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A Short Biomimetic Approach to the Fully Functionalized Bicyclic Framework of Type A Acylphloroglucinols

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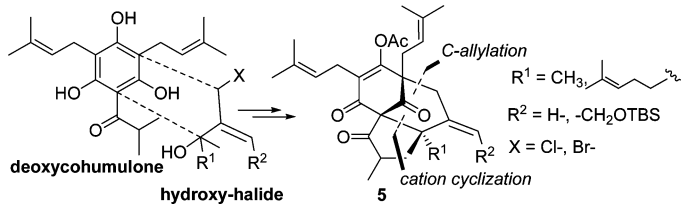
ABSTRACT



A biomimetic approach toward type A polyprenylated acylphloroglucinols (PPAPs) is described. The method is based on a *C-alkylation−cation cyclization* reaction sequence, leading to a convenient buildup of molecular complexity, employing the simple and readily available deoxycohumulone and an appropriately functionalized hydroxy halide. Thus, a versatile construction of the fully functionalized bicyclic framework of type A PPAPs (5) was achieved.

Polycyclic polyprenylated acylphloroglucinols (PPAPs), such as hyperforin (**1**), nemorosone (**2**), garsubelin A (**3**), clusianone (**4**), etc. (Scheme 1), have been attracting significant attention of many research groups for over 20 years. Due to their intriguing biological activities combined with their unique molecular architecture, these molecules and their analogues constitute extremely challenging synthetic targets as well as very promising substrates for biological evaluation.[1] Grossman first classified all known PPAPs into three main types (A−C) based on proposed biosynthetic pathways.[2]

Although many approaches for the synthesis of the 1-acylbicyclo[3.3.1]nonane-2,4,9-trione structure of type A PPAPs have been reported, only few led successfully to a total synthesis (garsubelin A and nemorosone).[3,4] Moreover, in most methods, installation of all oxygen functionalities or side chains results in a significant increase of the required synthetic steps.[5,6] It is evident that the most challenging features in the synthesis of PPAPs is the construction of an extremely congested carbon framework containing three quaternary carbon centers, two of which are on a bridgehead position of the bicyclic system (C-1 and C-5), while the third (C-8) is neighboring C-1.

Herein, we wish to demonstrate a general method leading efficiently and in few steps to the fully functionalized acyl bicyclo[3.3.1]nonane-2,4,9-trione core of type A PPAPs. Inspired by the biosynthetic pathways proposed for type A PPAPs,[1] we aimed at the construction of key intermediate **5** (Scheme 2), employing an annulation reaction, which would involve an intermolecular cation cyclization of colupulone analogue **6**, the latter being formed by C-allylation of deoxycohumulone **7** with hydroxyallyl halide **8**.

For the preparation of colupulone analogues **6**, deoxycohumulone **7** was prepared by prenylation of acylphloroglucinol **9** (Scheme 3) with dimethylallyl bromide **10**.[7] At a first attempt, C-allylation of **7** with bromide **8a** was

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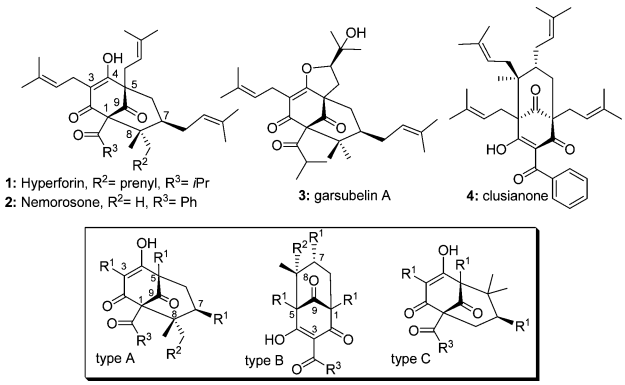
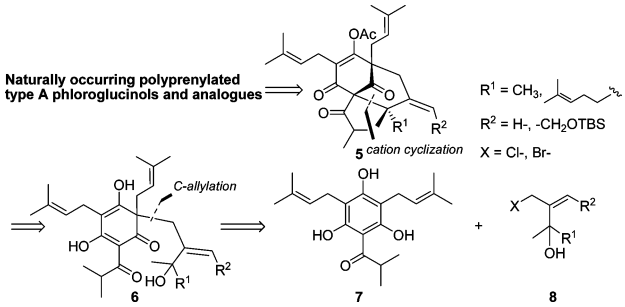
Scheme 1. Natural PPAPs

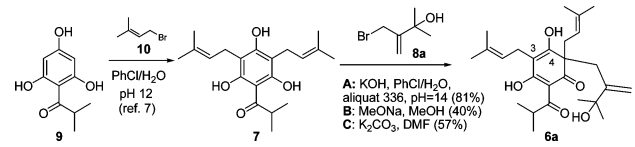


Scheme 2. Retrosynthetic Analysis



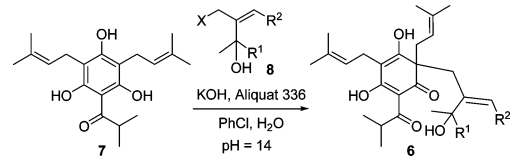
examined. Although **6a** was easily derived under alkaline conditions in protic or aprotic solvents (methods B and C), a significantly improved yield was achieved when a two-phase solvent system at pH 14 was applied (method A).

Scheme 3. C-Allylation of Deoxycohumulone **7**



Accordingly, colupulone analogues **6b**−**d** (Table 1) were similarly prepared utilizing method A. It was observed that when chlorides were used, improved yields of C-allylated products **6** were obtained, probably due to their higher stability.

Table 1. Allylation Studies: Preparation of Colupulone Analogues **6b**−**d**



entry	R-X	X	R^1	R^2	product	% yield
1	**8a**	Br	CH_3	H-	**6a**	81
2	**8b**	Br	CH_3	-CH_2OTBS	**6b**	79
3	**8c**	Cl	CH_3	-CH_2OTBS	**6b**	97
4	**8d**	Br		H-	**6c**[a]	62
5	**8e**	Cl		-CH_2OTBS	**6d**[a]	99
6	**8f**	Br		-CH_2OTBS	**6d**[a]	44

[a] Product was formed as ∼1:1 mixture of diastereoisomers (^{1}H NMR).

Proceeding to the annulation step, C-4 enol of **6a** was selectively acetylated prior to cyclization (Scheme 4).[8]

Direct generation of an intermediate cation on **11** by the use of acids, such as PPTS, CSA, or TsOH, in various solvents (CH_2Cl_2, toluene, NMP, THF) or $Pd(PPh_3)_4$ in THF proved completely unsuccesful leading to no reaction or degradation products. The same results were obtained when indirect methods involving transformation of the tertiary

(1) For a recent review refering to biological activity, biosynthesis, and synthetic efforts towards PPAPs, see: (a) Ciochina, R.; Grossman, R., B. *Chem. Rev.* **2006**, *106*, 3963. For more recent studies towards the synthesis of phloroglucinols, see: (b) Abe, M.; Nakada, M. *Tetrahedron Lett.* **2007**, *48*, 4873. (c) Kraus, A. G.; Jeon, I. *Tetrahedron Lett.* **2008**, *49*, 286. (d) Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2009**, *50*, 3519. For the synthesis of Hyperforin analogues and their biological evaluation, see: (e) Verotta, L.; Appendino, G.; Jakupovic, J.; Bombardelli, E. *J. Nat. Prod.* **2000**, *63*, 412. (f) Verotta, L.; Appendino, G.; Belloro, E.; Bianchi, F.; Sterner, O.; Lovati, M.; Bombardelli, E. *J. Nat. Prod.* **2002**, *65*, 433. (g) Verotta, L.; Appendino, G.; Bombardelli, E.; Brun, R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1544. For the synthesis of designed derivatives and their biological properties, see: (h) Gurtner, M.; Simon, J. C.; Giannis, A.; Sleeman, J. P. *ChemBioChem* **2005**, *6*, 171. (i) Grey, C.; Kyrylenco, S.; Hennig, L.; Nguyen, L.-H. D.; Büttner, A.; Pham, H. D.; Giannis, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5219. (j) Rothley, M.; Schmid, A.; Thiele, W.; Schacht, V.; Plaumann, D.; Gartner, M.; Yektaoglu, A.; Bruyère, F.; Noël, A.; Giannis, A.; Sleeman, J. P. *Int. J. Cancer* **2009**, *125*, 34. For recent reviews on the biological activity of hyperforin, see: (k) Quiney, C.; Billard, C.; Salanoubat, C.; Fourneron, J. D.; Kolb, J. P. *Leukemia* **2006**, *20*, 1519. (l) Medina, M. A.; Martinez-Poveda, B.; Amores-Sanchez, M. I.; Quesada, A. R. *Life Sci.* **2006**, *79*, 105.

(2) For a first attempt on classification of polyprenylated benzoylphloroglucinols, see: Cuesta-Rubio, O.; Velez-Castro, H.; Frontana-Uribe, B. A.; Cadena, J. *Phytochemistry* **2001**, *57*, 279.

(3) For total syntheses of garsubelin A, see: (a) Kuramochi, A.; Usada, H.; Yamatsugu, K.; Motomu, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200. (b) Siegel, D. R.; Danishefsky, S., J. *J. Am. Chem. Soc.* **2006**, *128*, 1048. (c) Ahmad, N. M.; Rodeschini, V.; Simpkins, N. S.; Ward, S. E.; Blake, A. J. *J. Org. Chem.* **2007**, *72*, 4803. For a total synthesis of nemorosone and clusianone, see: (d) Tsukano, C.; Siegel, D. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 840.

(4) For synthesis of a type B PPAP, clusianone, see: (a) Rodeschini, V.; Ahmad, N. M.; Simpkins, N. S. *Org. Lett.* **2006**, *8*, 5283. (b) Nuhant, P.; David, M.; Pouplin, T.; Marazano, C. *Org. Lett.* **2007**, *9*, 287. (c) Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 12682. (d) See also ref 3d.

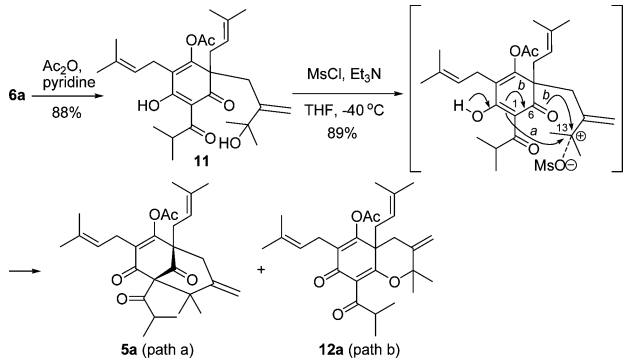
(5) To the best of our knowledge, methods establishing all quaternary centers and oxygen functionalities, during cyclization, have been developed for type B clusianone only. For two examples, see ref 4b,c.

(6) For an attempt to construct the bicyclic framework of type A PPAPs, in a direct way, under oxidative conditions which, nevertheless, led to polycyclic systems, indicating the difficulty of this approach, see: Mitasev, B.; Porco, J. A., Jr. *Org. Lett.* **2009**, *11*, 2285.

(7) US Patent 4,101,585, 1978.

(8) Cyclization attempts of unprotected colupulone **6a** resulted either in messy reactions or in O-cyclization of prenyl side chains due to participation of the C-4 enol.

Scheme 4. Annulation Studies Based on Cation Cyclization



hydroxyl group into a good leaving group (bromide, tosylate, or triflate) and subsequent cyclization were attempted. Gratifyingly, our efforts to convert the tertiary hydroxyl group of **11** into the corresponding methanesulfonic ester resulted in an unexpected rapid and direct transformation to the cyclized product **5a**. In addition to the desired C-cyclized product **5a** (path a), the formation of the O-cyclized product **12a** was also observed (ratio **5a/12a** 1.5:1, 89%), probably due to attack of enol hydroxyl on C-6 to the intermediate electrophilic carbon C-13 (path b). Moreover, since the same cyclization products were obtained when methanesulfonic anhydride was used, it is evident that the reaction pathway proceeds via the formation of a nondetectable methanesulfonic ester,[9] without the intermediacy of the corresponding chloride.

To confirm structure of **5a**, by single-crystal X-ray diffraction, compound **13** was prepared from **6a** using *p*-bromobenzoyl as a protective group (Scheme 5). Crystallization of the latter was unsuccesful; thus, it was reduced to the more crystallizable derivative **14**. The structure of **14** was unambiguously confirmed by X-ray analysis.[10] In the structure of **14** in Scheme 5 chiral carbons are highlighted in black.

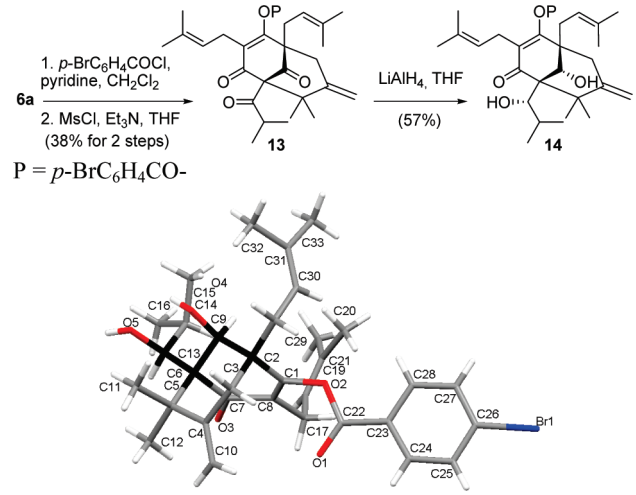
All other colupulone analogues **6b**−**d** were similarly acetylated, and their annulation was examined. The results are summarized in Table 2. As expected, cation cyclization of compounds **6b**−**d** (entries 2−5) proceeded under the same conditions leading to target intermediates **5b**−**d**.

We should note that the presence of a double bond, allylic to the tertiary alcohol, is necessary for the stabilization of the intermediate cation. Hence, any attempt to cyclize the "saturated" colupulone analogue **15** to **16** (Scheme 6),[11] either directly or indirectly (via the formation of an intermediate tosylate), resulted only in elimination or other degradation products.

In parallel to the development of the above strategy, Michael reaction was also examined as a possible annulation

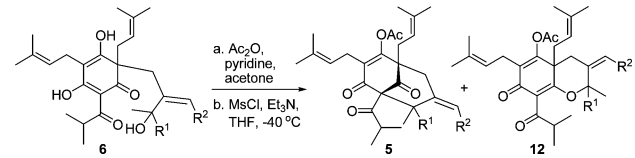
(9) Methanesulfonic ester could not be detected by TLC.
(10) See the Supporting Information for complete experimental details.
(11) In this case, for the preparation of **15**, alkylation of **7** with bromide **8g** was performed in MeONa/MeOH (method B), as method A resulted in no reaction.

Scheme 5



method toward type A PPAPs. Consequently, deoxycohumulone **7** was subjected to C-allylation with bromide **8h** or chloride **8i** to furnish colupulone analogues **17** and **18**, respectively (Scheme 7).

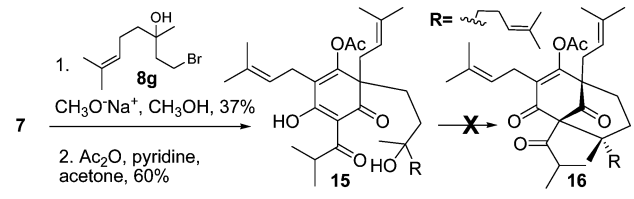
Table 2. Annulation Studies: Preparation of Key Intermediates **5**



entry	substrate	R^1	R^2	Products[a]	yield[b] %
1	**6a**	CH_3	H-	**5a:12a**	78
2	**6b**	CH_3	-CH_2OTBS	**5b:12b**	73
3	**6c**		H-	**5c:12c**[c]	79
4	**6d-A**		-CH_2OTBS	**5d-A:12d-A**	65
5	**6d-B**		-CH_2OTBS	**5d-B:12d-B**	73

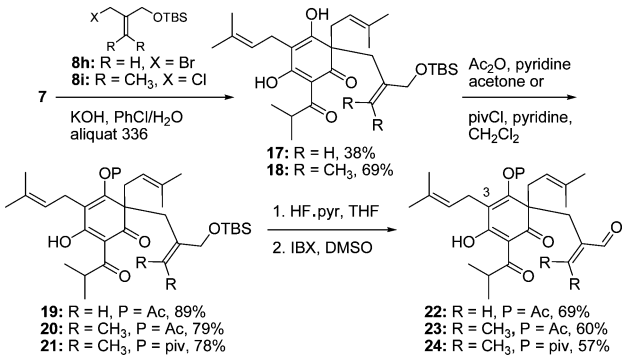
[a] C/O ratio was ~1.5:1. [b] Overall yields of cyclized products. [c] Products were isolated as 1:1 mixture of diastereoisomers (^{1}H NMR).

Scheme 6



After selective acetylation or pivaloylation, followed by desilylation and subsequent oxidation of **19**, **20**, and **21**, the corresponding Michael acceptors **22**, **23**, and **24** were prepared.

Scheme 7. Preparation of Michael Precursors

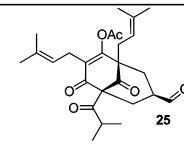
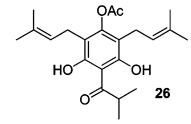
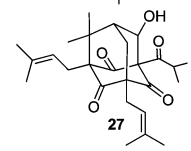
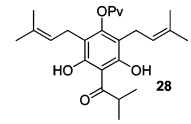


Several conditions were applied to induce an intermolecular Michael reaction (Table 3). It is worth noting that, during our experimentation, Qi and Porco published a successful application of a similar approach for the synthesis of type B, clusianone.[4c] Nevertheless, in our case, only disubstituted α,β-unsaturated aldehyde **22** cyclized to the desirable type A bicyclic framework **25** (entry 1). In contrast, the more substituted aldehyde **23** remained unreacted either under mild or strong alkaline conditions in low temperatures (entry 2). Further experimentation for cyclization of **23** or its more stable pivaloate analogue **24** under harsh conditions led either to adamantane derivative **27** (entry 4), in accordance with Qi and Porco's results,[12] or aromatization products **26** or **28**, due to removal of the allylic side chain (entries 3 and 5).

The above results confirm the difficulty in the construction of the fully functionalized bicyclic core met in type A PPAPs. Only colupulone analogues containing an allylic tertiary alcohol led to successful cyclization, and although minor variations, such as change of solvent, temperature, or salt addition, did not improve the C/O product ratio, this unprecenteded annulation step remains extremely advantageous for the course of this project. Employing this method, two quaternary centers were directly connected surpassing problems faced by other approaches. Thus, the highly stereochemically demanding systems of type A PPAPs, hyperforin and garsubelin A, established with all oxygen functionalities and quaternary carbon centers, were constructed in two key steps and an affordable overall yield. Moreover, the presence of an allylic hydroxyl group in key intermediates **5** provides suitable handle for further derivatization, as well as for the preparation of a large variety of acylphloroglucinol analogues useful for SAR studies. Current efforts are devoted to further optimizing the cyclization reaction, as well as expanding the scope of key intermediate **5**.

(12) Formation of **27** is due to deacetylation of **23**, in situ Michael addition on C-3 and subsequent aldol condensation, under the harsh conditons applied. See ref 4c.

Table 3. Michael Approach Results to Type a Bicyclic Framework

entry	substrate	conditions	product	% yield
1	**22**	$NaHCO_3$ $DMSO/H_2O$ 25 °C	 **25**	71
2	**23**	A[a]	-	-
3	**23**	$NaHCO_3$ $DMSO/H_2O$ 120 °C	 **26**	67
4	**23**	NaH, THF or KHMDS, toluene 0 – 60 °C	 **27**	54
5	**24**	B[b]	 **28**	52

[a] Conditions A: (a): $NaHCO_3$, $DMSO/H_2O$ or K_2CO_3, DMSO or Li_2CO_3, THF or Cs_2CO_3,THF or SiO_2/CH_2Cl_2, 25−60 °C; (b): NaH, THF or KHMDS, toluene, −78 to +15 °C. [b] Conditions B: piperidine, C_6H_6, 25 °C or $NaHCO_3$, $DMSO/H_2O$, 80 °C or KHMDS, toluene, 60 °C or LiHMDS, THF, 25 °C.

Acknowledgment. We thank Professor Dr. A. Giannis (University of Leipzig, Germany) for kindly providing high-resolution mass spectra and *pro*-ACTINA S.A. for low-resolution mass spectra.

Supporting Information Available: Experimental details and characterization data for selected compounds, as well as CIFs and single-crystal X-ray data for **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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