

# Synthesis of the Bridging Framework of Phragmalin-Type Limonoids

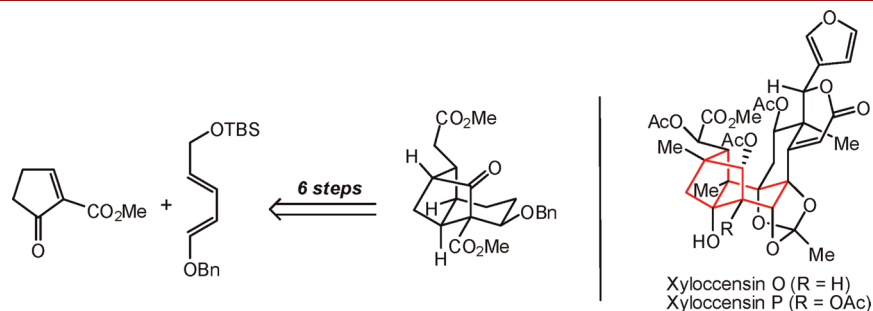
Terry P. Lebold, Gary M. Gallego, Christopher J. Marth, and Richmond Sarpong\*

Department of Chemistry, University of California, Berkeley, California 94720, United States

rsarpong@berkeley.edu

Received March 13, 2012

## ABSTRACT



An efficient synthesis of the octahydro-1*H*-2,4-methanoindene core of phragmalin-type limonoids, such as xyloccensins O and P, is reported. The success of the synthetic route is predicated on the use of network analysis in the retrosynthetic analysis and a Diels–Alder reaction for the synthesis of a key hydrindanone derivative.

The phragmalin-type limonoids (e.g., xyloccensin O and P, **2** and **3**, and trichagmalin A and C, **4** and **5**, Figure 1)<sup>1</sup> are highly oxygenated triterpenoid derivatives of daunting molecular complexity that, to date, have not succumbed to total synthesis. The intricate polycyclic and highly oxygenated nature of these compounds constitutes a significant challenge for modern chemical synthesis.<sup>2</sup> Central among the challenges associated with the chemical synthesis of this subset of limonoids is identifying effective approaches to the unusual octahydro-1*H*-2,4-methanoindene framework (highlighted in Figure 1). We reasoned that a synthetic endeavor aimed at this unique carbon skeleton would lead to the discovery of novel strategies and tactics applicable to the synthesis of a variety of phragmalin-type limonoids. An efficient synthetic route could enable further investigation into the already diverse bioactivities of the limonoid family (e.g., anticancer,<sup>3</sup>

anti-HIV,<sup>4</sup> antibiotic, anti-inflammatory,<sup>5</sup> and antifeedent<sup>6</sup> properties) and, potentially, improvement of their pharmacological profiles by derivitization.

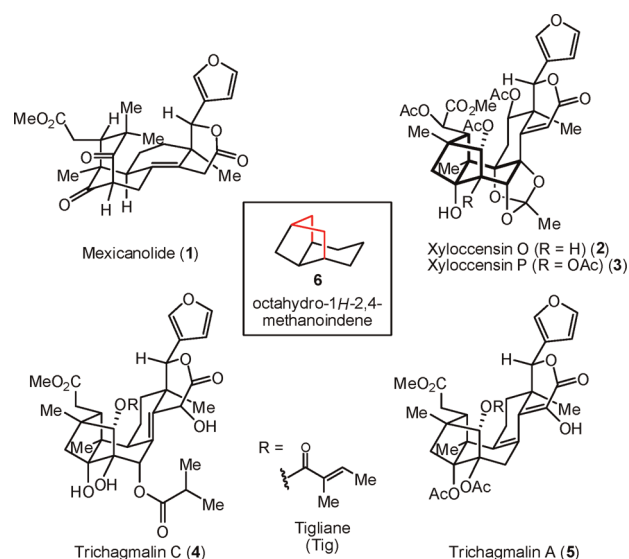


Figure 1. Selected limonoid natural products.

(1) Wu, J.; Xiao, Q.; Huang, J.; Xiao, Z.; Qi, S.; Li, Q.; Zhang, S. *Org. Lett.* **2004**, 6, 1841–1844.

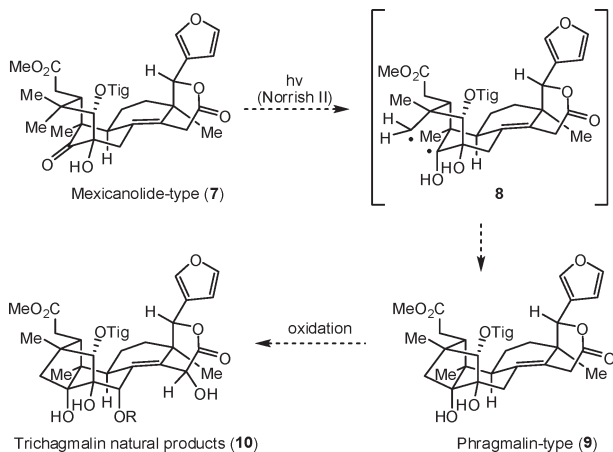
(2) For a recent review of limonoids, see: Heasley, B. H. *Eur. J. Org. Chem.* **2011**, 19–46.

(3) (a) Brandt, G. E.; Schmidt, M. D.; Prinszano, T. E.; Blagg, B. S. *J. Med. Chem.* **2008**, 51, 6495–6502. (b) Luo, J.; Wang, J.-S.; Wang, X.-B.; Luo, J.-G.; Kong, L.-Y. *Chem. Pharm. Bull.* **2011**, 59, 225–230. (c) Cui, J.; Deng, Z.; Xu, M.; Proksch, P.; Li, Q.; Lin, W. *Helv. Chim. Acta* **2009**, 92, 139–150.

(4) Kuo, R.-Y.; Qian, K.; Morris-Natschke, S. L.; Lee, K.-H. *Nat. Prod. Rep.* **2009**, 26, 1321–1344.

Biosynthetically, the phragmalin-type limonoids likely arise from the related mexicanolide-type natural products (e.g., **7**, Scheme 1). A possible biogenetic connection between the mexicanolide-type (**7**) and corresponding phragmalin derivatives (e.g., **9**), proposed by Hao and co-workers,<sup>7</sup> is outlined in Scheme 1. This process may begin with a photoinitiated Norrish type II reaction to afford the strained octahydro-1*H*-2,4-methanoindene framework. Given that the Norrish type II product (**9**) likely represents the photostationary state, highly strained systems of this type may be accessed.

**Scheme 1.** Proposed Biogenetic Connection between Mexicanolide-Type and Phragmalin-Type Limonoids



Biomimetic syntheses can often bring an unprecedented level of simplification to a challenging synthetic target,<sup>8</sup> however, the unique environment of an enzyme, should one be required, is not easily emulated by synthetic chemists. For the phragmalin-type limonoids in particular, the strict conformational requirements regarding the proximity of reacting partners in photoreactions, including the Norrish type II process, makes it unclear how high yielding the conversion of **7** to **9** would be outside of a biological context. As such, we decided to pursue alternative, more robust, strategies for the formation of the caged phragmalin framework.

Foremost among our considerations as to how to access the architecturally intricate phragmalin-type tricyclic

skeleton was to apply the method of network analysis.<sup>9</sup> To forge the caged methanoindene polycycle (see **6** in Figure 1), a disconnection of any of the bonds shown in red would realize the main goal of network analysis, namely, the simplification of the complex caged structure to a fused ring system.<sup>8b</sup> Despite the powerful reduction in complexity in the retrosynthetic sense that this approach offers, we were cognizant of the significant challenge that the forward C–C bond construction posed due to the accompanying increase in strain.<sup>10</sup>

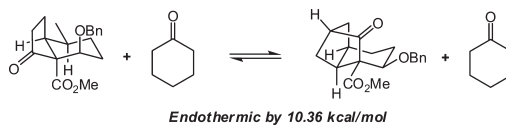
In this communication, we report the successful implementation of network analysis guidelines for forming functionalized octahydro-1*H*-2,4-methanoindene frameworks (**14** and **26**, Scheme 2 and 6, respectively), which serve as models for the challenging phragmalin-type caged architecture (e.g., in xylocensin **O**, **2**).

Initial studies focused on the construction of **14**. This undertaking would demonstrate the feasibility of the intramolecular cyclization by using an irreversible alkylation before attempting the bond construction using a potentially reversible Michael addition (*vide infra*). We envisioned that **14** could arise from conformer **13A** of hydrindanone derivative **13** by an alkylative C–C bond formation. Although conformations of hydrindane and hydrindanone systems have been studied,<sup>11</sup> there are no reports that describe these dynamics in highly functionalized systems. Despite preliminary computations suggesting conformer **13B** to be lower in energy, the irreversibility of the alkylation step arising from conformer **13A** was expected to lead to productive formation of **14**.<sup>12</sup> Hydrindanone derivative **13** could in turn arise from a Diels–Alder cycloaddition between cyclopentenone **11** and diene **12**.

Given that 2-methoxycarbonylcyclopent-2-enone (**11**) is readily available in multigram quantities,<sup>13</sup> our synthesis of **13** commenced with the preparation of diene **12** (Scheme 3).

(9) (a) Corey, E. J.; Ohno, M.; Vatakencherry, P. A.; Mitra, R. B. *J. Am. Chem. Soc.* **1961**, *83*, 1251–1253. (b) Corey, E. J.; Ohno, M.; Mitra, R. B.; Vatakencherry, P. A. *J. Am. Chem. Soc.* **1964**, *86*, 478–485. (c) Corey, E. J.; Howe, W. J.; Orf, H. W.; Pensak, D. A.; Petersson, P. G. *J. Am. Chem. Soc.* **1975**, *97*, 6116–6124. (d) Corey, E. J. *Angew. Chem., Int. Ed.* **1991**, *30*, 455–465.

(10) For example, the following homodesmotic calculation (Gaussian DFT; basis set B3LYP/6-31G(d,p); see the Supporting Information for details) indicates that formation of the tricycle from the bicycle is uphill by 10.36 kcal/mol. For a discussion on homodesmotic calculations, see: Wheeler, S. E.; Houk, K. N.; Schleyer, P. v. R.; Allen, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 2547–2560.



(11) (a) Sokolova, I. M.; Petrov, A. A. *Neftekhimiya* **1977**, *17*, 498; *Chem. Abstr.* **87**, 184059b. (b) Lo Cicero, B.; Weisbuch, F.; Dana, G. *J. Org. Chem.* **1981**, *46*, 914–919. (c) Schneider, H.-J.; Nguyen-Ba, N. *Org. Magn. Reson.* **1982**, *18*, 38. (d) Moniz, W. B.; Dixon, J. A. *J. Am. Chem. Soc.* **1961**, *83*, 1671–1675. (e) Lack, R. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1968**, *90*, 6997–7001.

(12) Our preliminary conformational search of **13** using MacroModel minimization/Monte Carlo search parameters has identified compound **13B** as more energetically stable than compound **13A**.

(13) Wang, C.; Gu, X.; Yu, M. S.; Curran, D. P. *Tetrahedron* **1998**, *54*, 8355–8370.

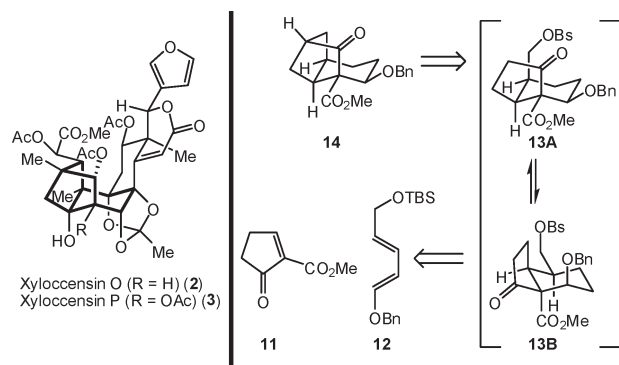
(5) (a) Ravangpai, W.; Sommit, D.; Teerawatananond, T.; Sinpranee, N.; Palaga, T.; Pengprecha, S.; Muangsins, N.; Pudhom, K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4485–4489. (b) Luo, J.; Wang, J.-S.; Luo, J.-G.; Wang, X.-B.; Kong, L.-Y. *Tetrahedron* **2011**, *67*, 2942–2948.

(6) Wu, J.; Xiao, Q.; Zhang, S.; Li, X.; Xiao, Z.; Ding, H.; Li, Q. *Tetrahedron* **2005**, *61*, 8382–8389.

(7) Zhang, Q.; Di, Y.-T.; He, H.-P.; Fang, X.; Chen, D.-L.; Yan, X.-H.; Zhu, F.; Yang, T.-Q.; Liu, L.-L.; Hao, X.-J. *J. Nat. Prod.* **2011**, *74*, 152–157. For other proposed biosynthetic pathways for more highly oxygenated limonoids, see: (a) Taylor, D. A. H. *Phytochemistry* **1983**, *22*, 1297–1299. (b) Abdelgaleil, S. A. M.; Okamura, H.; Iwagawa, T.; Sato, A.; Miyahara, I.; Doe, M.; Nakatani, M. *Tetrahedron* **2001**, *57*, 119–126.

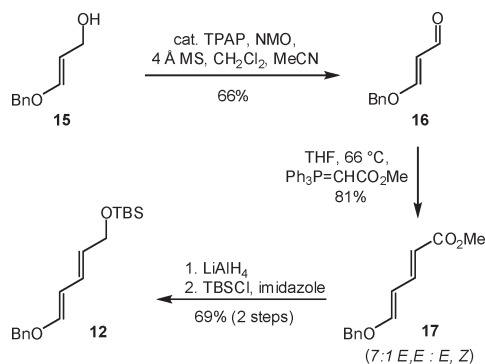
(8) (a) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551–564. (b) Heathcock, C. H. *Angew. Chem., Int. Ed.* **1992**, *31*, 665–681.

## Scheme 2. Retrosynthetic Analysis of 14



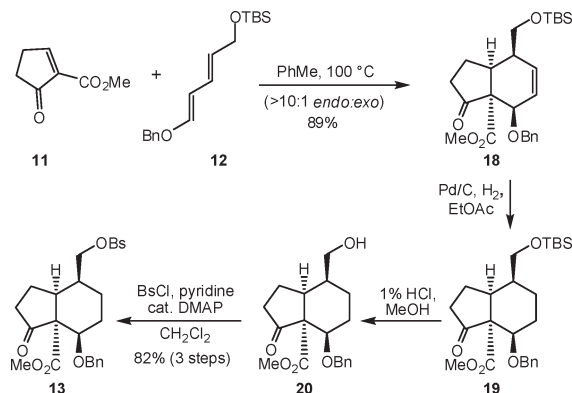
Building on precedents from d'Angelo<sup>14</sup> and Grierson,<sup>15</sup> we began with the Ley oxidation<sup>16</sup> of allylic alcohol **15** (prepared from ethyl propiolate),<sup>17</sup> affording aldehyde **16** in 66% yield. Wittig olefination using carbomethoxymethylidene phosphorane gave diene ester **17** in 81% yield as a separable 7:1 mixture of *E,E* and *E,Z* isomers. Subsequent reduction of the ester group (LiAlH<sub>4</sub>) and silylation using TBSCl and imidazole provided the desired diene (**12**) in 69% yield over the two steps.

## Scheme 3. Synthesis of Diene 12



With diene **12** and dienophile **11** in hand, we next pursued the Diels–Alder cycloaddition. Heating a mixture of diene **12** and freshly prepared **11** (1.45 equiv) provided

## Scheme 4. Synthesis of Hydrindanone Derivative 13



adduct **18** (Scheme 4) in 89% combined yield (> 10:1 *endo*/*exo* ratio).<sup>18,19</sup> Reduction of the double bond in **18** could be accomplished under carefully monitored hydrogenation conditions, which proceeded without hydrogenolytic cleavage of the benzyl ether. Treatment of the crude hydrogenation product (**19**) with 1% HCl in MeOH furnished alcohol **20**, which was sulfonated to produce keto-benzenesulfonate **13** in 82% yield over the three steps.

With keto-benzenesulfonate **13** in hand, the stage was set for the key alkylation reaction to build the tricyclic framework of the phragmalin-type limonoids. As shown in Table 1, several conditions were explored with varying levels of success. While excess KHMDS (Table 1, entry 1) led only to decomposition, the use of 1.1 equiv of KHMDS gave the desired octahydro-1*H*-2,4-methanoindene framework (entry 2). However, the yields were found to be highly variable, with significant amounts of hydrindene **21** often being formed. Ultimately, a 74% yield of **14** could be consistently obtained under carefully controlled conditions using KHMDS (1.1 equiv) as the base in the presence of triethylamine and tetrabutylammonium iodide (TBAI; 1 equiv) in THF at –78 °C with warming to room temperature over 20 min (entry 3). The structure of **14** was unambiguously confirmed by X-ray crystallographic analysis of the corresponding *p*-bromobenzoate derivative **22** (Figure 2).<sup>20</sup>

Table 1. Optimization of Alkylation Conditions

entry	conditions	result
1	KHMDS (2 equiv), THF, –78 °C to rt	decomposition
2	KHMDS (1.1 equiv), THF, –78 °C to rt	<b>14</b> (38–84%)
3	KHMDS (1.1 equiv), TBAI (1 equiv) THF/NEt <sub>3</sub> , –78 °C to rt	<b>14</b> (74%)

(14) Maddaluno, J.; d'Angelo, J. *Tetrahedron Lett.* **1983**, 24, 895–898.

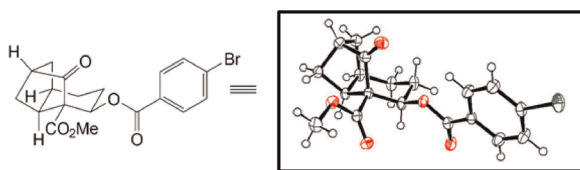
(15) Prabhakaran, J.; Lhermitte, H.; Das, J.; Sasi-Kumar, T. K.; Grierson, D. S. *Synlett* **2000**, 5, 658–662.

(16) (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627. (b) Hinzen, B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1907–1908.

(17) (a) Fujiwara, K.; Goto, A.; Sato, D.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, 46, 3465–3468. (b) Tellam, J. P.; Kociok-Köhn, G.; Carbery, D. R. *Org. Lett.* **2008**, 10, 5199–5202.

(18) The *endo* and *exo* diastereomers could be easily separated by column chromatography.

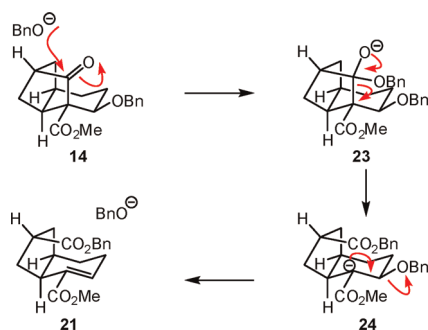
(19) Of note, the double bond in **18** could provide a functional handle for the annulation of the remainder of the phragmalin framework.



**Figure 2.** ORTEP representation of **22**.

The fragmentation product (i.e., hydrindene **21**) likely arises through a retro-Claisen reaction (Scheme 5) where initial nucleophilic attack on the ketone moiety by trace alkoxide generates tetrahedral intermediate **23**, which can collapse to form **21** via ester enolate **24** (E1cB type process).<sup>21,22</sup>

**Scheme 5.** Fragmentation Pathway of **14**



After the success of the intramolecular alkylative cyclization, we next investigated the potentially more challenging Michael addition, which would incorporate the required methylene ester present in the natural products.<sup>23</sup>

(20) Ortep-3 for Windows: Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.

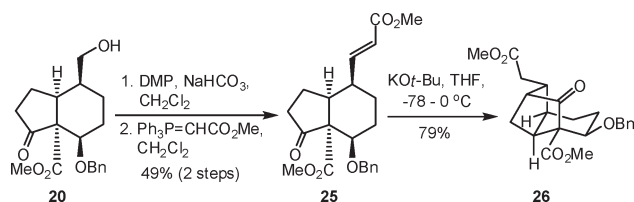
(21) Support for this hypothesis is found by treatment of **14** with KO<sup>t</sup>Bn which results in clean conversion to **21**.

(22) Interestingly, fragmentation of the polycyclic framework is not observed upon reduction of the carbonyl group of **14** with NaBH<sub>4</sub>. For more information, see the Supporting Information.

(23) The success of this cyclization illustrates the potential for further elaboration of this core towards the phragmalin-type limonoids.

(24) Stereochemistry of **26** predicated on A<sup>1,3</sup> considerations.

**Scheme 6.** Michael Addition



To this end, alcohol **20** was converted to enone **25** through sequential oxidation and Wittig olefination in 49% yield over two steps (Scheme 6). Gratifyingly, treating enone **25** with catalytic amounts of KO<sup>t</sup>-Bu in THF (−78–0 °C) led to the desired 1,4-adduct (**26**) as a single diastereomer in 79% yield.<sup>24</sup> Having accomplished the intramolecular 1,4-conjugate addition, we are currently focused on the preparation of more highly functionalized caged frameworks.

In conclusion, we have developed a rapid and efficient route to the octahydro-1*H*-2,4-methanoindene core of the phragmalin-type limonoids. Key to the success of this route was the synthesis of the highly substituted hydrindanone system **18**, which, in turn, provided access to intramolecular cyclization precursors **13** and **25**. This work illustrates the utility of network analysis in defining a rapid path to architecturally complex frameworks such as the octahydro-1*H*-2,4-methanoindene core of the highly complex phragmalin-type limonoids.

**Acknowledgment.** The authors are grateful to the NIH (NIGMS RO1 084906) and American Cancer Society (RSG-09-017-01 CDD) for support of this work. T.P.L. thanks the NSERC (Canada) for a postdoctoral fellowship. Kathleen A. Durkin (UC Berkeley) is also thanked for computational assistance (NSF CHE-0233882 and CHE-0840505).

**Supporting Information Available.** Experimental details and characterization for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.