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Synthesis of (+/–)-Clusianone: High-Yielding Bridgehead and Diketone Substitutions by Regioselective Lithiation of Enol Ether Derivatives of Bicyclo[3.3.1]nonane-2,4,9-triones

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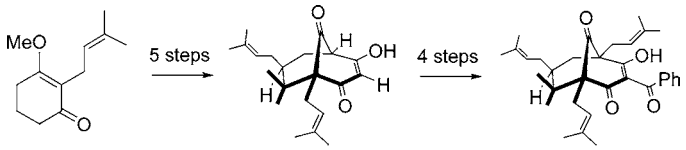
ABSTRACT



A concise synthesis of the polyprenylated acylphloroglucinol natural product, clusianone, in racemic form, is described. An Effenburger cyclization generated a core bicyclo[3.3.1]nonane-trione structure, which was then elaborated by means of regioselective lithiation reactions.

Plants and trees of the family Clusiaceae (Guttiferae) are a rich source of polyprenylated acylphloroglucinols (PPAPs), characterized by a bicyclo[3.3.1]nonane-trione core structure bearing additional acyl and prenyl substituents, e.g., garsubellin A (**1**), hyperforin (**2**), and clusianone (**3**) (Figure 1).[1]

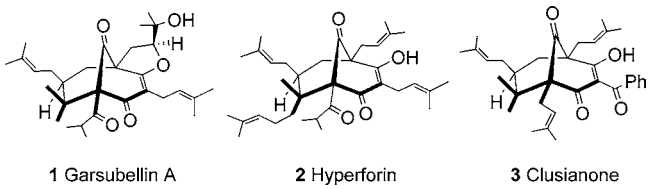


Figure 1. Representative PPAPs.

Garsubellin A (**1**) has attracted significant synthetic attention since its isolation from *Garcinia subelliptica* in 1997, due to its ability to induce choline acetyltransferase, a key enzyme involved in acetylcholine biosynthesis.[2] Hyperforin (**2**) is thought to be the major bioactive constituent from *Hypericum perforatum* (St. John's wort (SJW)), which has well-known antidepressant properties.[3] The use of SJW extracts for the treatment of mild to moderate depression is widespread in Europe but remains controversial in terms of efficacy, especially with regard to undesirable prescription drug interactions.[4] Clusianone (**3**) has been known since 1976, the structure originally being determined by X-ray crystallography,[5] although more recently there was some confusion of this compound with a C-7 epimer.[6] Recent

(1) (a) Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963−3986. (b) Verotta, L. *Phytochem. Rev.* **2002**, *1*, 389−407.

(2) Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull.* **1997**, *45*, 947−949.

(3) (a) Structure: Bystrov, N. S.; Chernov, B. K.; Dobrynin, V. N.; Kolosov, M. N. *Tetrahedron Lett.* **1975**, 2791−2794. (b) Biosynthesis: Adam, P.; Arigoni, D.; Bacher, A.; Eisenreich, W. *J. Med. Chem.* **2002**, *45*, 4786−4793.

(4) Madabushi, R.; Frank, B.; Drewelow, B.; Hartmut, D.; Butterweck, V. *Eur. J. Clin. Pharm.* **2006**, *62*, 225−233.

(5) McCandlish, L. E.; Hanson, J. C.; Stout, G. H. *Acta Cryst., Sect. B* **1976**, *32*, 1793−1801.

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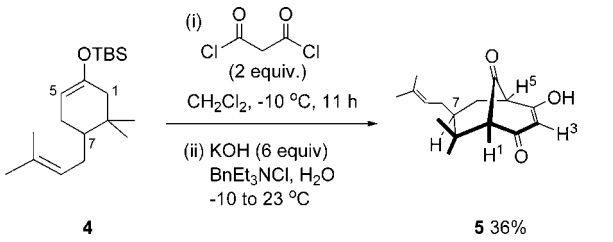
screening has ascribed potent anti-HIV and cancer chemopreventive properties to this compound and close natural relatives.[6a,7]

PPAPs have stimulated much synthetic activity; several groups have described progress toward specific members of the PPAP family,[8] but only very recently has **1** succumbed to total synthesis by the groups of Shibasaki[9] and Danishefsky.[10]

The idea of constructing either naturally occurring PPAPs or unnatural derivatives, by appending substituents to a common [3.3.1]-trione core system, is an attractive one in terms of accessing diverse structures for probing the SAR in these systems. In this context, we noted the very rapid access to an appropriate trione, described by Spessard and Stoltz in their elegant approach to garsubellin A (Scheme 1).[11]

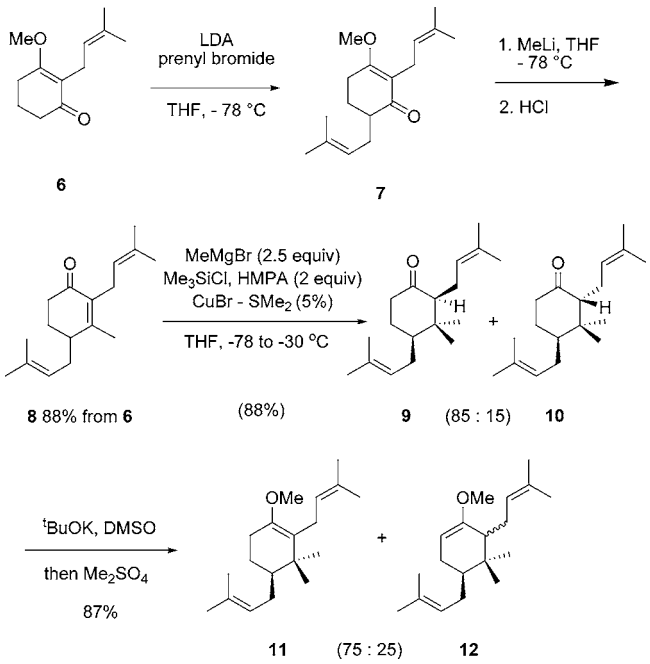
Scheme 1



They accomplished diastereoselective (at C-7) conversion of enol silane **4** into the bridged trione **5** by reaction with malonyl dichloride, in a modification of a procedure originally described by Effenburger and co-workers.[12] The yield of **5** was modest, but the ketone corresponding to **4** could also be recovered. Unfortunately, enol derivatives having additional α- and α′-substituents, destined to emerge as the C-1 and C-5 bridgehead groups in **5**, were even less satisfactory participants in the cyclization.

On the basis of our successful bridgehead lithiation−substitution results on related [3.3.1] systems,[13] we anticipated adopting this method for appending appropriate substituents onto a core structure **5** at either (or both) bridgehead substituent. Direct substitution at the vinylic position (C-3) by metalation also appeared viable.[14] Here we present preliminary results which serve to validate this strategy and which enable a very concise synthesis of **3** (Scheme 2).

Scheme 2



As installation of a substituent at the very hindered C-1 position of **5** was considered an extreme test of our strategy,[15] we instead opted to focus on substitution reactions at C-3 and C-5 of a core trione (or derivative thereof). With clusianone in mind as the ultimate target, we prepared an enol derivative incorporating the required C-1 prenyl substituent.

Prenylation of the known vinylogous ester **6** gave **7**,[16] which was then reacted with MeLi and hydrolyzed under mildly acidic conditions to give enone **8**. Copper-catalyzed Grignard addition to this tetrasubstituted system proved more effective than the use of stoichiometric cuprate reagents and provided the ketone product as a mixture of diastereoisomers **9** and **10**, with the former predominating. A regioisomeric mixture of enol ethers **11** and **12** was then easily prepared using established conditions.[17]

Our explorations of the Effenburger-type cyclization indicated rather similar effectiveness of methyl enol ethers such as **11**/**12** and the corresponding enol silanes (OTBS), and either regioisomer appears to participate in the process.

(6) (a) Piccinelli, A. L.; Cuesta-Rubio, O.; Chica, M. B.; Mahmood, N.; Pagano, B.; Pavone, M.; Barone, V.; Rastrelli, L. *Tetrahedron* **2005**, *61*, 8206−8211. (b) Delle Monache, F.; Delle Monache, G.; Gacs-Baits, E. *Phytochemistry* **1991**, *30*, 2003−2005.

(7) Ito, C.; Itoigawa, M.; Miyamoto, Y.; Onoda, S.; Sundar Rao, K.; Mukainaka, T.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **2003**, *66*, 206−209.

(8) For full listings of previous efforts, see refs 9 and 10 and also: (a) Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2006**, *47*, 689−692. (b) Kraus, G. A.; Jeon, I. *Tetrahedron* **2005**, *61*, 2111−2116. (c) Lavigne, R. M. A.; Riou, M.; Girardin, M.; Morency, L.; Barriault, L. *Org. Lett.* **2005**, *7*, 5921−5923.

(9) Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200−14201.

(10) Siegal, D. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1048−1049.

(11) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943−1946.

(12) Schönwälder, K.-H.; Kollatt, P.; Stezowski, J. J.; Effenburger, F. *Chem. Ber.* **1984**, *117*, 3280−3296.

(13) Giblin, G. M. P.; Kirk, D. T.; Mitchell, L.; Simpkins, N. S. *Org. Lett.* **2003**, *5*, 1673−1675.

(14) Miyata, O.; Schmidt, R. R. *Tetrahedron Lett.* **1982**, *23*, 1793−1796.

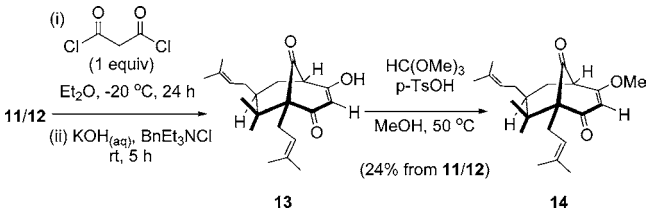
(15) The Danishefsky Garsubellin A synthesis features bridgehead substitution at this position, which proved less than trivial, due to a 25−36% yield in the key bridgehead iodination process (via lithiation−silylation).

(16) Majetich, G.; Hull, K.; Casares, A. M.; Khetani, V. *J. Org. Chem.* **1991**, *56*, 3958−3973.

(17) Heiszwolf, G. J.; Kloosterziel, H. *J. Chem. Soc., Chem. Commun.* **1966**, 51.

In the event, cyclization under conditions similar to those described by Effenburger was predictably low yielding but provided viable quantities of material for completion of our synthesis. Thus, reaction of the mixture **11**/**12** with malonyl dichloride under the described conditions gave the desired trione **13** (ca. 30% crude material), as a single diastereomer, which could be separated by base extraction from recovered ketones **9**/**10** (55% recovered) (Scheme 3).[18]

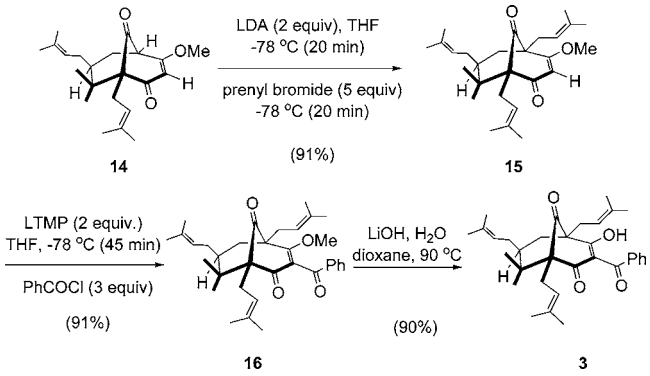
Scheme 3



Trione **13** was O-methylated under acidic conditions prior to purification, providing the single regioisomeric vinylogous ester **14** in 24% overall yield from **11** and **12**.[19]

The vinylogous ester, **14**, was then converted into the natural product clusianone, as shown in Scheme 4. First, treatment of **14** with excess LDA, followed by alkylation with prenyl bromide, gave **15**, with *bridgehead substitution occurring in 91% yield*.[20] Acylation at C-3 by the action of LTMP followed by benzoyl chloride was equally efficient.[21] Finally, hydrolysis of the vinylogous ester, under conditions akin to those described previously,[11] gave clusianone, as a mixture of enol tautomers spectroscopically identical with the reported data.[6a,22]

Scheme 4



The synthesis described here generates the naturally occurring PPAP in racemic form in only nine synthetic steps and in 12% overall yield (even accounting for a 24% yield for the crucial bridge-forming process) from **6**. The synthesis underlines the brevity imbued by teaming the powerful Effenburger cyclization with regioselective lithiation processes. The low yields that accompany the key cyclization are not easily rectified by minor variations to reaction conditions, and we are presently investigating a more substantial redesign of this process as a means to substantially improve its efficiency.

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Supporting Information Available: Complete experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The stereochemical assignment of **13** was initially made by analogy with the result of Spessard and Stoltz. The assignment was validated by the eventual conversion of this intermediate into the natural product. In addition, certain intermediates show distinctive large *J*-values between H-7 and one of the C-6 CH_2 protons in the ^1H NMR, demonstrating the pseudoaxial (therefore endo) nature of H-7.

(19) Methylation under basic conditions (K_2CO_3, Me_2SO_4, acetone) furnished an equimolar mixture of **14** and the regioisomeric vinylogous ester, methylated at C-2. Equilibration studies indicated that isomer **14** is the thermodynamically favoured one.

(20) The use of 2 equiv of base proved optimal, but we could find no evidence for dianion formation.

(21) For a recent example of a similar metalation, see: Zapf, C. W.; Harrison, B. A.; Drahl, C.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6533−6537.

(22) Further evidence for the identity of our synthetic sample was obtained by comparison of spectral data of intermediate **16** with those of a previously reported methylated derivative of clusianone (see Supporting Information): De Oliveira, C. M. A.; Porto, A. M.; Bittrich, V.; Vencato, I.; Marsaioli, A. J. *Tetrahedron Lett.* **1996**, *37*, 6427−6430.