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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 their challenging structures and promising biological activities, 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 *bis*-alkylation 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. Based on 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 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]

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In order 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 both the equivalents of 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** (d.r. = 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*).

In order to access clusianone, we considered use of α-acetoxy enal **27**[10] in the annulation process in order to install an aldehyde handle for prenyl installation (Scheme 3). Accordingly, treatment of **5** with KHMDS (2.1 equiv) and **27** (1.1 equiv.) in THF (65°C) led to the generation of desired annulation product. In order to facilitate isolation and further characterization, enol methylation afforded **28** (one methyl ether isomer shown for clarity) as a mixture of regioisomers (54% yield, two steps). 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*. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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References

1. Presented in part at the 233rd American Chemical Society National meeting; March 25–29, 2007; Chicago, Illinois. ORGN abstract 383
2. Ciochina C, Grossman RB. Chem. Rev 2006;106:3963. [PubMed: 16967926]
3. Mccandlish LE, Hanson JC, Stout GH. Acta Cryst 1976;B32:1793.
4. Cuesta-Rubio O, Velez-Castro H, Frontana-Uribe BA, Cardenas J. Phytochemistry 2001;57:279. [PubMed: 11382245]
5. Tanaka N, Takaishi Y, Shikishima Y, Nakanishi Y, Bastow K, Lee KH, Honda G, Ito M, Takeda Y, Kodzhimatov OK, Ashurmetov O. J. Nat. Prod 2004;67:1870. [PubMed: 15568778]
6. Select examples: (a) Spessard SJ, Stoltz BM. Org. Lett 2002;4:1943. [PubMed: 12027653] (b) Ciochina R, Grossman RB. Org. Lett 2003;5:4619. [PubMed: 14627398] (c) Nicolaou KC, Carenzi GEA, Jeso V. Angew. Chem. Int. Ed 2005;44:3895. (d) Mehta G, Bera MK. Tetrahedron Lett 2006;47:689.
7. (a) Kuramochi A, Usuda H, Yamatsugu K, Kanai M, Shibasaki M. J. Am. Chem. Soc 2005;127:14200. [PubMed: 16218611] (b) Siegel DR, Danishefsky SJ. J. Am. Chem. Soc 2006;128:1048. [PubMed: 16433500]
8. (a) Rodeschini V, Simpkins NS, Wilson C. J. Org. Chem 2007;72:4265. [PubMed: 17465570] (b) Nuhant P, David M, Pouplin T, Delpech B, Marazano C. Org. Lett 2007;9:287. [PubMed: 17217286] (c) Ahmad NM, Rodeschini V, Simpkins NS, Ward SE, Blake AJ. J. Org. Chem 2007;72:4803. [PubMed: 17530804]
9. Delle Monache F, Monache GD, Gacs-Baitz E. Phytochemistry 1991;30:2003.
10. See Supporting Information for complete experimental details.
11. Drewett KG, Laws DRJ. 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. [PubMed: 16209615] (c) Takagi R, Miwa Y, Nerio T, Inoue Y, Matsumura S. Org. Biomol. Chem 2007;5:286. [PubMed: 17205172]
13. Sun Y, Li Y, Zhao L, Xiao L. Hecheng Huaxue 1995;3:127.
14. Mondal M, Puranik VG, Argade NP. J. Org. Chem 2007;72:2068. [PubMed: 17298098]
15. Ma S, Yu S, Peng Z, Guo H. J. Org. Chem 2006;71:9865. [PubMed: 17168610]
16. (a) dos Santos MH, Nage TJ, Braz-Filho R, Lula IS, Speziali NL. Magn. Reson. Chem 2001;39:155. (b) Piccinelli AL, Cuesta-Rubio O, Chica MB, 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. [PubMed: 10814258]
18. Chatterjee AK, Sanders DP, Grubbs RH. Org. Lett 2002;4:1939. [PubMed: 12027652]

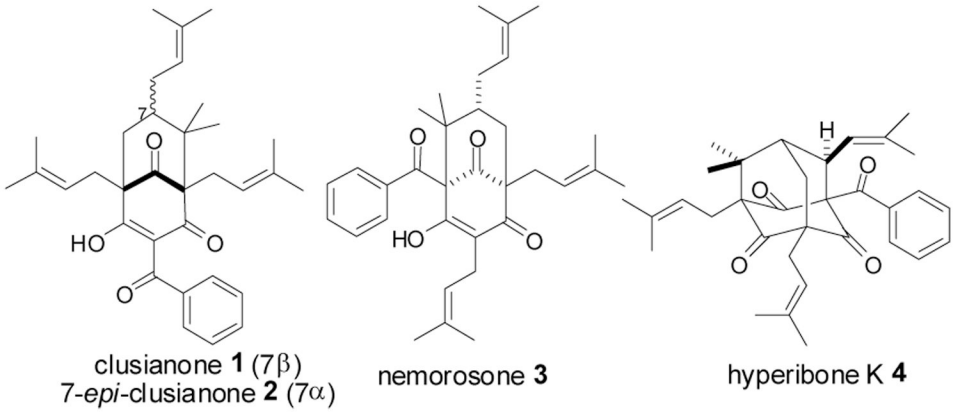
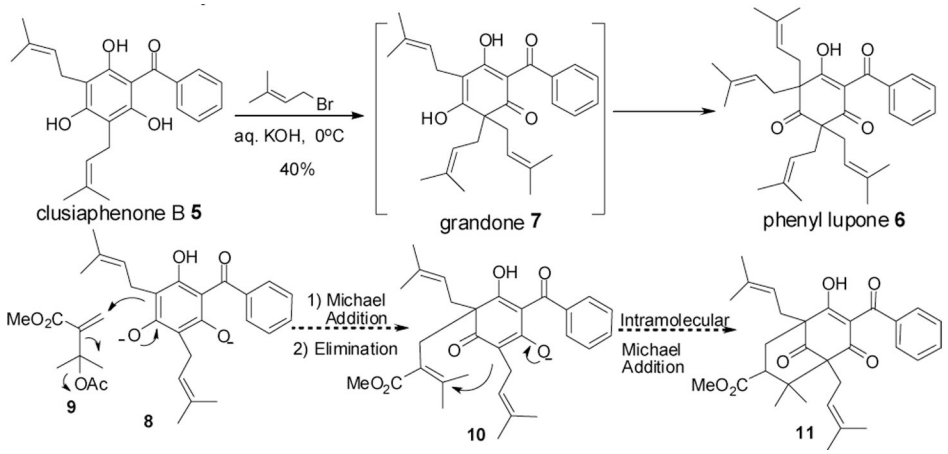
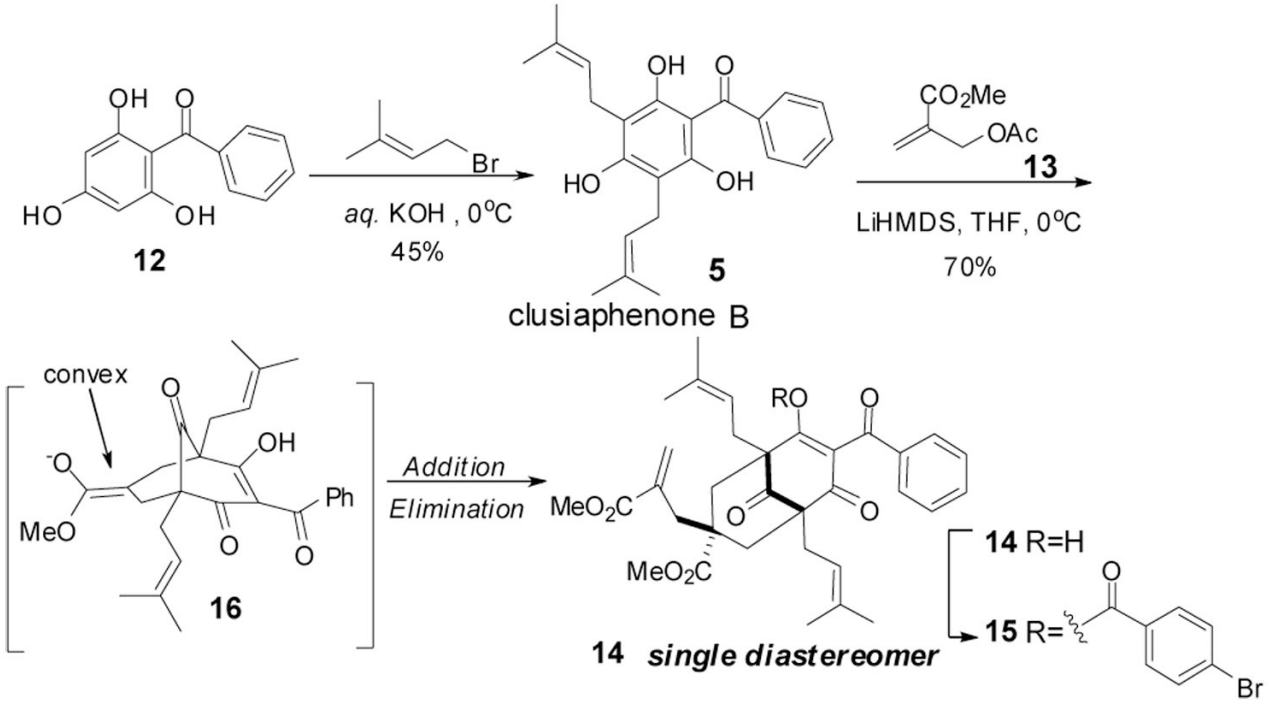


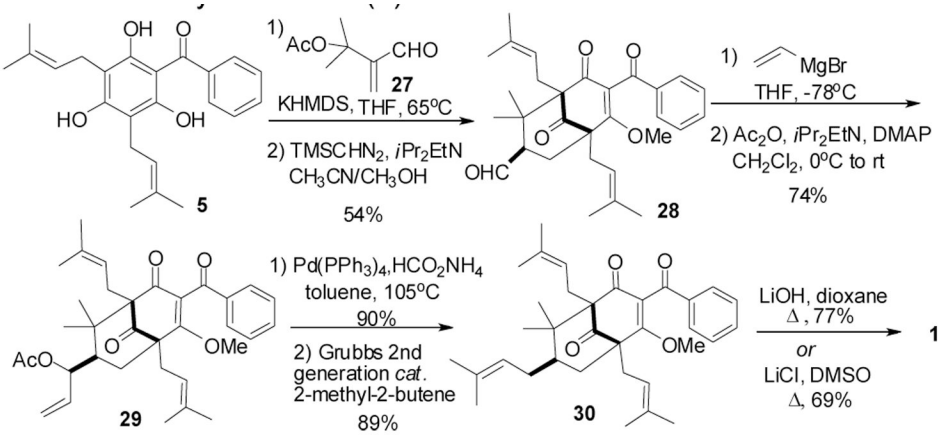
Figure 1.
Polyisoprenylated Phloroglucinol Natural Products



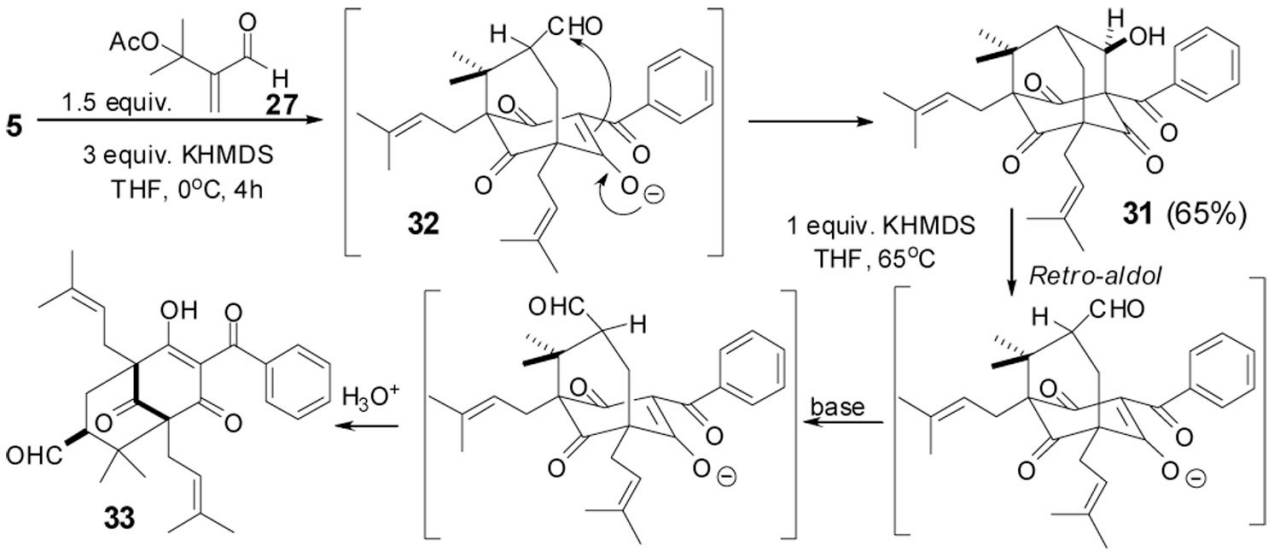
Scheme 1.
Synthetic Plan for Clusianone



Scheme 2.
Model Studies



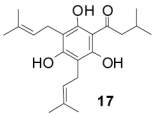
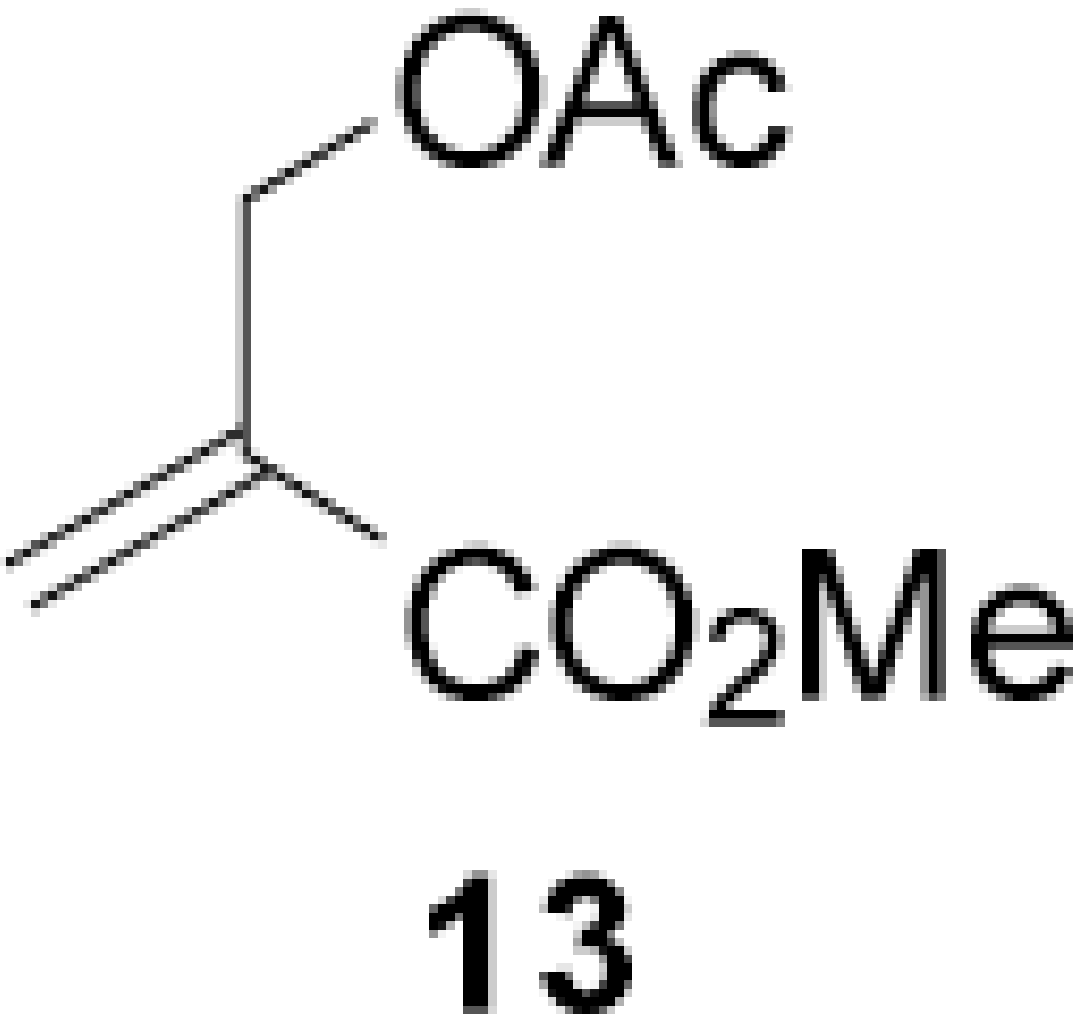
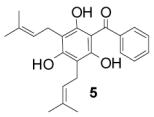
Scheme 3.
Synthesis of (±)-clusianone



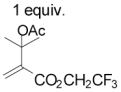
Scheme 4.
Access to an Adamantane Framework

Table 1

Alkylative Dearomatization-Annulation

entry	substrates	Michael acceptors
1	 17	2 equiv.  13
2	 5	1 equiv.  19

entry	substrates	Michael acceptors
3	**5**	 **9**

entry	substrates	Michael acceptors
4	**5**	1 equiv.  **23**
5	**5**	1 equiv.  **25**

[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.