ORGANIC LETTERS

2009
Vol. 11, No. 14
2988−2991

Biomimetic Synthesis of Dimeric Metabolite Acremine G via a Highly Regioselective and Stereoselective Diels−Alder Reaction

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Received May 8, 2009

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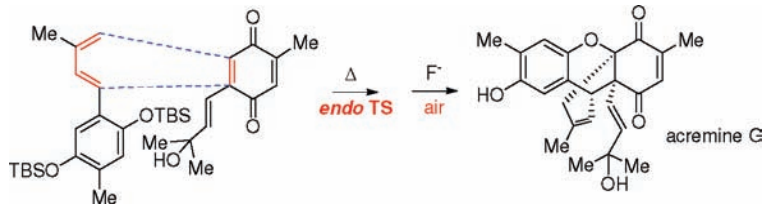
Published on June 18, 2009 on http://pubs.acs.org | doi: 10.1021/ol901004e

ABSTRACT



The dimeric metabolite acremine G was synthesized featuring a highly regioselective and stereoselective Diels−Alder reaction between a TBS-protected hydroquinone diene and a structurally related alkenyl quinone. The major *endo* [4 + 2] adduct slowly transforms to acremine G by the atmospheric air under the deprotection conditions (in situ generated HF).

Acremines A−F,[1] G,[2] and H−N[3] (Figure 1) are metabolites isolated from the cultures of the fungus *Acremonium byssoides*. They inhibit the germination of sporangia of *Plasmopara viticola*. Some of them exhibit modest cytotoxic activity against the tumor cell line H460, while acremine A inhibits lipoxygenase. Acremine A has also been isolated[4] from the methanolic extract of *Periploca aphylla*. Its initially misassigned structure was corrected later.[5] Of particular synthetic interest is acremine G which biosynthetically could derive from a Diels−Alder reaction between the so far nonisolated hydroquinone diene **1** and alkenyl quinone **2** (Scheme 1),[6] accompanied by an intermolecular oxidative coupling in the [4 + 2] adduct. Biomimetic Diels−Alder reactions and dimerizations have been proposed for a plethora of natural product biosyntheses and have been accomplished aesthetically[7] in several cases by synthetic organic chemists.

Monomer **2** which resembles acremines A and B could form **1** via dehydration/oxidation. A similar biosynthetic proposal had been postulated for the structurally related allomicrophyllone.[8] To test this postulated [4 + 2] biogenetic

(1) Assante, G.; Dallavalle, S.; Malpezzi, L.; Nasini, G.; Burruano, S.; Torta, L. *Tetrahedron* **2005**, *61*, 7686–7692.

(2) Arnone, A.; Nasini, G.; Panzeri, W.; de Pava, O. V.; Malpezzi, L. *J. Nat. Prod.* **2008**, *71*, 146–149.

(3) Arnone, A.; Assante, G.; Bava, A.; Dallavalle, S.; Nasini, G. *Tetrahedron* **2009**, *65*, 786–791.

(4) Aziz-ur, R.; Malik, A.; Riaz, N.; Nawaz, H. R.; Ahmad, H.; Nawaz, S. A.; Choudhary, M. I. *J. Nat. Prod.* **2004**, *67*, 1450–1454.

(5) Hoarau, C.; Pettus, T. R. R. *Org. Lett.* **2006**, *8*, 2843–2846.

(6) For a recent example of employing a Diels−Alder reaction between a quinone and a diene, as a key step towards the biomimetic synthesis of cordiaquinones in our lab, see: Arkoudis, E.; Stratakis, M. *J. Org. Chem.* **2008**, *73*, 4484–4490.

(7) Selected examples: (a) Nicolaou, K. C.; Snider, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698. (b) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078–3115. (c) Mehta, G.; Pan, S. C. *Org. Lett.* **2004**, *6*, 3985–3988. (d) Zhang, W.; Luo, S.; Fang, F.; Chen, Q.; Hu, H.; Jia, X.; Zhai, H. *J. Am. Chem. Soc.* **2005**, *127*, 18–19. (e) Gagnepain, J.; Castet, F.; Quideau, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1533–1535. (f) Dong, S.; Zhu, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2008**, *130*, 2738–2739. (g) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773–775. (h) Porco, J. A., Jr.; Su, S.; Bardhan, S.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5790–5792. (i) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393–5407. (j) Nicolaou, K. C.; Lim, Y. H.; Becker, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3444–3448.

(8) Yamamura, S.; Simpol, L. R.; Ozawa, K.; Ohtani, K.; Otsuka, H.; Kasai, R.; Yamasaki, K.; Padolina, W. G. *Phytochemistry* **1995**, *39*, 105–110.

10.1021/ol901004e CCC: $40.75 © 2009 American Chemical Society
Published on Web 06/18/2009

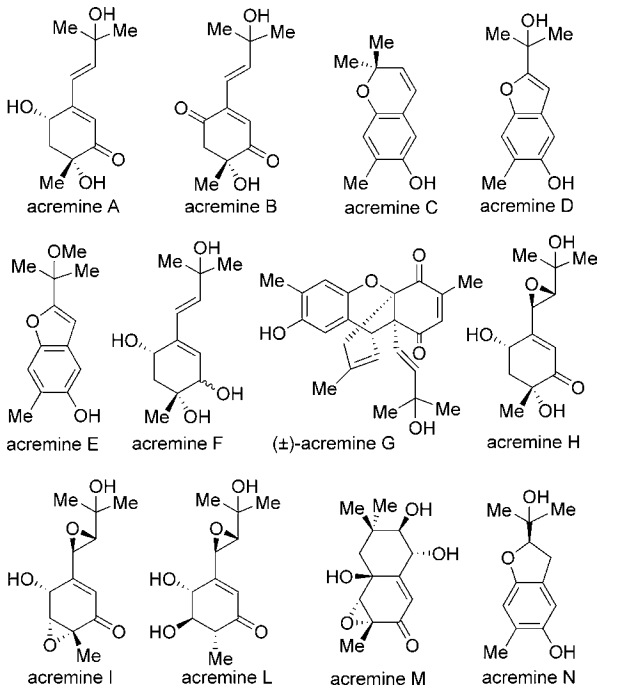
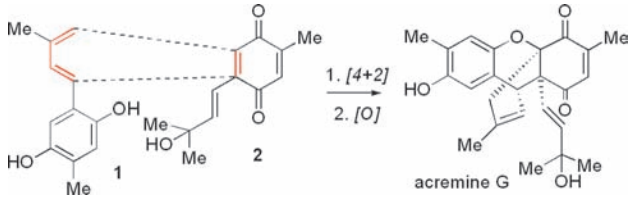


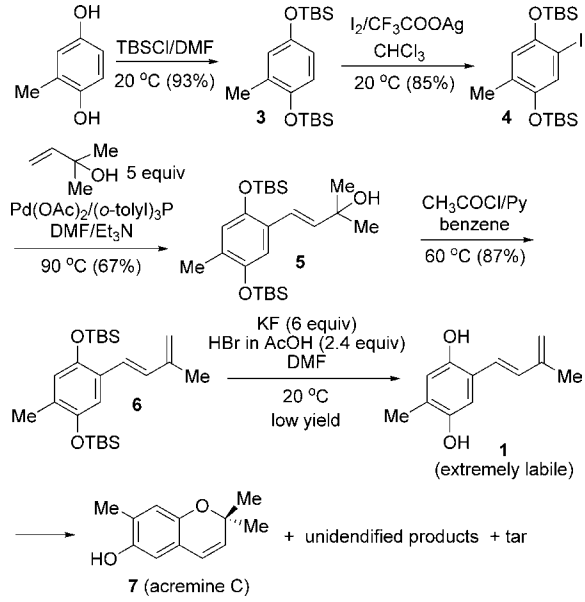
Figure 1. Acremines A−N.

pathway, we undertook the synthesis of the proposed monomers **1** and **2**. Regarding the attempted synthesis of diene **1** (Scheme 2), toluhydroquinone was used as the starting material. The TBS-protected toluhydroquinone **3** was iodinated selectively at C-5 with I_2/CF_3COOAg to form **4** in 85% yield, while the aryl iodide **4** underwent a Heck coupling ($Pd(OAc)_2$, (*o*-tolyl)$_3$P, Et_3N, DMF) with 2-methylbut-3-en-2-ol[9] to afford **5** in 67% isolated yield. The allylic alcohol **5** was easily dehydrated to diene **6** on treatment with acetyl chloride/pyridine.[9] We observed that even on standing **5** slowly dehydrates to **6**. While the silyl-protected diene **6** is quite stable for a long time, all initial attempts to deprotect the TBS groups (TBAF, $Pd(CH_3CN)_2Cl_2$,[10] catal. TMSBr,[11] LiOAc,[12] $CuBr_2$,[13] and other) failed to provide any hydroquinone diene. The desired diene **1** is, as expected, sensitive to acidic or basic conditions and rather polymerizes very fast leaving behind a tary residue. By using a mild desilylation procedure modified by Hudson[14] (KF, HBr/CH_3COOH, dry DMF), the deprotection proceeded efficiently after 4−5 h at room temperature.

Scheme 1. Postulated Biosynthesis of Acremine G via a Tandem Diels−Alder Dimerization/Oxidation



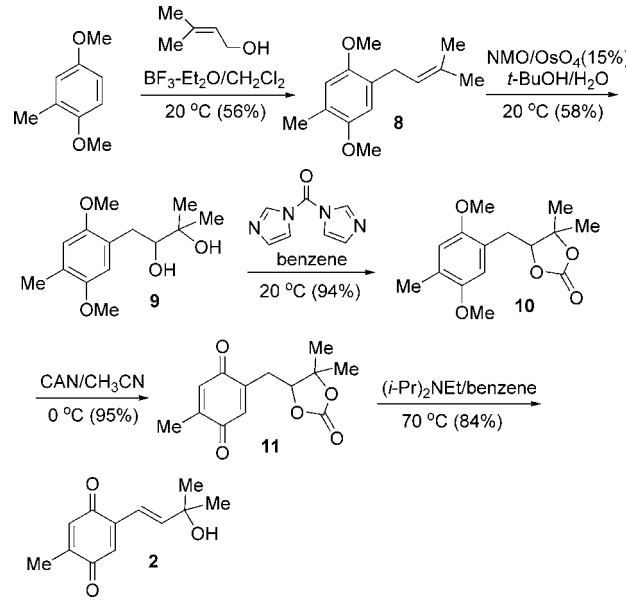
Scheme 2. Attempted Synthesis of Diene Monomer **1**



Diene **1** is extremely labile and decomposes within a few minutes. In one of our numerous attempts, luckily enough **1** was seen by ^{1}H NMR before undergoing decomposition. It partially transforms, among other unidentified products and tar, to chromene **7**, whose spectral data are in agreement with those of acremine C[1] (Figure 1). The cyclization of **1** to **7** is obviously catalyzed by acidic impurities. Hence, we decided to use the silyl-protected diene **6** en route to accomplish the [4 + 2] scenario shown in Scheme 1.

The synthesis of the desired dienophile **2** was accomplished in five steps (Scheme 3) from the commercially

Scheme 3. Synthesis of the Alkenyl Quinone **2**



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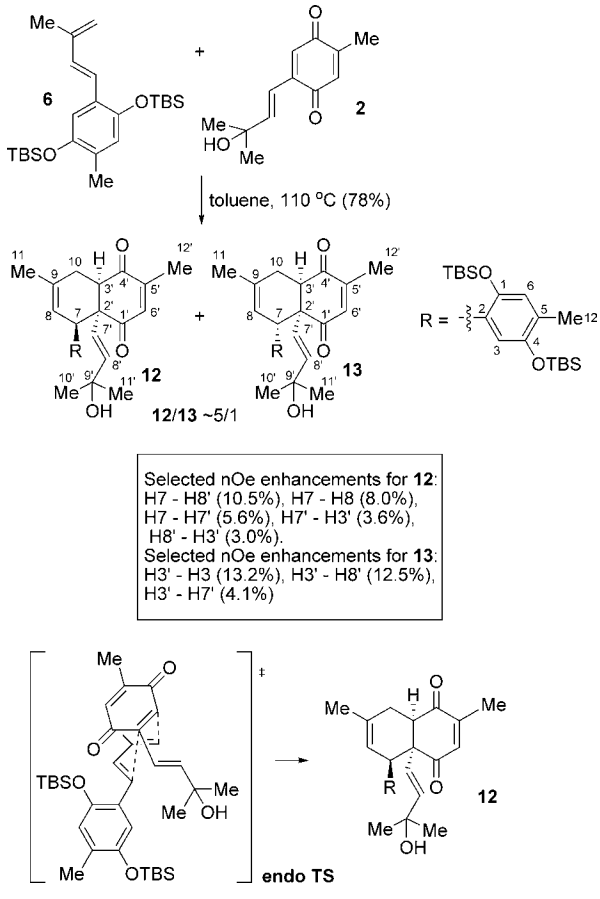
available 2-methyl-1,4-dimethoxybenzene. Thus, prenylation[15] at C-5 under Friedel−Crafts conditions (prenol, BF_3 etherated) afforded **8**,[16] which after dihydroxylation (cat. OsO_4, NMO), protection of the 1,2-diol **9** as carbonate **10** with 1,1′-carbonyldiimidazole (CDI), and reaction of **10** with ceric ammonium nitrate, afforded quinone **11** in 52% yield over the three last steps. Finally, treatment of **11** with Hunig's base[17] (15 equiv) in refluxing benzene cleanly afforded **2** in 84% isolated yield. It should be noted that regarding the last step, the reactant dilution must be kept as low as 0.01 M, otherwise a mixture of products is formed in low yield.

Having in our hands diene **6** and dienophile **2**, we performed their [4 + 2] cycloaddition in refluxing toluene. The reaction was complete after 24 h to afford a mixture of **12** (endo product) and **13** (exo product) in 78% yield and in a relative ratio **12**/**13** ∼ 5/1. The structural assignment of the products was performed by NOE experiments, with some key enhancements shown in Scheme 4. The selective formation of **12** among seven other possible regio/stereoisomers could be explained considering the *endo* transition state (Scheme 4), where a nonbonding interaction between the alkenyl chain of quinone and the aryl substituent of diene **1** possibly dictates the regiochemical and stereochemical outcome. On the other hand, the regiochemical preference for cycloaddition on the vinyl-substituted double bond of 2-monovinyl-substituted 1,4-quinones is known,[18] as a result of the larger coefficients of its LUMO (semiempirical calculations).

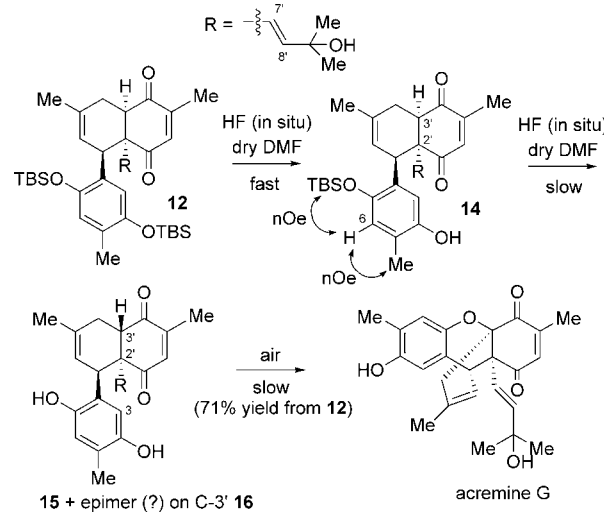
The endo adduct **12**, which from the stereochemical point of view is the suitable precursor of acremine G, underwent deprotection (6.0 equiv of KF, 2.5 equiv of HBr 33% in CH_3COOH, dry DMF).[14] These deprotection conditions (in situ generated HF) are the only effective ones, as all variations discussed above during the attempted deprotection of **6** failed, providing either a mixture of products and/or tar. After 1 h, a new product had been primarily formed (TLC), which was isolated and characterized by NMR as the selectively monodeprotected on the less hindered −OTBS group **14** (NOE interaction of H-6 with the TBS group, Scheme 5). The cis stereochemistry among the fused six-membered rings was retained in **14** as revealed by the NOE enhancement (4.4%) among the hydrogen atoms on C-3′ and the olefinic hydrogens on the alkenyl (C7′−C8′) side chain. Leaving the reaction mixture for a longer time, a new more polar product gradually appeared. After 24 h, it was isolated and ascribed as the dideprotected starting material. The completely deprotected **12** was a mixture of two epimers in a ratio ∼5/1 with the major assigned as the trans-fused **15** (Scheme 5). In **15**, the lack of NOE enhancement between the hydrogen atom H-3′ and the alkenyl (C7′−C8′) side chain is characteristic, while a strong enhancement of the hydrogen atom on C-3 was observed (13.7%) upon irradiating the hydrogen atom on C-3′, in agreement with our stereochemical

Scheme 4. Diels−Alder Reaction between **6** and **2** and the Stereochemical Assignment of the Cycloadducts[a]



[a] The atom numbering of **12** and **13** was arbitrarily considered after the numbering of acremine G in the isolation paper.

Scheme 5. Deprotection of the Diels−Alder Adduct **12** with in Situ Generated HF, Leading to Acremine G



(9) Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.* **1987**, *109*, 4335–4338.
(10) Wilson, N. S.; Keay, B. A. *Tetrahedron Lett.* **1996**, *37*, 153–156.
(11) Shah, S. T. A.; Guiry, P. J. *Org. Biomol. Chem.* **2008**, *6*, 2168–2172.

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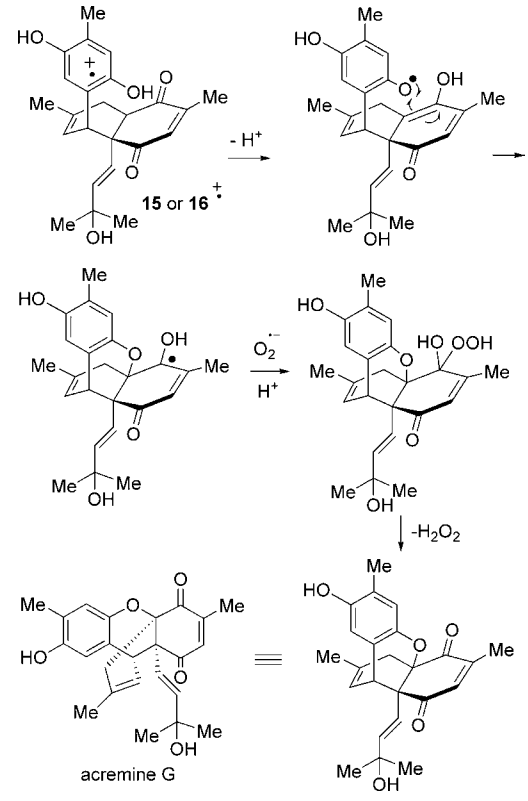
assignment. Obviously, the cis stereochemistry among the fused rings observed in **12** or **14** was not retained in the fully deprotected cycloadduct **15** due to an epimerization under the slightly acidic reaction conditions. The minor dideprotected product **16** could not be separated from **15** by column chromatography, and we tentatively assigned its structure as the epimer of **15** on C-3′. However, in the mean time, besides monoprotected **14** and fully deprotected **15**/**16**, a new product with an intermediate polarity among them started to form and became the major after 24 h, while after 36 h it was almost the only reaction product. We were pleased to realize that the newly formed product was acremine G[19] (71% isolated yield from **12**). Additionally, acremine G was also exclusively formed after 24 h on leaving the mixture of **15**/**16** in DMF, having added acetic acid (5 equiv).

We postulate that the oxidation of **15**/**16** to acremine G occurs by molecular oxygen via a radical pathway (Scheme 6). A reasonable mechanism requires formation of the radical cation of the hydroquinone moiety in **15**/**16** by electron transfer either intramolecularly from the semiquinone moiety or intermolecularly by molecular oxygen (affording superoxide anion). The radical cation eliminates a proton, and the resulting oxygen centered radical couples with the double bond of the common enol form of **15**/**16**. Finally, the cyclized C-centered radical reacts with the superoxide anion to form a labile hydroperoxy hemiacetal, which eliminates H_2O_2 to yield acremine G. We postulate that the slightly acidic conditions during the deprotection process facilitate the oxidative coupling through catalyzing the formation of the necessary enol. Notably, we did not observe any product resulting from the coupling among C3 and C3′ that would provide a compound related to hydroxymicrophyllone.[8] A profound reason is that a more strained system is thus generated, relative to the six-membered ring coupling which generates acremine G.

Scheme 6. Postulated Mechanism for the Oxidation of **15**/**16** to Acremine G by Electron Transfer to Molecular Oxygen



In conclusion, we have presented an efficient biomimetic route to acremine G featuring a highly regioselective and stereoselective Diels−Alder reaction. Synthetic studies toward microphyllones[8] (structurally related to acremine G natural products) as well as an exploration of the hydroquinone−ketone oxidative coupling are in progress.

Acknowledgment. E.A. thanks IKY for a 4 year fellowship. We thank professor A. Berkessel (Cologne University) for obtaining some HRMS.

Supporting Information Available: Experimental details for the synthesis of monomers **2** and **6** and their cycloaddition. Copies of ^{1}H, ^{13}C NMR, HRMS, and MS spectra of key compounds and reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Wang, B.; Sun, H.-X.; Sun, Z.-H. J. *J. Org. Chem.* **2009**, *74*, 1781–1784.
(13) Bhatt, S.; Nayak, S. K. *Tetrahedron Lett.* **2006**, *47*, 8395–8399.
(14) Suleman, A. S.; Tillekeratne, L. M. V.; Hudson, R. A. *Synth. Commun.* **2001**, *31*, 3303–3308.
(15) Misiti, D.; Moore, H. W.; Folkers, K. *Biochemistry* **1965**, *4*, 1156–1160.
(16) Scheepers, B. A.; Klein, R.; Davies-Coleman, M. T. *Tetrahedron Lett.* **2006**, *47*, 8243–8246.
(17) Lindsey, C. C.; Gomez-Diaz, C.; Villalba, J. M.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 4559–4565.
(18) Irngartinger, H.; Stadler, B. *Eur. J. Org. Chem.* **1998**, 605–626.
(19) For a comparison of the NMR spectroscopic data of natural and synthetic acremine G, see the Supporting Information.