J|A|C|S
COMMUNICATIONS

Published on Web 04/26/2006

An Unusual Cationic [2 + 2] Cycloaddition in a Divergent Total Synthesis of Hongoquercin A and Rhododaurichromanic Acid A

Aleksey V. Kurdyumov and Richard P. Hsung*

Division of Pharmaceutical Sciences and Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53705

Received July 20, 2005; E-mail: rhsung@wisc.edu

(+)-Hongoquercin A (**1**) was isolated from an unidentified terrestrial fungus[1a] and exhibits antibacterial properties toward methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*.[1,2a] We envisioned a bioinspired strategy[3] for the construction of **1** that would feature a Stork−Eschenmoser−Johnson polyene cyclization[4−8] employing daurichromenic ester **2**,[9] which can be synthesized via a formal *oxa*-[3 + 3] cycloaddition.[10−13] There are vast precedents in polyene cyclizations, including those closely related and reported by Õmura and Smith[14,15] as well as Parker,[16] using **5**. The proposed cationic polyene cyclization is unusual[7] given that the position of the third olefin in the chromene nucleus is three carbons away from the second olefin and *exo* to the pending ring. Thus, pursuit of this *exo*-polyene cyclization could lead to an unexpected outcome. We report here this unique polyene cyclization and an unusual cationic [2 + 2] cycloaddition that led to a divergent total synthesis of hongoquercin A and rhododaurichromanic acid A.Initial unsuccessful attempts involved various Lewis acids[8] and mercury reagents[17] as highlighted in Table 1 (entries 1−3). However, treating daurichromenic ester **2** with Brønsted acids, such as trifluoroacetic acid (TFA), changed the outcome especially when it was used at ≥30 equiv or as a cosolvent with CH_2Cl_2 (entries 4−10), as we isolated two products **6** and **7** with each as a single diastereomer,[18] and with no other relevant products or related stereoisomers being found.

To confirm our structural assignment of **6**, (+)-**6** was synthesized independently from enal (+)-**8**[19] (Scheme 2). Chromene (+)-**6** spectroscopically matched with (±)-**6** isolated from the polyene cyclization. To complete the total synthesis, reduction of (+)- or (±)-**6** was accomplished with TFA/TESH,[20] and the ensuing saponification gave (+)- or (±)-**1** as a single diastereomer in 95% overall yield that spectroscopically matched completely with Mori's report,[1a] and date for the potassium salt of our sample also matched with that reported in the isolation.[2a,18]

We did not know the identity of **7** initially except that it was the major product in all cases. In addition, **7** appeared to be more sensitive toward TFA and decomposed under prolonged reaction time (entries 5 and 8 in Table 1). Interconversion between **6** and **7** was not observed when individual pure samples were subjected to the reaction conditions.

Ultimately, X-ray structure of a *para*-bromobenzoate derivative **10** was obtained (Scheme 3). We were surprised to find that it possessed a caged tricyclic structural motif with a cyclobutane that closely matched rhododaurichromanic acid A (see **12**) and B, which only differs from A stereochemically at C19-Me (see hollow arrow in **10**).[21,22] A subsequent total synthesis of rhododaurichromanic acid A (**12**) was achieved from **7**.[23]

Mechanistically, as postulated in Scheme 4, the formation of **6** likely proceeds through the classic polyene cyclization via **13** and **14**. The observed high diastereoselectivity is remarkable given that the existing stereocenter at C8 is rather remote from C3−4 olefin, which is the initiating site. This stereochemical control is likely a result of geometric and conformational arrangement of the triene motif required during the cyclization.[7]

The cyclobutane formation in **7** is, however, much more intriguing and can be rationalized as follows. Daurichromenic ester **2** could be ionized first through protonation of the chromene oxygen to give allyl cation **15**, which is stabilized by the aromatic ring. The C15−10 bond formation could then occur to give **16**. It is noteworthy that the other possibility could have been the formation of the C15−5 bond from **15**, which would have been a six-membered

Scheme 1

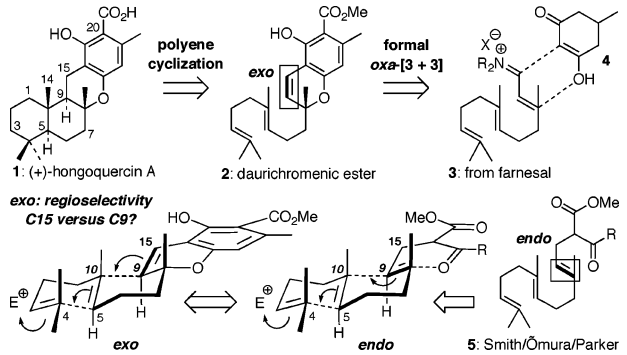
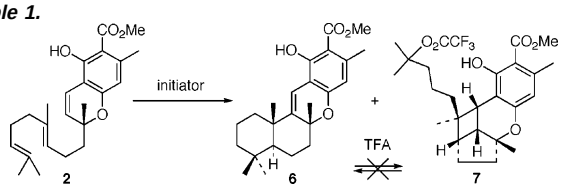
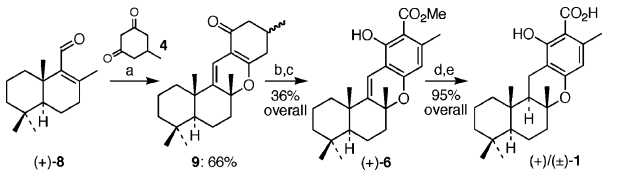


Table 1.



entry	initiator (equiv)		solvent	temp (°C)	time yields (h)	6	7
1	$SnCl_4$ (2.0)		CH_2Cl_2	0	2	no reaction	
2	BF_3-Et_2O (6.0)		CH_2Cl_2	−78 to −10	2	no reaction	
3	$Hg(OTf_2)$ (1.5)		CH_3Cl_2	−78	3	no reaction	
4	TFA (5.0-10.0)		CH_2Cl_2	−78 to rt	0.5−48	trace	trace
5	TFA (30.0)		CH_2Cl_2	−78 to −10	0.5−16	16%	20%
6	TFA	1:3	CH_2Cl_2	−78 to rt	1	19%	35%
7	TFA	1:5	CH_2Cl_2	−78 to rt	3.5	16%	36%
8	TFA	1:5	CH_2Cl_2	−78 to 0	17	23%	trace
9	TFA/TFAA	1:20	CH_2Cl_2	0 to rt	0.5	19%	35%
10	TFA	1:20	CH_2Cl_2	0 to rt	3	17%	27%

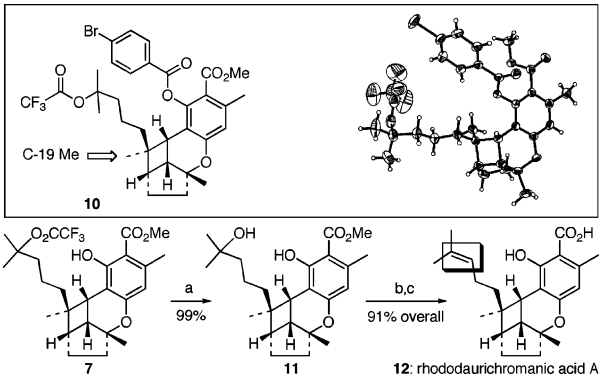
Scheme 2 [a]



[a] Conditions: (a) piperidinium acetate, EtOAc, 85 °C, 16 h; (b) LDA, −78 °C, $NCCO_2Me$; (c) DDQ, PhH, 2 days, 60 °C; (d) TFA, TESH, CH_2Cl_2, reflux; (e) aq KOH, MeOH/THF.

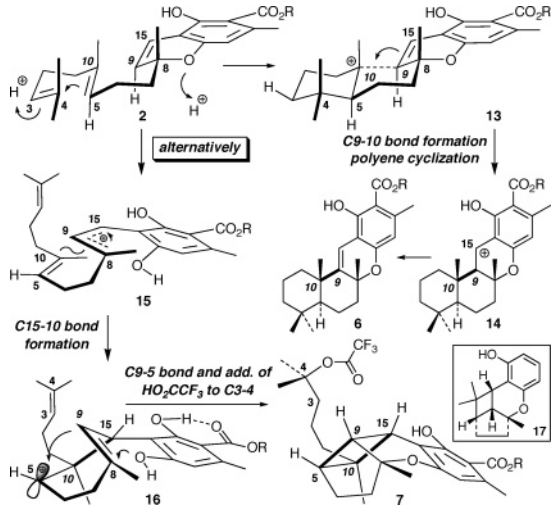
10.1021/ja054872i CCC: $33.50 © 2006 American Chemical Society

Scheme 3 [a]



[a] Conditions: (a) K_2CO_3, MeOH/THF, rt; (b) Burgess reagent, toluene, reflux; (c) 6 M aq NaOH, MeOH, rt.

Scheme 4



ring formation instead of the seven-membered ring shown in **16**. However, this would lead to a *trans*-olefin within the six-membered ring. In addition, the geometric constraint of the allyl cation, which is conserved throughout the cyclization, likely prevents this bond formation. The ensuing addition of C8−9 olefin to the secondary carbocation at C5 would follow to give the C9−5 bond formation. The subsequent trapping of the tertiary C8 cation with the non-hydrogen bonded phenolic oxygen should reconstitute the chromene nucleus, although both phenoxide groups could potentially trap the C8 cation.

The formation of the tertiary trifluoroacetate is likely independent of the process, or could inhibit the classic polyene cyclization if the addition of TFA to the C3−4 olefin occurs first. A related system devoid of the C3−4 olefin also led to the respective cyclobutane in 60% yield as a single diastereomer (see the box),[18] thereby suggesting that the C3−4 olefin has no impact on the cyclobutane formation. An optically enriched sample of **2** was rather very difficult to attain, although its cyclization could lead to further mechanistic insight.[24] Overall, the proposed pathway appears to be reasonable and resembles a Gassman-like cationic [2 + 2] cycloaddition.[25]

We have described an unusual polyene cyclization and cationic [2 + 2] cycloaddition that led to a divergent total synthesis of hongoquercin A and rhododaurichromanic acid A. The uncovered cationic cyclobutane formation could be relevant to the biosynthetic pathway for other cyclobutane-containing terpenoids.

Acknowledgment. The authors thank NIH (NS38049) for support, and Dr. Victor Young for X-ray analysis.

Supporting Information Available: Experimental procedures, NMR spectra and characterizations for all new compounds, and X-ray data (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Roll, D. M.; Manning, J. K.; Carter, G. T. *J. Antibiot.* **1998**, *51*, 635. (b) For fermentation studies, see: Abbanat, D. A.; Singh, M. P.; Greenstein, M. *J. Antibiot.* **1998**, *51*, 708.

(2) For the sole total synthesis, see: (a) Tsujimori, H.; Bando, M.; Mori, K. *Eur. J. Org. Chem.* **2000**, 297. (b) Tsujimori, H.; Mori, K. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 1410.

(3) For a review, see: Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131.

(4) (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.

(5) Stadler, P. A.; Eschenmoser, A.; Schinz, H.; Stork, G. *Helv. Chim. Acta* **1957**, *40*, 2191.

(6) Also see: (a) Woodward, R. B.; Block, G. *J. Am. Chem. Soc.* **1953**, *75*, 2023. (b) Johnson, W. S.; Crandall, J. K. *J. Org. Chem.* **1965**, *30*, 1785.

(7) For reviews, see: (a) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1. (b) Barlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, pp 341−409. Also see: (c) Crombie, L.; Ponsford, R. *Chem. Commun.* **1968**, 894. (d) Yagen, B.; Mechoulam, R. *Tetrahedron Lett.* **1969**, *10*, 5353.

(8) For some recent examples, see: (a) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc*. **2004**, *126*, 11122. (b) Kumazawa, K.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2004**, *6*, 2551. (c) Zhang, J.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3215. (d) Barrero, A. F.; Cuerva, J. M.; Herrador, M. M.; Valdivia, M. V. *J. Org. Chem.* **2001**, *66*, 4074.

(9) Jpn. Kokai Tokyo Koho, JP 82−28080, 1982.

(10) For reviews, see: (a) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem.* **2005**, *3*, 1349. (b) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23.

(11) (a) Kurdyumov, A. V.; Gullickson, G. C.; Lin, N.; Cole, K. P.; Swidorski, J. J.; Sydorenko, N.; Hsung, R. P. *Org. Lett.* **2006**, *8*, 191. (b) Shen, H. C.; Wang, J.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Liu, J.; Wei, L.-L.; Sklenicka, H. M.; Zehnder, L. R.; Zificsak, C. A. *J. Org. Chem.* **2003**, *68*, 1729.

(12) (a) Hsung, R. P.; Cole, K. P.; Zehnder, L. R.; Wang, J.; Wei, L.-L.; Yang, X.-F.; Coverdale, H. A. *Tetrahedron* **2003**, *59*, 311. (b) Cole, K. P.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4843.

(13) For some recent examples, see: (a) Olson, B. S.; Trauner, D. J. *Synlett* **2005**, 700. (b) Itoh, K.; Hasegawa, M.; Tanaka, J.; Kanemasa, S. *Org. Lett.* **2005**, *7*, 979. (c) Pettigrew, J. D.; Cadieux, J. A.; So, S. S. S.; Wilson, P. D. *Org. Lett.* **2005**, *7*, 467. (d) Grecian, S.; Wrobleski, A. D.; Aubé, J. *Org. Lett.* **2005**, *7*, 3167. (e) Sagar, R.; Singh, P.; Kumar, R.; Maulik, P. R.; Shaw, A. K. *Carbohydr. Res.* **2005**, *340*, 1287. (f) Lee, Y. R.; Kim, D. H. *Synthesis* **2006**, 603. (g) Lee, Y. R.; Lee, W. K.; Noh, S. K.; Lyoo, W. S. *Synthesis* **2006**, 853.

(14) Ḥanda, M.; Sunzazuka, T.; Sugawara, A.; Harigaya, Y.; Otoguro, K.; Ōmura, S. *J. Antibiot.* **2003**, *56*, 730.

(15) (a) Smith, A. B., III; Kinsho, T.; Sunazuka, T.; Ōmura, S. *Tetrahedron Lett.* **1996**, *37*, 6461. (b) Tomoda, H.; Tabata, N.; Nakata, Y.; Nishida, H.; Kaneko, T.; Obata, R.; Sunzazuka, T.; Ōmura, S. *J. Org. Chem.* **1996**, *61*, 882.

(16) Parker, K. A.; Resnick, L. *J. Org. Chem.* **1995**, *60*, 5726.

(17) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806.

(18) Procedures and characterizations can be found in Supporting Information.

(19) (a) Hua, D. H.; Huang, X.; Chen, Y.; Battina, S. K.; Tamura, M.; Noh, S. K.; Koo, S. I.; Namatame, I.; Tomoda, H.; Perchellet, E. M.; Perchellet, J.-P. *J. Org. Chem.* **2004**, *69*, 6065. (b) Chackalamannil, S.; Wang, Y.; Xia, Y.; Czarniecki, M. *Tetrahedron Lett.* **1995**, *36*, 5315.

(20) Hydrogenation of **10** using Pd−C gave a 10:1 isomeric mixture.

(21) For isolation, see: Kashiwada, Y.; Yamzaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioko, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559.

(22) For total syntheses, see: (a) Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935. (b) Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett*. **2003**, *5*, 4481. (c) Hu, H.; Harrison, T. J.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 3782. (d) Lee, Y. R.; Wang, X. *Bull. Korean Chem. Soc.* **2005**, *26*, 1933.

(23) The Burgess elimination also gave the terminal olefinic isomer; see Supporting Information.

(24) We thank one of the reviewers for suggesting this informative experiment. We are currently still pursuing the synthesis and cyclization of an enantiomerically pure substrate to examine the stereochemical outcome in terms of inversion, retention, or racemization.

(25) (a) Gassman, P. G.; Chavan, S. P.; Fertel, L. B. *Tetrahedron Lett.* **1990**, *31*, 6489. (b) Gassman, P. G.; Lottes, A. C. *Tetrahedron Lett.* **1992**, *33*, 157.

JA054872I