf)_2$ provided the silylene derivative **26** in excellent yield.[16] Gratifyingly, this

Scheme 3



Scheme 4



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(10) Kwon, B. S.; Tae, J. *Heterocycles* **2004**, *62*, 137.

(11) For example, attempts to hydrolyze the amide with concentrated sulfuric acid led to loss of the *tert*-butyl moiety and the formation of the primary amide.

(12) Keck, G. E.; McLaws, M. D.; Wager, T. T. *Tetrahedron* **2000**, *56*, 9875.

(13) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86.

(14) Keck's work indicated that the TBS moiety would be removed under the conditions used for the amide hydrolysis, and thus this sequence was more efficient.

(15) Baba, Y.; Ogoshi, Y.; Hirai, G.; Yanagisawa, T.; Nagamatsu, K.; Mayumi, S.; Hashimoto, Y.; Sodeoka, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2963.

enyne on conversion to the $Co_2(CO)_6$ complex, followed by thermal activation at 70 °C in PhMe, led to conversion to the desired tetracyclic adduct **27** in 70% yield as a single diastereomer.[17] While we have been unable to unequivocally assign the stereochemistry of the cycloadduct, it is of no real consequence as the hydroxyl center will become sp^2-hybridized in subsequent intermediates. However, on the basis of the usual stereochemical biases of the intramolecular PK reaction leading to the placement of the peripheral substituents *exo*, we propose the indicated stereochemistry (Scheme 4).[18]

In summary, we have developed an efficient 10-step sequence from 4-methylsalicylic acid to the complete carbon framework of several members of the hamigeran family of natural products. The key step involves an intramolecular Pauson−Khand reaction of an aryl enyne. Critical to the success of this cyclization is the presence of a bulky silylene protecting group which tethers the two reacting fragments, thereby facilitating the reaction by reducing the entropic penalty and provides steric acceleration through buttressing effects. Current efforts are directed toward the completion of the total synthesis of hamigeran B from **27** and the preparation of nonracemic precursors.

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Supporting Information Available: Detailed experimental procedures and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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