An Unusual Michael-Induced Skeletal Rearrangement of a Bicyclo[3.3.1]nonane Framework of Phloroglucinols to a Novel Bioactive Bicyclo[3.3.0]octane

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ABSTRACT
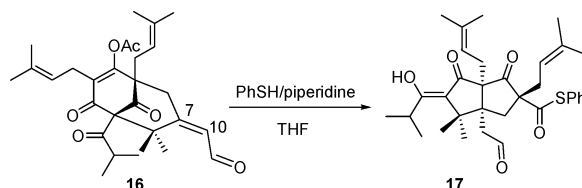
A novel skeletal rearrangement of bicyclo[3.3.1]nonane-2,4,9-trione (16) to an unprecedented highly functionalized bicyclo[3.3.0]octane system (17), induced by an intramolecular Michael addition, is presented. This novel framework was found to be similarly active to hyperforin (1), against PC-3 cell lines. A mechanistic study was examined in detail, proposing a number of cascade transformations. Also, reactivity of the $\Delta^{7,10}$-double bond was examined under several conditions to explain the above results.

Polycyclic polyprenylated acylphloroglucinols (PPAPs) contain a bicyclo[3.3.1]nonane framework, which is often found in nature, as a constituent of many biologically active metabolites.[1] The chemistry of this carbon skeleton has been intensively explored for the construction of complex natural products, as well as various ring systems.[2]

Particularly, the great biological properties of hyperforin (1), garsubelin A (2), and other PPAPs (Figure 1) have intrigued many researchers to focus on the total synthesis

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of these natural products,[3] as well as on the preparation of analogues for SAR studies.[4] Our approach to the bicyclo[3.3.1]nonane system of type A PPAPs is depicted in Scheme 1. The fully functionalized carbon skeleton of hyperforin (**1**) and garsubelin A (**2**) was constructed in three steps, employing the readily available deoxycohumulone **5**.[5]
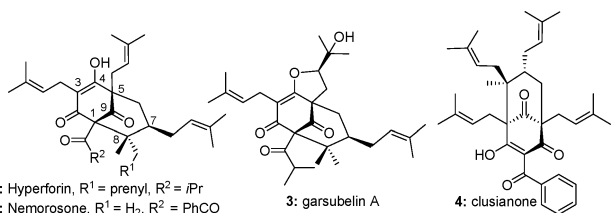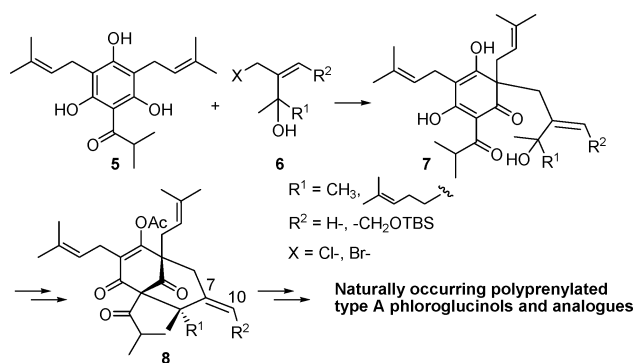

Figure 1. Natural PPAPs.

Scheme 1. Synthetic Approach to Type A PPAPs

Consequently, our research efforts focused on the removal of the remaining $\Delta^{7,10}$-double bond from the bicyclic system **8**, in a regioselective manner. However, the neopentyl position of this exocyclic double bond proved

to be an unsurpassed obstacle. Many attempts to remove the $\Delta^{7,10}$-double bond (Table 1) via either hydrogenation (entries 1−3) or regioselective isomerization of an allylic alcohol to the corresponding carbonyl compound (entries 4, 5)[6] proved unsuccesful. The difficulty in accessing C-7 was further revealed during the attempted 3,3-sigmatropic rearrangement of allylic thiocarbonate ester **13** (entry 6). The molecule refused to furnish a saturated C-7 through the expected 1,2-sigmatropic rearrangement[7] yielding instead ester **14** *via* an 1,3-sigmatropic rearrangement.

Table 1. Selected Examples of Attempts on $\Delta^{7,10}$-Double Bond Removal[a]

entry	substrate	conditions	product
1		a. H_2, Pd/C, MeOH, 60 °C b. H_2, PtO_2, $NaHCO_3$, THF 25 °C c. $RhP(Ph)_3Cl$, H_2, CH_2Cl_2, 40 °C d. Crabtree's catalyst (1 equiv), H_2 (3.5 atm) CH_2Cl_2, 25 °C	No reaction
2		Crabtree's catalyst (0.1 equiv), H_2 (1 atm), CH_2Cl_2, 25 °C	No reaction
3		Crabtree's catalyst (2 equiv), H_2 (1 atm), CH_2Cl_2, 25 °C	
4		TPAP, decanol, C_6H_5F, reflux	messy reaction
5		$Fe(CO)_5$, pentane, hv	decomposition
6		170 °C	

[a] Crabtree's catalyst = [Ir(COD)Py(PCy$_3$)]PF$_6$.

(3) For total synthesis of hyperforin, see: (a) Sparling, B. A.; Moebius, D. C.; Shair, M. D. *J. Am. Chem. Soc.* **2013**, *135*, 644. (b) Shimizu, Y.; Shi, S. L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1103. (c) Uwamori, M.; Nakada, M. *Tetrahedron Lett.* **2013**, *54*, 2022. For total syntheses of garsubelin A, see: (d) Kuramochi, A.; Usada, H.; Yamatsugu, K.; Motomu, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200. (e) Siegel, D. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1048. For a total synthesis of nemorosone and clusianone, see: (f) Tsukano, C.; Siegel, D. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 840. For synthesis of a type B PPAP, clusianone, see: (g) Rodeschini, V.; Ahmad, N. M.; Simpkins, N. S. *Org. Lett.* **2006**, *8*, 5283. (h) Nuhant, P.; David, M.; Pouplin, T.; Marazano, C. *Org. Lett.* **2007**, *9*, 287. (i) Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 2682. For total synthesis of plukenetione, see: (j) Zhang, Q.; Mitasev, B.; Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2010**, *132*, 14212.

(4) For analogues and SAR studies, see: (a) Verotta, L.; Appendino, G.; Belloro, E.; Jakupovic, J.; Bombardelli, E. *J. Nat. Prod.* **1999**, *62*, 770. (b) Verotta, L.; Appendino, G.; Jakupovic, J.; Bombardelli, E. *J. Nat. Prod.* **2000**, *63*, 412. (c) Shan, M. D.; Hu, L. H.; Chen, Z. L. *J. Nat. Prod.* **2001**, *64*, 127. (d) Verotta, L.; Appendino, G.; Belloro, E.; Bianchi, F.; Sterner, O.; Lovati, M.; Bombardelli, E. *J. Nat. Prod.* **2002**, *65*, 433. (e) Gartner, M.; Muller, T.; Simon, J. C.; Giannis, A.; Sleeman, J. P. *ChemBioChem* **2005**, *6*, 171.

(5) Couladouros, E. A.; Dakanali, M.; Demadis, K. D.; Vidali, V. P. *Org. Lett.* **2009**, *11*, 4430.

(6) (a) Marko, I. E.; Gautier, A.; Tsukazaki, M.; Llobet, A.; Plantalech-Mir, E.; Urch, C. J.; Brown, S. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1960. (b) Cherkaoui, H.; Soufiaoui, M.; Gree, R. *Tetrahedron* **2001**, *57*, 2379.

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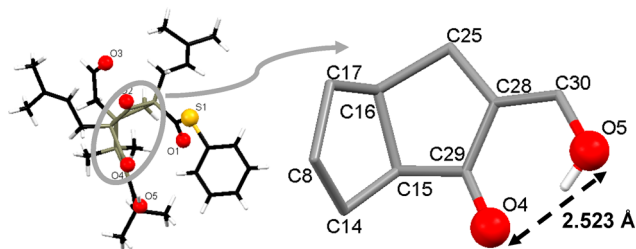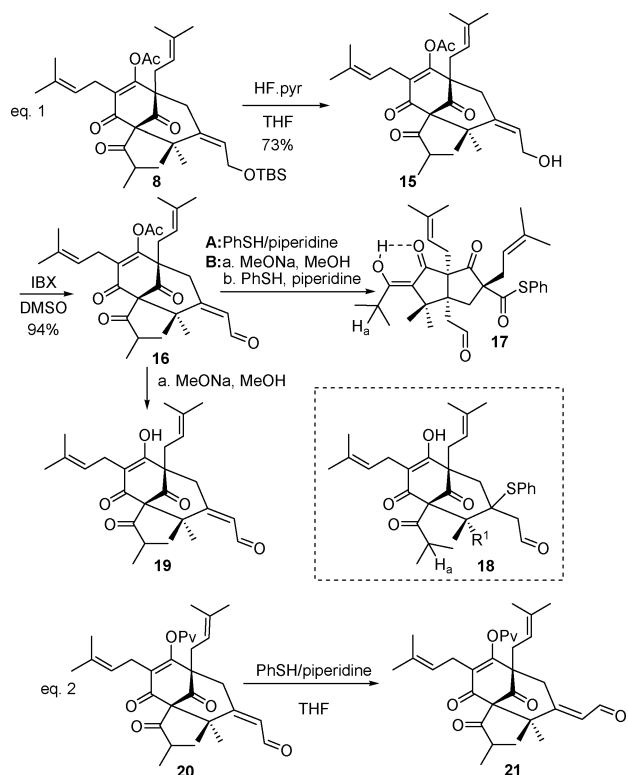**Scheme 2.** Michael Approach to PPAPs

Figure 2. Molecular structure of **17** (left) and detailed view of the bicyclic core with the intramolecular H-bond (right). O (red) and S (yellow) atoms are presented as exaggerated spheres.

In parallel, further differentiation of the $\Delta^{7,10}$-double bond of system **8** was attempted, by converting it to the more polarized α,β-unsaturated aldehyde **16**, after desilylation and oxidation of **15** (Scheme 2). All attempted conditions are summarized in Table 2. Typical Michael conditions (e.g., PhSH, Et₃N, THF) resulted in messy reaction mixtures (Table 2, entries 6−8).[8]

After several attempts, subjection of **16** to PhSH/piperidine (Scheme 2, eq 1, method A) furnished a single product, whose ^{1}H NMR spectrum supported the desired deacetylated structure **18**, except for a significant shift observed for Ha (δ 2.04→2.78). To our surprise, X-ray

(8) Other attempts for hydride addition on α,β-unsaturated alcohol **11** (e.g., [(PPh₃)CuH]₆ or NaBH₄/AcOH) also failed.

Table 2. Michael Addition Attempts on Aldehyde **16**

entry	base/Nu/solvent	t	product (% yield)
1	−/PhSH/THF	25 to 60 °C	no reaction
2	−/PhSH/CH₂Cl₂	25 to 40 °C	no reaction
3	−/PhSH/−	25 to 60 °C	no reaction
4	pyridine/PhSH/THF	25 to 60 °C	no reaction
5	PPTS/PhSH/THF	0 to 60 °C	no reaction
6	DMAP/PhSH/THF	25 °C	messy reaction[a]
7	Et₃N/PhSH/THF	0 to 25 °C	messy reaction[a]
8	Et₃N/PhSH/CH₂Cl₂	0 to 25 °C	messy reaction[a]
9	a. MeONa/MeOH	25 °C	no reaction
	b. DBU/PhSH/THF		
10	piperidine/PhSH/THF	25 °C	**17** (73%)
11	a. MeONa/MeOH	25 °C	
	b. piperidine/PhSH/THF		**17** (81%)
12	a. MeONa/MeOH	25 °C	
	b. Bu₂NH/PhSH/THF		**17** (70%)
13	a. MeONa/MeOH	25 °C	
	b. BuNH₂/PhSH/THF		**17** (79%)
14	MeONa/MeOH	25 °C	**19**

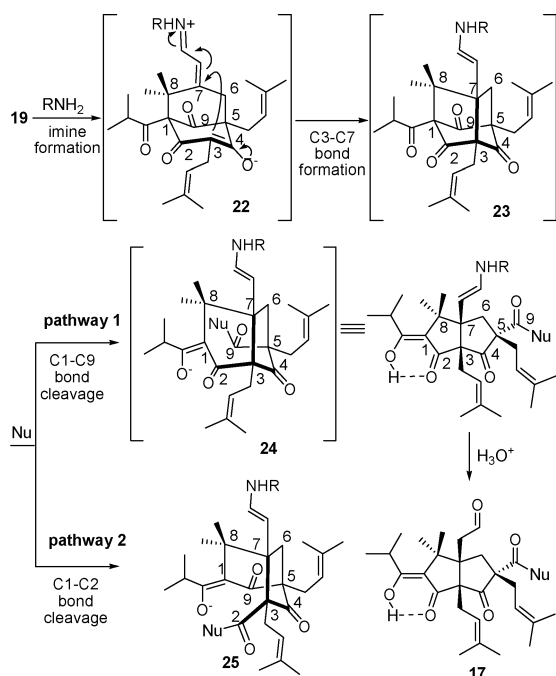[a] Deacetylation product **19** was initially formed.

analysis revealed the structure of the deacetylated 5,5-bicyclic framework **17** (Figure 2), which is locked in an intramolecular hydrogen bonded ring (O···O 2.523 Å), explaining Ha deshielding (see Supporting Information (SI) for complete experimental details).

Further experimentation on Michael coupling conditions was needed in order to clarify the mechanism of the new reaction. Application of the same conditions on the pivaloate derivative **20** (Scheme 2, eq 2) resulted only in $\Delta^{7,10}$-double bond isomerization product **21**, proving that protective group removal was necessary for the rearrangement to proceed. Additionally, deprotection of **16** using MeONa/MeOH resulted in the formation of unstable alcohol **19** which was subsequently converted to **17** using PhSH/piperidine.

Several other bases were also used (Table 2), clarifying that this skeletal rearrangement is not related to pH, but it proceeds only in the presence of a primary or a secondary amine (entries 10−13 vs entries 6−9).

The latter findings suggest the formation of a possible imine intermediate. Accordingly, we propose the following mechanism (Scheme 3). The exposed allylic aldehyde **19** should be the most accessible carbonyl against amines. Imine formation of the above moiety augments the electrophilicity at C-7, enabling thus an attack of the C-3 enolate anion, derived from the resonated unprotected C-4 hydroxyl group (**22**→**23**). Had this highly strained tricyclic system **23** been formed, it may release strain *via* eight possible retro-aldol reactions (two from C4-carbonyl, three from C2-carbonyl, and three from C9-carbonyl). Cleavage of C1−C9 or C1−C2 bonds (pathway 1 or 2) should be more favorable, since they both could lead to a delocalized enolate system. Noticeably, out of all the possible derivatives, **23** affords the 5,5-ring system **24** versus the 6,5-ring system **25**, in a high yield.

Scheme 3. Proposed Mechanism of Michael-Induced Skeleton Rearrangement

Table 3. Antiproliferative Efficacy (IC in μg/mL)

compound	IC_{20}	IC_{50}	IC_{80}
α-TOS[a]	17.25	43.13	69.01
1	7.54	18.85	30.17
17	9.62	24.05	38.48

[a] α-TOS = α-tocopherol succinate.

activation of the Akt1 pathway. Surprisingly, compound **17** showed similar antiproliferative efficacy with **1** (Table 3), while both were more potent than reference compound α-TOS[9] (SI).

In conclusion, the reactivity of the $\Delta^{7,10}$-double bond of bicyclic acyl phloroglucinol systems **8** and **16** were examined, under various conditions. Due to severe steric hindrance, the only successful tranformation was that to the bicyclic[3.3.0]octane system via an intramolecular rearrangement. The above findings open a new route to a novel class of bioactive acylphloroglucinol analogues. Current efforts focus on extending the utility of this novel transformation, as well as further dissecting the molecular mechanism of its bioactivity.

Supporting Information Available. Experimental details and characterization data for all new compounds, as well as crystallographic data (cif file, deposited in the CCDC as 912255) and bioactivity data for **17** and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

Preliminary screening of this novel framework was performed. Hyperforin (**1**) and its derivatives have been reported to show target specific antitumor activity through the Akt1-mediated antiproliferative and apoptotic pathway.[9] Thus, **1** and **17** were assessed for antiproliferative activity in the androgen-unresponsive, grade IV, PC-3 cell line. PC-3 cells are highly metastatic with constitutive expression of the EGFR oncogene and downstream

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