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Oxidative Rearrangement of Imidazoles with Dimethyldioxirane

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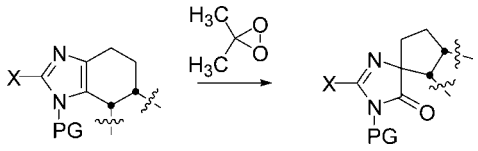
ABSTRACT



Tetrahydrobenzimidazoles, on treatment with dimethyldioxirane, rearrange to provide 5-imidazolones exclusively. These rearrangements proceed with a broad range of substrates and with good to excellent levels of diastereoselectivity.

The oroidin-derived alkaloids are a diverse family of marine natural products that result from various modes of functionalization and cyclization of the parent heterocycle (**1**, Figure 1).[1,2] Among the most complex members of this family of natural products are the oroidin dimers palau'amine **2**,[3] massadine **3**,[4] and axinellamine A **4**.[5] Although these molecules differ in their connectivity and relative stereochemical relationships, they result from the formal dimerization of two molecules of oroidin (or derivatives), and each possesses one spiro-fused cyclopentylimidazole system. The structural complexity found in these systems coupled with their potentially useful biological activity renders them attractive synthetic targets.[3−5] One of the notable challenging features of these three molecules lies in the hexasubstituted cyclopentane ring system (e.g., the E-ring of palau'amine).[6] Our

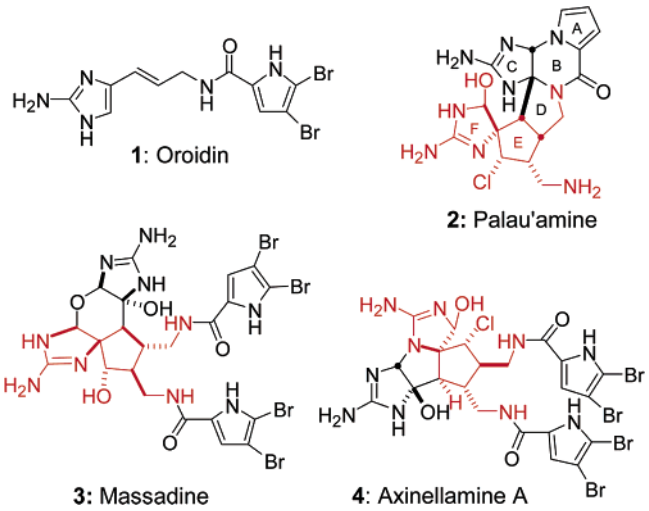


Figure 1. Some oroidin-derived dimers.

laboratories[7] and those of Romo[8] recognized that the Diels−Alder/rearrangement sequence proposed by Kinnel and Scheuer[3a] as a possible biosynthetic pathway represented an

(1) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, 1.
(2) (a) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237. (b) Hoffman, H.; Lindel, T. *Synthesis* **2003**, 1753.
(3) (a) Kinnel, R. B.; Gehrken, H. P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376. (b) Kinnel, R.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281.
(4) Nishimura, S.; Matsunaga, S.; Shibazaki, M.; Suzuki, K.; Furihata, K.; van Soest, R. W. M.; Fusetani, N. *Org. Lett.* **2003**, *5*, 2255.
(5) Urban, S.; de Almeida Leone, P.; Carroll, A. R.; Fechner, G. A.; Smith, J.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **1999**, *64*, 731.
(6) For other approaches to the cyclopentane core, see: (a) Overman, L. E.; Rogers, B. N.; Tellow, J. E.; Trenkle, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7159. (b) Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8793. (c) Belanger, G.; Hong, F.-T.; Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Org. Chem.* **2002**, *67*, 7880. (d) Koenig, S. G.; Miller, S. M.; Leonard, K. A.; Loewe, R. S.; Chen, B. C.; Austin, D. J. *Org. Lett.* **2003**, *5*, 2203.

(7) (a) Lovely, C. J.; Du, H.; Dias, H. V. R. *Org. Lett.* **2001**, *3*, 1319. (b) Lovely, C. J.; Du, H.; Dias, H. V. R. *Heterocycles* **2003**, *60*, 1. (c) He, Y.; Chen, Y.; Wu, H.; Lovely, C. J. *Org. Lett.* **2003**, *5*, 3623.

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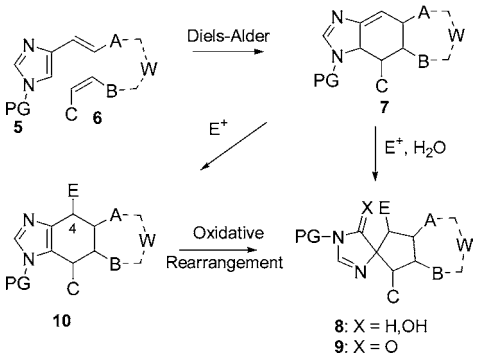
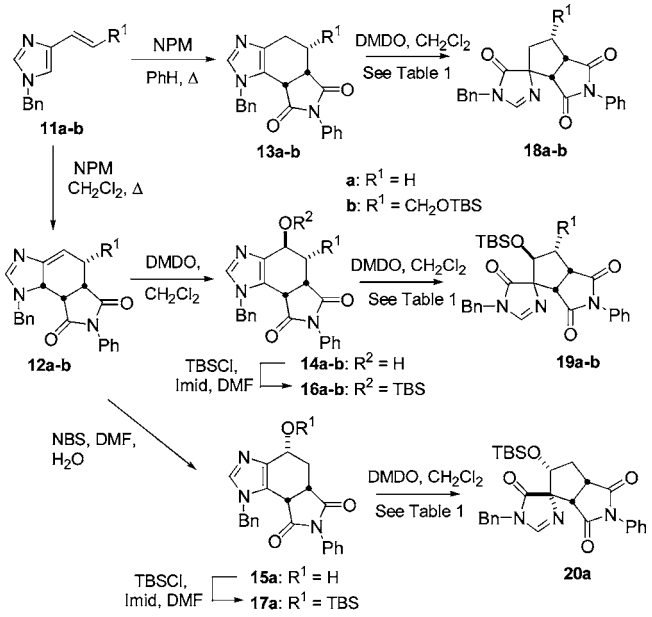
Scheme 1



attractive strategy to fashion this congested ring system (Scheme 1, **5** + **6** → **7** → **8**). We have recently demonstrated that 4-vinylimidazoles can participate as dienes in the Diels−Alder (DA) reaction, both inter- and intramolecularly to provide the tetrahydrobenzimidazoles (cf. Scheme 2, **11a** → **12a** or **13a**).[7] This communication describes our efforts to convert these DA adducts into spirobicyclic systems related to those found in **2**−**4** and the discovery of a novel oxidative rearrangement reaction.

Scheme 2



NPM = *N*-Phenylmaleimide

Our initial investigations centered on electrophile-induced rearrangement of the DA adduct (Scheme 1, **7** → **8**) akin to that proposed by Kinnel and Scheuer[3a] as a possible biosynthetic route to **2**.[9] Experiments in this vein were singularly unsuccessful due to aromatization (Scheme 1, **7** → **10**) rather than rearrangement and installation of the new functionality with the incorrect stereochemistry (at least for **2**).[10,11] During the course of these studies we became aware of two reports that suggested a related but alternate strategy. It had been demonstrated that tetrahydrobenzimidazoles rearrange, on treatment with base, an alkyl halide and singlet oxygen to provide a spiro cyclopentyl 4-imidazolone in low yield.[12] More recently, the groups of both Foote and Adam have demonstrated that *N*-acylindoles would rearrange via the 2,3-epoxyindole to 2-indolones on treatment with dimethyldioxirane (DMDO).[13] On the basis of these precedents, it appeared that the rearrangement of tetrahydrobenzimidazoles to spiroimidazolones with DMDO might be possible (Scheme 1, **10** → **9**). Further, if the substrates were functionalized in the 4-position (E = Cl or OH), then the net transformation proposed by Scheuer and Kinnel would have been achieved, albeit in separate steps.

Accordingly, we were delighted to discover that when DA adduct **13a**[7b] was treated at room temperature with a slight excess of DMDO, two spiro imidazolones were obtained in 56 and 27% yields.[14] The isolation of two products was not entirely unexpected given that (a) the faces of the imidazole are diastereotopic and (b), in principle, either 4- or 5-imidazolones could be produced; therefore, there is the potential for the formation of up to four isomeric rearrangement products. Fortunately, the major rearrangement product was amenable to study by X-ray crystallography, the results of which indicated that it was in fact the *exo* 5-imidazolone (Table 1, entry 1, *exo*-**18a**).[15] The other product was assigned as the corresponding *endo* 5-imidazolone (Table 1, entry 1, *endo*-**18a**).[16] Enamine **12a**[7b] can be converted into either the *exo* alcohol **14a** (89%) by oxidation with DMDO or the *endo* alcohol **15a** (91%, dr = 5:1) by reaction with NBS/H_2O. The alcohols, after protection as silyl ethers (**16a**, **17a**), were treated with DMDO and in each case 5-imidazolones, *endo*-**19a** and *exo*-**20a**, were obtained (Table 1, entries 2 and 3). X-ray analysis of each of these products revealed that the imidazolone carbonyl and the silyl ether were anti to one another. These results suggested that the stereochemistry of the rearrangement could be controlled through steric effects

(8) Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535.

(9) For related rearrangements, see: (a) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 557. (b) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147. (c) Ganesan, A.; Wang, H. *J. Org. Chem.* **2000**, *65*, 4685.

(10) Dilley and Romo encountered a similar problem in their approach to the spiro cyclic portion of palau'amine; see ref 8.

(11) Details of these studies will be reported elsewhere.

(12) Bernhart, C. A.; Perreaut, P. M.; Ferrari, B. P.; Muneaux, Y. A.; Assens, J.-L. A.; Clement, J.; Haudricourt, F.; Muneaux, C. F.; Taillades, J. E.; Vignal, M.-A.; Gougat, J.; Guiraudou, P. R.; Lacour, C. A.; Roccon, A.; Cazaubon, C. F.; Breliere, J.-C.; Le Fur, G.; Nisato, D. *J. Med. Chem.* **1993**, *36*, 3371.

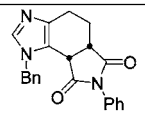
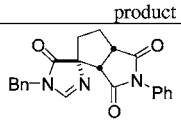
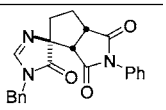
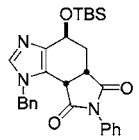
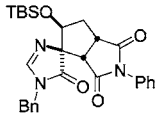
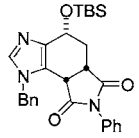
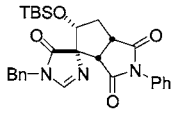
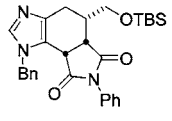
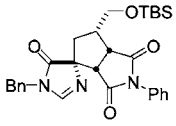
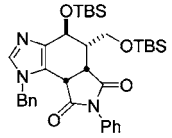
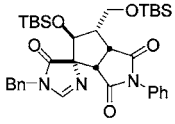
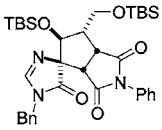
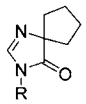
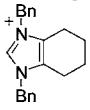
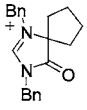
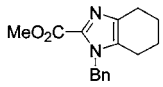
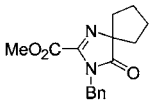
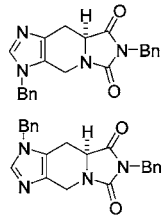
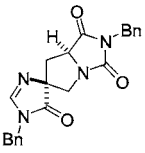
(13) (a) Adam, W.; Ahrweiler, M.; Sauter, M.; Schmiedeskamp, B. *Tetrahedron Lett.* **1993**, *34*, 5247. (b) Adam, W.; Ahrweiler, M.; Peters, K.; Schmiedeskamp, B. *J. Org. Chem.* **1994**, *59*, 2733. (c) Zhang, X.; Foote, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 8867.

(14) A third, as yet unidentified product was obtained from this reaction.

(15) Stereochemical descriptors *endo/exo* are used to indicate the orientation of the imidazolone carbonyl moiety with respect to the azabicyclo[3.3.0]octane.

(16) Supportive of this assignment is the ^{13}C NMR chemical shift of the imidazolone carbonyl carbon (δ = 180.4), which is consistent with those obtained for other 5-imidazolones prepared in this study, a number of which were characterized by X-ray crystallography.

Table 1. Yields and Products from the Oxidative Rearrangement

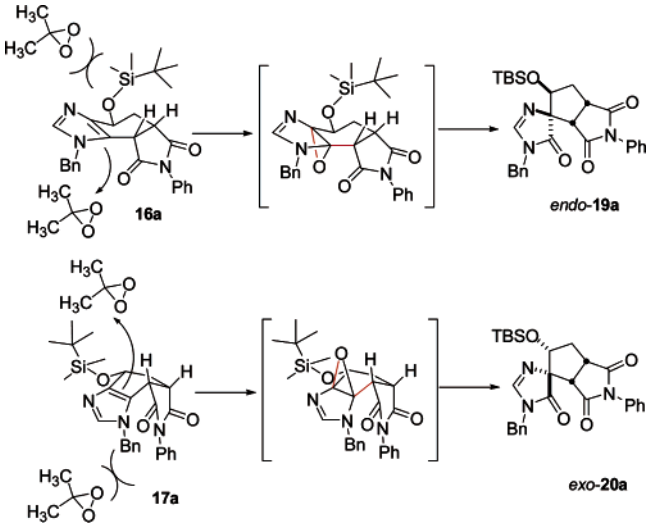
entry	substrate	product - yield/%[a]		
1	 **13a**	 *exo*-**18a**	56[b]	 *endo*-**18a**	27
2	 **16a**	 *endo*-**19a**	82[b]		
3	 **17a**	 *exo*-**20a**	44[b]		
4	 **13b**	 *exo*-**18b**	60		
5	 **16b**	 *exo*-**19b**	56[b]	 *endo*-**19b**	14
6	 **21** R = Bn	 **25**	73[c]		
7	**22** R = Me	**26**	70		
8	**23** R = MOM	**27**	60		
9	**24** R = SO_2NMe_2	**28**	0		
10	 **29**	 **30**	0		
11	 **31**	 **32**	40		
12	 4-**33**/5-**33**	 *exo*-**34**	45		

[a] See Supporting Information for reaction conditions. [b] Relative configuration was determined by X-ray analysis. [c] Regiochemistry was confirmed through unambiguous synthesis of the corresponding 4-imidazolone.

and that the 4-OTBS moiety directed oxidation from the opposite face (Scheme 3).

To further probe the potential of this rearrangement, the structurally more elaborate substrates (**13b** and **16b**) were prepared through a DA reaction of the urocanic acid-derived

Scheme 3



diene **11b**[17] with *N*-phenylmaleimide (NPM) from which, depending on the reaction conditions, either the enamine **12b** (76%) or the aromatic **13b** (88%) adduct could be obtained.[17] The former was subjected to treatment with DMDO to provide the corresponding *exo*-alcohol (**14b**, confirmed by X-ray analysis), which was then protected as the TBS-ether (**16b**). Exposure of **13b** to DMDO resulted in a smooth rearrangement to provide a single spiro 5-imidazolone. The stereochemistry of the newly installed center is believed to be *exo*, based on the $TBSOCH_2$-directing epoxidation in the *exo* direction (Table 1, entry 4, *exo*-**18b**). The more highly functionalized substrate **16b** was subjected to the DMDO-mediated rearrangement, providing two 5-imidazolones (Table 1, entry 5, *endo*- and *exo*-**19b**). Surprisingly, the major product was *exo*-**19b**, which was contrary to our expectation based on the anticipated stereodirecting effect of the 4-OTBS moiety (cf. **16a** → *endo*-**19a**. Examination of the X-ray structures for *exo*-**19b** (and to some extent **14b**)[17] provides a clue to some of the steric elements that may play a role in controlling the stereochemical outcome of this reaction.[18] In both cases, the hydroxymethyl group is disposed such that this moiety forces the succinimide to twist out of the plane to reduce the steric clash between the OTBS moiety and C6 in **16b** (Figure 2). The net effect of this is to force the other carbonyl substituent (C8) to adopt a pseudoaxial orientation, which then renders approach of the DMDO along this vector more difficult, leading to the observed preference for oxidation from the *exo* face.

All of these initial substrates possess similar electronic character (C2-substituent = H, and N1 = Bn) in the imidazole moiety, and therefore it was of interest to establish the influence of substituents on this rearrangement. To simplify product analysis, the parent tetrahydrobenzimidazole was selected for investigation, thus removing the complicat-

(17) See Supporting Information for the preparation of these substrates.
(18) Although we have no direct evidence, it is reasonable to assume a similar orientation for the hydroxymethyl group in **16b** since it would avoid a steric clash with the 4-OTBS moiety.

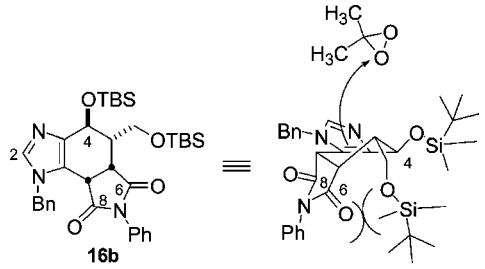
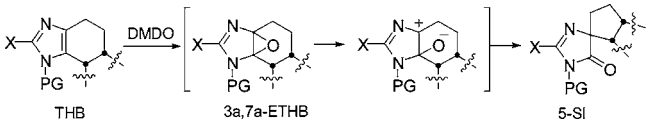


Figure 2. Proposed stereochemical model.

ing stereochemical component. After protection of tetrahydrobenzimidazole[19] with CH_3, Bn (one or two), MOM, or SO_2NMe_2 groups, the N-substituted derivatives (**21**−**24**, **29**) were treated with DMDO. Three of these derivatives, **21**−**23**, rearranged to provide 5-imidazolones in modest to good yields (Table 1, entries 6−8), whereas two, **24** and **29**, did not (Table 1, entries 9, 10). These results suggested that there was a requirement for the substrates to possess some minimal level of electron density for the oxidation to proceed. The 2-carboxymethyl derivative (**31**)[20] was prepared and evaluated; gratifyingly, this substrate underwent rearrangement to provide the corresponding imidazolone (**32**) in moderate yield. The histidine-derived substrate **33**[21] effectively rearranges under these conditions to provide a 5-imidazolone (**34**) as a single diastereomer.

One of the notable features of this rearrangement is the exclusive formation of 5-imidazolones rather than the isomeric 4-imidazolones (Scheme 4).[22] These results can be

Scheme 4



interpreted in terms of two factors. Sterically, the 5-imidazolone is less crowded than the isomeric 4-imidazolone since the spiro cyclopentyl ring is further removed from the N1-substituent. Second the carbocation (or electron-deficient carbons) leading to the 5-imidazolone is more stabilized than the corresponding carbocation leading to the 4-imidazolone.

In summary, we have identified a novel oxidative rearrangement of tetrahydrobenzimidazoles that selectively provides 5-imidazolones in good yields. These reactions proceed with moderate to excellent stereoselectivity via preferential oxidation at the least sterically hindered face. In addition, spiroimidazolones *exo*-**18b** and *exo*-**19b** contain the structural features of the DEF-rings of deschloropalau'amine and palau'amine, respectively, suggesting that the strategy outlined in Scheme 1 represents a workable approach to these targets. We are continuing to investigate the scope and limitations of this reaction in conjunction with its application in total synthesis efforts.

Acknowledgment. This work was supported by the Robert A. Welch Foundation (Y-1362) and the Texas Advanced Research Program (003656-0004-1999). X-ray diffraction studies on compounds **14b**, *exo*-**19b**, and *exo*-**20a** were performed at the Texas Center for Crystallography at Rice University funded by the Robert A. Welch Foundation.[23]

Supporting Information Available: Experimental procedures and characterization data for all of the compounds (^{1}H and ^{13}C NMR, IR, MS, and elemental analysis) and X-ray data (CIF) for compounds **14b**, *exo*-**18a**, *endo*-**19a**, *exo*-**19b**, *exo*-**20a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL036403W

(19) Tetrahydrobenzimidazole was prepared by the partial reduction of benzimidazole (Pd−C/H_2 at 75 psi, HOAc, 95 °C) in a minor modification of a literature procedure. Butula, I. *Croat. Chem. Acta* **1973**, *45*, 297.

(20) These compounds were prepared from 1-benzyltetrahydrobenzimidazole. For details see Supporting Information.

(21) Klutchko, S.; Hodges, J. C.; Blankley, C. J.; Colbry, N. L. *J. Heterocycl. Chem.* **1991**, *28*, 97. This material was obtained as a 1:1 mixture of 4- and 5-regioisomers

(22) The exact mechanism of this oxidative rearrangement is unknown at this time, and alternative mechanisms are certainly possible; however, it is convenient to formulate the rearrangement with the participation of the 3a,7a-epoxide and the resulting zwitterionic intermediate. See also: Wasserman, H. H.; Yoo, J. U.; DeSimone, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 9772.

(23) Inquiries regarding X-ray determinations should be directed to Dr. Simon Bott (University of Houston) at sbott@uh.edu.