ORGANIC LETTERS

2003
Vol. 5, No. 24
4619−4621

A New Synthetic Approach to the Polycyclic Polyprenylated Acylphloroglucinols

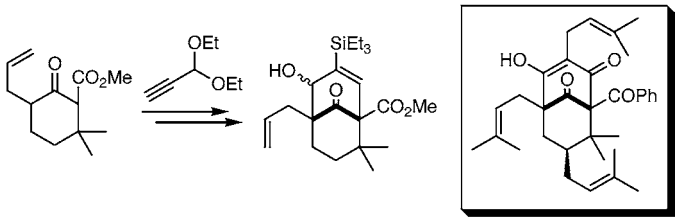
Roxana Ciochina and Robert B. Grossman*

Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506-0055

robert.grossman@uky.edu

Received September 16, 2003

ABSTRACT



The three-carbon α,α′-annulation of a sterically hindered cyclic β-keto ester can be achieved by alkynylation with 3,3-diethoxypropyne, syn reduction of the alkyne with $Co_2(CO)_8$ and Et_3SiH, and an intramolecular aldol reaction. The method is potentially useful for the synthesis of nemorosone, hyperforin, and other polycyclic polyprenylated acylphloroglucinols.

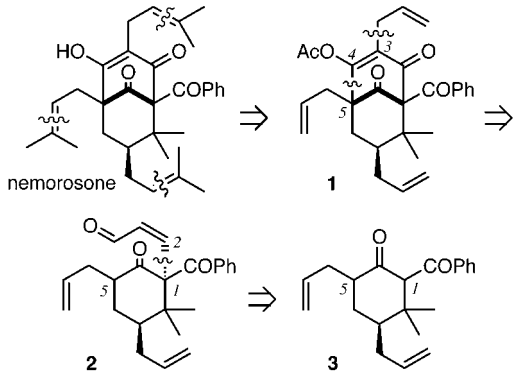
In recent years, widespread interest in the antidepressant activity of *Hypericum perforatum* (St. John's wort) has stimulated much investigation into metabolites from the Guttiferae. Studies of the plants from this family have revealed a class of compounds, the polycyclic polyprenylated acylphloroglucinols (PPAPs), with fascinating chemical structures and intriguing biological activities. The PPAPs feature a highly oxygenated and densely substituted bicyclo-[3.3.1]nonane-2,4,9-trione core to which are attached an acyl group at C(1) or C(3) and prenyl or $C_{10}H_{17}$ side chains.[1] Secondary cyclizations may involve the β-diketone and pendant olefinic groups, affording adamantanes, homoadamantanes, or pyrano-fused structures. Various PPAPs have been found to be antibiotics against multidrug-resistant *S. aureus*,[2] stimulators of choline acetyltransferase,[3] and inhibitors of DNA topoisomerase I and II,[4] tubulin depolymerization,[5] and neurotransmitter reuptake.[6]

The combination of intriguing biological activity and challenging structure makes the PPAPs appealing targets for organic synthesis, but surprisingly few model studies and no total syntheses of these compounds have appeared. The five model studies that have appeared to date have used an α,α′-annulation of a cyclohexanone derivative to construct the key bicyclo[3.3.1]nonane skeleton. In their garsubellin A model studies, Shibasaki used a complex sequence that included C−C bond-forming addition−elimination and aldol reactions,[7] Nicolaou used a "biomimetic" selenocyclization of a cyclic β-keto ester onto a pendant prenyl group,[8] and Stoltz used a tandem Claisen−Dieckmann reaction of malonyl dichloride.[9] In their hyperforin model studies, Kraus

(1) Cuesta-Rubio, O.; Velez-Castro, H.; Frontana-Uribe, B. A.; Cárdenas, J. *Phytochemistry* **2001**, *57*, 279.
(2) Iinuma, M.; Tosa, H.; Tanaka, T.; Kanamaru, S.; Asai, F.; Kobayashi, Y.; Miyauchi, K.; Shimano, R. *Biol. Pharm. Bull.* **1996**, *19*, 311. Schempp, C. M.; Pelz, K.; Wittmer, A.; Schöpf, E.; Simon, J. C. *Lancet* **1999**, *353*, 2129.
(3) Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull.* **1997**, *45*, 947.
(4) Tosa, H.; Iinuma, M.; Tanaka, T.; Nozaki, H.; Ikeda, S.; Tsutsui, K.; Tsutsui, K.; Yamada, M.; Fujimori, S. *Chem. Pharm. Bull.* **1997**, *45*, 418.
(5) Roux, D.; Hadi, H. A.; Thoret, S.; Guénard, D.; Thoison, O.; Païs, M.; Sévenet, T. *J. Nat. Prod.* **2000**, *63*, 1070.
(6) Chatterjee, S. S.; Bhattacharya, S. K.; Wonnemann, M.; Singer, A.; Müller, W. E. *Life Sci.* **1999**, *63*, 499.
(7) Usuda, H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2002**, *4*, 859. Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 3621.
(8) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q.; Kim, S.; Kessabi, J. *Org. Lett.* **1999**, *1*, 807. Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724.
(9) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943.

10.1021/ol0357907 CCC: $25.00
Published on Web 11/01/2003

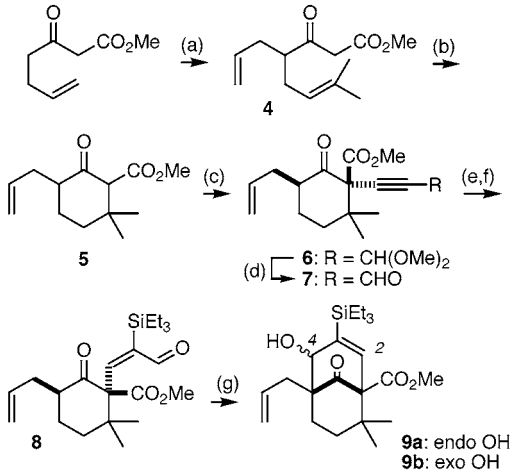
Scheme 1



used an allylation followed by Mn-mediated oxidative cyclization,[10] and, in a very creative approach, Young used an intramolecular allene−nitrile oxide cycloaddition.[11] Nicolaou's disconnection was unique: he annulated the *gem*-dimethyl-containing ring onto an existing cyclohexanone, whereas the others annulated the β-diketone-containing ring onto an existing one.

We decided to focus our own initial efforts in this area on the type A PPAP, nemorosone (Scheme 1),[1,12] because we thought that its fairly simple structure relative to other PPAPs would present fewer hurdles as we developed our methodology. Our retrosynthetic analysis of nemorosone had us mask the sensitive prenyl groups as more robust, tractable allyl groups until the very end of the synthesis, when they could be installed by Ru-catalyzed cross-metathesis of **1** with $Me_2C{=}CHMe$.[9,13] We thought that the C(3) allyl group of **1** could be installed by alkylation of the β-diketone group, the C(4−5) bond of **1** by an intramolecular aldol reaction of **2**, and the C(1−2) bond of **2** by alkylation of β-diketone **3**. Our previous experience with synthesizing sterically congested compounds by the use of CN groups[14] led us to speculate that a 1-alkynyl group could be added to C(1) of **3** without much steric impedance from the adjacent *gem*-dimethyl group. In fact, the Hashimoto and Moloney groups developed $Pb(OAc)_4$-mediated alkynylations of β-keto esters in the late 1980s,[15,16] although they did not investigate substrates so hindered as **3**. The C-selectivity of the Pb-mediated alkynylations appealed to us, as did their irreversibility and neutral conditions, the latter because we did not want any sterically compressed intermediates to fragment by retro-Michael, -Claisen, or -Dieckmann reactions. We

Scheme 2[a]



[a] (a) NaH, BuLi, DMPU, prenyl bromide, 67%. (b) $SnCl_4$, CH_2Cl_2, 84%. (c) $(EtO)_2CHC{\equiv}CSnBu_3$, $Pb(OAc)_4$, 48%. (d) HCO_2H, 71%. (e) $Co_2(CO)_8$, 87%. (f) Et_3SiH, $Me_3SiC{\equiv}CSiMe_3$, 94%. (g) cat. 6 N aq HCl, 72%, ca. 1:1 dr.

decided to alkynylate **3** with commercially available 3,3-diethoxypropyne; after syn reduction of the C≡C bond[15] and acetal hydrolysis to give **2**, the unmasked aldehyde could then engage in an intramolecular aldol reaction at C(5).

We decided to begin our investigation with a model study (Scheme 2). Addition of prenyl bromide to the dianion of methyl 3-oxo-6-heptenoate[17] in the presence of DMPU gave diene **4** in 67% yield, and cyclization of **4** with $SnCl_4$ provided cyclohexanone-2-carboxylate **5** in 84% yield.[18] The $Pb(OAc)_4$-mediated α-alkynylation of β-keto ester **5** with lithiated 3,3-diethoxypropyne failed;[15] instead, the major product was derived from oxidative dimerization of the alkyne. However, when the corresponding tributylstannylated alkyne was added to a mixture of **5** and $Pb(OAc)_4$, the desired alkynylated β-keto ester **6**, which contained the two contiguous quaternary centers of the PPAPs, was obtained in 48% yield.[16] Even after flash chromatography, ester **6** was contaminated with some Bu_3SnX residue, but this impurity was removed in subsequent steps.

Catalytic hydrogenation of the C≡C bond of **6** failed, even at very high pressures (ca. 1000 psi). To reduce the steric encumbrance around the alkyne, acetal **6** was hydrolyzed to the aldehyde **7** in neat HCO_2H in 71% yield.[19] Although hydrogenation of the C≡C bond of **7** proceeded with several catalysts, reduction of the allyl and formyl groups was often competitive, and those catalysts that did not also reduce the allyl group caused the nascent cis enal to isomerize to the trans isomer.

A literature survey revealed very few alternatives to Lindlar-type hydrogenation for the syn reduction of alkynes

(10) Kraus, G. A.; Nguyen, T. H.; Jeon, I. *Tetrahedron Lett.* **2003**, *44*, 659.
(11) Young, D. G. J.; Zeng, D. *J. Org. Chem.* **2002**, *67*, 3134.
(12) de Oliveira, C. M. A.; Porto, A. L. M.; Bittrich, V.; Vencato, I.; Marsaioli, A. J. *Tetrahedron Lett.* **1996**, *37*, 6427. de Oliveira, C. M. A.; Porto, A. L. M.; Bittrich, V.; Marsaioli, A. J. *Phytochemistry* **1999**, *50*, 1073. Cuesta-Rubio, O.; Cuellar Cuellar, A.; Rojas, N.; Velez Castro, H.; Rastrelli, L.; Aquino, R. *J. Nat. Prod.* **1999**, *62*, 1013.
(13) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939.
(14) Grossman, R. B. *Synlett* **2001**, 13.
(15) Hashimoto, S.; Miyazaki, Y.; Shinoda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1990**, 1100.
(16) Moloney, M. G.; Pinhey, J. T.; Roche, E. G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 333.
(17) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(18) White, J. D.; Skeean, R. W.; Trammell, G. L. *J. Org. Chem.* **1985**, *50*, 1939.
(19) Gorgues, A.; Simon, A.; Le Coq, A.; Hercouet, A.; Corre, F. *Tetrahedron* **1986**, *42*, 351.

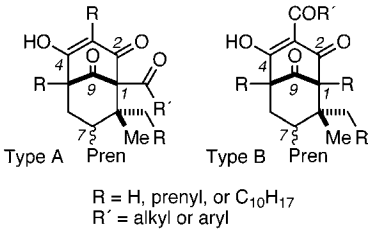


Figure 1. The polycyclic polyprenylated acylphloroglucinols (PPAPs).

in the presence of unhindered alkene and carbonyl groups. Only one precedent stood out: an alkyne was syn hydrosilylated with Et_3SiH via its $Co_2(CO)_6$ complex, and terminal alkenes in the substrate were unaffected.[20] We obtained the $Co_2(CO)_6$ complex of **7** in 87% yield, despite the steric encumbrance around the C≡C bond in **7**, and treatment of the complex with excess Et_3SiH in the presence of $Me_3SiC{\equiv}CSiMe_3$ gave the (*E*)-α-silyl enal **8** in 94% yield with complete regio- and stereoselectivity. Furthermore, acid-catalyzed cyclization of **8** cleanly gave separable aldols **9a** and **9b** in 72% combined yield (ca. 1:1 crude dr). The faster-moving, crystalline diastereomer was initially proposed to be **9a** because its ^{1}H NMR spectrum showed long-range allylic coupling between H(2) and H(4), whereas that of the slower, liquid diastereomer did not. The assignment of the former compound as **9a** was later confirmed by X-ray crystallographic analysis. Also, a NOESY spectrum of the latter compound showed a cross-peak between a resonance attributed to H(4) and one attributed to H(6) or H(7), confirming it as **9b**. Aldols **9** not only contain the bicyclo[3.3.1]nonane skeleton and all three quaternary centers of the type A PPAPs (Figure 1), but they also contain functionality that is suitable for elaboration into the 2-prenyl-1,3-diketone moiety of nemorosone (Scheme 1) and several other type A PPAPs.

To our knowledge, the conversion of **5** to **9** constitutes the first application of 3,3-diethoxypropyne to α,α′-annulation, in which it acts as a synthetic equivalent to *cis*-*β*-chloroacrolein. Undoubtedly, Shibasaki was expecting a *cis*-*β*-chloroacrylate to behave similarly when he combined it with a 2-acylcyclohexanone,[7] but in this case, reaction occurred at the *γ*-position, not the α-position, of the nucleophile, and the acrylate-derived *π* bond of the adduct had isomerized to the trans configuration, necessitating a lengthy, awkward, and technically difficult sequence of steps to achieve the desired aldol reaction.

In conclusion, we have developed a short and efficient synthetic approach to the bicyclo[3.3.1]nonane skeleton of the PPAPs that involves a novel three-carbon α,α′-annulation of a sterically hindered cyclic *β*-keto ester with 3,3-diethoxypropyne. The alkynylation reaction permits the construction of the two contiguous quaternary centers of the PPAPs in reasonable yield and without complications from O-alkylation or retro-Michael, -Claisen, or -Dieckmann reactions. We have also successfully applied a recently developed syn hydrosilylation[20] to the very hindered product of this alkynylation reaction. The greatest remaining obstacle to the synthesis of a PPAP is probably the transformation of the 2-silyl-2-alken-1-ol moiety of **9** into a 2-prenyl-1,3-diketone. Studies along this line are underway.

Acknowledgment. We thank the NIH (GM61002) for its support of this work. NMR instruments used in this research were obtained with funds from NSF's CRIF program (CHE-997841) and the University of Kentucky's Research Challenge Trust Fund.

Supporting Information Available: Experimental details for the preparation and full characterization of compounds **4**−**9**, X-ray data for **9a**, ^{1}H and ^{13}C NMR spectra of **5**−**7**, and NOESY spectrum of **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0357907

(20) Hosokawa, S.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 2609. Kira, K.; Tanda, H.; Hamajima, A.; Baba, T.; Takai, S.; Isobe, M. *Tetrahedron* **2002**, *58*, 6485.