ORGANIC LETTERS

2006
Vol. 8, No. 5
819−821

Diels–Alder Reactions of Oroidin and Model Compounds

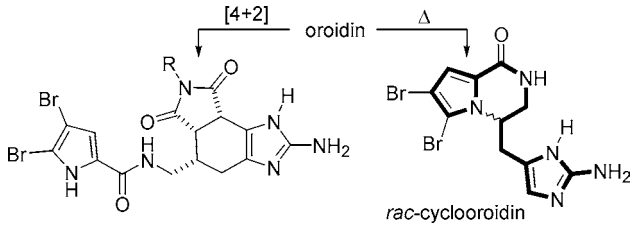
Christoph Pöverlein, Gregor Breckle, and Thomas Lindel*

Department of Chemistry and Biochemistry, Ludwig Maximilian University, Butenandtstrasse 5-13, D-81377 Munich, Germany

thomas.lindel@cup.uni-muenchen.de

Received October 28, 2005

ABSTRACT



It is shown that the marine key metabolite oroidin undergoes Diels–Alder reactions with electron-poor dienophiles. However, on heating of oroidin in the absence of any reaction partner, cyclization to the natural product cyclooroidin takes place. This is the first direct conversion of oroidin to another pyrrole-imidazole alkaloid.

Oroidin (**1**) is the parent compound of the pyrrole-imidazole alkaloids, a structurally versatile family of marine natural products with various biological activities.[1,2] Dibromoageliferin (**2**) from the sponge *Agelas* sp. formally arises through a Diels−Alder cyclodimerization of oroidin (**1**), followed by double bond migration into the aromatic imidazole ring (Figure 1).[3] Recently, Baran et al. have synthesized ageliferin through ring expansion of the cyclobutanoid [2 + 2] dimer sceptrin.[4] In this communication, we would like to report on the behavior of the parent compound oroidin and a few model compounds in the presence and absence of dienophiles under thermal conditions.

Quite a few cycloadditions have been investigated with 2-unsubstituted 4(5)-alkenylimidazoles. Walters and Lee reported the [4 + 2] cycloaddition of electron-rich N-alkylated 5-alkenylimidazoles and *N*-phenylmaleimide.[5] Lovely et al. reported inter- and intramolecular Diels−Alder reactions of various N-functionalized 4-alkenylimidazoles as diene component with electron-poor dienophiles including *N*-phenylmaleimide[6] and covalently bound urocanic amide.[7]

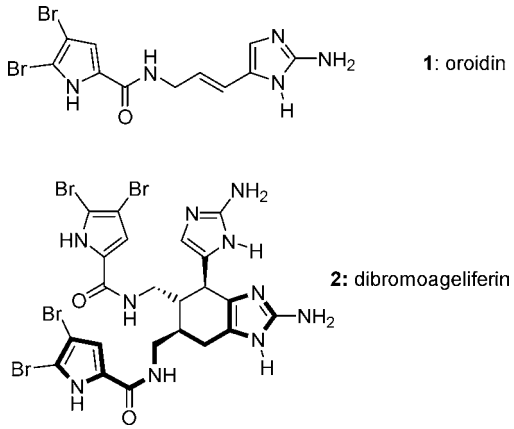


Figure 1. Oroidin (**1**) and the dimer dibromoageliferin (**2**).

(1) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237−243.
(2) Reviews on the synthesis of the pyrrole-imidazole alkaloids: (a) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753−1783. (b) Jacquot, D. E. N.; Lindel, T. *Curr. Org. Chem.* **2005**, *9*, 1551−1565.
(3) (a) Kobayashi, J.; Tsuda, M.; Murayama, T.; Nakamura, H.; Ohizumi, Y.; Ishibashi, M.; Iwamura, M.; Ohta, T.; Nozoe, S. *Tetrahedron* **1990**, *46*, 5579−5586. (b) Keifer, P. A.; Schwartz, R. E.; Koker, M. E. S.; Hughes, R. G., Jr.; Rittschof, D.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 2965−2975. (c) Assmann, M.; Köck, M. *Z. Naturforsch., C: Biosci.* **2002**, *57*, 157−160.
(4) Baran, P. S.; O'Malley, D. P.; Zografos, A. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 2674−2677.

10.1021/ol0526219 CCC: $33.50
Published on Web 02/04/2006

Romo et al. analyzed the Diels−Alder reaction of N,N′-disubstituted 2-imidazolones with unsaturated lactames.[8] Furthermore, 2-silylated[9] and 2-sulfanylated 5-alkenylimidazoles have been studied, the latter leading Ohta et al.[10] to the synthesis of 15,15′-dimethylageliferin.

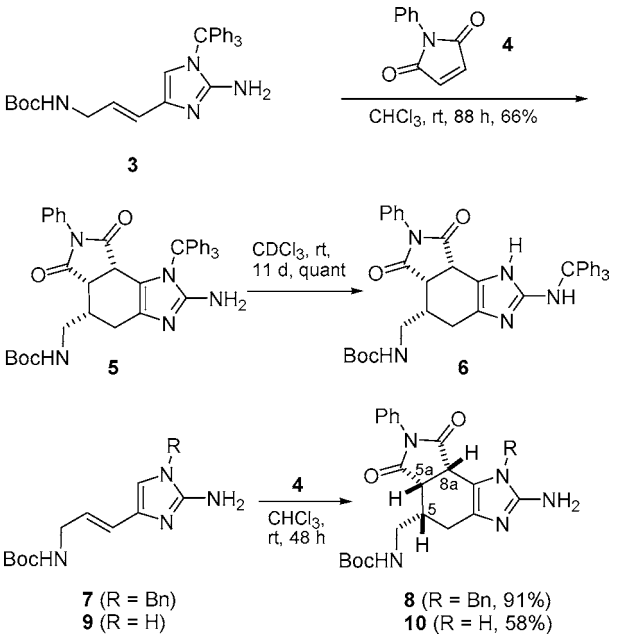
However, no [4 + 2] cycloaddition has been reported for oroidin itself or for any related 4(5)-alkenylimidazole bearing an amino substituent in the imidazole 2-position, although this may be relevant for the chemical understanding of the pyrrole-imidazole alkaloids.[11]

The 2-amino group renders electron density to the alkenylimidazole system. Al Mourabit et al. discussed the ambivalent reactivity of various tautomers of 2-amino-4(5)-alkenylimidazoles, which, according to ab initio calculations, should be energetically almost equal.[12]

We started with model studies on dienes **3**,[13] **7**, and **9** representing the amino component of the amide oroidin ("eastern section", Scheme 1). Compound **7** is accessible from 1-benzyl-4-iodoimidazole via Sonogashira coupling with Boc-protected propargylic amine, followed by azidation at C-2 and reduction with Red-Al. Diene **9** was obtained via chemoselective detritylation of **3** on treatment with MeOH/HOAc (10:1) under reflux (12 h, 95%) retaining the Boc group. For reasons of comparability with earlier studies,[5,6] we chose *N*-phenylmaleimide and maleimide as reactive dienophiles.

Conversions were almost quantitative by TLC. Cycloadduct **5** was obtained at room temperature on reaction of **3** with *N*-phenylmaleimide. Already during workup of **5** we observed some conversion to the rearranged product **6** with the trityl group now attached to the terminal amino group. Prolonged standing in $CDCl_3$ led to complete conversion of **5** to **6**. However, cycloadduct **8** obtained from the benzyl analogue **7** was stable. Cycloaddition also occurred starting from diene **9** in the absence of an imidazole protecting group providing **10** in 58% yield after workup. The polar character of the unprotected 2-amino imidazole moiety led to some loss of material during chromatography on silica. We did not observe any of the initial Diels−Alder products with the double bond in the exocyclic position of the imidazole ring, probably because rapid tautomerization occurs via the NH groups of the 2-aminoimidazole moiety.

Scheme 1. Model Study on the Diels−Alder Reaction of 2-Amino-4-alkenylimidazoles with *N*-Phenylmaleimide



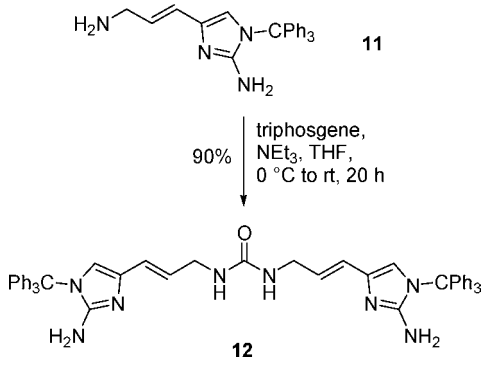
MM2 and PM3 calculations indicate that the energy difference between the endo and exo products is smaller than 2 kcal/mol. However, NOESY spectra of **5**, **6**, and **8** indicate that the endo products were formed. In particular, correlations between 5-H/5a-H and 5a-H/8a-H were observed. The endo selectivity of the cycloaddition is in agreement with earlier observations by Romo et al.[8] and Lovely et al.[6] The endo product should be kinetically preferred.[5] On treatment with [D_4]MeOH, we observed exchange of 8a-H. However, no diastereomeric product was formed, even on prolonged reaction times. Reprotonation at C-8a appears to always occur from the same side.

We did not observe any Diels−Alder homodimerization of the 2-aminoimidazoles competing with the reaction of maleimide. Heating of **3** or **9** in the absence of maleimide did not yield any isolable product either. Even if two eastern sections of oroidin were covalently connected to each other by a urea linkage (conversion of compound **11**[13] to **12**; Scheme 2), we were not able to thermally induce a [4 + 2] cycloaddition. We had been encouraged to that experiment by the fact that N,N′-disubstituted ureas can be cyclized to seven-membered rings, for instance, via intramolecular Heck reaction.[14]

In which manner would the natural product oroidin itself behave? Reflecting the reactivity of our model compounds, oroidin (**1**·HCO_2H, obtained by total synthesis as the formate[15]) starts to react with *N*-phenylmaleimide and maleimide already at room temperature. Addition of $Y(OTf)_3$ (20 mol %) led to acceleration of the Diels−Alder reactions

(5) Walters, M. A.; Lee, M. D. *Tetrahedron Lett.* **1994**, *35*, 8307−8310.
(6) (a) Lovely, C. J.; Du, H.; Dias, H. V. R. *Org. Lett.* **2001**, *3*, 1319−1322. (b) Lovely, C. J.; Du, H.; Dias, H. V. R. *Heterocycles* **2003**, *50*, 1−7. (c) Lovely, C. J.; Du, H.; He, Y.; Dias, H. V. R. *Org. Lett.* **2004**, *6*, 735−738.
(7) He, Y.; Chen, Y.; Wu, H.; Lovely, C. J. *Org. Lett.* **2003**, *5*, 3623−3626.
(8) (a) Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535−1538. (b) Dransfield, P. J.; Wang, S.; Dilley, A.; Romo, D. *Org. Lett.* **2005**, *7*, 1679−1682.
(9) Deghati, P. Y. F.; Wanner, M. J.; Koomen, G. J. *Tetrahedron Lett.* **1998**, *39*, 4561−4564.
(10) Kawasaki, I.; Sakaguchi, N.; Fukushima, N.; Fujioka, N.; Nikaido, F.; Yamashita, M.; Ohta, S. *Tetrahedron Lett.* **2002**, *43*, 4377−4380.
(11) The amino component of the amide oroidin has been dimerized with concomitant oxidation: Olofson, A.; Yakushijin, K.; Horne, D. A. *J. Org. Chem.* **1997**, *62*, 7918−7919.
(12) Abou-Jneid, R.; Ghoulami, S.; Martin, M.-T.; Dau, E. T. H.; Travert, N.; Al-Mourabit, A. *Org. Lett.* **2004**, *6*, 3933−3936.
(13) Breckle, G.; Polborn, K.; Lindel, T. *Z. Naturforsch., B: Chem. Sci.* **2003**, *58*, 451−456.
(14) Hayashi, M.; Sai, H.; Horikawa, H. *Heterocycles* **1998**, *48*, 1331−1335. A discussion on the estimated energetics of the putative cyclization of **12** is included in the Supporting Information.
(15) Oroidinium formate was obtained by refluxing *N*-trityloroidin (synthesized via compound **3**, ref 13) in $CHCl_3$−MeOH−HCO_2H (2:2:1).

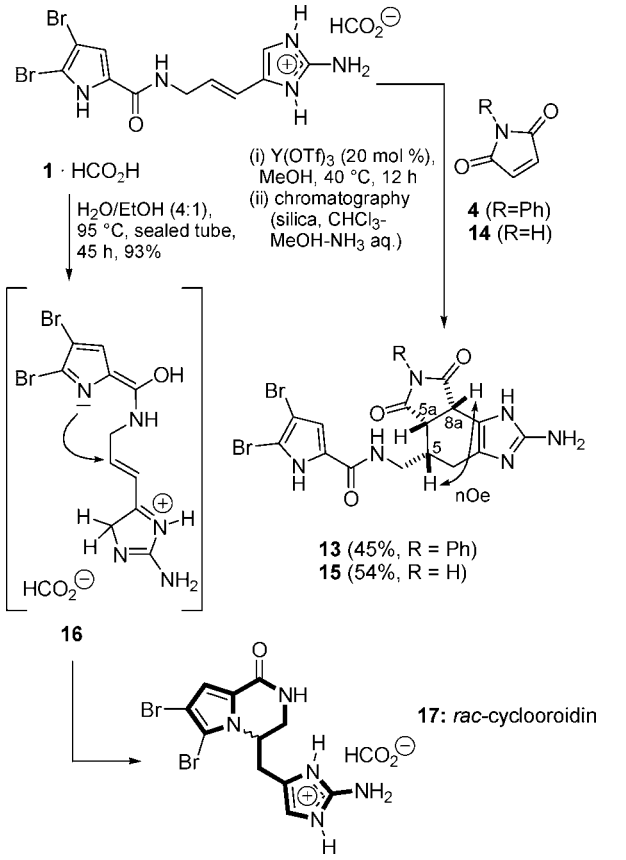
Scheme 2. Covalently Linked Eastern Sections of Oroidin



of oroidin, providing the endo cycloadducts **13** and **15** in good yields.[16] The stereochemistry of **15** was determined by NOESY experiments. Compounds **13** and **15** constitute the first Diels−Alder adducts of oroidin (Scheme 3).

A surprising product was formed on heating of oroidin formate (**1**·HCO_2H) in the absence of maleimides above 65 °C in protic solvents. The double bond had disappeared, but the product had a molecular formula identical to that of oroidin. Instead of a Diels−Alder reaction, cyclization had taken place affording *rac*-cyclooroidin formate (**17**) in almost quantitative yield. As an intermediate, the azafulvene tautomer **16** is proposed. Our chemical study shows that, in the absence of enzymes under thermal conditions in protic solvent, cyclization of oroidin to cyclooroidin is preferred over [4 + 2] cyclodimerization to dibromoageliferin. According to PM3 calculations, the reaction enthalpies of both alternative reactions are expected to be comparable. However, formation of cyclooroidin (**17**) is entropically favored. In the sponge, this process may be enzyme-assisted, since cyclooroidin had been reported as an optically active natural product from *Agelas oroides*.[17] The cyclization of oroidin (**1**) to *rac*-cyclooroidin (**17**) constitutes the first conversion of that marine key metabolite to another pyrrole-imidazole alkaloid.[18−20]

Scheme 3. Diels-Alder Reaction and Cyclization of Oroidinium Formate (**1**·HCO_2H)



Acknowledgment. We thank Mrs. Petra Böhrer for the synthesis of oroidin. Thomas Schwarz is thanked for the preparation of **7**.

Supporting Information Available: Detailed experimental procedures, characterization data for all new compounds, and molecular modeling. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0526219

(16) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* **2001**, 439−455.

(17) Fattorusso, E.; Taglialatela-Scafati, O. *Tetrahedron Lett.* **2000**, *41*, 9917−9922.

(18) For a pioneer cyclization of dihydrooroidin, see: Foley, L. H.; Büchi, G. *J. Am. Chem. Soc.* **1982**, *104*, 1776−1777.

(19) For an oxidative cyclization of oroidin in DMSO/TFA, see: Lindel, T.; Breckle, G.; Hochgürtel, M.; Volk, C.; Grube, A.; Köck, M. *Tetrahedron Lett.* **2004**, *45*, 8149−8152.

(20) While this manuscript was under review, an alternative total synthesis of *rac*-cyclooroidin was published: Papeo, G.; Gómez-Zurita Frau, M. A.; Borghi, D.; Varasi, M. *Tetrahedron Lett.* **2005**, *46*, 8635−8638.