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Novel Formal Synthesis of Cephalotaxine via a Facile Friedel–Crafts Cyclization

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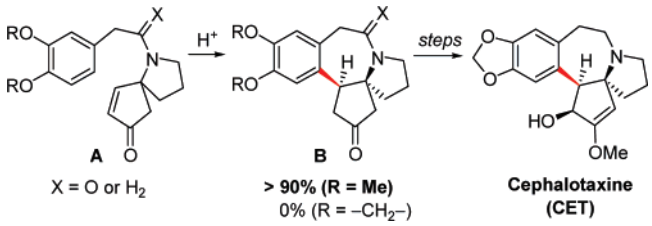
ABSTRACT



A novel formal synthesis of cephalotaxine (CET), the parent structure of the antileukemia *Cephalotaxus* alkaloids, was achieved via a facile Friedel–Crafts cyclization of the amino (or amido) spiro-cyclopentenone precursor (A) mediated by a protic acid leading to tetracyclic ketone B. A remarkable stereoelectronic effect of the methylenedioxy substituent (R) and an interesting skeletal isomerization of the CET core ring system (B, X = H_2) were observed.

Cephalotaxine (CET) is the parent structure of a rare family of plant antileukemia *Cephalotaxus* alkaloids,[1] possessing a unique spiro-annulated polycyclic ring system. The structural characteristics of CET and the clinically proven yet intriguing antitumor therapeutic potentials of its naturally occurring ester derivatives (i.e., harringtonine and homoharringtonine) have attracted a long-standing interest in their chemical synthesis.[1b,2] A variety of innovative synthetic strategies have been developed since the landmark total synthesis of CET by Weinreb and Semmelheck in the 1970s,[3] by focusing on the construction of the tetracyclic core ring system (ABCD, Figure 1).

One of the most commonly employed strategic approaches is the B-ring closure of a spirocyclic precursor (A-CD) leading to the formation of the *central benzazepine* system (bond highlighted in red in Figure 1). Some typical B-ring closure approaches used in previous CET synthesis (or a relevant model study) include: (1) Lewis (or protic) acid mediated Friedel−Crafts-type cyclization as employed by the Kuehne,[4] Royer,[5] Sha,[6] and Mori[7] groups (Figure 2),[8] among which a remarkable stereoelectronic effect of the

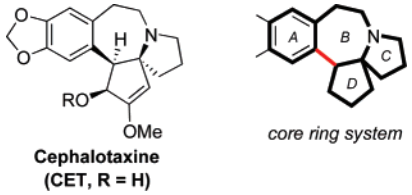


Figure 1. Cephalotaxine (CET) and its core ring system.

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(1) For reviews, see: (a) Huang, L.; Xue, Z. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1984; Vol. 23, pp 157−226. (b) Jalil Miah, M. A.; Hudlicky, T.; Reed, J. W. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1998; Vol. 51, pp 199−269.

(2) For a recent total synthesis, see: Eckelbarger, J. D.; Wilmot, J. T.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 10370 and references therein.

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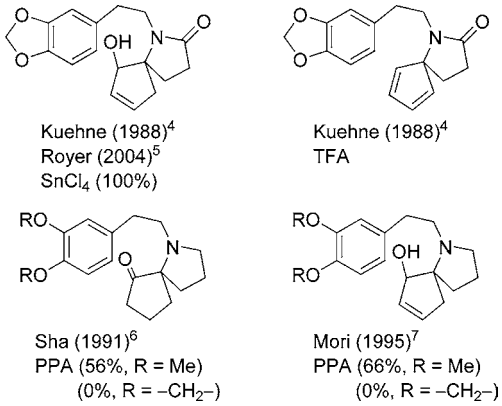


Figure 2. Typical Friedel−Crafts cyclization approaches.

methylenedioxy substituent (R) was first noticed by Sha and co-workers;[6] (2) Pd(0)-catalyzed Heck-type coupling of an unsaturated spirocyclic aryl halide precursor as exemplified by the Tietze,[9] Ikeda,[10] Suga-Yoshida,[11] and Hayes[12] groups (Figure 3); and (3) radical cyclization approaches as used by the Semmelheck[13] and Taniguchi[14] groups (Figure 4).

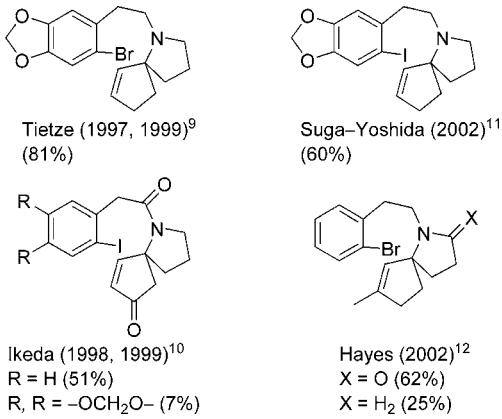


Figure 3. Typical Pd^0-catalyzed Heck-type coupling approaches.

As a continuation of our study toward CET synthesis,[15] we envisioned that an alternative Friedel−Crafts-type cyclization (Scheme 1, arrows) of a spiro-cyclic enone precursor **I** would produce the tetracyclic ring structure **II** of CET

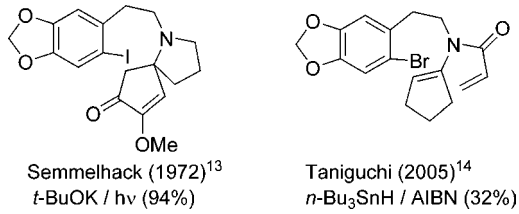
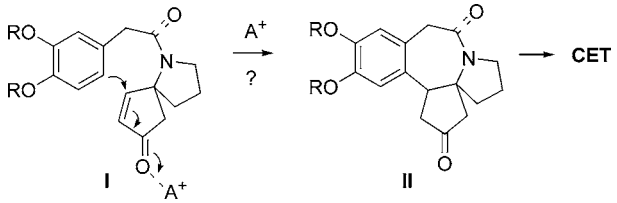


Figure 4. Alternative radical cyclization approaches.

directly, which is known to be readily transformed into CET.[16]

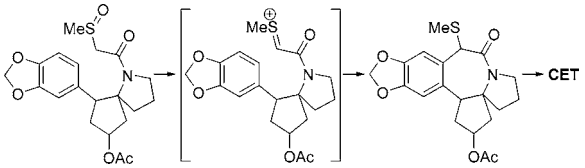
Scheme 1. Enone Friedel−Crafts Cyclization Approach (?)



To test the feasibility of this B-ring closure approach, the amido spiro-cyclopentenone **4a** (or **4b**) was prepared[17] conveniently from proline-derived spirocyclic amino enone **2** and acid chloride **3** in good yield (Scheme 2) by following procedures reported by Ikeda et al.[10b] Although the *methylenedioxy*-substituted precursor **4a** did not cyclize under various Lewis or protic acid conditions, we found that a

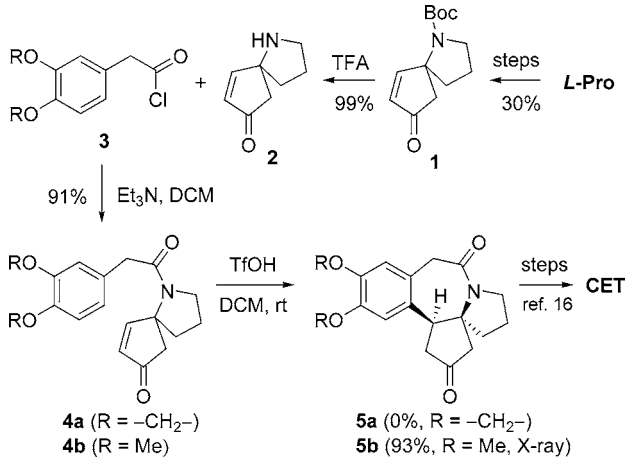
(3) For an account, see: Weinreb, S. M.; Semmelhack, M. F. *Acc. Chem. Res.* **1975**, *8*, 158.
(4) Kuehne, M. E.; Bornmann, W. G.; Parsons, W. H.; Spitzer, T. D.; Blount, J. F.; Zubieta, J. *J. Org. Chem.* **1988**, *53*, 3439.
(5) Planas, L.; Perard-Viret, J.; Royer, J. *J. Org. Chem.* **2004**, *69*, 3087.
(6) Sha, C. K.; Young, J. J.; Yeh, C. P.; Chang, S. C.; Wang, S. L. *J. Org. Chem.* **1991**, *56*, 2694.
(7) Isono, N.; Mori, M. *J. Org. Chem.* **1995**, *60*, 115.

(8) For an alternative B-ring cyclization approach involving a cationic intermediate, see: Ishibashi, H.; Okano, M.; Tamaki, H.; Maruyama, K.; Yakura, T.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1436.

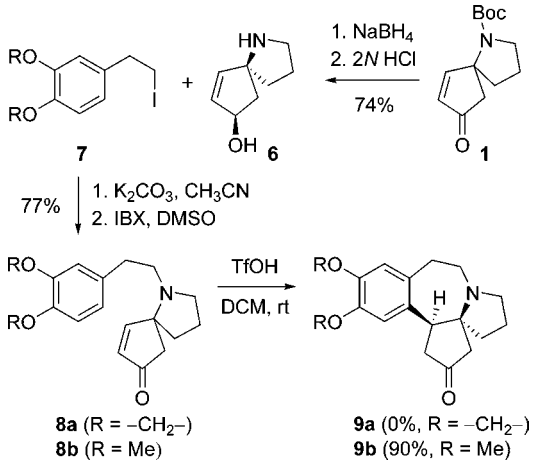


(9) (a) Tietze, L. F.; Shirok, H. *Angew. Chem., Int. Ed.* **1997**, *36*, 1124. (b) Tietze, L. F.; Shirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264.
(10) (a) Ikeda, M.; Hirose, K.; El Bialy, S. A. A.; Sato, T.; Yakura, T.; Bayomi, S. M. M. *Chem. Pharm. Bull.* **1998**, *46*, 1084. (b) Ikeda, M.; El Bialy, S. A. A.; Hirose, K.; Kotake, M.; Sato, T.; Bayomi, S. M. M.; Shehata, I. A.; Abdelal, A. M.; Gad, L. M.; Yakura, T. *Chem. Pharm. Bull.* **1999**, *47*, 983.
(11) Suga, S.; Watanabe, M.; Yoshida, J. I. *J. Am. Chem. Soc.* **2002**, *124*, 14824.
(12) Worden, S. M.; Mapitse, R.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6011.
(13) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507.
(14) Taniguchi, T.; Ishita, A.; Uchiyama, M.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *J. Org. Chem.* **2005**, *70*, 1922.
(15) (a) Li, W.-D. Z.; Wang, Y.-Q. *Org. Lett.* **2003**, *5*, 2931. (b) Li, W.-D. Z.; Ma, B.-C. *J. Org. Chem.* **2005**, *70*, 3277. (c) Ma, B.-C.; Wang, Y.-Q.; Li, W.-D. Z. *J. Org. Chem.* **2005**, *70*, 4528.
(16) Yasuda, S.; Yamada, T.; Hanaoka, M. *Tetrahedron Lett.* **1986**, *27*, 2023.
(17) See Supporting Information for experimental details.

Scheme 2. Novel Formal Synthesis of Cephalotaxine



Scheme 3. Friedel−Crafts Enone Cyclization of **8**



smooth (conjugate) Friedel−Crafts-type enone cyclization of an analogous *dimethoxy* derivative **4b** occurred on treatment with triflic acid (2.5 equiv, as a slurry mixture in CH_2Cl_2) at ambient temperature and the cyclization product **5b** (mp 222−224 °C) was obtained in 93% yield.[18] It is obvious that the remarkable stereoelectronic effect of the methylenedioxy substituent[6] is responsible for the *deactivation* of the aryl group (leading to an electron-deficient arene system). It is noteworthy that the corresponding iodo analogue of **4a** used by the Ikeda group[10] in their Heck cyclization approach (Figure 3) gave the corresponding cyclization product in quite low yield (ca. 7%) as well, which may underline the significance of a stereoelectronic effect similar to that above.

The spectroscopic features of **5b** are identical to those reported by Hanaoka et al.[16] and its *cis*-cyclopentanone configuration was further confirmed by a single-crystal X-ray diffraction analysis.[19] A simple yet effective formal synthesis of CET via a facile Friedel−Crafts enone cyclization was thus realized.

As shown in Scheme 3, the amino spiro-cyclopentenone **8a** (or **8b**) was prepared analogously via N-alkylation of spiro amino alcohol **6** derived from enone **1** and followed by IBX oxidation.[17] Similarly, the protic acid mediated Friedel−Crafts cyclization of the *dimethoxy* enone **8b** (R = Me) proceeded cleanly to give tetracyclic ketone **9b** in 90% isolated yield, whereas the corresponding *methylenedioxy* derivative **8a** failed to cyclize under the same or forcing acidic conditions.[20]

This Friedel−Crafts enone cyclization is equally applicable for the six-membered ring formation from various spirocyclic enone substrates **10**−**13** as summarized in Figure 5 under similar acidic conditions.[21] The deactivation of the aryl system by the methylenedioxy substituent is obvious in the cases of **10b** vs **11b**. The electron-deficient aryl system (i.e., **13b**) is very reluctant to participate in the conjugated arylative enone cyclization.

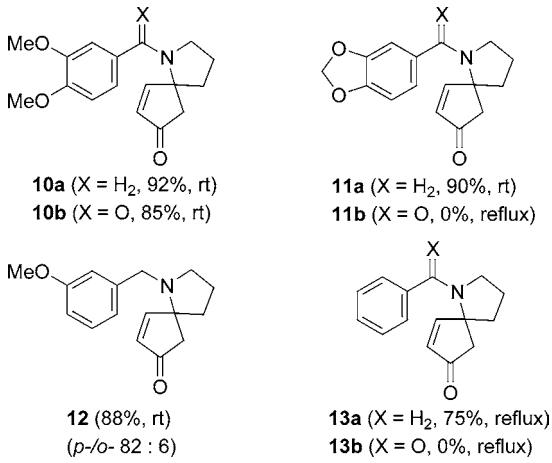
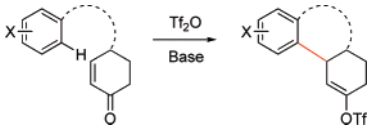


Figure 5. Friedel−Crafts cyclization of spiro enones **10**−**13**.

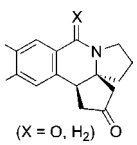
(18) During the preparation of this manuscript, we have noticed a recent report by Trauner et al. (Grundl, M. G.; Kaster, A.; Beaulieu, E. D.; Trauner, D. *Org. Lett.* **2006**, *8*, 5429.) on a similar *triflative* Friedel−Crafts cyclization of an aryl enone precursor:



(19) X-ray crystallographic data of **5b**: $C_{18}H_{21}NO_4$, FW 315.36, monoclinic, space group $P2(1)/c$, a = 8.576(2) Å, b = 7.6040(18) Å, c = 24.573(6) Å, β = 99.323(4), Z = 4, d_{calcd} = 1.325 g/cm^3, R_1 ($I > 2\sigma(I)$) = 0.0454, wR_2 (all data) = 0.0903. See Supporting CIF file for more details.

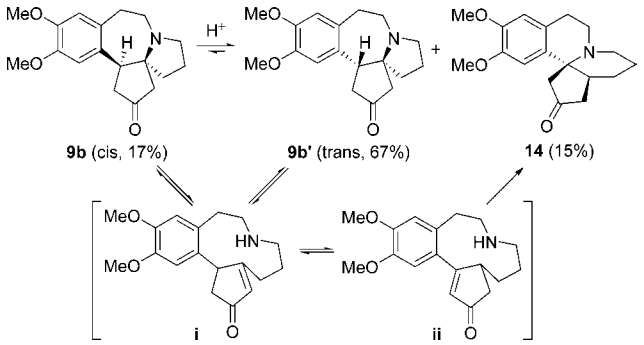
(20) For example, enlongated refluxing of **8a** with triflic acid in CH_2Cl_2 led to gradual decomposition.

(21) Mediated by triflic acid in a slurry mixture of CH_2Cl_2, see Supporting Information for detailed spectral data of the corresponding cyclization products with a general structure of



Interestingly, we found that the cis-tetracyclic ketone **9b** readily underwent a ring skeletal isomerization (Scheme 4)

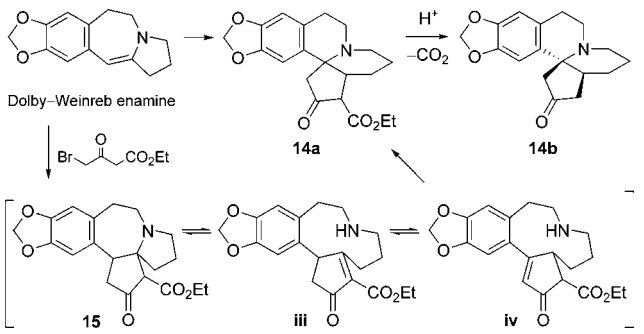
Scheme 4. Ring Skeletal Isomerization of **9b**



upon exposure to mild acidic conditions (i.e., long-standing in a $CHCl_3$ solution), from which a more polar major isomer (67%, monohydrate of hydrochloride salt, mp. 223−225 °C) was identified by single-crystal X-ray diffraction analysis as the trans-isomer **9b′**[22] and a less polar isomer (ca. 15%, mp 171−172 °C) was found to be the known ketone **14**.[23] Apparently, an acid-mediated equilibration between *cis*-**9b** and macrocyclic enones **i** and **ii** via retro-Michael and cyclopentenone isomerization is attributed to the observed skeletal rearrangement. It was noted that the crystalline trans-isomer **9b′** was more stable and less prone toward isomerization than the corresponding cis-isomer **9b**. This skeletal isomerization can be accelerated under some forcing conditions (i.e., refluxing in toluene with a catalytic amount of PPTs).

These observations are coincident with an intriguing ring system isomerization process proposed previously by Dolby and co-workers (Scheme 5)[24] during their pioneering synthetic study on CET, in which the Dolby−Weinreb enamine alkylation product **15** was assumed to undergo a fast

Scheme 5. Dolby Rearrangement[24] Proposal to Cyclic Ketones **14a** and **14b**



equilibration with macrocyclic enone intermediates **iii** and **iv** and ring skeletal rearrangement product **14a** was identified as the sole isolable product. The presence of an α-ethoxycarbonyl group on the cyclopentanone ring and the relatively electron-deficient aryl system with the methylenedioxy substituent in **15** may be responsible for the extremely facile isomerization to **14a** and **14b**.

In summary, we have accomplished a simple and effective formal synthesis of cephalotaxine via a facile Friedel−Crafts-type enone cyclization of a spiro-cyclopentenone precursor. The remarkable stereoelectronic effect of the aryl methylenedioxy substituent demonstrated in this work implies the π-electronic demanding character for the above cyclization reaction. This facile Friedel−Crafts enone cyclization may be applicable in other heterocyclic syntheses of potential medicinal use.

Acknowledgment. Dedicated to Dr. L. J. Dolby of Organic Consultants, Inc. (Eugene, Oregon 97401). We thank the National Natural Science Foundation (QT 20021001 and 20572047) for financial support. The Cheung Kong Scholars program and the Outstanding Scholars program of Nankai University are gratefully acknowledged.

Supporting Information Available: Experimental procedures, spectral data, copies of spectra for compounds **4a**, **4b**, **5b**, **8a**, **8b**, **9b**, **9b′**, and **10**−**13**, the corresponding cyclization products of **10**−**13**, and crystallographic information files (CIFs) for compounds **5b** and **9b′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) X-ray crystallographic data for the monohydrate of the hydrochloride salt of **9b′**: $C_{18}H_{26}NClO_4$, FW 355.85, triclinic, space group $P1$, a = 7.477(9) Å, b = 10.370(13) Å, c = 11.376(14) Å, α = 92.785(14), β = 94.308(16), γ = 92.272(15), Z = 2, d_{calcd} = 1.348 g/cm^3, R_1 ($I > 2\sigma(I)$) = 0.0484, wR_2 (all data) = 0.0714. See Supporting CIF file for more details.

(23) For an alternative preparation and X-ray structure, see ref 15b.

(24) Dolby, L. J.; Nelson, S. J.; Senkovich, D. *J. Org. Chem.* **1972**, *37*, 3691.