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Abstract— A Diels-Alder/rearrangement sequence has been pursued in our lab en route to a number of oroidin dimers. In order to access the fully substituted core of these molecules, 1',2'-disubstituted 4-vinylimidazoles were required as dienes. The preparation of a series of 4-vinylimidazoles containing substituents on the vinyl moiety via hydroalumination/electrophilic trapping or hydrosilylation are described. These derivatives undergo Diels-Alder reactions with *N*-phenylmaleimide to provide the tetrahydrobenzimidazole derivatives. The cycloadducts derived from halosubstituted systems generally undergo elimination, leading to the corresponding dihydrobenzimidazole, whereas the silyl and stannyl derivatives provide the corresponding 4-substituted tetrahydrobenzimidazole. ©2017 Elsevier Science. All rights reserved

Palau'amine (1) was isolated several years ago from a marine sponge found off the Caroline Islands by Scheuer and coworkers.¹ In the initial reports, the Scheuer lab determined that the molecule was a hexacyclic oroidin dimer and was characterized by the presence of an all *cis* hexasubstituted cyclopentane in which all of the substituents were arrayed on the more hindered *endo* face of the E-ring, including the chloride at C17. The subsequent isolation of other dimers containing related carbocycles, e.g., axinellamine A (3)² and massadine (4),³ but with substituents on adjacent positions displaying *trans* relationships, led to speculation that the structure of palau'amine (1) may have been misassigned. This was subsequently confirmed upon the re-isolation of palau'amine and related derivatives.⁴ Further confirmation has come from the recent total synthesis of palau'amine by the Baran group.⁵

Figure 1: Palau'amine and related oroidin dimers

The intrinsic structural challenges presented by the oroidin alkaloids have resulted in a significant number of research groups developing approaches to the total syntheses of these marine alkaloids, in particular axinellamine (3), massadine (4) and palau'amine (2).⁶ Our lab has pursued an approach to this group of alkaloids based on a Diels-Alder/rearrangement⁸ strategy as a means to access the spiro fused EF-rings.⁹ Part of the motivation behind this strategy derived from the ability to

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use the known stereochemical characteristics of the Diels-Alder (DA) reaction as a means to establish the stereochemical relationships in the E-ring. An additional attractive feature of this approach arose from the idea that in principle substituents at all positions on the lone carbocycle could be incorporated on the diene **5** (vinylimidazole), which led to the notion that one of the substituents could be chloride (**5**, X = Cl) and this would then allow the direct incorporation of this key substituent (Scheme 1).¹⁰ Furthermore, based on our understanding of the reactivity of the initial adduct, we had high hopes that this chemistry would lead to the installation of the chloride in an *endo* fashion – i.e., protonation would occur from the *exo* face leading to the correct stereochemistry for the originally reported structure of palau'amine (**1**). Although the reassignment of the stereochemistry at this position would mean that this approach affords the incorrect configuration at C17, it would still provide a strategy to construct the polysubstituted E-ring of the natural product, simply requiring adjustment of the configuration at a suitable point in the sequence. The concise nature of this strategy motivated us to explore the use of heterosubstituted vinylimidazoles early on in our investigation of the DA chemistry of vinylimidazoles.

Scheme 1: Overview of approach to polysubstituted tetrahydrobenzimidazoles

Briefly, we converted the 4-iodoimidazole **10a** into the corresponding methyl ketone **11** via reaction of the Grignard derivative, prepared by halogen-magnesium exchange with EtMgBr, with the Weinreb amide (Scheme 2). The ketone then served as the precursor to the TBS-silyl ether and vinyl chloride. Deprotonation of **11** and trapping with TBSCl delivered the enol ether **13**; unfortunately this material was rather unstable and decomposed quite rapidly. Attempted DA reactions of

this enol with *N*-phenylmaleimide (NPM) were not successful. On the other hand, the vinyl chloride **12**, which was obtained by treatment of ketone **11** with POCl₃,¹¹ engaged in cycloaddition. However, unlike the parent system, heating at 90 °C was required with NPM for reaction to occur. Interestingly, rather than isolating the expected chlorosubstituted adduct, a 2+1 adduct **15** was obtained as the major adduct, although the yield was quite modest. We had isolated this material previously, and characterized it by X-ray crystallography.^{7c} Presumably it arises through the dehydrochlorination of the cycloadduct to produce **14** followed by a second DA reaction with NPM. Based on this result and other discoveries from our lab, specifically obtaining cycloadducts related to **7** (X = H) and subsequent ability to introduce a hydroxyl group through oxidation we moved away from this strategy for a period of time.^{8a} As our program matured to intramolecular variants, we were unable to isolate the primary cycloadduct (c.f. **7**) unless highly activated dienophiles were employed.^{7b, 7g} As a result, we decided to revisit the approach of using heterosubstituted dienes to access molecules related to **5**.

Scheme 2: First generation 1-heterosubstituted vinylimidazoles

In our initial investigation, we decided to employ substrates that are readily prepared from the corresponding iodoimidazoles and propargyl alcohol via a Sonogashira reaction to provide the substituted propargylic alcohols **16a-b** (Scheme 3).¹² As we have learned more about these heterocyclic systems, we have determined that either the electron rich Bn-protected or the electron poor DMAS (dimethylaminosulfonyl)-protected systems provide good yields of DA products as well as providing electronically complementary heterocycles. The DMAS-protected systems were of particular interest as the corresponding cycloadducts are less prone to rearomatization. Treatment of the propargylic alcohol **16a-b** with Red-Al and then an *N*-halosuccinimide provided the 3-halo-substituted derivatives **17-19** in moderate to good yields (Table 1). Conversion of the alcohol to the TBS-ether provided the required DA substrates **21-23** (Scheme 3, Table 1).

Scheme 3: Second generation substrates – Reagents and conditions: (a) i. $\text{HC}\equiv\text{CCH}_2\text{OTHP}$, CuI, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, K_2CO_3 , THF, 60 °C, 47%. ii. *p*-TsOH, MeOH, H_2O , 88%. (b) $\text{HC}\equiv\text{CCH}_2\text{OH}$, CuI, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, Et_3N , THF, 60 °C, 72%. (c) Red-Al ($\geq 60\%$ wt in PhMe), THF, 0 °C then NXS, rt, see Table 1. (d) TBSCl, imidazole, CH_2Cl_2 , 0 °C to rt, for **21–23** see Table 1; for **24b** = 88%. (e) PhMe_2SiH , $[\text{Cp}^*\text{Ru}(\text{MeCN})_3]\text{PF}_6$, acetone, 0 °C to rt (f) Red-Al ($\geq 60\%$ wt in PhMe), THF, then Bu_3SnCl , 60%.

Table 1: Yields for hydrohalogenation and silylation of propargyl alcohols **16a–b**

PG = Bn	Halogenation, %	Silylation, %
X = Cl	17a 35	21a 92
X = Br	18a 81	22a 91
X = I	19a 88	23a 90
PG = DMAS	%	%
X = Cl	17b 34	21b 87
X = Br	18b 78	22b 88
X = I	19b 82	23b 92

Initial cycloaddition experiments were conducted with NPM in CH_2Cl_2 and heated until cycloaddition occurred. The iodo- and bromosubstituted systems engaged in cycloaddition upon heating to between 50–65 °C. However with the Bn-protected systems **22a–23a**, rather than the halosubstituted cycloadduct we obtained the dehydrohalogenated products **29a** in moderate yields (entries 2–3, Table 2). Presumably, the expected cycloadduct formed, but undergoes elimination. On the other hand, with the DMAS-protected derivatives **22b–23b**, we observed formation of the bromo- or iodo-containing cycloadducts **31** and **32** in modest yield (entries 5–6, Table 2). The chloro substituted derivatives **21a–b** were much less reactive; below 75 °C no reaction occurred, but at significantly higher temperatures than that decomposition occurred.¹³ We assume that the chloro substituent retards the cycloaddition inductively by reducing the electron density of the dienyl system.

While these experiments demonstrated that halo substitution was tolerated on the vinyl group, unwanted postcycloaddition elimination compromised the approach with the Bn-derivatives; these substrates are suitable for oxidative rearrangement (c.f. **8**→**9**, Scheme 1), whereas the DMAS-protected systems are not.⁸ However, if a substituent could be introduced that was not prone to elimination and would ultimately serve a surrogate for chlorine or oxygen then a potential solution to this issue would be forthcoming. Accordingly, we began to investigate the preparation of silyl substituted vinylimidazoles.¹⁴ Initial attempts to accomplish this via metallation of the vinyl halides **21–23** with either organolithiums or Grignards and electrophilic trapping were unsuccessful.¹⁵ The propargyl alcohols again serve as substrates and were subjected to hydrosilylation using the method described by Ball and Trost.¹⁶ Reaction of either the Bn- and DMAS-systems with Me_2PhSiH and either the TBS-ether for **27a** or the alcohol for **27b** gave an approximately 2.2–2.3:1 mixture of the required hydrosilylation derivative and the corresponding regioisomer (Scheme 3). After chromatographic separation of the regioisomers and silylation in the case of the DMAS-derivative, the vinylimidazoles **27a–b** were subjected to DA reaction with NPM. In the case of the Bn-protected derivative **27a**, two inseparable cycloadducts **33** were obtained, which based on their spectroscopic properties, were assigned as epimers at the C4-silyl bearing carbon (entry 7, Table 2). On the other hand, the DMAS-protected derivative **27b** on reaction with NPM resulted in the formation of the initial adduct **34** as a single stereoisomer (entry 8, Table 2). An X-ray crystal structure of this cycloadduct clearly indicates both the relative stereochemistry and that it is the initial cycloadduct (Figure 2).¹⁷ The relative stereochemistry is

consistent with an *endo* transition state, similar to the stereochemical outcome in the non-substituted systems.^{7d}

Table 2: Yields and products from the cycloaddition reactions with *N*-phenylmaleimide

Entry	Substrate	Product %
1	21a , X = Cl	29 0
2	22a , X = Br	29 20
3	23a , X = I	29 45
4	21b , X = Cl	30 0
5	22b , X = Br	31 24 (dr = 1:1)
6	23b , X = I	32 45 (<i>endo</i>)
7		
	27a	33 85 (dr = 1.0:0.6)
8		
	27b	34 85
9		
	24b	35 72

Figure 2: X-ray crystal structure of **34** (hydrogen atoms omitted for clarity)

A final substrate **24b** containing a vinylstannane was evaluated as a diene. The substrate was prepared by transmetalation of the vinylalane with Bu_3SnCl , which in turn was obtained from the reaction of propargyl alcohol **16b** and Red-Al and protection as the TBS-ether (Scheme 2). Gratifyingly, this substrate upon reaction with NPM delivered the initial adduct **35** as a single stereoisomer (entry 9, Table 2).

Scheme 4: Postcycloaddition manipulations

Finally, the utility of the C4-silyl derivative **34** to post cycloaddition functionalization was examined through oxidation using a mixture of $\text{Hg}(\text{OAc})_2$ and peracetic acid,¹⁸ the corresponding diol **36** was obtained as a single stereoisomer (Scheme 4).¹⁹ Subjection of diol **36** to protection as the silyl ether delivered the mono protected derivative **37** in good yield. Previously, we have prepared a related alcohol **38** through oxidation of an initial DA reaction giving a single alcohol which was characterized

through X-ray crystallography.^{8a} The newly synthesized alcohol was clearly different from this alternative preparation and thus we tentatively assigned it as the *endo* alcohol **36** based on this and several key nOe interactions (Scheme 4).

In summary, we have investigated the use of heterosubstituted vinylimidazoles in DA reactions with NPM. Halo substituted systems gave mixed results, the benzyl-protected systems resulted in cycloaddition followed by dehydrohalogenation whereas the DMAS-protected systems afforded the 4-halo substituted cycloadducts. On the other hand, silyl and stannyl substituted systems delivered cycloadducts retaining the heteroatom. The precise identity of the cycloadduct was dependent on the N-protecting group and is presumably related to the propensity of the system to undergo rearomatization. In one case, we were able to subject the cycloadduct to a subsequent oxidative transformation to deliver the polysubstituted alcohol **36**.

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1. (a) Kinnel, R. B.; Gehrken, H. P.; Scheuer, P. J., *J. Am. Chem. Soc.* **1993**, *115*, 3376-3377; (b) Kinnel, R.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J., *J. Org. Chem.* **1998**, *63*, 3281-3286.
2. 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*, 731-735.
3. Nishimura, S.; Matsunaga, S.; Shibazaki, M.; Suzuki, K.; Furihata, K.; van Soest, R. W. M.; Fusetani, N., *Org. Lett.* **2003**, *5*, 2255-2258.
4. (a) Buchanan, M. S.; Carroll, A. R.; Quinn, R. J., *Tetrahedron Lett.* **2007**, *48*, 4573-4574; (b) Kobayashi, H.; Kitamura, K.; Nagai, K.; Nakao, Y.; Fusetani, N.; van Soest, R. W. M.; Matsunaga, S., *Tetrahedron Lett.* **2007**, *48*, 2127-2129.
5. Seiple, I. B.; Su, S.; Young, I. S.; Nakamura, A.; Yamaguchi, J.; Jørgensen, L.; Rodriguez, R. A.; O'Malley, D. P.; Gaich, T.; Köck, M.; Baran, P. S., *J. Am. Chem. Soc.* **2011**, *133*, 14710-14726.
6. (a) Al-Mourabit, A.; Zancanella, M. A.; Tilvi, S.; Romo, D., *Nat. Prod. Rep.* **2011**, *28*, 1229-1260; (b) Hoffmann, H.; Lindel, T., *Synthesis* **2003**, 1753-1783; (c) Ma, Y.; De, S.; Chen, C., *Tetrahedron*, doi:10.1016/j.tet.2014.11.056.
7. (a) Lovely, C. J.; Du, H.; Dias, H. V. R., *Org. Lett.* **2001**, *3*, 1319-1322; (b) He, Y.; Chen, Y.; Wu, H.; Lovely, C. J., *Org. Lett.* **2003**, *5*, 3623-3626; (c) Lovely, C. J.; Du, H.; Dias, H. V. R., *Heterocycles* **2003**, *60*, 1-7; (d) Lovely, C. J.; Du, H.; Sivappa, R.; Bhandari, M. R.; He, Y.; Dias, H. V. R., *J. Org. Chem.* **2007**, *72*, 3741-3749; (e) Sivappa, R.; Hernandez, N. M.; Yong He; Lovely, C. J., *Org. Lett.* **2007**, *9*, 3861-3864; (f) Sivappa, R.; Mukherjee, S.; Dias, H. V. R.; Lovely, C. J., *Org. Biomol. Chem.* **2009**, *7*, 3215-3218; (g) He, Y.; Krishnamoorthy, P.; Lima, H. M.; Chen, Y.; Wu, H.; Sivappa, R.; Dias, H. V. R.; Lovely, C. J., *Org. Biomol. Chem.* **2011**, *9*, 2685-2701.
8. (a) Lovely, C. J.; Du, H.; He, Y.; Dias, H. V. R., *Org. Lett.* **2004**, *6*, 735-738; (b) Sivappa, R.; Koswatta, P.; Lovely, C. J., *Tetrahedron Lett.* **2007**, *48*, 5771-5774.
9. (a) Walters, M. A.; Lee, M. D., *Tetrahedron Lett.* **1994**, *35*, 8307-8310; (b) Kawasaki, I.; Sakaguchi, N.; Fukushima, N.; Fujioka, N.; Nikaido, F.; Yamashita, M.; Ohta, S., *Tetrahedron Lett.* **2002**, *43*, 4377-4380; (c) Deghati, P. Y. F.; Wanner, M. J.; Koomen, G.-J., *Tetrahedron Lett.* **1998**, *39*, 4561-4564; (d) Cotterill, L. J.; Harrington, R. W.; Clegg, W.; Hall, M. J., *J. Org. Chem.* **2010**, *75*, 4604-4607; (e) Watson, L. J.; Harrington, R. W.; Clegg, W.; Hall, M. J., *Org. Biomol. Chem.* **2012**, *10*, 6649-6655; (f) Pöverlein, C.; Breckle, G.; Lindel, T., *Org. Lett.* **2006**, *8*, 819-821.
10. Lewis, N. J.; Knight, D. B.; Collins, W. J., *J. Med. Chem.* **1979**, *22*, 1505-1509.
11. Barrero, A. F.; Sanchez, J. F.; Oltra, J. E.; Teva, D., *J. Heterocycl. Chem.* **1991**, *28*, 939-944.
12. (a) Bhandari, M. R.; Yousufuddin, M.; Lovely, C. J., *Org. Lett.* **2011**, *13*, 1382-1385; (b) Bhandari, M. R.; Sivappa, R.; Lovely, C. J., *Org. Lett.* **2009**, *11*, 1535-1538.
13. In one experiment with the DMAS-protected derivative 17b, we were able to observe the formation of the initial Diels-Alder adduct, but despite several attempts to reproduce this observation, we have been unable to do so.
14. Choudhury, P. P.; Junker, C. S.; Pidaparthy, R. R.; Welker, M. E., *J. Organomet. Chem.* **2014**, *754*, 88-93.
15. We attempted to introduce both sulfur and silicon via this metallation-trapping sequence unsuccessfully.
16. Trost, B. M.; Ball, Z. T., *J. Am. Chem. Soc.* **2005**, *127*, 17644-17655.
17. The X-ray data obtained for compound 34 has been deposited at the Cambridge Crystallographic Data Center - CCDC 1044753.
18. Fleming, I.; Sanderson, P. E. J., *Tetrahedron Lett.* **1987**, *28*, 4229-4232.
19. Although the diastereomeric mixture of cycloadducts was subjected to oxidation, only a single diastereomeric diol was isolated. However, given that the yield for this reaction is low, it is our belief that this is result is circumstantial and reflects differential reactivity of the two isomers. At this stage, we have been unable to establish the fate of the other isomer.