

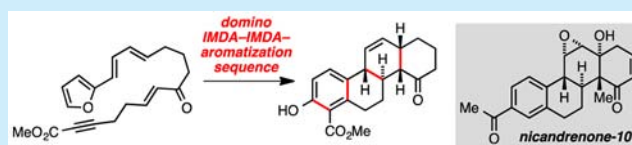
A Domino Diels–Alder Approach toward the Tetracyclic Nicandrenone Framework

Emily G. Mackay, Marck Nörret, Leon S.-M. Wong, Ignace Louis, Andrew L. Lawrence, Anthony C. Willis, and Michael S. Sherburn*

Research School of Chemistry, Australian National University, Canberra, ACT 2601, Australia

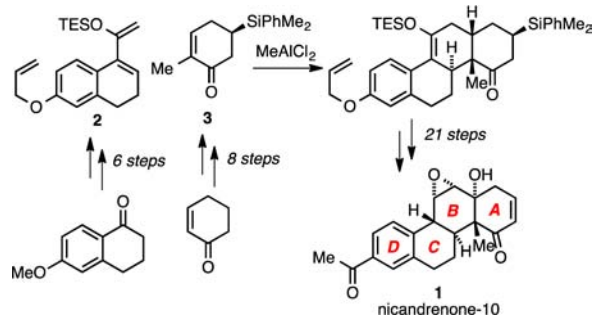
S Supporting Information

ABSTRACT: The tetracycyclic framework of the nicandrenone natural products is formed in one step from a linear precursor via a domino intramolecular Diels–Alder/intramolecular furan Diels–Alder/aromatization sequence. The approach represents a new 0 → ABCD strategy for the preparation of aromatic steroids.

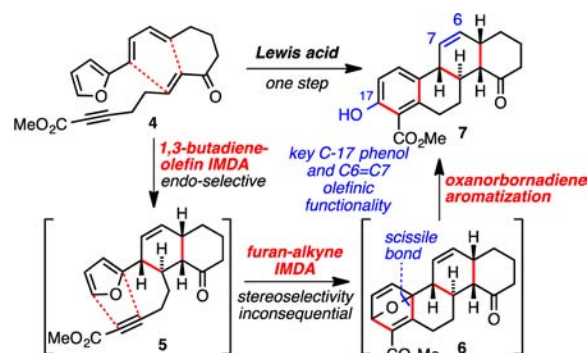


The nicandrenone natural products are a structurally unusual group of ring-D aromatic homosteroids that are responsible for the insect repellent and antifeedant properties of *Nicandra physaloides*, a member of the Solanaceae plant family.¹ Corey and Stoltz reported the enantioselective total synthesis of nicandrenone-1 and nicandrenone-10 (**1**) in 2000 employing a Diels–Alder reaction between a tetralone-derived diene **2** and substituted cyclohexanone dienophile **3**.² This A + CD → ABCD approach remains the only reported synthesis of any ring-D aromatic homosteroid (Scheme 1).³

Scheme 1. Corey–Stoltz Synthesis of Nicandrenone-10



Scheme 2. Proposed One Step 0 → ABCD Aromatic Steroid Synthesis



two Lewis acid promoted IMDA reactions,^{5,6} the latter (**5** → **6**) involving a furan diene and alkyne dienophile, followed by an *in situ* aromatization of the thus formed oxabicyclonorbornene ring system to afford tetracycle **7**.

Specifically, an initial *endo*-selective 1,7,9-decatrien-3-one-type IMDA reaction⁶ between the internal, acyclic 1,3-butadiene residue and acyl-activated olefin would form bicycle **5**, and a subsequent IMDA reaction between the furan diene and carbomethoxy-activated alkyne⁷ would generate oxabicyclonorbornene-containing pentacycle **6**. Under Lewis acidic conditions, the doubly allylic, tertiary C–O bond of the strained oxa-bridged ring system should cleave and aromatize to phenol **7**.⁷ This unprecedented tetracyclization sequence would also install useful functionality for further manipulation into the natural product. Thus, the same phenolic residue was used by Corey and Stoltz to introduce the C-17 side chain by cross-coupling,² and the cyclohexene generated in the initial Diels–Alder reaction would also serve as a convenient handle for incorporation of the epoxyalcohol.

Received: August 20, 2015

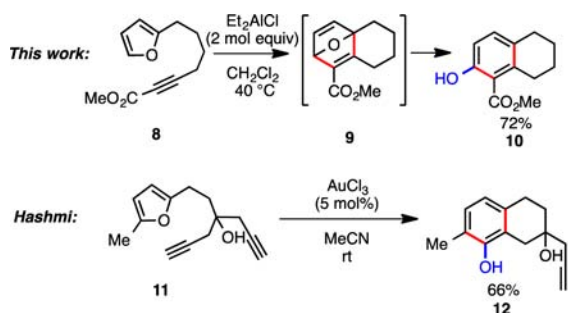
Published: November 2, 2015

The nicandrenones clearly represent a significant synthetic challenge, as evidenced by the step count from Corey's landmark synthesis. Herein we describe a new approach that permits rapid synthetic access to the core tetracyclic framework of the nicandrenones with both the potential for elaboration into the natural products and broader application in aromatic steroid synthesis.

Our strategy focuses on an early stage assembly of all four rings of the tetracycyclic framework of the nicandrenones through a domino, triple reaction sequence (Scheme 2). This 0 → ABCD method for aromatic steroid synthesis builds upon our double intramolecular Diels–Alder (IMDA) approach to nonaromatic tetracyclic systems.⁴ Specifically, we anticipated that linear precursor **4** might undergo a domino sequence of

IMDA reactions involving furan dienes and olefinic dienophiles have enjoyed widespread use.⁸ The corresponding processes involving alkynic dienophiles, however, have received relatively little attention.⁹ Furthermore, whereas the Brønsted acid mediated formation of phenols from 7-oxanorbornadienes is a well established process,⁷ the deployment of Lewis acids has not found widespread application. There have been several reports describing a furan–alkyne IMDA reaction followed by an aromatization.^{9c,g,h,10} Since none matched the structure of our intended intermediate, it was considered pertinent to model the furan–alkyne IMDA–aromatization sequence, *viz.* 5 → 6 → 7, prior to embarking upon the synthesis of domino reaction precursor 4. Pleasingly, exposure of readily prepared¹¹ alkyne–furan 8 to Et₂AlCl (a Lewis acid commonly used to promote IMDA reactions⁵) gave bicyclic phenol 10 in 72% yield, by way of putative oxa-bridged intermediate 9 (Scheme 3).

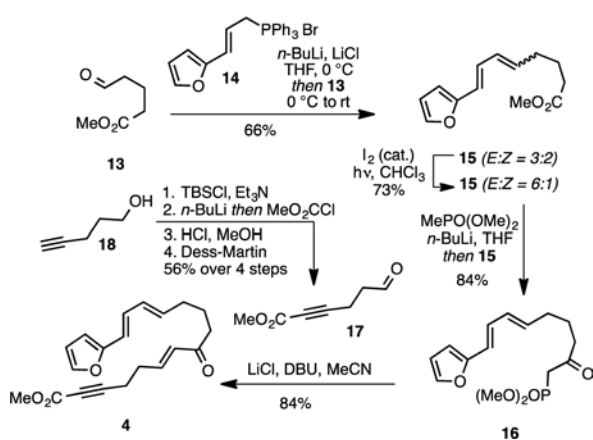
Scheme 3. Alkyne–Furan Cyclization–Aromatization Sequences



The intramolecular union of alkynes and furans to form bicyclic phenols is the basis of the Hashmi AuCl₃-catalyzed phenol synthesis (Scheme 3, 11 → 12).¹² The Lewis acid promoted furan–alkyne IMDA–aromatization reaction (8 → 10) delivers a hydroxytetralin product with complementary regiochemistry to that of Hashmi's useful transformation.

Building upon this encouraging model study, we embarked upon the synthesis of fully armed linear precursor 4. A short and highly convergent synthesis of this compound, with a longest linear sequence of six steps, and allowing the preparation of multigram quantities of 4, is depicted in Scheme 4. Known aldehyde 13 (available in two steps from δ -valerolactone)¹³ underwent a Wittig reaction with the semistabilized phosphorane

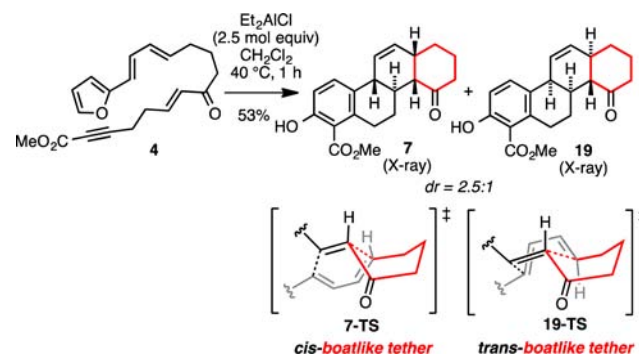
Scheme 4. Multigram Scale Synthesis of Domino Tetracyclization Precursor 4



derived from phosphonium salt 14 (made in two steps from furfural)^{4b} to form ester 15 as a 3:2 (*E:Z*) mixture of geometrical isomers about the newly formed bond. This ratio was improved to 6:1 (*E:Z*) by equilibration with catalytic elemental iodine in sunlight. Transformation into phosphonate 16, by way of phosphono-Claisen condensation, proceeded in good yield and was followed by a Roush–Masamune Horner–Wadsworth–Emmons¹⁴ reaction with aldehyde 17 (available from 4-pentyn-1-ol 18 in four steps) affording desired linear precursor 4.

With precursor 4 accessible in useful quantities, attention turned to the key domino sequence. We were delighted to find that certain Lewis acids proved effective for the transformation of precursor 4 into a mixture of two diastereomeric tetracycles, 7 and 19. Of the Lewis acids investigated (ZnCl₂, SnCl₄, MeAlCl₂, Me₂AlCl, EtAlCl₂, Et₂AlCl, Me₃Al, AlCl₃), 2.5 mol equiv of Et₂AlCl gave the highest yield of 53% (Scheme 5). An

Scheme 5. Domino Tetracyclization of Linear Precursor 4



initial substrate concentration of ca. 10 mM was also needed for optimal yield, delivering a 2.5:1 mixture of products in refluxing CH₂Cl₂. Stereoisomeric tetracycles 7 and 19 (structures secured by single crystal X-ray analyses) are the result of an initial *endo*- and *exo*-mode cycloaddition, respectively, between the acyclic 1,3-butadiene and olefinic dienophile of substrate 4, presumably through boatlike transition states 7-TS and 19-TS.¹⁵

In summary, all four rings of the nicandrenone homosteroid framework have been accessed in a single step transformation from a readily prepared precursor.¹⁶ This striking increase in molecular complexity was accomplished through a new, Lewis acid promoted, domino IMDA/IMDA/aromatization sequence.¹⁷ Applications and extensions of this strategy for step economic natural product synthesis are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02412.

Experimental procedures, product characterizations, and ¹H and ¹³C and NMR spectra (PDF)
X-ray data for compound 7 (CIF)
X-ray data for compound 19 (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: michael.sherburn@anu.edu.au.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Australian Research Council.

■ REFERENCES

- (1) (a) Nalbandov, O.; Yamamoto, R. T.; Fraenkel, G. S. *J. Agric. Food Chem.* **1964**, *12*, 55. (b) Fraenkel, G. S.; Nayer, J.; Nalbandov, O.; Yamamoto, R. T. *Int. Kongr. Entomol. Verh., 11th* **1960**, *3*, 122. (c) Bates, R. B.; Eckert, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 8258. (d) Bates, R. B.; Morehead, S. R. *J. Chem. Soc., Chem. Commun.* **1974**, 125. (e) Begley, M. J.; Crombie, L.; Ham, P. J.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1972**, 1108a. (f) Begley, M. J.; Crombie, L.; Ham, P. J.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1972**, 1250. (g) Begley, M. J.; Crombie, L.; Ham, P. J.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1976**, 304.
- (2) Stoltz, B. M.; Kano, T.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9044.
- (3) For a review on the synthesis of steroids using a Diels–Alder reaction, see: (a) Mackay, E. G.; Sherburn, M. S. *Synthesis* **2014**, *47*, 1. For reviews on the synthesis of steroids, see: (b) Zeelen, F. *Nat. Prod. Rep.* **1994**, *11*, 607. (c) Nising, C. F.; Bräse, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 9389.
- (4) (a) Turner, C. I.; Williamson, R. M.; Turner, P.; Sherburn, M. S. *Chem. Commun.* **2003**, 1610. (b) Norret, M.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 4074.
- (5) For reviews on the IMDA reaction, see: (a) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (b) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. (c) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 820. (d) Takao, K.-i.; Munakata, R.; Tadano, K.-i. *Chem. Rev.* **2005**, *105*, 4779.
- (6) Roush, W. R. Stereochemical and Synthetic Studies of the Intramolecular Diels–Alder Reaction. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, 1990; Vol. 2, p 91.
- (7) For a review, see: Vogel, P.; Cossy, J.; Plumet, J.; Arjona, O. *Tetrahedron* **1999**, *55*, 13521.
- (8) (a) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179. (b) Keay, B. A.; Hunt, I. R. Aspects of the Intramolecular Diels–Alder Reaction of Furan Dienes Leading to the Formation of Epoxydecalin Systems. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press: Stamford Connecticut, 1999; Vol. 6, p 173.
- (9) Reported examples of alkyne–furan IMDA reactions in synthesis: (a) Grootaert, W. M.; De Clercq, P. J. *Tetrahedron Lett.* **1986**, *27*, 1731. (b) Harwood, L. M.; Jackson, B.; Jones, G.; Prout, K.; Thomas, R. M.; Witt, F. J. *J. Chem. Soc., Chem. Commun.* **1990**, 608. (c) Li, C. C.; Liang, S.; Zhang, X. H.; Xie, Z. X.; Chen, J. H.; Wu, Y. D.; Yang, Z. *Org. Lett.* **2005**, *7*, 3709. (d) Liu, L.; Gao, Y.; Che, C.; Wu, N.; Wang, D. Z.; Li, C. C.; Yang, Z. *Chem. Commun.* **2009**, 662. (e) Che, C.; Liu, L.; Gong, J.; Yang, Y.; Wang, G.; Quan, J.; Yang, Z. *Org. Lett.* **2010**, *12*, 488. (f) Gordon, C. P.; Young, K. A.; Robertson, M. J.; Hill, T. A.; McCluskey, A. *Tetrahedron* **2011**, *67*, 554. (g) Chen, Y.; Wang, L.; Liu, Y.; Li, Y. *Chem. - Eur. J.* **2011**, *17*, 12582. (h) Fang, L.; Chen, Y.; Huang, J.; Liu, L.; Quan, J.; Li, C.-C.; Yang, Z. *J. Org. Chem.* **2011**, *76*, 2479. (i) Samanta, K.; Kar, S.; Sarkar, A. K. *Tetrahedron Lett.* **2012**, *53*, 1376. (j) Nieto-Garcia, O.; Alonso, R. *J. Org. Chem.* **2013**, *78*, 2564.
- (10) (a) Yamaguchi, Y.; Yamada, H.; Hayakawa, K.; Kanematsu, K. *J. Org. Chem.* **1987**, *52*, 2040. (b) Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595. (c) Padwa, A.; Reger, T. S. *Can. J. Chem.* **2000**, *78*, 749. (d) Claeys, S.; Van Haver, D.; De Clercq, P. J.; Milanesio, M.; Viterbo, D. *Eur. J. Org. Chem.* **2002**, *2002*, 1051. (e) Muller, K. M.; Keay, B. A. *Synlett* **2008**, *2008*, 1236. (f) He, Y.; Zhang, X.; Cui, L.; Wang, J.; Fan, X. *Green Chem.* **2012**, *14*, 3429. (g) LaPorte, M.; Hong, K. B.; Xu, J.; Wipf, P. *J. Org. Chem.* **2013**, *78*, 167. (h) Chen, J.; Ferreira, A. J.; Beaudry, C. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 11931.
- (11) See the [Supporting Information](#) for full details.
- (12) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553.
- (13) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7559.
- (14) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essendorf, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
- (15) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915.
- (16) For the only reported 0 → ABCD method for aromatic steroid synthesis, involving an aromatic B-ring steroid synthesis, see: Lecker, S. H.; Nguyen, N. H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 856.
- (17) For a review on Diels–Alder sequences, see: Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167.