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Concise synthesis of the xenibellols core

Woo Han Kim [a], Angie R. Angeles [a], Jun Hee Lee [b], Samuel J. Danishefsky [a,b,*]

[a] Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, NY 10065, USA
[b] Department of Chemistry, Columbia University, 3000 Broadway, New York, NY 10027, USA

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ABSTRACT

We describe herein a concise synthesis of an intermediate, via 2,3-Wittig rearrangement and Williamson etherification, en route to the natural products, xenibellols A and B.

In 2005, Duh and co-workers reported the isolation of two novel diterpenoids, xenibellols A (**1**) and B (**2**) from the Formosan soft coral *Xenia umbellata* of Green Island, Taiwan[1] (Fig. 1). These natural products were found to exhibit cytotoxicity against P-388 cell with ED_{50} levels of 3.6 (**1**) and 2.8 μg/mL (**2**). In the same year, Xenibellol A (**1**) was separately isolated from *Xenia florida* samples collected in Taiwan by Shen et al., who assigned it the name xeniolactone A (**1**).[2] The researchers found **1** to exhibit mild cytotoxicity against human colon adenocarcinoma (WiDr) and medullocarcinoma (Daoy) tumor cells at 13.6 and 15.3 μg/mL, respectively. The key structural features of the xenibellols include an unusual oxolane linkage between C_8 and C_{11} in the context of a bicyclo[4.3.0]nonane skeleton, in conjunction with a conjugated (*E*,*E*)-dienol moiety. The dialdehyde motif of xenibellol B (**2**) has been suggested as the precursor to the lactone ring of xenibellol A (**1**). The gross structure of the xenibellols was elucidated by the analysis of one- and two-dimensional NMR spectroscopy, including COSY, HMQC, and HMBC experimentation. The assignments of the relative stereochemical relationships of **1** and **2** rest on a combination of NOESY correlations and comparison of their spectroscopic data to those of the xenia diterpenes. The absolute stereochemistries of the xenibellols have not yet been established.

We sought to undertake a program directed toward the synthesis of the xenibellols primarily due to their interesting structural features. We report herein a concise synthesis of the common xenibellol core, **7**.

Using the logic of pattern recognition[3] to guide retrosynthetic analysis,[4] one could discern a cis-fused hydrindane matrix, with the caveat that the bridgehead is further engaged in a tetrahydrofuran motif. The pattern analysis soon leads one back to the Hajos–Parrish ketone (**3**),[5] with its rich and informing history. For the case at hand, we envisioned, as outlined in Scheme 1, that key intermediate **5** could be derived from the Hajos–Parrish ketone.[5] Under appropriate conditions, it was hoped that **5** would undergo 2,3-Wittig rearrangement to afford **6**, possessing the quaternary bridgehead carbon. We expected that **6** could be converted to the target compound, **7**, through a short sequence featuring a Williamson etherification.

The synthesis of proposed intermediate **5** commenced with selective LiAl(O-*t*Bu)$_3$H-mediated reduction of the Hajos–Parrish ketone (**3**). Silyl protection of the resultant secondary alcohol furnished the α,β-unsaturated ketone **8** in good yield and selectivity.[6] Elongation of the carbon chain was accomplished through the treatment of **8** with methyl magnesium carbonate,[6] and the global reduction of the corresponding keto-acid with LAH provided the desired diol, **9**. Following protection of the primary alcohol, the 2,3-Wittig rearrangement precursor **5** was obtained through reaction of the secondary alcohol, **10**, with *n*Bu$_3$SnCH$_2$I (Scheme 2).[7]

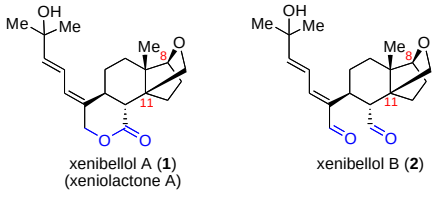
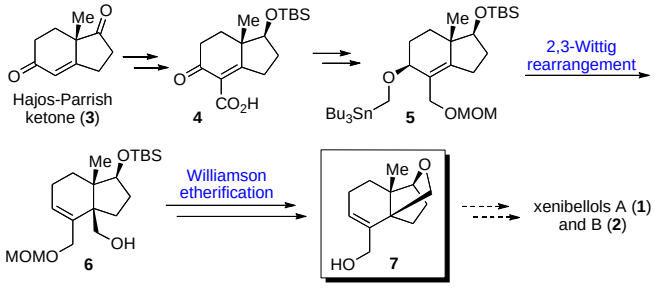


Figure 1. Xenibellols A and B.



Scheme 1. Synthetic strategy toward **7**.

* Corresponding author.
E-mail address: s-danishefsky@ski.mskcc.org (S.J. Danishefsky).

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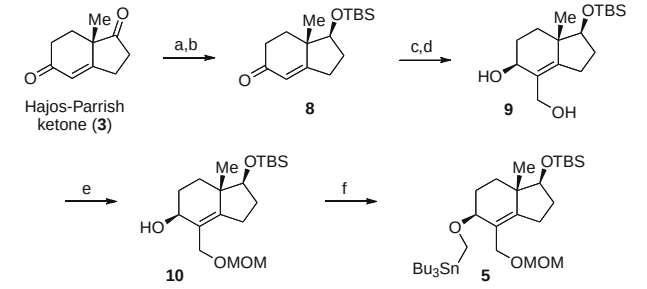
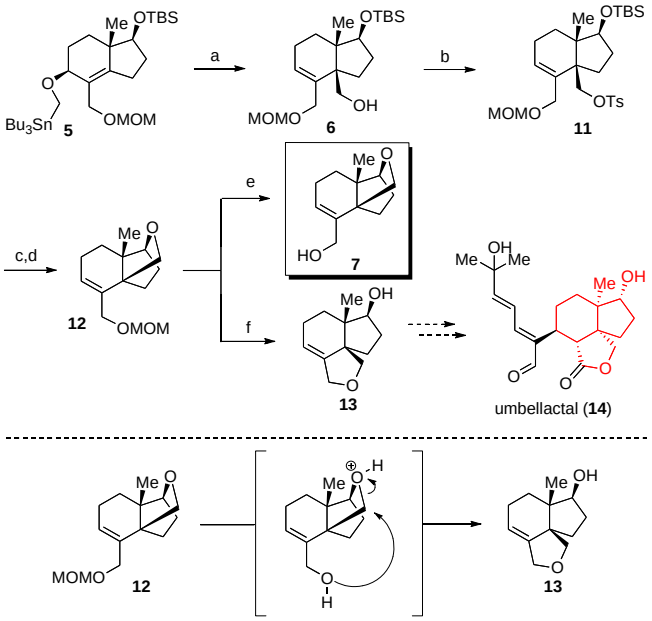


Scheme 2. Synthesis of the 2,3-Wittig rearrangement precursor **5**. Reagents and conditions: (a) LiAl(O-*t*Bu)$_3$H, THF, 0 °C, 40 min; (b) TBSCl, imidazole, DMF, rt, 12 h, 70% for two steps; (c) magnesium methyl carbonate, DMF, 125 °C, 2 h, 71%; (d) LAH, THF, −78 °C to rt, 4 h, 66% (dr = 7.5:1); (e) MOMCl, Hünig's base, DCM, −78 °C to 0 °C, 12 h, 83%; and (f) KH, THF, 0 °C, 10 min; then *n*Bu$_3$SnCH$_2$I, rt, 3 h, 71%.



Scheme 3. Synthesis of the xenibellols core, **7**. Reagents and conditions: (a) *n*BuLi, THF, −78 °C to rt, 12 h, 31%; (b) TsCl, pyridine, DMAP, rt, 12 h, 89%; (c) TBAF, THF, reflux, 3 h; (d) KH, 18-crown-6, THF, 0 °C, 1 h, 87% for two steps; (e) EtSH, MgBr$_2$–OEt$_2$, Et$_2$O, 0 °C, 1 h, 95%; and (f) 1 N HCl, THF, 50 °C, 8 h, 96%.

With intermediate **5** in hand, we next sought to investigate the key 2,3-Wittig rearrangement[8] of **5**, which would serve to install the bridgehead quaternary carbon (Scheme 3). As shown, upon exposure to *n*BuLi, the desired rearrangement product **6** was obtained, albeit in only 31% yield. The efficiency of the rearrangement was compromised by two competing pathways. One involves simple reduction, and the other entails 1,2-Wittig rearrangement. With compound **6** in hand, we next examined the formation of the oxolane moiety of the xenibellol core. Thus, treatment of the primary alcohol **6** with *p*-TsCl in pyridine at room temperature afforded tosylate **11**. The TBS group was removed with TBAF, and the resulting secondary alcohol was treated with KH in the presence of 18-crown-6-ether to furnish the desired oxolane derivative **12**. Finally, we explored deprotection of the MOM group to complete construction of the xenibellols core, **7**. Interestingly, the allylic alcohol formed under conventional acidic conditions was found to open the oxolane moiety to produce the secondary alcohol **13** in 96% yield. We note that this tricyclic compound, **13**, constitutes the core of another structurally related natural product, umbellactal (**14**).[9] After conducting careful studies on the deprotection of the MOM group, we found Kim's protocol[10] to be optimal, successfully providing the desired xenibellol core, **7**, in 95% yield.

In summary, a concise, though not yet high yielding approach to the construction of the core structure of xenibellols A (**1**) and B (**2**) has been developed. The heterotricyclic skeleton of the bicyclo[4.3.0]nonane system was constructed efficiently, with 2,3-Wittig rearrangement and classical Williamson etherification serving as the key transformations. Efforts to complete the total syntheses of xenibellols A (**1**) and B (**2**) continue beyond these milestones.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.131.

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