ORGANIC LETTERS

2007
Vol. 9, No. 2
287−289

α,α′-Annulation of 2,6-Prenyl-Substituted Cyclohexanone Derivatives with Malonyl Chloride: Application to a Short Synthesis of (±)-Clusianone. Formation and Rearrangement of a Biogenetic-Like Intermediate

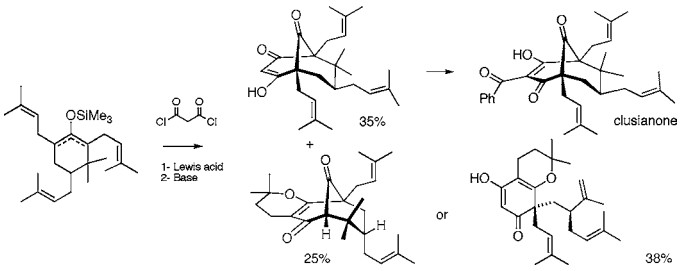
Philippe Nuhant, Marc David, Thomas Pouplin, Bernard Delpech,* and Christian Marazano*

Institut de Chimie des Substances Naturelles, CNRS, 1 Avenue de la Terrasse, 91198 Gif-sur-Yvette, France

marazano@icsn.cnrs-gif.fr

Received November 8, 2006

ABSTRACT



Conditions were found for the successful Effenberger α,α′-annulation of 3,3-dimethyl-2,4,6-triprenyl cyclohexanone silyl enol ethers with malonyl chloride to give the corresponding bicyclo[3.3.1]nonane-trione in 35% yield, this result allowing a short synthesis of (±)-clusianone. An isomeric rearranged bicyclo[3.3.1]nonane-trione was also isolated in 25% yield, and changing the Lewis acid resulted in formation of a lavandulyl-substituted phloroglucinol derivative in 38% yield. The mechanism of formation of these two last products mimics the biogenetic pathway to PPAPs.

A number of polyprenylated acylphloroglucinol derivatives (PPAPs) have been isolated from plants and trees of the family Clusiaceae (Guttiferae).[1] Some representative examples are depicted in Figure 1. Clusianone **1**[2] is one of the simplest members in this series, and hyperforin **2** and garsubellin A **3**, considering their interesting biological activities, recently became targets for total synthesis.[3] Our interest in this field came from the observation[4] that xanthochymol **4** was active in vitro in a tubulin disassembly

(1) For recent reviews, see: (a) Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963−3986. (b) Cuesta-Rubio, O.; Piccinelli, A. L.; Rastrelli, L. In *Studies in Natural Product Chemistry* (*Bioactive Natural Products, Part L*); Atta-ur Rahman, Ed.; Elsevier: Amsterdam, 2005; Vol. 32, pp 671−720.

(2) Piccinelli, A. L.; Cuesta-Rubio, O.; Chica, M. B.; Mahmood, N.; Pagano, B.; Pavone, M.; Barone, V.; Rastrelli, L. *Tetrahedron* **2005**, *61*, 8206−8211.

(3) Two total syntheses of garsubellin A were published recently: (a) Siegel, D. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1048−1049. (b) Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200−14201.

(4) Roux, D.; Hadi, H. A.; Thoret, S.; Guénard, D.; Thoison, O.; Païs, M.; Sévenet, T. *J. Nat. Prod.* **2000**, *63*, 1070−1076.

10.1021/ol062736s CCC: $37.00
Published on Web 12/22/2006

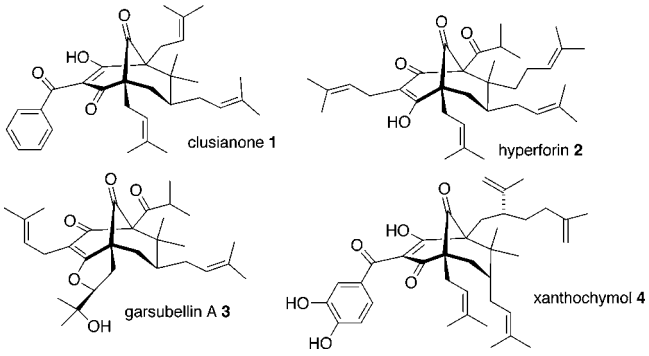
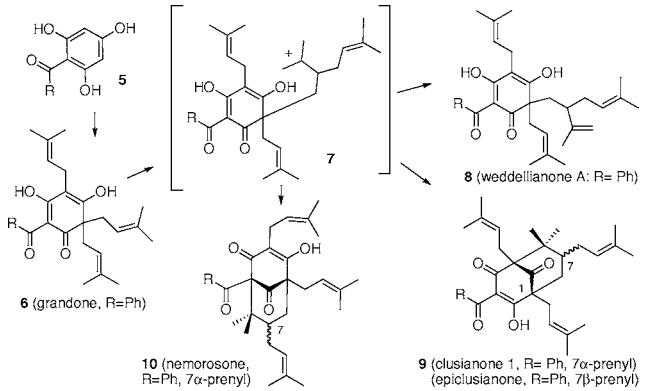


Figure 1. Some PPAPs of current interest.

inhibition test and from our recent results concerning isolation of analogues, oblongifolins A−D.[5]

The biosynthetic pathway to natural PPAPs is summarized in Scheme 1.[1a] Prenyl transfer to the phloroglucinol ring of

Scheme 1. Biosynthetic Pathways to Natural PPAPs



5 produces intermediate **6**. The addition of a fourth prenyl unit generates a lavandulyl cation **7**. This cation can eliminate a proton to give a lavandulyl-substituted derivative **8** or cyclizes to give triones **9** (type B cyclization) or **10** (type A cyclization).

Several strategies have emerged concerning PPAP synthesis.[1] Among them, α,α′-annulation of substituted cyclohexanones with malonyl chloride[6,7] is particularly attractive because it has the capability to form the key bicyclo[3.3.1]-nonane-2,4,9-trione system in one step.

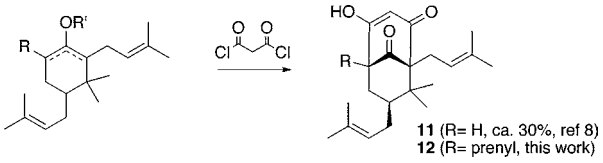
Very recently, Simpkins et al. reported the synthesis of the bicyclic methyl enol ether **11** (Scheme 2) and the first total synthesis of (±)-clusianone starting from this intermediate.[8] For our study, we targeted a short synthesis of the bicyclo[3.3.1]nonane-trione **12**.

(5) Hamed, W.; Brajeul, S.; Mahuteau-Betzer, F.; Thoison, O.; Mons, S.; Delpech, B.; Hung, N. V.; Sevenet, T.; Marazano, C. *J. Nat. Prod.* **2006**, *69*, 774−777.

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

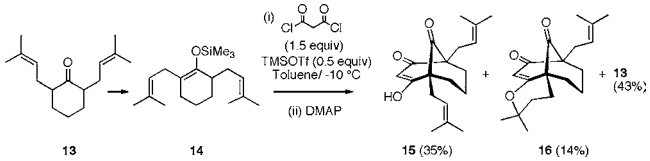
(7) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943−1946.

Scheme 2



We first investigated the reaction starting from the trimethylsilyl enol ether of 2,6-diprenyl cyclohexanone **14**. We were pleased to find rapidly satisfying conditions leading to the bicyclo[3.3.1]nonane-trione **15** (Scheme 3). Thus,

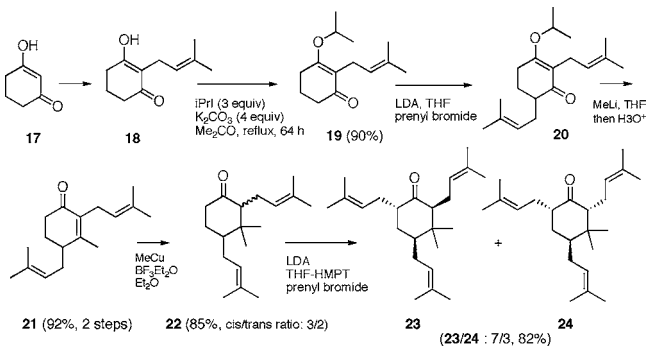
Scheme 3



treatment, at −10 °C, of a toluene solution of the silyl enol ether **14** with a slight excess of malonyl chloride and TMS triflate as a Lewis acid, followed by base treatment (DMAP), afforded three products. The desired cycloadduct **15** was obtained after chromatography over silica gel in 35% yield. It was accompanied by the corresponding cyclic ether **16** and cyclohexanone **13** (43%). Considering cyclohexanone **13** as recovered starting material, the corrected yield of the cyclization process is 86% (61% and 25% for **15** and **16**, respectively).

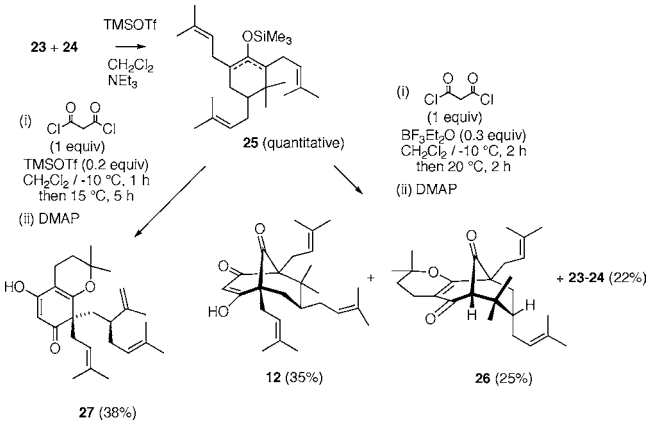
Encouraged by these first observations, we then directly devoted our efforts to the study of the reaction sequence of Scheme 2 (R = prenyl). For this purpose, an isomeric mixture of cyclohexanones **23** and **24** was prepared in five steps and in an overall yield of 58% from substituted dione **18** according to the route depicted in Scheme 4.[9]

Scheme 4



A mixture of silyl enol ethers **25** was then prepared from the mixture of cyclohexanones **23** and **24** (Scheme 5).

Scheme 5



Treatment of **25** with malonyl chloride in the presence of TMSOTf in toluene (conditions used for the preparation of bicyclononane-trione **15**, see Scheme 3) was unsuccessful. Using dichloromethane as solvent at −10 °C, the desired bicyclononane-trione **12** was obtained after chromatography over silica gel, but only in a disappointing yield of 6%. Another product was isolated in 11% yield. Allowing the reaction mixture to warm to 15 °C during 5 h, before base treatment, resulted only in an increased yield of 38% for this last product, the structure of which was established by spectroscopic methods as lavandulyl-substituted phloroglucinol derivative **27**. The relative stereochemistry of this compound was assigned considering its probable mechanism of formation (vide infra). Changing the Lewis acid to $BF_3{\cdot}Et_2O$ gave finally an appreciable 35% yield of **12** with recovery of the mixture of cyclohexanones **23**−**24** in 22% yield. It is thus a remarkable result considering that two quaternary carbon centers, with one being contiguous to an another one (*gem*-dimethyl), are formed during this crucial step. To our surprise, another bicyclononane-trione was isolated from the reaction mixture in 25% yield, the structure of which was established as **26** using intensive spectroscopic methods. The formation of lavandulyl derivative **27** was not observed with $BF_3{\cdot}Et_2O$ as a Lewis acid, meaning that the reaction pathway can be controlled by changing the nature of the Lewis acid.

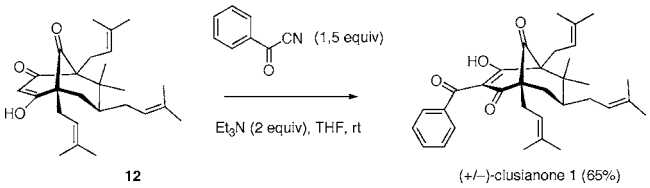
Completion of (±)-clusianone total synthesis from **12** was achieved by C-acylation with benzoyl cyanide,[10] according to Scheme 6. This clusianone synthesis involves seven steps from readily available intermediate **19** with an overall yield of approximately 14% (Simpkins et al. reported a nine-step synthesis and a similar overall yield from the methyl enol ether analogue of **19**).[10]

(8) Rodeschini, V.; Ahmad, N. M.; Simpkins, N. S. *Org. Lett.* **2006**, *8*, 5283−5285.

(9) Slight variations of now classical procedures have been used. See refs 7 and 8 and refs therein as well as the Supporting Information section for more details.

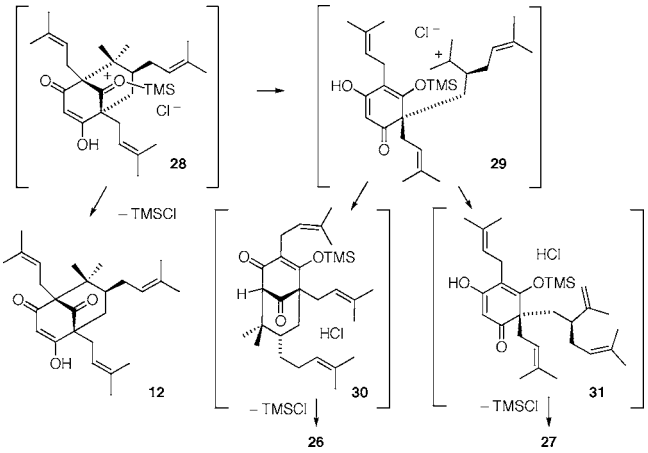
(10) Nicolaou, K. C.; Vassilikogiannakis, G.; Montagnon, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3276−3281.

Scheme 6. Completion of (±)-Clusianone Synthesis



A mechanism for the formation of rearrangement products **26** and **27** is proposed in Scheme 7.[11] Formation of the

Scheme 7



second carbon−carbon bond, in the reaction with malonyl chloride, is likely to produce an oxonium intermediate **28** which can produce a cationic species **29** by a fragmentation process. Cationic intermediate **29** can recyclize to give trione **30** or afford the lavandulyl derivative **31**. Liberation, in both cases, of one molecule of acid leads to the observed cyclic ether derivatives **26** or **27**. Intermediate cation **29** possesses striking analogies with the biogenetic cationic intermediate **7** in Scheme 1, whereas derivatives **30** and **31** can be considered as analogues of 7-*epi* nemorosone and weddellianone A, respectively.

Future work will try to take advantage of these new observations to extend the scope of this chemistry to natural PPAP synthesis.

Supporting Information Available: Experimental procedures, copies of NMR spectra for compounds **1**, **12**−**16**, **23**, **24**, **26**, and **27**, and nOe data for **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062736S

(11) For a rather similar discussion, see: Le Roux, C.; Mandrou, S.; Dubac, J. *J. Org. Chem.* **1996**, *61*, 3885−3887.