

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

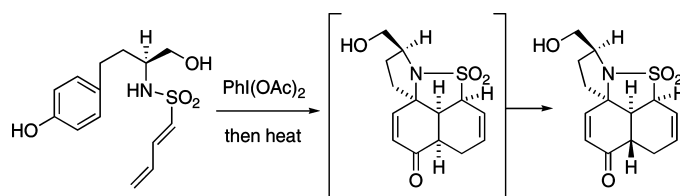
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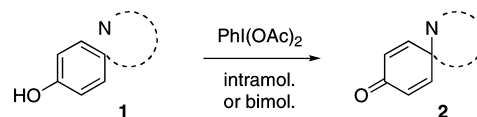
ABSTRACT



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 reagents¹ such as $\text{PhI}(\text{OAc})_2$ (“DIB”) and $\text{PhI}(\text{OCOCF}_3)_2$ (“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 intramolecular³ or in the bimolecular⁴ regime. While dienones **2** are “locally symmetrical”, various artifices enable their stereocontrolled desymmetrization. This causes the N-bearing spiro C atom to become

Scheme 1. The Oxidative Amidation of Phenols



stereogenic and to acquire a specific configuration. Desymmetrization may be accomplished via 1,4-addition⁵ 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

(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.

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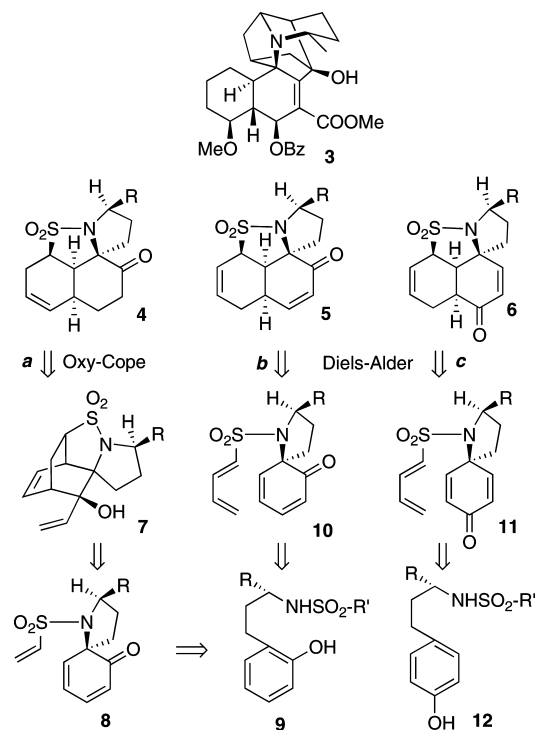
(6) (a) Mendelsohn, B.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539. (b) Frie, J.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 5394.

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

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

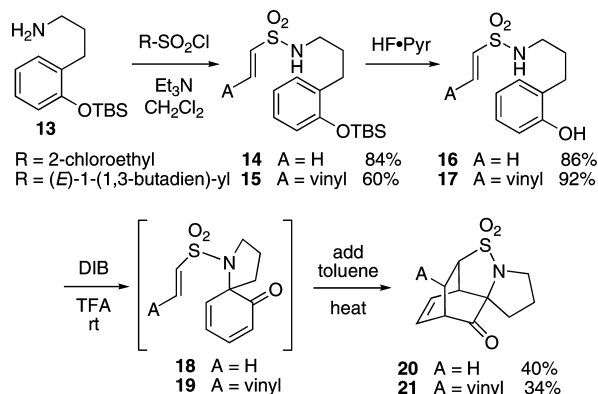


intermediates **4–6**, each one of which, in turn, could conceivably derive from the oxidative cyclization of a phenolic sulfonamide,^{3d} followed by IMDA reaction. An oxy-Cope rearrangement⁹ (cf. **7**) would also be required to elaborate **8** into **4**. We note that the decalin segment of **3** 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 ($\Delta E > 4$ 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

13¹⁰ with commercial 2-chloroethylsulfonyl chloride and with 1-(1,3-butadienyl)sulfonyl 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 TMEDA¹⁵ or CeCl_3 ,¹⁶ as well as vinyl-lithium 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.

20 $\xrightarrow{\text{TMS-C}\equiv\text{C-MgBr}}$ 93% $\xrightarrow{\text{LAH}}$ 66% 24 $\downarrow$ 5 (R = H)

TBAF 95% 22 R = TMS 23 R = H

25 $\xrightarrow[\text{THF, 87\%}]{\text{KH 18-cr-6}}$ 26

[ref 22]

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

1. BOC₂O, DMAP
 Et₃N, CH₂Cl₂, 88%
 2. *t*-BuOK, acrolein
 79%
 3. HF·Py, 92%

27 → 28 (DIB, TFA, rt)

29 → 30 (add toluene, heat, 39%)

(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.

The reaction scheme illustrates the Diels-Alder reaction of two cyclopentadiene derivatives, *syn*-31 and *anti*-31, to form bicyclic products *syn*-32 and *anti*-32.

Top Row:

- syn*-31:** A cyclopentadiene ring with a sulfonamide group (-NH-SO₂-R) and a vinyl group in a *syn* configuration. A dashed line indicates a "nonbonding interaction" between the hydrogen of the sulfonamide group and the vinyl group.
- anti*-31:** A cyclopentadiene ring with the same substituents in an *anti* configuration.

An equilibrium arrow points between *syn*-31 and *anti*-31.

Bottom Row:

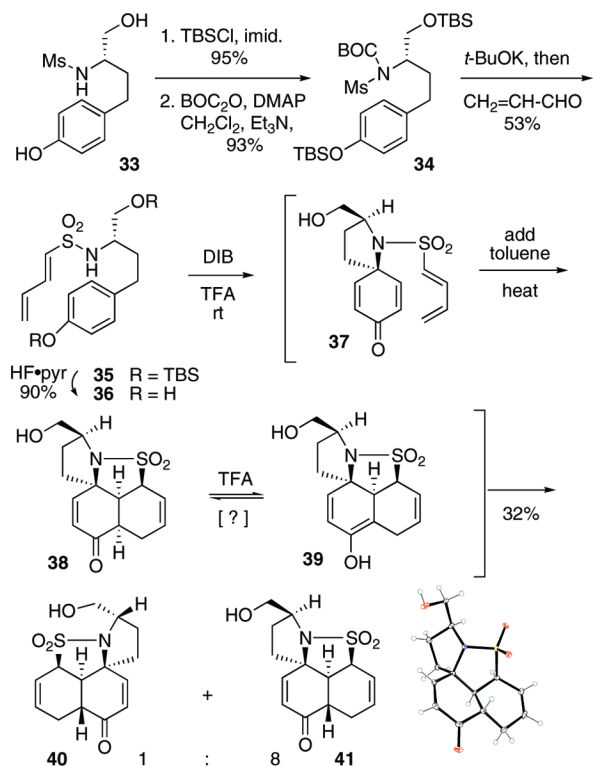
- syn*-32: expected minor product:** A bicyclic adduct where the sulfonamide and vinyl groups have ended up on the same face of the bicyclic system, with "opposite configurations" indicated by dashed lines.
- anti*-32: expected major product:** A bicyclic adduct where the sulfonamide and vinyl groups have ended up on opposite faces of the bicyclic system.

Vertical arrows indicate the reaction of *syn*-31 to *syn*-32 and *anti*-31 to *anti*-32.

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

(2b) The conversion of **2** into **3** effects 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, substance **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 (¹H NMR) of the anticipated *anti* adduct (major component) and of its *syn* diastereomer (minor, not fully characterized), in a

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

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 (¹H and ¹³C) spectra of several molecules. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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