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Synthesis of Highly Functionalized Bicyclo[*m*.*n*.1]alkanones via a Cationic Reaction Cascade

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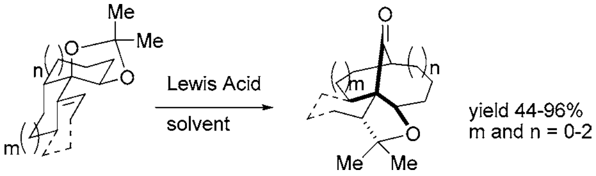
ABSTRACT



The acid-mediated Prins/pinacol and the triple domino reactions Diels–Alder/Prins/pinacol were used to construct highly functionalized bicyclo[*m*.*n*.1]alkanones 19–29 and 33a–c possessing various ring sizes from ketals 8–18 and 31a–c in 44–96% yields. This approach proves to be highly efficient and reliable to generate high molecular complexity in a single step.

The rapid synthesis of bicyclo[*m*.*n*.1]alkanone cores possessing quaternary carbon centers adjacent to a bridged ketone constitutes a significant synthetic challenge. This type of architectural feature is embedded in various complex biologically active compounds such as garsubellin A (**1**),[1] ingenol (**2**),[2] and penostatin F (**3**)[3] (Figure 1). In recent years, a number of clever methods have been developed to construct the bicyclo[*m*.*n*.1]alkanone framework.[4] However, most are specific to a particular scaffold. Therefore, it is of paramount importance to develop efficient methods of general applicability for the construction of various ring size combina-

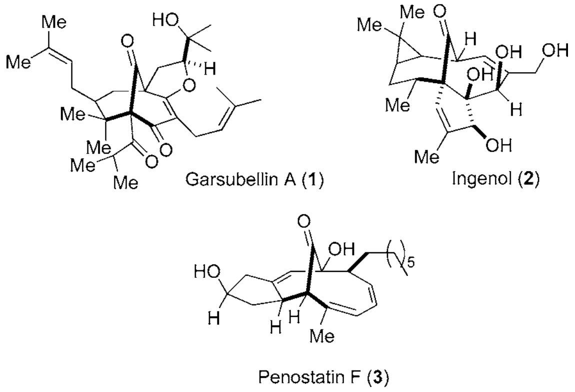


Figure 1.

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[1] For isolation of garsubellin A, see: (a) Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull.* **1997**, *45*, 947. Total synthesis of garsubellin A, see: (b) Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai,; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200. For related synthetic studies, see: (c) Nicolaou, K. C.; Carenzi, G. E. A.; Jeso, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 3895 and references therein. (d) Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2004**, *45*, 1113. (e) Takagi, R.; Nerio, T.; Miwa, Y.; Matsumura, S.; Ohkata, K. *Tetrahedron Lett.* **2004**, *45*, 7401. (f) Kraus, G. A.; Nguyen, T. H.; Jeon, I. *Tetrahedron Lett.* **2003**, *44*, 659. (g) Ciochina, R.; Grossman, R. B. *Org. Lett.* **2003**, *5*, 4619. (h) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943. (i) Young, D. G.; Zeng, D. *J. Org. Chem.* **2002**, *67*, 3134.

[2] For isolation of ingenol, see: (a) Hecker, E. *Cancer Res.* **1968**, *28*, 2338. (b) Zechmeister, K.; Brandl, F.; Hoppe, W.; Hecker, E.; Opferkuch, H. J.; Adolf, W. *Tetrahedron Lett.* **1970**, *11*, 4075. For total synthesis, see: (c) Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726. (d) Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498. (e) Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300. (f) Watanabe, K.; Suzuki, Y.; Aoki, K.; Sakakura, A.; Suenaga, K.; Kigoshi, H. *J. Org. Chem.* **2004**, *69*, 7802.

[3] (a) For isolation of penostatin F, see: Numata, A.; Iwamoto, C.; Minoura, K.; Hagishita, S.; Nomoto, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 449. For synthetic studies, see: (b) Barriault, L.; Ang, P. A. J.; Lavigne, R. M. A. *Org. Lett.* **2004**, *6*, 1317.

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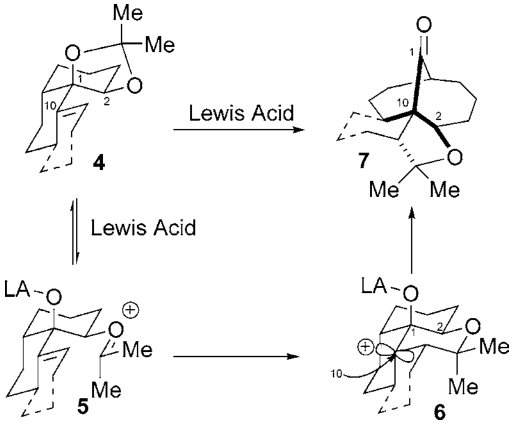
tions. To this end, cascade reactions represent an attractive and efficient strategy for the diastereoselective formation of multiple carbon−carbon bonds.[5]

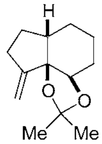
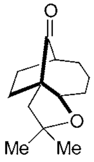
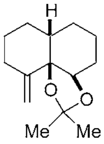
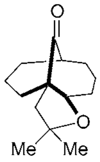
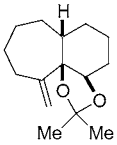
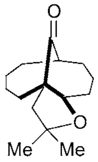
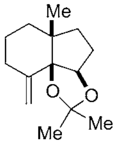
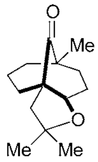
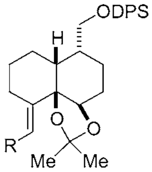
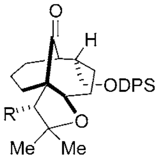
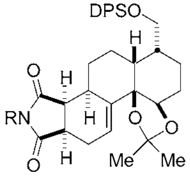
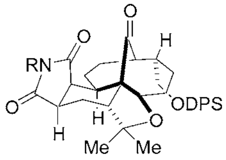
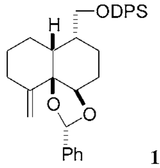
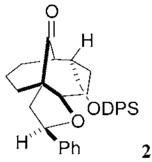
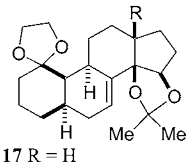
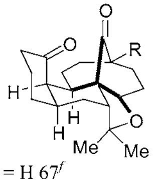
In the course of our studies toward the development of novel strategies to construct polycyclic structures using tandem reactions, we hypothesized that ketal **4** could be transformed into bicyclo[4.3.1]decanone **7** in a single operation via an acid-mediated Prins/pinacol reaction[6] (Scheme 1). Subjection of ketal **4** to a Lewis acid gives the corresponding oxacarbenium **5**, which is poised to undergo a Prins cyclization to furnish intermediate **6**. The empty p orbital in **6** (at C10) is aligned periplanar to the C1−C2 bond thus allowing this bond to migrate to form bicyclic ketone **7** bearing a quaternary center at C10.

Scheme 1



The attractive feature of the proposed method resides in the ability to generate various sizes of bicyclic ketone systems as well as the rapid achievement of high architectural molecular complexity. To the best of our knowledge, no examples for the synthesis of bicyclo[*m*.*n*.1]alkanones using the tandem Prins/pinacol reaction have been reported in the literature.

Table 1. Prins/Pinacol Cyclization

entry	substrate	product[a] (yield)
1	 **8**	 **19** (87%)[b]
2	 **9**	 **20** (61%)[c]
3	 **10**	 **21** (56%)[d]
4	 **11**	 **22** (53%)[c]
5	 **12** R = H	 **23** R = H (86%)[c]
6	**13** R = (CH$_2$)$_3$OTBS	**24** R = (CH$_2$)$_3$OH (67%)[e]
7	 **14** R = Ph	 **25** R = Ph (62%)[c]
8	**15** R = Bn	**26** R = Bn (77%)[c]
9	 **16**	 **27** (80%)[d]
10	 **17** R = H	 **28** R = H 67[f]
11	**18** R = Me	**29** R = Me 53[f]

[a] The structure of the compounds was established by NMR spectroscopy and X-ray diffraction (**19**, **24**, and **28**). [b] TMSOTf (1.2 equiv) in MeCN at −40 °C. [c] SnCl$_4$ (1.0−3.0 equiv) in CH$_2$Cl$_2$ at −78 °C. [d] SnCl$_4$ (1.0−3.0 equiv) in toluene at −78 °C. [e] BiCl$_3$ (1.0 equiv) in CH$_2$Cl$_2$ at 25 °C. [f] SnCl$_4$ (1.2−2.0 equiv) in chlorobenzene at −20 to 0 °C.

To verify the hypothesis depicted in Scheme 1, ketal **8** was treated with TMSOTf (1.2 equiv) in MeCN at −40 °C to produce the corresponding bicyclic[4.2.1]nonanone **19** in

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(4) For a review on the synthesis of bicyclo[3.3.1]nonane, see: (a) Butkus, E. *Synlett* **2001**, 1827. For a detailed review on the synthesis of bicyclo[4.3.1]decenone of phomoidrides, see: (b) Spiegel, D. A.; Njardason, J. T.; McDonald, I. M.; Wood, J. L. *Chem. Rev.* **2003**, *103*, 2691. For a review that summarizes different approaches for the synthesis of bicyclo-[5.3.1]undecene of taxol, see: (c) Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemp. Org. Synth.* **1994**, *1*, 47. (d) Sheehan, S. M.; Lalic, G.; Chen, J. S.; Shair, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2714.

(5) (a) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992. (b) Ziegler, F. *Comprehensive Organic Synthesis*, *Combining C−C* α *Bonds*; Paquette, L. A., Ed.; Permagon Press: Oxford, UK, 1991; Vol. 5, Chapter 7.3. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131. For recent reviews, see: (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (e) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (f) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167. (g) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (h) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (i) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207. (j) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (k) Malacria, M. *Chem. Rev.* **1996**, *96*, 289. (l) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.

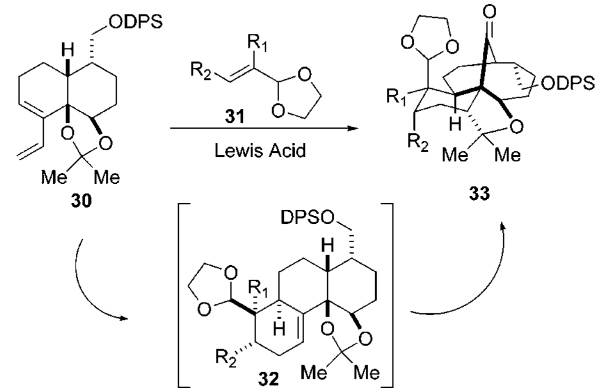
(6) (a) Martinet, P.; Mousset, G. *Bull. Soc. Chim. Fr.* **1970**, 1071. (b) Hopkins, M. H.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 4748. For a detailed review on Prins/pinacol and its clever application to total synthesis of complex natural products, see: (c) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143 and references therein.

87% yield (Table 1, entry 1). With this result in hand, we examined the scope and limitations of this acid-mediated process. A broad evaluation of various Lewis acids and a careful optimization of the reaction conditions indicated that $SnCl_4$ and TMSOTf gave the best results in most cases. The treatment of ketals **9** and **10** with $SnCl_4$ afforded bicyclo[4.3.1]decanone **20** and bicyclo[4.4.1]undecanone **21** in 61% and 56% yield, respectively (entries 2 and 3). The Lewis acid-mediated conversion of ketal **11** to the desired bicyclo[3.3.1]nonanone **22** was achieved in 53% yield. Notably, this core bears the two bridgehead quaternary centers present in garsubellin A (**1**) and related natural bicyclic phloroglucin products.

The compatibility of this transformation with various functional groups was also examined. The reaction tolerated *N*-phenyl and *N*-benzylimide moieties present on the ketals **14** and **15** as well as the DPS group. The desired ketones **23**, **25**, and **26** were obtained in 86%, 62%, and 77% yield, respectively (entries 5, 7, and 8). The efficient conversion of **16** into ketone **27** in 80% yield revealed that the benzylidene group also can be utilized in the tandem process. The transformation of ketals **13, 17**, and **18**, however, gave the unprotected polycyclic ketones **24, 28**, and **29** (entries 6, 10, and 11) demonstrating that 1,3-dioxolane and TBS protecting groups are labile under these reaction conditions.

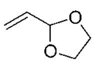
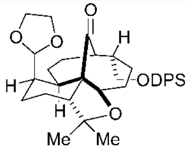
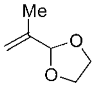
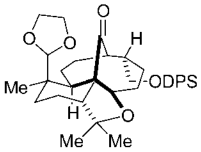
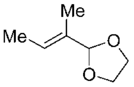
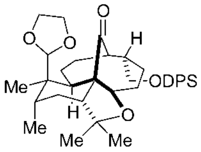
To further probe the scope of this transformation and increase the molecular complexity realized in a single step, we envisioned combining the Prins/pinacol with a Diels−Alder reaction.[7] We proposed that diene **30** and a Gassman type dienophile such as 2-vinyl-1,3-dioxolane **31** in the presence of a Lewis acid would generate the *endo* cycloadduct **32** in situ, which would undergo a Prins/pinacol sequence to afford ketone **33** in one step (Scheme 2).

Scheme 2



To demonstrate the feasibility of this tandem process, diene **30** and 2-vinyl-1,3-dioxolane **31a** were subjected to $SnCl_4$ in dichloromethane at −78 °C. As expected, ketone **33a** was isolated in 48% yield, in which the acetal moiety was not hydrolyzed during the process (Table 2, entry 1). We found that the addition of 25 mol % of TMSOTf dramatically increased the chemical yield to 96%. Other dienophiles such as **31b**,**c** were also subjected to the optimized reaction conditions; however, it was noticed that the degree of substitution of the dienophile has a direct effect on the reaction yields. One might suggest that the steric hindrance of the R1 and R2 groups is detrimental to the Diels−Alder/Prins/pinacol process.

Table 2. Tandem Diels−Alder/Prins/Pinacol

entry	dienophile	product	yield (%)
1	 **31a**	 **33a**	96[a] (48)[b]
2	 **31b**	 **33b**	62[b]
3	 **31c**	 **33c**	44[c]

[a] The reaction was performed with 1.0 equiv of $SnCl_4$ and 0.25 equiv of TMSOTf in CH_2Cl_2 at −78 °C. [b] Only $SnCl_4$. [c] 3.0 equiv of $SnCl_4$ and 0.25 equiv of TMSOTf.

In summary, we have developed a novel method for the construction of highly functionalized bicyclo[*m.n*.1]alkanones using tandem cationic cyclizations. We demonstrated the generality of the method by producing various ring sizes and realizing highly functionalized bicyclic frameworks. Further studies to extend the scope of this method and its application to the synthesis of garsubellin A (**1**) are underway and will be reported in due course.

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Supporting Information Available: High-field ^1H and ^{13}C NMR spectra and experimental procedures for compounds **19−29** and **33a−c**; ORTEP view of **19**, **24** (as a benzoate derivative), and **28** (CIF files). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) (a) Gassman, P. G.; Chavan, S. P. *J. Org. Chem.* **1988**, *53*, 2392. (b) Danishefsky, S. J.; Sepp-Lorenzino, L.; Magnuson, S. R.; Rosen, N. *J. Am. Chem. Soc.* **1998**, *120*, 1615.