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Tandem Phenolic Oxidative Amidation−Intramolecular Diels−Alder Reaction: An Approach to the Himandrine Core

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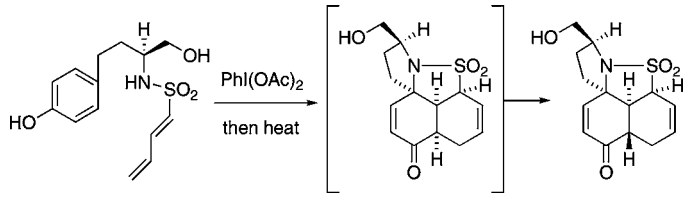
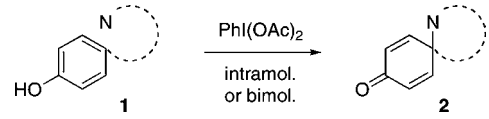
ABSTRACT



An oxidative cyclization of dienic sulfonamides mediated by iodobenzene diacetate in TFA, followed by a tandem intramolecular Diels−Alder reaction, achieves desymmetrization of a "locally symmetrical" dienone with good levels of diastereoselectivity and leads to valuable synthetic intermediates for the himandrine alkaloids.

Exposure of phenolic substrates **1** to hypervalent iodine reagents[1] such as $PhI(OAc)_2$ ("DIB") and $PhI(OCOCF_3)_2$ ("PIFA") induces formation of dienones **2** (Scheme 1), which are valuable educts in alkaloid synthesis. This transformation is described as the oxidative amidation of phenols,[2] and it may be carried out in the intramolecular[3] or in the bimolecular[4] regime. While dienones **2** are "locally symmetrical", various artifices enable their stereocontrolled desymmetrization. This causes the N-bearing spiro C atom to become stereogenic and to acquire a specific configuration. Desymmetrization may be accomplished via 1,4-addition[5] or 1,3-dipolar cycloaddition reactions.[6] In this paper, we demonstrate dienone desymmetrization via a diastereoselective intramolecular Diels−Alder reaction (IMDA),[7] which leads to densely functionalized intermediates that are generally useful in synthetic chemistry, but that may be especially

Scheme 1. The Oxidative Amidation of Phenols



(1) Reviews: (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (b) Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (c) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (d) Kita, Y. *Yakugaku Zasshi* **2002**, *122*, 1011. (e) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. Monograph: (f) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, CA, 1997.

(2) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, 3759.

(3) (a) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E.-M. *Tetrahedron Lett.* **1998**, *39*, 4667. (b) Braun, N. A.; Bray, J.; Ciufolini, M. A. *Tetrahedron Lett.* **1999**, *40*, 4985. (c) Braun, N. A.; Bray, J.; Ousmer, M.; Peters, K.; Peters, E.-M.; Bouchu, D.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397. (d) Canesi, S.; Belmont, P.; Bouchu, D.; Rousset, L.; Ciufolini, M. A. *Tetrahedron Lett.* **2002**, *43*, 5193.

(4) (a) Liang, H.; Ciufolini, M. A. *J. Org. Chem.* **2008**, *73*, 4299. (b) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Org. Lett.* **2005**, *7*, 175.

(5) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4336; *Angew. Chem.* **2004**, *116*, 4436.

(6) (a) Mendelsohn, B.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539. (b) Frie, J.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 5394.

(7) Ciganek, E. *Org. React.* **1984**, *32*, 1.

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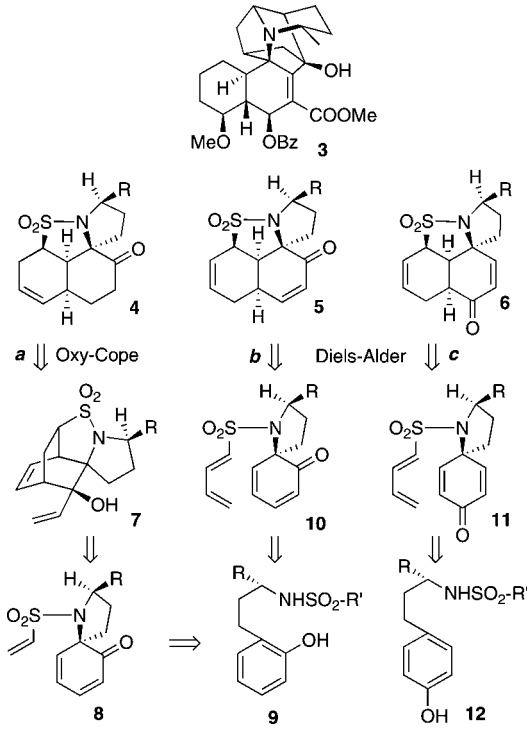
valuable for the assembly of the core unit of the structurally unique alkaloid, himandrine, **3**.[8]

The studies described here were motivated by the realization that the spirocyclic core of **3** may be brought within the scope of oxidative amidation chemistry as adumbrated in Scheme 2. Indeed, a key subunit of **3** is embedded in

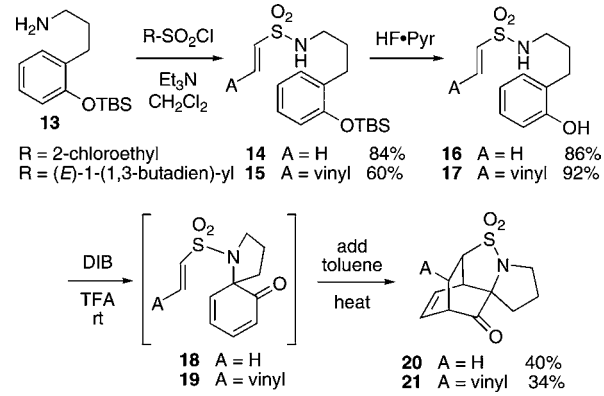
Scheme 2. Retrosynthetic Hypotheses for Himandrine



intermediates **4**−**6**, each one of which, in turn, could conceivably derive from the oxidative cyclization of a phenolic sulfonamide,[3d] followed by IMDA reaction. An oxy-Cope rearrangement[9] (cf. **7**) would also be required to elaborate **8** into **4**. We note that the decalin segment of **3** displays the trans ring junction, whereas the sequences leading to **4**−**6** would produce the *cis*-fused diastereomers. An MM+ study indicated that the *trans*-isomers of **4**−**6** were considerably more stable (ΔE > 4 kcal/mol). We thus anticipated that **5** and **6** would epimerize to the *trans*-isomers under mildly basic conditions, while **4** could be epimerized after conversion into an enone of the type **5**.

The exploration of pathways a−b required compounds **16** and **17**, which were obtained respectively by reaction of amine **13**[10] with commercial 2-chloroethylsulfonyl chloride and with 1-(1,3-butadien)ylsulfonyl chloride,[11] followed by desilylation (Scheme 3). While the original procedure for the oxidative

Scheme 3. Substrates for Ortho-Oxidative Amidation



cyclization of similar substrates utilized costly hexafluoroisopropanol as the solvent,[3d] we found that the reaction proceeds as efficiently, if not better, in neat trifluoroacetic acid (TFA). Treatment of **16**−**17** with DIB in TFA thus furnished **18**−**19**. This is an example of ortho-oxidative amidation of phenols.[12] Chromatographic purification of these sensitive materials caused unacceptable losses. We found it expedient to dilute the crude reaction mixture with toluene and heat to reflux to induce IMDA cyclization. Products **20**−**21** emerged in 40% and 34% yield after chromatography,[13] and their structures were ascertained by X-ray diffractometry.[14] Somewhat surprisingly, the sulfonyldiene moiety of **19** had thus behaved exclusively as a dienophile, while the dienone played the role of the diene, presumably thanks to its constrained s-*cis*-type diene geometry. The finding that **19** cyclizes to form exclusively a bicyclo[2.2.2]octenone system, and none of the desired product of the type **5** (R = H), signaled the demise of pathway b.

The investigation of pathway a continued with compound **20**, which according to the logic of Scheme 2 would now undergo addition of a vinyl nucleophile to the C=O group. Unexpectedly, this reaction was problematic. Thus, vinylmagnesium bromide in THF, with or without added HMPA or other promoters, such as TMEDA[15] or $CeCl_3$,[16] as well as vinyllithium prepared from either vinyltributyl tin/BuLi[17] or tetravinyl

(8) Isolation: (a) Brown, R. F. C.; Drummond, R.; Fogerty, A. C.; Hughes, G. K.; Pinhey, J. T.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1956**, *9*, 283. Bioactivity: (b) Cobbin, L. B.; Thorp, R. H. *Aust. J. Exptl. Biol. Med. Sci.* **1957**, *35*, 15. Structural work: (c) Guise, G. B.; Mander, L. N.; Prager, R. H.; Rasmussen, M.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1967**, *20*, 1029. (d) Willis, A. C.; O'Connor, P. D.; Taylor, W. C.; Mander, L. N. *Aust. J. Chem.* **2006**, *59*, 629. Synthetic studies: O'Connor, P. D.; Mander, L. N.; McLachlan, M. M. W. *Org. Lett.* **2004**, *6*, 703. Total synthesis: Movassaghi, M.; Tjandra, M.; Qi, J. *J. Am. Chem. Soc.* **2009**, *131*, 9648.

(9) Key reviews: (a) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971. (b) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. See also ref 22.

(10) Prepared as detailed in the Supporting Information.

(11) Lee, Y. S.; Ryu, E. K.; Yun, K.-Y.; Kim, Y. H. *Synlett* **1996**, 247. This method furnishes a mixture of *trans*- and *cis*-isomers. Remarkably, these were chromatographically separable with only modest losses (see the Supporting Information).

(12) For the first example of *ortho*-oxidative amidation of phenols see: Canesi, S. Dissertation, University Claude Bernard Lyon 1, 2004.

(13) For a similar reaction see: Drutu, I.; Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2002**, *4*, 493.

(14) The structure of **20** is published: Liang, H.; Canesi, S.; Patrick, B. O.; Ciufolini, M. A. *Z. Kristallogr.-New Cryst. Struct.* **2009**, *224*, 83.

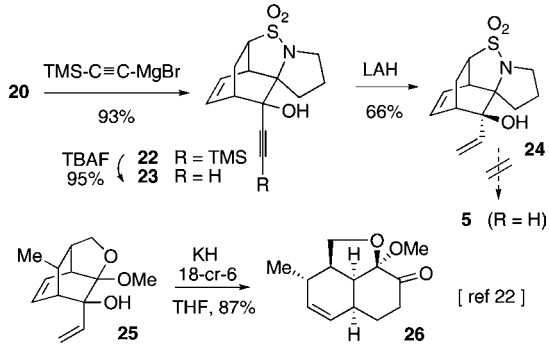
(15) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.

(16) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

(17) Seyferth, D.; Weiner, M. A.; Vaughan, L. G.; Raab, G.; Welch, D. E.; Cohen, H. M.; Alleston, D. L. *Bull. Soc. Chim. Fr.* **1963**, *7*, 1364.

tin/BuLi[18] at various temperatures, fared uniformly poorly (10−15% yield after a difficult purification). Conversely, addition of the bromomagnesio derivative of TMS-acetylene[19] was efficient and stereoselective (Scheme 4). Deprotection

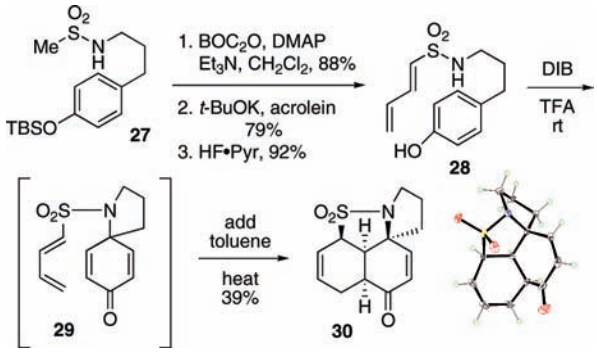
Scheme 4. Failed Oxy-Cope Rearrangement of **24**



(TBAF) and LAH reduction of the triple bond[20] converted **22** into **24**.[21] While solid precedent exists for the oxy-Cope rearrangement of systems similar to **24**, e.g, the isomerization of **25** to **26**,[22] thermal activation of **24** gave none of the rearranged product. The substrate was recovered virtually intact after heating to 200 °C, above which temperature it decomposed. Attempts to induce rearrangement in the anionic mode[23] also failed.

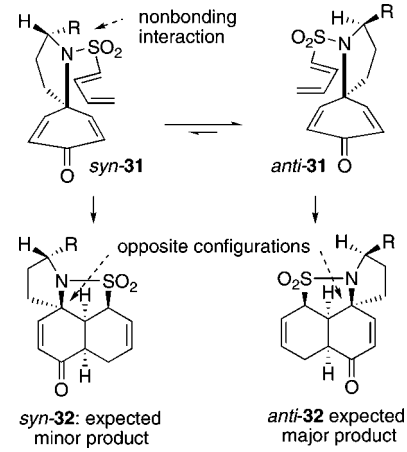
We thus turned to pathway c, which entailed the initial creation of **28** (Scheme 5). The (*E*)-1-(1,3-butadienyl)sul-

Scheme 5. Tandem Oxidative Amidation−IMDA Reaction of **28**



fonamide moiety of the substrate was installed on **27** by a Tozer-type condensation.[24] Accordingly, the *N*-BOC derivative of **27** was reacted with acrolein in the presence of *t*-BuOK and the resulting product was desilylated to deliver **28**. Pleasingly, exposure of the latter to DIB in TFA, followed by addition of toluene and heating to reflux, produced **30** in 39% yield after chromatography.[25] The structure of this compound was ascertained by X-ray diffractometry, and its configuration is consistent with the anticipated occurrence of the IMDA step in the *endo* mode. This encouraging outcome induced us to address the problem of exerting stereocontrol at the level of the spirocenter. The spiro carbon in **29** is chirotopic and nonstereogenic, but it becomes stereogenic during the IMDA step. To produce a given configuration of the spirocenter in **30**, the sulfonyldiene must interact selectively with the *pro-R* or the *pro-S* double bond of the dienone. Precedent[5,6a] suggested that such an objective might be attained with substrate **31** (Scheme 6), wherein the

Scheme 6. Expected Course of the IMDA Reaction of **31**



N-atom bearing carbon is now stereogenic. An *endo*-Diels−Alder cyclization of **31** may proceed through either of two diastereomeric conformers, which may be described as *syn*-**31** and *anti*-**31** (Scheme 6), leading respectively to diastereomers *syn*-**32** and *anti*-**32** of the cycloadduct. Presumably, the sulfonyl group will tend to avoid nonbonding interactions with substituent R during the reaction; therefore, product *anti*-**32** should be dominant.

The foregoing hypothesis was probed with use of substrate **36**, obtained from L-tyrosinol methanesulfonamide, **33**,[26] as shown in Scheme 7. Accordingly, bis-*O*-silylation and *N*-BOC-derivatization afforded **34**. Tozer reaction of the

(18) Dunne, K. S.; Lee, S. E.; Gouverneur, V. *J. Organomet. Chem.* **2006**, *691*, 5246.

(19) Prepared *in situ* by reaction of the acetylene with EtMgBr in THF.

(20) Chanley, J. D.; Sobotka, H. *J. Am. Chem. Soc.* **1949**, *71*, 4140.

(21) It should be noted that: (i) The acetylenic Grignard was superior to the lithium variant in the addition reaction. (ii) Lindlar hydrogenation [(a) Lindlar, H.; Dubuis, R. *Org. Synth.* **1973**, *5* (Collect.), 880. (b) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446.] of the alkyne failed, presumably on steric grounds. Thus, attempted Lindlar hydrogenation of **23** resulted in exclusive reduction of the olefin (iii) Schwartz hydrozirconation [Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115.] of the ethynyl group also failed; (iv) the configuration of **23** was ascertained by NOESY spectroscopy.

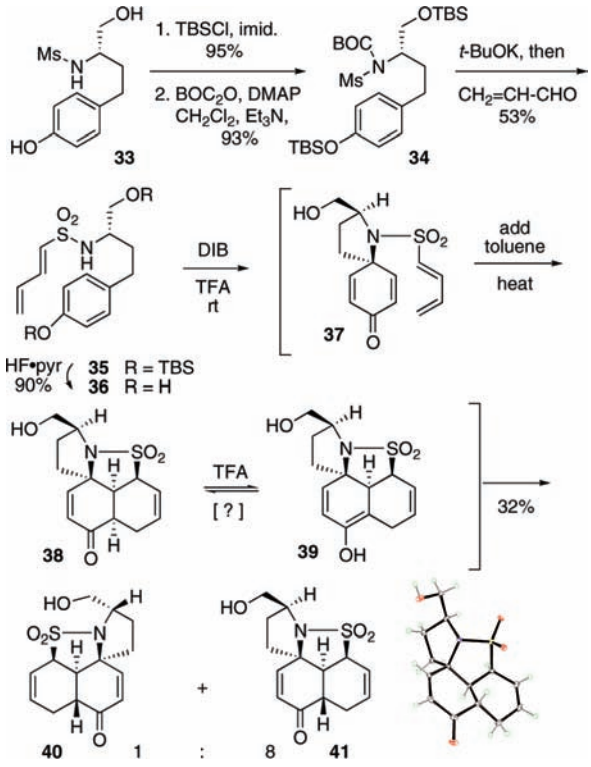
(22) (a) Juo, W.-J.; Lee, T.-H.; Liu, W.-C.; Ko, S.; Chittimalla, S. K.; Rao, C. P.; Liao, C.-C. *J. Org. Chem.* **2007**, *72*, 7992. (b) Lee, T.-H.; Liao, C.-C.; Liu, W.-C. *Tetrahedron Lett.* **1996**, *37*, 5897.

(23) Lutz, R. *Chem. Rev.* **1984**, *84*, 205. Deprotonation of the OH group was effected with KH, NaH, or KHMDS, with and without 18-crown-6, in benzene, toluene, THF, and DMSO.

(24) Tozer, M. J.; Woolford, A. J. A.; Linney, I. D. *Synlett* **1998**, 186.

(25) The conversion of **29** into **30** reflects an unprecedented mode of reactivity. However, related Diels−Alder reactions of quinone monoketal cognates of **29** are documented: (a) Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1559. (b) Yu, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 2783. (c) Hayden, A. E.; DeChancie, J.; George, A. H.; Dai, M.; Yu, M.; Danishefsky, S. J.; Houk, K. N. *J. Org. Chem.* **2009**, *74*, 6770.

Scheme 7. Desymmetrization of the "Locally Symmetrical" Dienone via Stereocontrolled IMDA Reaction of **37**



latter with acrolein in the presence of *t*-BuOK as seen previously gave **35**, desilylation of which delivered **36**. Notice that relative to himandrine, susbtance **36** has the opposite configuration of the nitrogen-bearing center. But of course, whatever diastereoselectivity might be attained during the crucial oxidative cyclization/IMDA reaction would later be duplicated in an enantiomeric series of compounds produced from D-**33**. The now familiar oxidative treatment of **36** with DIB in TFA afforded an 8:1 mixture (^{1}H NMR) of the anticipated *anti* adduct (major component) and of its *syn* diastereomer (minor, not fully characterized), in a cumulative 32% yield. The two compounds were difficult to separate, but a chromatographic fraction enriched in the major product deposited crystals suitable for an X-ray diffractometric study. Surprisingly, the material thus obtained proved to be the trans-fused isomer **41** of the presumed primary product **38**. Thus, the tandem oxidative amidation/IMDA cyclization had produced directly a compound with the himandrine-like trans-fusion of the decalin system. We suppose that this unexpected result is due to epimerization of **38** through TFA-promoted equilibration with enol **39**.

No such isomerization occurred in the sequence leading to the unsubstituted congener **30**. Attempts to rationalize such a difference in behavior have been unfruitful. For instance, an MM+ calculation estimated that the energy difference between the cis and trans isomers of the cycloadducts is very similar regardless of substitution at the nitrogen-bearing carbon ($\Delta E = -5.6$ kcal/mol for **30** vs -5.2 kcal/mol for **38**), as are the energy differences between the cis-adducts and the corresponding enols ($\Delta E = -7.5$ kcal/mol for **30** vs -7.4 kcal/mol for **38**), signifying that the more facile isomerization of **38** is unattributable to a greater thermodynamic drive to attain the trans-fused arrangement of the decalin domain. Then, the different behavior of **30** and **38** must be due to subtle kinetic factors. It would be imprudent to speculate on the nature of these at the present time.

In summary, we have extended the desymmetrization of "locally symmetrical" dienones emerging from the oxidative amidation of phenols to the IMDA mode. Reaction pathways a−c have served as platforms to explore aspects of the chemistry of a number of heretofore unknown systems. Finally, intermediates of the type **41** could be useful as building blocks for himandrine.

Acknowledgment. We thank the University of British Columbia, the Canada Research Chair Program, NSERC, CIHR, and MerckFrosst Canada for financial support.

Supporting Information Available: Experimental procedures and characterization data for new compounds, plus NMR (^{1}H and ^{13}C) spectra of several molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Available from commercial homotyrosine as detailed in ref. 5.