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Rapid Access to Polyprenylated Phloroglucinols via Alkylative Dearomatization−Annulation: Total Synthesis of (±)-Clusianone[1]

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A number of polyprenylated phloroglucinol natural products bearing densely functionalized bicyclo[3.3.1]nonane-1,3,5-trione core structures have been reported from plant sources (Figure 1).[2] These include clusianone **1** and its C7 epimer **2**,[3] isolated from the floral resins of *Clusia* species, nemorosone **3**,[4] a regioisomer of **1**, and the adamantane-containing polyprenylated phloroglucinol hyperibone K **4**.[5] In light of the challenging structures and promising biological activities of these compounds, a number of synthetic efforts have been reported.[6] Recently, impressive syntheses of (±)-garsubellin **A**[7] and (+)-clusianone **1**[8] have been accomplished, further underscoring interest in this target class. In this Communication, we report our initial studies on the synthesis of polyprenylated phloroglucinols employing a tandem alkylative dearomatization−annulation process to rapidly construct the bicyclo[3.3.1]nonane-1,3,5-trione core.

Our approach to clusianone (Figure 1, **1**) and related polyprenylated phloroglucinols was inspired by biosynthetic considerations[4] as well as the facile alkylative dearomatization observed for clusiaphenone B **5**[9] (Scheme 1). Prenylation of **5** (prenyl bromide, aq KOH) afforded **6** (40% yield),[10] presumably through the intermediacy of grandone **7**.[11] This transformation underscored the propensity for sequential bisalkylation of the phloroglucinol core and suggested a concise approach to clusianone and related targets involving alkylative dearomatization−annulation. Recent reports[12] have described sequential Michael-elimination reactions of enolates with acrylates to prepare bicyclo[3.3.1]nonane core structures. On the basis of the alkylation sequence **5** → **7** → **6**, we considered whether an anionic species **8** derived from clusiaphenone B **5** may participate in conjugate addition with a Michael acceptor such as **9** to afford dearomatized product **10**. Intramolecular conjugate addition completes the synthesis of **11** which possesses the clusianone framework.

The synthesis of the polyisoprenylated benzophenone clusiaphenone B **5** commenced with *C*-prenylation[13] of acylphloroglucinol **12** (Scheme 2).[14] After considerable experimentation, we found that treatment of **5** with LiHMDS (3 equiv) followed by the addition of α-acetoxymethyl acrylate **13**[12a] (2 equiv) at 0 °C led to an efficient, highly diastereoselective dearomatization−annulation process in which an additional Michael-elimination event had unexpectedly occurred to afford **14** (70% yield). The backbone structure of **14** was suggested by computational-assisted structure elucidation based on ^{1}H, ^{13}C, ^{1}H-^{1}H COSY, HMQC, and HMBC data.[10] The relative stereochemistry of **14** was determined by acylation and X-ray crystal structure analysis of the derived *p*-bromobenzoate ester **15**. The stereochemistry of the final Michael-elimination event is likely dictated by the approach of **13** from the convex face of the enolate intermediate **16** which has been observed for transformations in related compounds.[7b]

To evaluate the scope of the dearomatization−annulation process, we examined the reaction of substituted phloroglucinols with a variety of substituted α-acetoxyacrylates (Table 1). Phloroglucinol **17** bearing an alkyl−aryl ketone reacted with **13** in a similar manner to **5** (LiHMDS, THF, 0 °C) to afford the bicyclo[3.3.1]nonane derivative **18** (entry 1). Reaction of acrylonitrile **19**[15] with **5** under similar conditions afforded a mixture of products. Reduction of

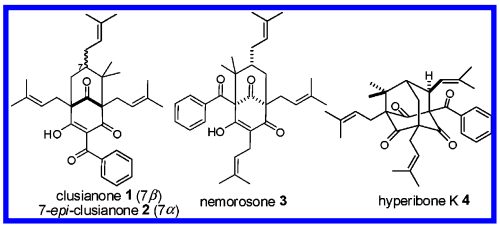
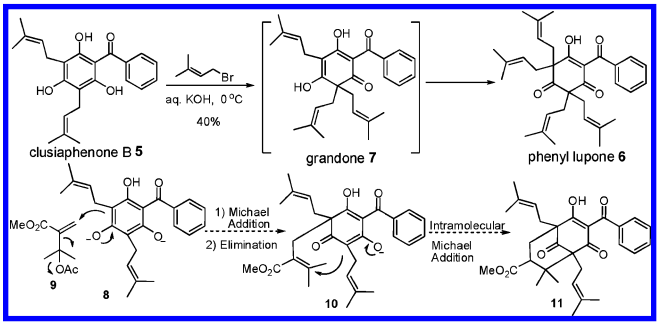
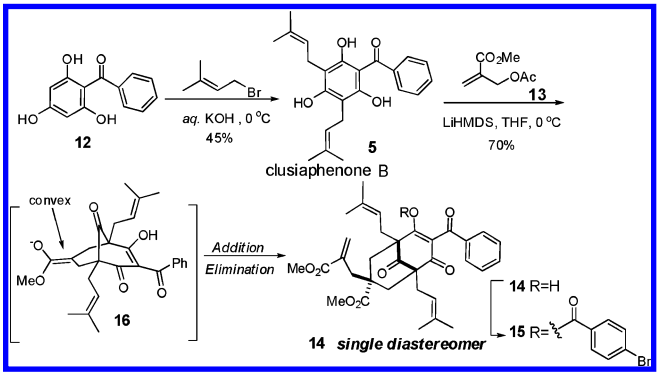


Figure 1. Polyisoprenylated phloroglucinol natural products.

Scheme 1. Synthetic Plan for Clusianone



Scheme 2. Model Studies



both equivalents of the Michael acceptor and base led to the production of **20** (41% yield) after enol methylation (entry 2). This result supports the lower reactivity of acrylonitriles as Michael acceptors in comparison to acrylate **13**. Using the more sterically hindered α-acetoxymethyl acceptor **9**[10] (entry 3), annulation and enol methylation were found to proceed cleanly to afford the clusianone-type compound **21** and its epimer **22** (dr = 4:1). The stereochemical assignment of **21** and **22** were based on NOE experiments and comparison to coupling constants reported for **1** and **2**.[16] Reactions of the electron deficient Michael acceptors trifluoroethyl ester **23**[10] (entry 4) and sulfone **25**[10] (entry 5) afforded products **24** and **26** leading us to suspect epimerization of the C7 stereocenter during the tandem process (vide infra).

To access clusianone, we considered use of α-acetoxy enal **27**[10] in the annulation process to install an aldehyde handle for prenyl installation (Scheme 3). Accordingly, treatment of **5** with KHMDS

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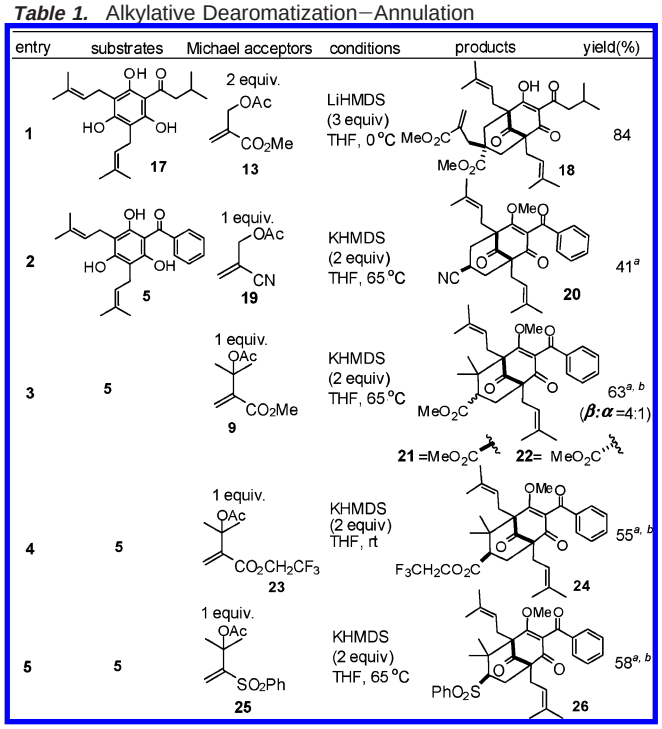
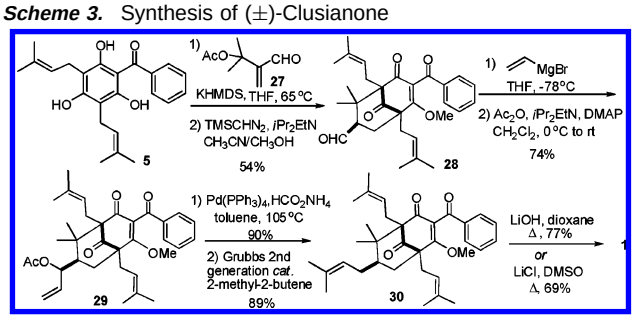
Table 1. Alkylative Dearomatization−Annulation



[a] Yield after enol methylation using $TMSCHN_2$ (2 equiv) and iPr_2EtN (1.5 equiv). [b] Mixture of enol ether isomers produced, one shown for clarity.

Scheme 3. Synthesis of (±)-Clusianone



(2.1 equiv) and **27** (1.1 equiv) in THF (65 °C) led to the generation of desired annulation product. To facilitate isolation and further characterization, enol methylation afforded **28** as a mixture of regioisomers (54% yield, two steps, one methyl ether isomer shown for clarity). The addition of vinyl magnesium bromide to aldehyde **28**, followed by acetylation of the emerged secondary alcohol, afforded allylic acetate **29**. Palladium-catalyzed formate reduction[17] of allylic acetate **29** was followed by olefin cross-metathesis with 2-methyl-2-butene according to the Grubbs's protocol[18] to afford clusianone methyl ether **30** (80%, two steps). Final nucleophilic demethylation[8a,c] generated (±)-clusianone as a mixture of enol tautomers.[16b]

As previously described, we have found that the dearomatization−annulation process favors production of clusianone-type stereoisomers. We thus initiated experiments to probe details of the suspected epimerization of the aldehyde-bearing stereocenter leading to **28** (Scheme 3). Interestingly, treatment of **5** with enal **27** in the presence of KHMDS at 0 °C unexpectedly led to the production of the complex adamantane **31** (Scheme 4). The structure of **31** is closely related to the natural product hyperibone K (Figure 1, **4**). This compound is apparently produced from the kinetic protonation product **32** followed by a stereoselective intramolecular aldol reaction. Further treatment of **31** with KHMDS at 65 °C led to the formation of **33** via a retro-aldol epimerization process. These initial studies support base-catalyzed epimerization leading to clusianone precursor **28** (Scheme 3) and related compound (cf.

Scheme 4. Access to an Adamantane Framework

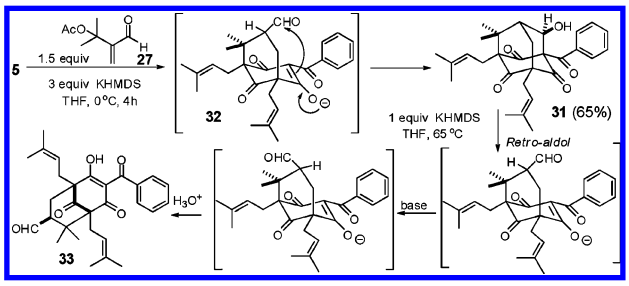


Table 1) and establish a possible route to adamantane-containing polyprenylated phloroglucinols including hyperibone K (**4**, Figure 1).

In summary, we have developed a concise approach to the bicyclo[3.3.1]nonane framework of the polyprenylated phloroglucinol natural products utilizing alkylative dearomatization−annulation. A related approach has been used to access an adamantane structure with four all carbon quaternary centers formed in one step from a phloroglucinol precursor. Further applications of the methodology to the synthesis of additional polyprenylated phloroglucinol natural products are currently in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds; X-ray crystal structure coordinates and files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Presented in part at the 233rd American Chemical Society National meeting, Chicago, Illinois, March 25−29, 2007; ORGN abstract 383.
(2) Ciochina, C.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963.
(3) Mccandlish, L. E.; Hanson, J. C.; Stout, G. H. *Acta Cryst.* **1976**, *B32*, 1793.
(4) Cuesta-Rubio, O.; Velez-Castro, H.; Frontana-Uribe, B. A.; Cardenas, J. *Phytochemistry* **2001**, *57*, 279.
(5) Tanaka, N.; Takaishi, Y.; Shikishima, Y.; Nakanishi, Y.; Bastow, K.; Lee, K. H.; Honda, G.; Ito, M.; Takeda, Y.; Kodzhimatov, O. K.; Ashurmetov, O. *J. Nat. Prod.* **2004**, *67*, 1870.
(6) Select examples: (a) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943. (b) Ciochina, R.; Grossman, R. B. *Org. Lett.* **2003**, *5*, 4619. (c) Nicolaou, K. C.; Carenzi, G. E. A.; Jeso, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 3895. (d) Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2006**, *47*, 689.
(7) (a) Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200. (b) Siegel, D. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1048.
(8) (a) Rodeschini, V.; Simpkins, N. S.; Wilson, C. *J. Org. Chem.* **2007**, *72*, 4265. (b) Nuhant, P.; David, M.; Pouplin, T.; Delpech, B.; Marazano, C. *Org. Lett.* **2007**, *9*, 287. (c) Ahmad, N. M.; Rodeschini, V.; Simpkins, N. S.; Ward, S. E.; Blake, A. J. *J. Org. Chem.* **2007**, *72*, 4803.
(9) Delle Monache, F.; Monache, G. D.; Gacs-Baitz, E. *Phytochemistry* **1991**, *30*, 2003.
(10) See Supporting Information for complete experimental details.
(11) Drewett, K. G.; Laws, D. R. J. *J. Inst. Brew.* **1970**, *76*, 188.
(12) (a) Takagi, R.; Nerio, T.; Miwa, Y.; Matsumura, S.; Ohkata, K. *Tetrahedron Lett.* **2004**, *45*, 7401. (b) Takagi, R.; Miwa, Y.; Matsumura, S.; Ohkata, K. *J. Org. Chem.* **2005**, *70*, 8587. (c) Takagi, R.; Miwa, Y.; Nerio, T.; Inoue, Y.; Matsumura, S. *Org. Biomol. Chem.* **2007**, *5*, 286.
(13) Sun, Y.; Li, Y.; Zhao, L.; Xiao, L. *Hecheng Huaxue* **1995**, *3*, 127.
(14) Mondal, M.; Puranik, V. G.; Argade, N. P. *J. Org. Chem.* **2007**, *72*, 2068.
(15) Ma, S.; Yu, S.; Peng, Z.; Guo, H. *J. Org. Chem.* **2006**, *71*, 9865.
(16) (a) dos Santos, M. H.; Nage, T. J.; Braz-Filho, R.; Lula, I. S.; Speziali, N. L. *Magn. Reson. Chem.* **2001**, *39*, 155. (b) Piccinelli, A. L.; Cuesta-Rubio, O.; Chica, M. B.; Mahmood, N.; Pagano, B.; Avone, M.; Barone, V.; Rastrell, L. *Tetrahedron* **2005**, *61*, 8206.
(17) Hughes, G.; Lautens, M.; Wen, C. *Org. Lett.* **2000**, *2*, 107.
(18) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939.

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