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Concise Total Synthesis of (±)-Cephalotaxine via a Transannulation Strategy: Development of a Facile Reductive oxy-Nazarov Cyclization

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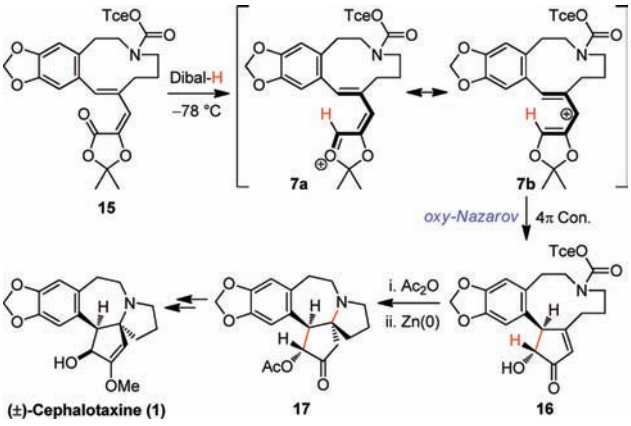
ABSTRACT



A concise total synthesis of (±)-cephalotaxine (1) has been achieved from dioxolanone derivative 15 via a transannulation strategy. The key transformation is a facile reductive oxy-Nazarov cyclization as illustrated above, involving presumably a tethered 1,2-oxidopentadienyl cation species 7a or 7b, which represents a new variant of the oxy-Nazarov cyclization and constitutes an effective, regio- and stereospecific 5-hydroxy cyclopentenone annulation protocol under mild hydride reduction conditions.

The Nazarov reaction is a unique electrocyclization of a formal oxidopentadienyl cation species leading to cyclopentenone derivatives.[1] This mechanistically interesting and synthetically valuable cyclopentannulation has enjoyed ever-increasing attention.[2] Despite recent advances in directed control and catalysis,[3] it is still desirable to explore new variants of this reaction under mild conditions. We present here the development of a facile reductive oxy-Nazarov (RON) cyclization[4] in conjunction with our

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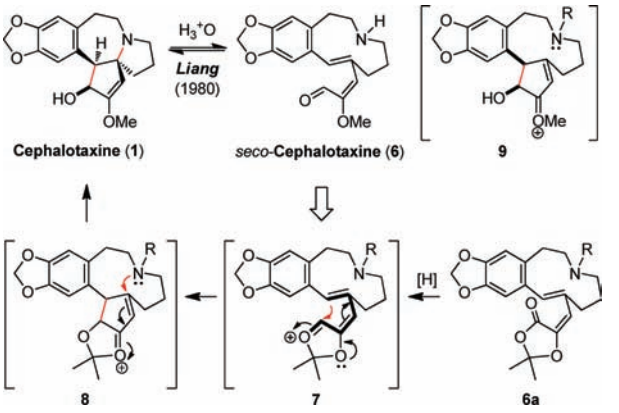
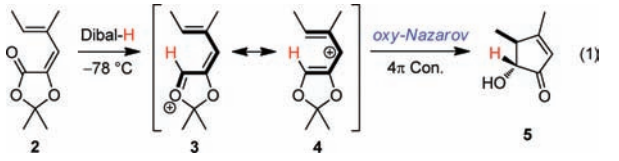


Figure 1. Liang's hypothesis and transannulation strategy.

synthetic studies toward cephalotaxine (**1**, CET, Figure 1). This transformation (eq 1) constitutes an effective, regio- and stereospecific cyclopentannulation of vinylalkylidene dioxolanone **2** to 5-hydroxy cyclopentenone **5** under mild hydride reduction conditions,[5] which is formulated tentatively as the thermally conrotatory ring closure of a tethered 1,2-oxidopentadienyl cation species **3** or resonance hybrid form **4**.[6] An expedient total synthesis of (±)-**1** was achieved by employing this RON cyclization as a key step.



CET (**1**) is the parent structure of the *Cephalotaxus* alkaloids.[7] The unusual cyclic architecture and potent antileukemic activity of its ester derivatives (i.e., homoharringtonine) render **1** an attractive target for total synthesis.[7b,8] An intriguing stereochemical problem associated with **1** is its optical lability.[9] An appealing mechanistic speculation concerning the racemization of **1** was invoked by Liang in 1980 (Figure 1)[10] in which *seco*-CET (**6**) was proposed as a transient structure in a reversible addition of the amine to the aldehyde function across the macrocyclic olefin. Inspired by this hypothesis,[11] we reasoned that a tethered oxonium species **7** could serve as a functional equivalent of **6** that might undergo a formal electrocyclization to give the cyclopentenone species **8**. Subsequent transannular cyclization would lead to the core ring system of **1**. In continuation of our strategic exploration of CET synthesis,[12] we envisioned a transannulation approach[13] starting from an equivalent macrocyclic dioxolanone derivative **6a** (Figure 1). It was our assumption that the fragmentation of **1** to **6** might involve a formal *retro*-Nazarov process[14] of a cationic species **9**,[11] which could shed light on the puzzling racemization mechanism of CET.[15]

To explore the above transannulation strategy, condensation[16] of norhydrastinine (**10**)[17] with iodo enolsilane **11** in DMF afforded the annulation product **12** (mp 92–93 °C)[18] in 45% yield (Scheme 1).[19] Upon exposure of aldehyde **12** to a mixture of 10 equiv of 2,2,2-trichloroethyl chloroformate (TrocCl) and 8 equiv of $KHCO_3$ in $CHCl_3$, macrocyclic aldehyde **13** (mp 156–158 °C)[18] was obtained in 91% yield.[20] Wittig olefination[19] of **13** with triphenylphosphoranylidene dioxolanone (**14**) in toluene at reflux furnished the (*E*)-dioxolanone **15** (mp 122–123 °C) in 68% isolated yield, along with the separable (*Z*)-isomer (14%). This convergent three-step procedure produced the designated macrocyclic dioxolanone derivative **15** (cf. **6a**) in a

(3) For a recent review, see: Harmata, M. *Chemtracts–Org. Chem.* **2004**, *17*, 416.

(4) For a variant of the *intercepted* Nazarov cyclization by hydride transfer reduction which was termed also as the *Reductive Nazarov Cyclization*, see: Giese, S.; West, F. G. *Tetrahedron Lett*. **1998**, *39*, 8393. *idem, Tetrahedron* **2000**, *56*, 10221.

(5) To the best of our knowledge, the only documentation on the reduction of a geometric mixture of cinnamylidene dioxolanones by Dibal-H (Toluene, −78 °C) was recorded to give a product mixture of hydroxyl aldehyde and stereochemically unspecified hydroxyl cyclopentenone in an attempted synthesis of α-keto aldehyde, see: Ramage, R.; Griffiths, G. J.; Shutt, F. E.; Sweeney, J. N. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1531.

(6) For a recent synthesis of 5-hydroxycyclopent-2-enones via an *interrupted* Nazarov cyclization, see: Marx, V. M.; Burnell, D. J. *Org. Lett*. **2009**, *11*, 1229.

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(15) Studies are underway in our laboratory to verify this mechanistic reasoning.

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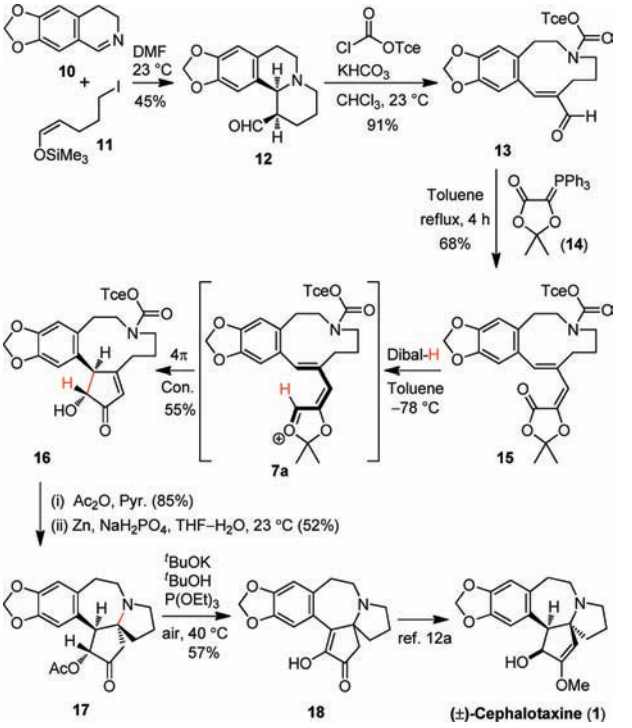
(18) Structure characterized by single crystal X-ray analysis.[19] CCDC 735679, 735678, 735677, 735680, 735707, and 735676 contain the supplementary crystallographic data for compounds **12**, **13**, **17**, **20a**, **23a**, and s-**5** (SI-1), respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(19) See Supporting Information (SI-1) for details.

(20) (a) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc*. **1992**, *114*, 4403. (b) Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, L.; Deluca, M.; Merritt, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc*. **1993**, *115*, 8116.

Scheme 1. Concise Total Synthesis of (±)-Cephalotaxine (**1**)



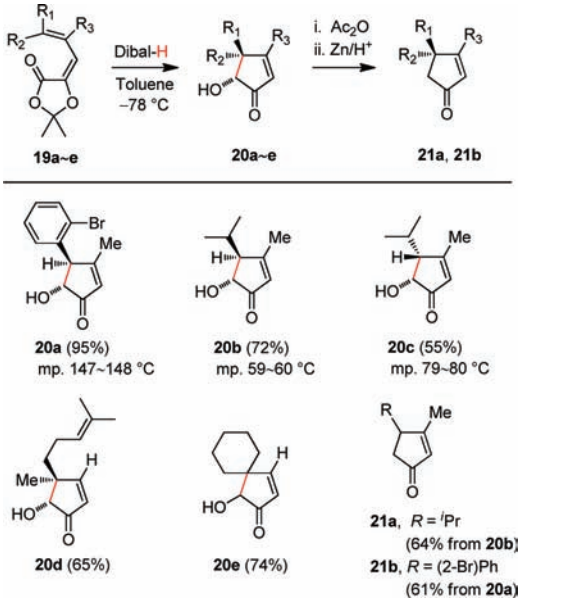
multigram quantity from readily available components **10**, **11**, and **14**.

Various reductive conditions were next examined on dioxolanone **15**. To our delight, upon exposure to Dibal-H (1.2 equiv) in toluene at −78 °C and subsequent aqueous workup with an aqueous *Rochelle* salt solution, hydroxy cyclopentenone **16** (mp 177−179 °C)[21] was isolated (55% *borsm*) as the sole product (Scheme 1). The facile and stereospecific transformation of **15** → **16** indicated that an oxy-Nazarov cyclization took place effectively under mild hydride reduction conditions, presumably via the tethered 1,2-oxidopentadienyl cation species **7a**. Notably, the carbamate function in **15** was not affected by the action of Dibal-H. Acetylation of hydroxy enone **16** followed by selective cleavage of the *N*-Troc group by zinc reduction afforded the corresponding transannular cyclization product **17** (mp 156−158 °C)[18] as a single diastereomer. Demethylcephalotaxinone (**18**) was prepared by oxidation of **17** in 57% yield, and this was converted to (±)-CET via a well-established two-step procedure.[9b,12a] Thus an expedient total synthesis of (±)-CET has been achieved from dioxolanone **15** via a 5-step sequence.

To delineate the general scope of this novel RON cyclization, we examined a range of vinylalkylidene dioxolanones **19a**−**e** (Scheme 2). Cyclization proceeded smoothly with Dibal-H (1.2 equiv) in toluene at −78 °C to give the corresponding 5-hydroxy cyclopentenones **20a**−**e** stereospecifically in satisfactory yield. Diastereomeric cyclopentenones **20b**

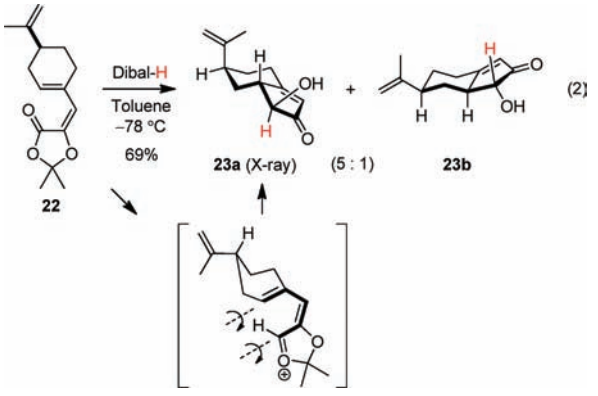
(21) Stereostructure characterized by an X-ray analysis of the corresponding *p*-nitrobenzoate of an analogously cyclized *N*-Eoc derivative s-**5**.[18,19]

Scheme 2. Reductive oxy-Nazarov (RON) Cyclization



and **20c**[22] were obtained from the respective geometric isomers **19b** and **19c**. Cyclopentenone **20d** with a quaternary carbon and spiro-cyclopentenone **20e** were constructed effectively. Reductive deoxygenation[23] of **20a** and **20b** to **21a** and **21b** was realized via the corresponding acetates with metallic zinc in glacial acetic acid.[19]

Chiral dioxolanone derivative **22**, readily prepared from (*S*)-perillaldehyde, underwent smooth RON annulation (eq 2) to give the bicyclic diastereomers **23a** (mp 108−109 °C)[18] and **23b** in a ratio of 5:1, which implies a substantial torquoselective control by the isopropenyl group.[24]



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(23) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223.

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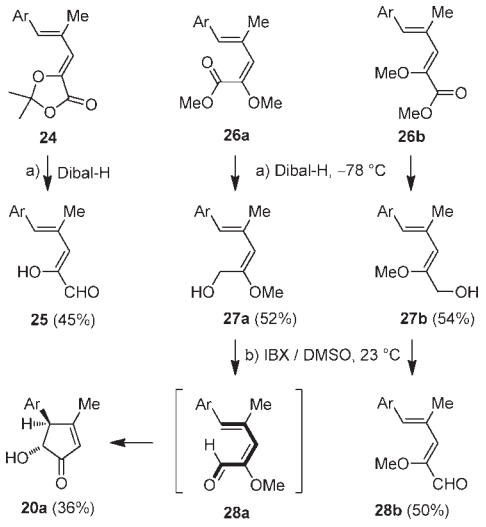
Scheme 3. Dibal-H Reduction of **24** and **26(a,b)** (Ar = 2-BrPh)



It is evident that the alkylidene geometry of the dioxolanone **2** must be (*E*)-configured. Hydride reduction of the (*Z*)-isomer **24** resulted in a moderate yield of the hydroxy aldehyde **25** (Scheme 3) as the sole isolable product (Ar = (2-Br)Ph).[19] Furthermore, the tethered acetal function in **2** facilitates the RON cyclization significantly as the hydride reduction of dienyl esters **26a** and **26b** afforded the corresponding alcohols **27a** and **27b** in moderate yield, respectively (Scheme 3). Oxidation of **27a** with IBX led to the cyclopentenone **20a** in 36% yield, which corresponds to the iso-Nazarov cyclization[25] of an aldehyde intermediate **28a**. In contrast, the IBX oxidation of **28b** produced the corresponding aldehyde **27b** as the sole product.[26]

(25) For examples of *iso*-Nazarov cyclization involving a 1-oxidopentadienyl cation or equivalents, see: (a) Jung, M. E.; Yoo, D. *J. Org. Chem.* **2007**, *72*, 8565. (b) Miller, A. K.; Banghart, M. R.; Beaudry, C. M.; Suh, J. M.; Trauner, D. *Tetrahedron* **2003**, *59*, 8919. (c) de Lera, Á. R.; Rey, J. G.; Hrovat, D.; Iglesias, B.; López, S. *Tetrahedron Lett.* **1997**, *42*, 7425. (d) Denmark, S. E.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 195. (e) Tius, M. A.; Astrab, D. P. *Tetrahedron Lett.* **1984**, *25*, 1539.

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(27) For examples, see: (a) Muxfeldt, H.; Weigele, M.; Van Rheenen, V. *J. Org. Chem.* **1965**, *30*, 3573. (b) Weinreb, S. M.; Auerbach, J. *J. Am. Chem. Soc.* **1975**, *97*, 2503. (c) Kim., S. H.; Cha, J. K. *Synthesis* **2000**, *14*, 2113. (d) Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4972. (e) Dhoro, F.; Tius, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 12472. (f) Prandi, C.; Deagostino, A.; Venturello, P.; Occhiato, E. G. *Org. Lett.* **2005**, *7*, 4345.

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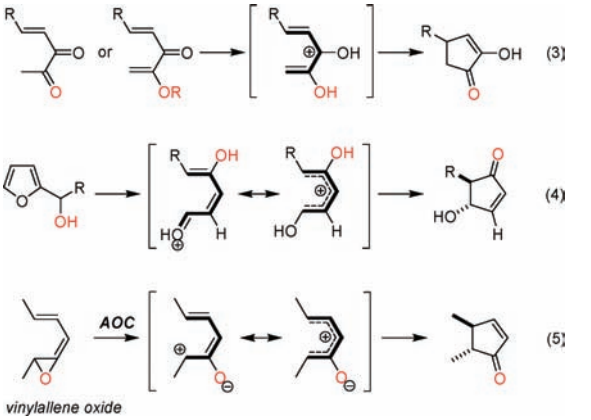
(29) For a relevant review, see: (a) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757. For examples, see: (b) Corey, E. J.; Ritter, K.; Yus, M.; Najera, C. *Tetrahedron Lett.* **1987**, *28*, 3547. (c) Kim, S. J.; Cha, J. K. *Tetrahedron Lett.* **1988**, *29*, 5613. (d) Hess, B. A., Jr.; Smentek, L.; Brash, A. R.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 5603. (e) López, C. S.; Faza, O. N.; York, D. M.; De Lera, Á. R. *J. Org. Chem.* **2004**, *69*, 3635.

Other mechanistically relevant variants of the general oxy-Nazarov cyclization include those of α-ketoenone or functional equivalents (eq 3),[2e,p,27] 2-furyl carbinol (Piancatelli rearrangement, eq 4),[28] and vinylallene oxide (eq 5),[2h,29] in which the oxy-substituents at C(2) or C(4) of the corresponding pentadienyl cations facilitate their respective pericyclic ring-closure process.[30] Thus, the RON cyclization (eq 1) developed in this work represents a new variant of the typical oxy-Nazarov reaction, featuring the incorporation of a tethered oxy-substituent at C(2) in the presumably bis-oxidopentadienyl cation species **3** and **4**, which might explain the rapid and effective 4π electrocyclization of dioxolanone **2** under mild hydride reduction conditions.



In summary, a facile RON cyclization of vinylalkylidene dioxolanones of type **2** has been developed which provides an efficient, regio- and stereospecific oxy-cyclopentannulation protocol,[31] as demonstrated in an expedient synthesis of (±)-CET. Further investigations on the scope, mechanistic details, asymmetric variant, and synthetic applications of this reaction is ongoing in our laboratory and will be reported in due course.

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Supporting Information Available. Experimental procedures, spectral data, and copies of ^{1}H and ^{13}C NMR spectrum for compounds **12**, **13**, **15**−**18**, **19a**−**e**, **20a**−**e**, **21(a,b)**, **22**, **23a**, **24**, **25**, **26(a,b)**, **27(a,b)**, **28b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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