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Intramolecular Diels–Alder Reactions of 4-Vinylimidazoles

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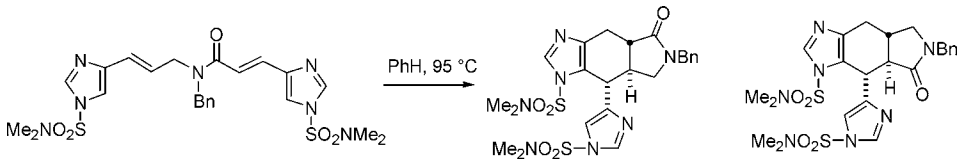
ABSTRACT



The synthesis of a variety of unsaturated ethers, esters, and amides derived from urocanic acid and their Diels–Alder reactions are reported. Propargylic ethers and esters cyclize with reasonable efficiencies, but the related mono- and unactivated olefins did not cyclize. On the other hand, the corresponding amines and amides, along with the doubly activated ester/amide derivatives participate in the cycloaddition reaction.

Our laboratory has been interested for some time in the development of methods for elaborating simple imidazoles into complex, marine-derived natural products.[1,2] Of particular interest have been several members of the oroidin class of molecules (Figure 1). The parent heterocycle (**1**), through various modes of cyclization and/or dimerization, provides a large variety of structurally interesting and biologically active natural products.[3] Among this class of marine alkaloids, we have been interested in developing approaches to palau'amine **2**,[4] ageliferin **3**,[5] and axinellamine A **4**.[6] This interest arises as a result of the possibility of utilizing Diels−Alder chemistry of vinylimidazoles to access

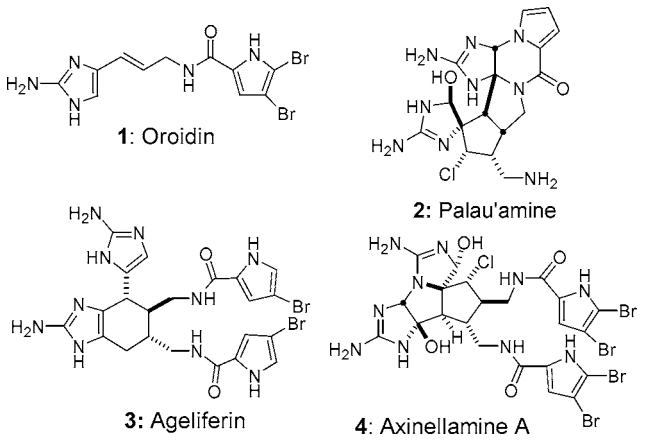


Figure 1. Oroidin and some oroidin-derived alkaloids.

the polysubstituted carbocycle in these alkaloids.[1a,7] When this project was initiated, little was known concerning the Diels−Alder reaction of imidazoles or vinylimidazoles,[8] although subsequently our own efforts[1a,b] and those of Ohta[5d]

(1) (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) Chen, Y.; Dias, H. V. R.; Lovely, C. J. *Tetrahedron Lett.* **2003**, *44*, 1379. (d) Lovely, C. J.; Du, H.; He, Y.; Dias, H. V. R. Manuscript in preparation.

(2) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, 1.

(3) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237.

(4) Isolation: Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281. Synthetic approaches: Overman, L. E.; Rogers, B. N.; Tellew, 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) Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535. (d) Belanger, G.; Hong, F.-T.; Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Org. Chem.* **2002**, *67*, 7880. (e) Koenig, S. G.; Miller, S. M.; Leonard, K. A.; Loewe, R. S.; Chen, B. C.; Austin, D. J. *Org. Lett.* **2003**, *5*, 2203.

(5) Isolation: (a) Kobayashi, J.; Tsuda, M.; Murayama, T.; Nakamura, H.; Ohizumi, Y.; Ishibashi, M.; Iwamura, M.; Ohta, T.; Nozoe, S. *Tetrahedron* **1990**, *46*, 5579. (b) Williams, D. H.; Faulkner, D. J. *Tetrahedron* **1996**, *52*, 5381. (c) Keifer, P. A.; Schwartz, R. E.; Koker, M. E. S.; Hughes, R. G.; Rittschof, D.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 2965. (d) Synthetic approaches: Kawasaki, I.; Sakaguchi, N.; Fukushima, N.; Fujioka, N.; Nikaido, F.; Yamashita, M.; Ohta, S. *Tetrahedron Lett.* **2002**, *43*, 4377.

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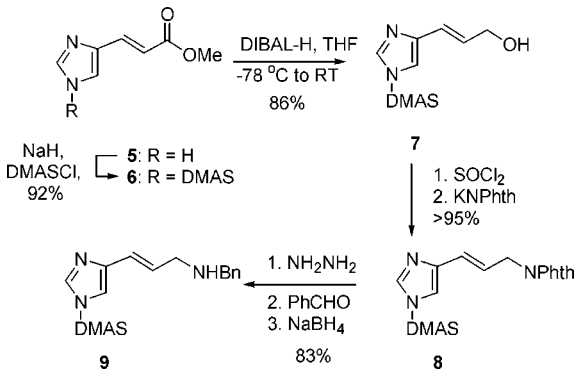
have shed some light on these latter substrates as Diels−Alder dienes (and dienophiles). In related work, Romo's group, in their approach to palau'amine, have investigated the Diels−Alder chemistry of vinylimidazol-2-ones.[4c] To date, all of these reported examples are intermolecular in nature, and so recently our attention has been directed to the extension of this methodology to the then unknown intramolecular variants. It was our eventual intent to employ this Diels−Alder variant as the key step in approaches to ageliferin **3** and axinellamine A **4**. Therefore the studies described in this Letter serve as feasibility studies for this undertaking.

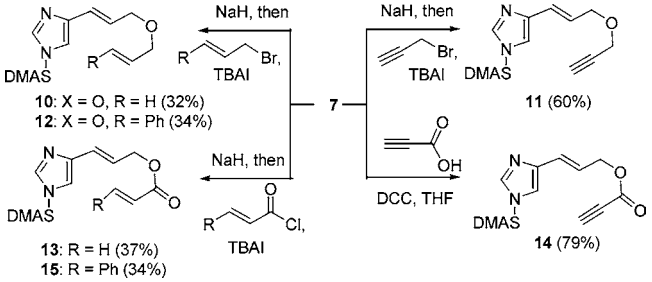
Our investigation commenced with the protection of methyl urocanoate (**5**)[9] with dimethylaminosulfonyl chloride (DMASCl) to provide **6**, which upon subsequent reduction with DIBAL-H gave the key allylic alcohol (**7**, Scheme 1).[10]

Scheme 1



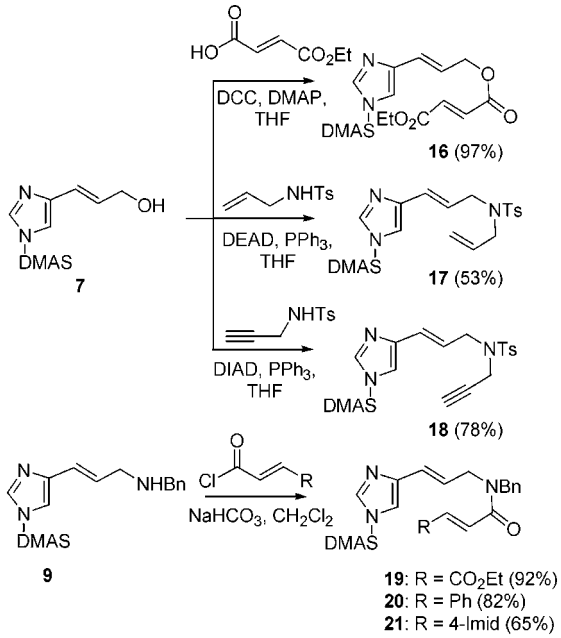
At this point the alcohol was alkylated with a variety of representative allyl or propargyl halides or acylated with related acyl chlorides or carboxylic acids (suitably activated) to provide the corresponding ethers or esters, respectively (Scheme 2, **10**−**15**, Scheme 3, **16**). The analogous amino-

Scheme 2



or amide-linked substrates were prepared from either the alcohol, by a Mitsunobu amination[11] with the allyl sulfona-

Scheme 3



mide (Scheme 3, **7** → **17**)[12] or the propargyl sulfonamide (Scheme 3, **7** → **18**),[13] or by acylation of the *N*-benzylamine (Scheme 3, **9** → **19**−**21**). The *N*-benzylamine (**9**) was prepared from **7** by chlorination and subsequent treatment with potassium phthalimide (Scheme 1, **7** → **8**).[14] Cleavage of the *N*-alkylated phthalimide was achieved with hydrazine, and the resulting primary amine was then reductively alkylated with benzaldehyde in the presence of $NaBH_4$ (Scheme 1, **8** → **9**).

With this variety of trienes in hand, they were subjected to a thermal Diels−Alder reaction in benzene. The outcome of these reactions is summarized in Table 1. In the *O*-linked series, it is evident that only the acetylenic systems participate effectively in cycloaddition (Table 1, entries 2 and 5), with the notable exception of the fumarate derivative (Table 1, entries 7 and 8). While the poor reactivity of the unactivated systems can be understood in terms of unfavorable energetics,

(6) Isolation: 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. Synthetic approaches: (a) Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8793. (b) See also ref 4c.

(7) In the case of palau'amine and axinellamine, a ring contraction of the Diels−Alder adduct would be necessary to access the cyclopentane. For our efforts toward this end see ref 1d and Romo's report, ref 4c

(8) (a) Kosaka, K.; Maruyama, K.; Nakamura, H.; Ikeda, M. *J. Heterocycl. Chem.* **1991**, *28*, 1941. (b) Xu, Y.-Z.; Yakushijin, K.; Horne, D. A. *Tetrahedron Lett.* **1993**, *34*, 6981. (c) Walters, M. A.; Lee, M. D. *Tetrahedron Lett.* **1994**, *35*, 8307. (d) Wan, Z.-K.; Woo, G. H. C.; Synder, J. K. *Tetrahedron* **2001**, *57*, 5497. (e) Neipp, C. E.; Ranslow, P. B.; Wan, Z.; Snyder, J. K. *J. Org. Chem.* **2003**, *68*, 4345. (f) Deghati, P. Y. F.; Wanner, M. J.; Koomen, G.-J. *Tetrahedron Lett.* **1998**, *39*, 4561. See also (g) Rothenburg, A. S.; Daulplaise, D. L.; Panzer, H. P. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 560.

(9) Pirrung, M. C.; Pei, T. *J. Org. Chem.* **2000**, *65*, 2229.

(10) This compound has been described in the patent literature. Tozer, M. J.; Kalindjian, S. B.; Linney, I. D.; Steel, K. I. M.; Pether, M. J.; Cooke, T. PCT Int. Appl. WO 9905114 A2, 1999; *Chem. Abstr.* **1999**, *130*, 168369

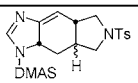
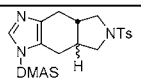
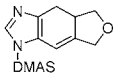
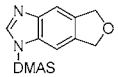
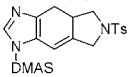
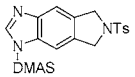
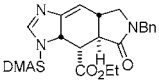
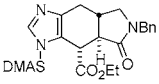
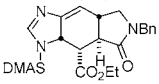
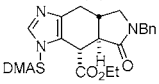
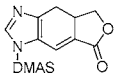
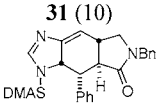
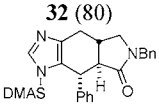
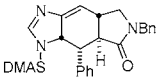
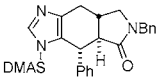
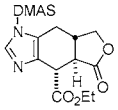
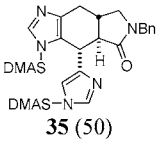
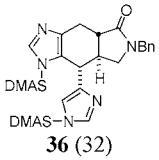
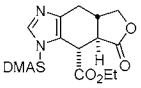
(11) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.

(12) Tehrani, K. A.; Nguyen Van, T.; Karikomi, M.; Rottiers, M.; De Kimpe, N. *Tetrahedron* **2002**, *58*, 7145.

(13) Oppolzer, W.; Ruiz-Montes, J. *Helv. Chim. Acta* **1993**, *76*, 1266.

(14) Sellier, C.; Buschauer, A.; Elz, S.; Schunack, W. *Liebigs Ann. Chem.* **1992**, 317.

Table 1. Intramolecular Diels−Alder Cycloaddition Reactions of Vinylimidazoles

entry	substrate	conditions	cycloadduct (yield/%)[a]	entry	substrate	conditions	cycloadduct (yield/%)[a]
1	**10**	160 °C	Decomposition	9	**17**	190 °C, 72 h	 **27** (8)  **28** (54)
2	**11**	170 °C, 72 h	 **22** (65)  **23** (1)	10	**18**	160 °C, 72 h	 **29** (38)  **30** (8)
3	**12**	160 °C	Decomposition	11	**19**	68 °C, 12 h	 **31** (95)  **32** (0)
4	**13**	160 °C	Decomposition	12	**19**	68 °C, 10 h[b]	 **31** (10)  **32** (80)
5	**14**	180 °C, 48 h	 **24** (30)	13	**20**	130 °C, 25 h	 **33** (61)  **34** (32)
6	**15**	160 °C	Decomposition	14	**20**	130 °C, 45 h	 **33** (27)  **34** (51)
7	**16**	160 °C, 96 h	 **25** (20)	15	**21**	95 °C, 70 h	 **35** (50)  **36** (32)
8	**16**	135 °C, 72 h	 **26** (20)				

[a] Yields are not optimized. [b] Amide was used directly after aqueous workup.

the lack of reactivity of the acrylate and cinnamate systems requires further explanation (Table 1, entries 4 and 6). It has been found in intermolecular variants that there is a regiochemical preference for orientation of an electron-deficient substituent proximal to the imidazole;[15] therefore it is reasonable to assume that the entropic advantage conferred by intramolecularity does not overcome the intrinsic electronic bias of the system. This notion is supported to some degree by the successful cycloaddition of the fumarate-derived diester, which provides cycloadduct **25** in a modest 20% yield (Table 1, entry 7). Interestingly, the DMAS-moiety appears to have migrated to the other imidazole nitrogen (N3 in **16**). There are reports in the literature of the migration of DMAS groups on imidazoles, and it has been assumed that this is a result of the relief of steric crowding, leading to the thermodynamically most stable isomer.[16] A similar explanation can be forwarded in this instance, since migration of the DMAS moiety would relieve steric crowding between the CO_2Et moiety and the DMAS group.[17] Ultimately it was found by reducing the temperature to 135 °C and reducing the reaction time (Table 1, entry 8) that the anticipated cycloadduct (**26**) could be obtained, although the yield was fairly low.[18]

The corresponding amino-linked substrates (**17**−**21**) were investigated, and it was found that these were more effective substrates, although for the unactivated systems rather high temperatures and extended reaction times were required. The *N*-allyl substrate provided two products (Table 1, entry 9), a ca. 1:1 mixture of *cis*/*trans* aromatized cycloadducts (**28**, 54%), along with a 4:1 diastereomeric mixture of the initial cycloadduct (**27**, 8%, *cis*/*trans* unassigned).[19] The propargyl system successfully cyclized (Table 1, entry 10), affording the expected adduct **29** in 38% yield, plus a small amount

(15) Du, H.; Lovely, C. J. Unpublished results.

(16) (a) Kim, J.-W.; Abdelaal, S. M.; Bauer, L.; Heimer, N. E. *J. Heterocycl. Chem.* **1995**, *32*, 611. (b) Bhagavatula, L.; Premchandran, R. H.; Plata, D. J.; King, S. A.; Morton, H. E. *Heterocycles* **2000**, *53*, 729.

(17) We were concerned that under the reaction conditions employed, migration of the DMAS group may have occurred with other substrates. NOESY experiments were conducted on **22**, **24**, **29**, **33**, and **34**, the results of which indicated that the initially expected products were obtained.

(18) In an attempt to improve the yield of this cycloadduct, the reaction was allowed to proceed for 9 days at 135 °C; however, under these conditions the yield did not improve and migration of the DMAS group occurred to provide **25**.

of the fully aromatized adduct (**30**, 8%). By far the best substrate was the fumaramide derivative (**19**); heating a sample of this material in benzene at 68 °C led to the formation of a single cycloadduct in 90% yield (Table 1, entry 11). It was found that this substrate underwent cycloaddition during purification as small amounts of cycloadduct were detected in the ^{1}H NMR spectrum of **19**; therefore in subsequent reactions it was directly subjected to cycloaddition after preparation. Under these circumstances, the major product was the aromatized adduct (**32**), plus small amounts of the initial adduct (**31**, Table 1, entry 12). Presumably, under these conditions trace amounts of acid catalyze the aromatization of the imidazole ring. Analysis of the aromatized adduct by X-ray indicated that the ring fusion was *trans*, resulting from an *endo* transition state. The cinnamide **20** also participates in a cycloaddition reaction providing two adducts (Table 1, entry 13), the initial adduct (**33**, 61%) and the aromatized adduct (**34**, 32%). Prolonged heating led to the formation of more of the aromatized adduct (Table 1, entry 14), which is consistent with previous results obtained in the intermolecular series.[1a,b] Each of these adducts was obtained as a single diastereomer, which on the basis of coupling constant data appear to contain a *trans* fused lactam ($J_{4a,7a}$ = 13.1, 12.8 Hz respectively). Given this, it appears that these products are formed via an *endo* transition state. The final system evaluated was the dimeric imidazolyl substrate **21**, which was to serve as a model for approaches to ageliferin (and possibly axinellamine A). As can be seen, this too is a competent substrate (Table 1, entry 15), providing two products (**35** and **36**),[20] although the reaction rate is somewhat attenuated. Perhaps the most notable feature of this derivative is that there is an additional selectivity issue regarding the diene/dienophile pairing. Aromatic products arising from both possible pairings were obtained, although it appears that there is some intrinsic selectivity for the allylic amine functioning as the diene. Furthermore, there is an interesting disparity in the outcome of the cycloaddition reactions of **20** and **21**. Presumably, in the case of **21** the cost of dearomatizing either imidazole (as required for cycloaddition) is similar, whereas with **20** the energetics for dearomatizing the benzene moiety are too prohibitive.[21] Both adducts appear to possess *trans* ring fusions as judged by the magnitude of the coupling constant for the diaxial protons ($J_{4a,7a}$ = 12.8, 12.8 Hz respectively), which is consistent with those observed for **25** and **32** for which X-ray structures have been secured.

There is an interesting contrast in the results obtained with the ether/ester series and the amine/amide series. Only the acetylenic dienophiles participated in cycloaddition with the *O*-linked systems, whereas all of the *N*-linked systems react albeit with varying efficiencies. These results can be interpreted in terms of reactive rotamer effects, that is, the amines/amides have a greater population of the reactive rotamer as a result of unfavorable nonbonded interactions between the *N*-substituent (Ts or Bn) and the dienophilic component.[22,23]

In summary, we have demonstrated that intramolecular Diels−Alder reactions are feasible with 4-vinylimidazoles derived from urocanic acid. The most efficient cycloadditions are obtained with *N*-substituted amino-linkers, in particular with activated dienophiles. In these cases, the reactions appear to proceed via *endo* transition states, providing *trans* ring-fused products as the major adduct.[24] Both cycloadducts **35** and **36** contain the appropriate structural and stereochemical elements for elaboration into ageliferin. We are currently investigating the scope of this reaction with respect to imidazole substitution patterns and its application in natural product total synthesis. The results of these studies will be reported in due course.

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Supporting Information Available: Experimental and characterization data for all new compounds and X-ray plots and data (in CIF format) for compounds **25** and **32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) We cannot rule out the possibility that this mixture of products is in fact the 4- and 5-isomers, through migration of the *N*-sulfamoyl group, rather than the *cis*/*trans* isomers on the basis of the NMR data.

(20) This cycloadduct was obtained as a mixture of products, which were separable by preparative thin-layer chromatography.

(21) For comparison, see: Oppolzer, W.; Achini, R.; Pfenninger, E.; Weber, H. P. *Helv. Chim. Acta* **1976**, *59*, 1186

(22) (a) He, Y.; Mahmud, H.; Wayland, B. R.; Dias, H. V. R.; Lovely, C. J. *Tetrahedron Lett.* **2002**, *43*, 1171. (b) Gschwend, H. W.; Lee, A. O.; Meier, H. P. *J. Org. Chem.* **1973**, *38*, 2169. (c) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224. (d) Jung, M. E. *Synlett* **1990**, 186. (e) Jung, M. E. *Synlett* **1999**, 843. (f) Bur, S. K.; Lynch, S. M.; Padwa, A. *Org. Lett.* **2002**, *4*, 473.

(23) It was found that the NH-congener of **19** did not undergo cyclization at temperatures up to 160 °C.

(24) The use of *endo* here refers to the relative location of the terminal substituent on the dienophilic component rather than the carbonyl of the amide.

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