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A Novel and Efficient Total Synthesis of Cephalotaxine

Wei-Dong Z. Li* and Yong-Qiang Wang

National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

wdli@fas.harvard.edu; liwd@lzu.edu.cn

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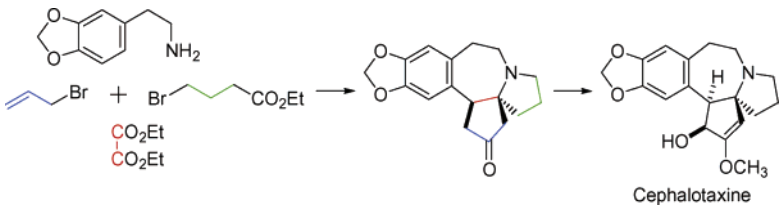
ABSTRACT



Total synthesis of cephalotaxine (CET), the parent member of a class of structurally unique antileukemia *Cephalotaxus* alkaloids, was accomplished on the basis of a conceptually novel strategy featuring transannular reductive skeletal rearrangements as the key transformations for the construction of the pentacyclic ring skeleton of CET. The synthetic potential of the designated Clemmensen–Clemo–Prelog–Leonard reductive rearrangement was demonstrated for the first time in a facile synthesis of the benzazepine subunit of CET. A novel endocyclic enamine (cyclopentenone) annulation was discovered and rationalized as an unusual azo-Nazarov-type cyclization.

Cephalotaxine (**1**, CET), the parent member of the *Cephalotaxus* alkaloids,[1] processes a unique benzazepine-bearing pentacyclic ABCDE-ring skeleton. Naturally occurring esters of CET (harringtonine and homoharringtonine) have been found to be highly effective for the treatment of acute human leukemia and are currently undergoing advanced clinical trials.[2] Homoharringtonine is also a potent agent against strains of chloroquinine-resistant *Plasmodium f.* malaria parasite in vitro.[3] The unique structure and the therapeutic potential of this group of alkaloids have stimulated much synthetic research that has produced several elegant total syntheses of CET[1b,4] and numerous studies on the construction of the pentacyclic ring system.[1b,5] Nonetheless, an even more efficient and practical synthesis of CET is desirable in light of the potential pharmaceutical needs. We describe herein a novel and highly efficient synthesis of CET.

The unique heterocyclic ABCDE-ring system of CET has continued to be a proving ground for new strategy and synthetic methods.[1b] Our strategic thinking for elaborating the key pentacyclic precursor, ketone **2**[6] (Figure 1), was based

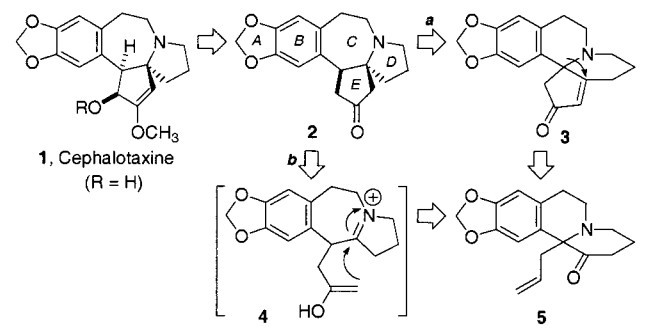


Figure 1. Strategic plan.

on a transannular skeletal rearrangement (path *a*) of cyclic enone **3** that parallels the biogenesis of CET postulated by Parry et al.[7] Enone **3** could in turn be derived from cyclic ketone **5**. A more conventional strategy is outlined as path *b*, which involves a transannular rearrangement of ketone **5** to benzazepine precursor **4**.

(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 review, see: Kantarjian, H. M.; Talpaz, M.; Santini, V.; Murgo, A.; Cheson, B.; O'Brien, S. M. *Cancer* **2001**, *92*, 1591.

(3) Whaun, J. M.; Brown, N. D. *Ann. Trop. Med. Parasitol.* **1990**, *84*, 229. See also: *Chem. Abstr.* **1990**, *113*, 165042.

(4) For recent examples, see: (a) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824. (b) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885. (c) Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264.

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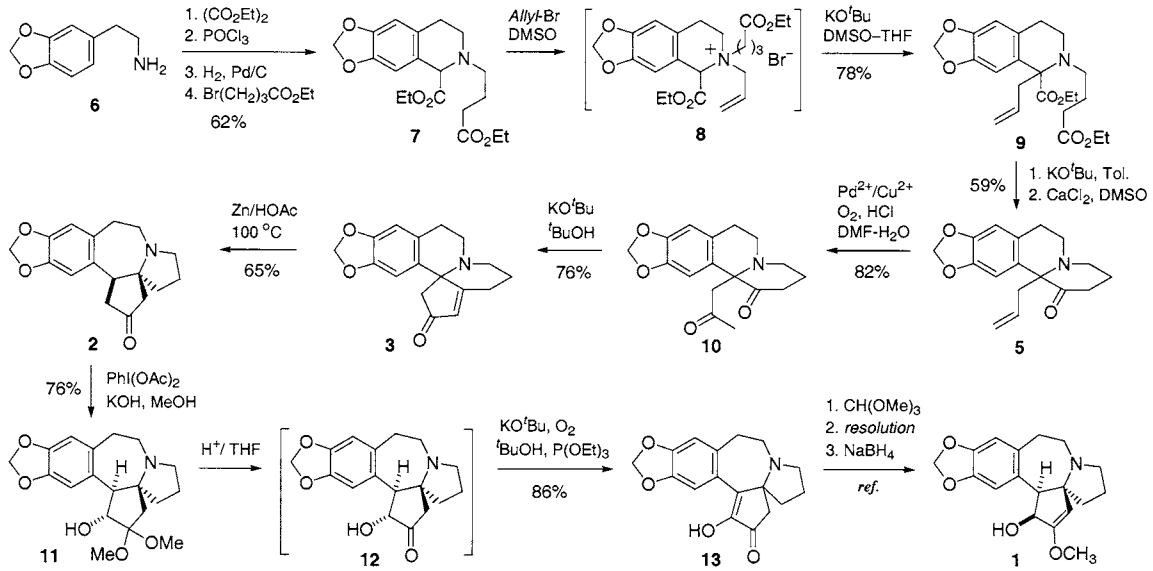
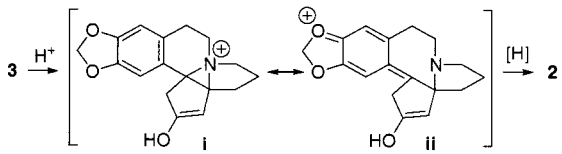
Scheme 1. Total Synthesis of Cephalotaxine



As shown in Scheme 1, the synthesis commenced from *β*-(3, 4-methylenedioxy)phenethylamine (**6**), which was converted to **7** in quantity in 62% overall yield by the following sequence: (1) Bischler−Napieralski cyclization of corresponding oxalamide, (2) catalytic hydrogenation, and (3) N-alkylation with ethyl 4-bromobutyrate.[8] Reaction of diester **7** with allyl bromide in DMSO at 35 °C for 48 h followed by treatment with KO^{t}Bu in DMSO−THF (1:1) at −15 °C → rt gave the allylation product **9** in 78% yield,[9] presumably via a facile 2,3-sigmatropic rearrangement[10] of the corresponding *N*-ylide of ammonium salt **8**. Dieckmann cyclization of diester **9** (KO^{t}Bu, toluene, reflux) and subsequent decarboxylation ($CaCl_2$, DMSO, 150 °C) produced the cyclic ketone **5** in 59% yield. Wacker oxidation of **5** (10 mol % $PdCl_2$, $CuCl_2$, O_2, 0.2 N HCl−DMF, 65 °C) furnished the diketone **10** in 82% yield, which was cyclized (KO^{t}Bu, ^{t}BuOH, 40 °C) to form the pentacyclic enone **3** (76%). Upon short exposure to zinc dust in hot (100 °C) glacial acetic acid, enone **3** was transformed into the desired pentacyclic ketone **2** (mp 129−131 °C) in 65% isolated yield[11] along with ca. 5% of enone conjugate reduction product (mp 173−174 °C).[6a] This remarkably facile transformation can be rationalized as a transannular reductive rearrangement via a transient bridged aziridinium[12] intermediate as shown in Scheme 2. This type of skeletal rearrangement can be found in Büchi's synthesis of *Iboga* alkaloids.[13]

Scheme 2. Transannular Rearrangement Pathway for **3** → **2**

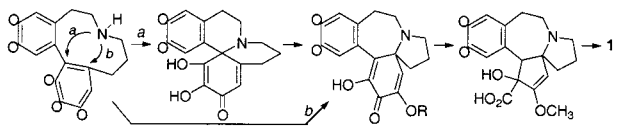


Attempted direct hydroxylation of the corresponding enolate of cyclic ketone **2** using Büchi's procedure (KO^{t}Bu, ^{t}BuOH, O_2, $P(OEt)_3$)[14] resulted in a facile dehydrogenation of **2** to an enone **17** (vide infra). Subjecting **2** to Moriarty oxidation ($PhI(OAc)_2$, KOH, MeOH, 0 °C)[15] gave a hydroxy dimethylketal as the sole product (mp 74−75 °C) in 76%

(5) For recent examples, see: (a) Worden, S. M.; Mapitse, R.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6011. (b) Booker-Milburn, K. I.; Dudin, L. F.; Anson, C. E.; Guile, S. D. *Org. Lett.* **2001**, *3*, 3005. (c) Kim, S.-H.; Cha, J. K. *Synthesis* **2000**, 2113. (d) Beall, L. S.; Padwa, A. *Tetrahedron Lett.* **1998**, *39*, 4159. (e) Molander, G. A.; Hiersemann, M. *Tetrahedron Lett.* **1997**, *38*, 4347. (f) De Oliveira, E. R.; Dumas, F.; D'Angelo, J. *Tetrahedron Lett.* **1997**, *38*, 3723.

(6) (a) Dolby, L. J.; Nelson, S. J.; Senkovich, D. *J. Org. Chem.* **1972**, *37*, 3691. (b) Weinreb, S. M.; Auerbach, J. *J. Am. Chem. Soc.* **1975**, *97*, 2503. (c) Weinreb, S. M.; Semmelhack, M. F. *Acc. Chem. Res.* **1975**, *8*, 158. (d) Weinstein, B.; Craig, A. R. *J. Org. Chem.* **1976**, *41*, 875.

(7) Parry, R. J.; Chang, M. N. T.; Schwab, J. M.; Foxman, B. M. *J. Am. Chem. Soc.* **1980**, *102*, 1099 (cf. path *a* below).



(8) See the Supporting Information for details.

(9) Direct allylation of diester **7** with allyl bromide by the action of KO^{t}Bu in THF or DMF resulted in a low and irreproducible yield of **9**.

(10) This was evidenced by the slowness and incompleteness of direct methylation (MeI, KO^{t}Bu) as compared to allylation or crotylation of diester **7** or corresponding 3, 4-dimethoxy analogue. For a review, see: Brückner, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp 873−908.

(11) The putative pentacyclic ketone **2** had not been actually synthesized prior to this work; cf. refs 1b and 6.

(12) For a review, see: Nagata, W. In *Lectures in Heterocyclic Chemistry*; Castle, R. N., Elslager, E. F., Eds.; J. Heterocyclic Chemistry, Inc.: Orem, 1972; Vol. 1, pp S29−S37.

(13) Büchi, G.; Coffen, D. L.; Kocsis, K.; Sonnet, P. E.; Ziegler, F. E. *J. Am. Chem. Soc.* **1966**, *88*, 3099.

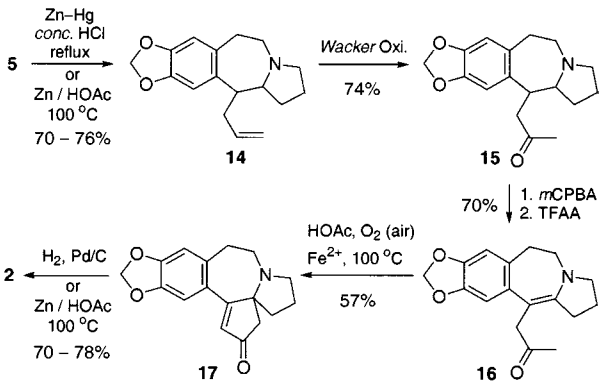
(14) Büchi, G.; Kulsa, P.; Ogasawara, K.; Rosati, R. L. *J. Am. Chem. Soc.* **1970**, *92*, 999.

(15) Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett.* **1981**, *22*, 1283. For a review, see: Moriarty, R. M.; Prakash, O. *Org. React.* **1999**, *54*, 273.

yield, which was deduced to be **11** by spectroscopic analysis.[16] Deketalization of **11** in THF followed by autoxidative dehydrogenation[17] (KO^{t}Bu, ^{t}BuOH, O_2, $P(OEt)_3$, 40 °C) of the resulting crude hydroxy ketone **12** (*epi*-desmethylcephalotaxine) afforded desmethylcephalotaxinone (**13**) (mp 105−107 °C) in 86% yield,[6b] identical in every respect with a sample prepared from natural (−)-CET[18] by hydrolysis[7] and autoxidative dehydrogenation as for **11** → **13**. Since the conversion of desmethylcephalotaxinone (**13**) to natural (−)-CET via methylation, optical resolution with L-tartaric acid,[19] and borohydride reduction has been demonstrated,[1b] the sequence outlined in Scheme 1 constitutes a total synthesis of CET with an overall yield of ca. 12% to desmethylcephalotaxinone (**3**) from diester **7** through an eight-stage sequence.

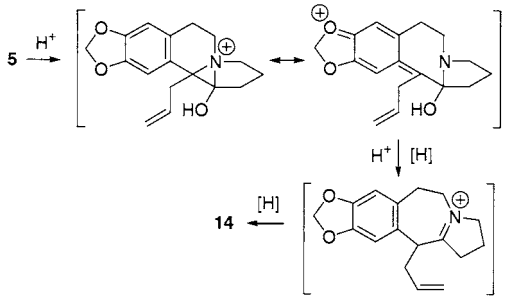
The synthesis described above evolved from an initial strategic plan (Figure 1, path *b*) that was based on an intramolecular Mannich cyclization[20] of the iminium intermediate **4** for the *E*-ring formation. We envisioned that the corresponding precursor to **4** would be generated from cyclic ketone **5** by a Clemmensen reductive rearrangement. The anomalous Clemmensen reduction of cyclic α-amino ketone was first noticed by Clemo in 1931,[21] clarified by Prelog,[22] and later studied systematically by Leonard and co-workers.[23] Surprisingly, the potential of this interesting reductive rearrangement in organic synthesis has not been recognized. We took advantage of this unique Clemmensen−Clemo−Prelog−Leonard reductive rearrangement for constructing the benzazepine-bearing ABCD-ring system of CET. To our delight, standard Clemmensen reduction (Zn−Hg, concentrated HCl, reflux) of α-amino ketone **5** led to allyl benzazepine derivative **14** in 76% isolated yield (Scheme 3). Furthermore, we found that anhydrous Clemmensen

Scheme 3. Enamine Cyclopentenone Annulation Pathway to **2**



reduction conditions,[24] with zinc dust in hot glacial acetic acid, were also equally effective for this reductive rearrangement. This convenient and mild procedure is well suited to multifunctional substrates.[25]

Scheme 4. Reductive Rearrangement Pathway for **5** → **14**



This facile rearrangement can be generalized (Scheme 4) as an acid-catalyzed transannular interaction[26] of N:→C═OH^+ (leading to a transient aziridinium intermediate), which would facilitate the benzylic C−N bond reductive cleavage.[27] The electron-rich aromatic system certainly contributed to this facile process.

Acidic Wacker oxidation (vide supra) of **14** gave methyl ketone **15** in 74% yield. However, the attempted generation of iminium intermediate **4** from **15** by the oxidative action[28] of $Hg(OAc)_2$ resulted in a slow decomposition of **15** under a variety of reaction conditions. In case an alternative Polonovski−Potier protocol[29] might be more selective, the corresponding amine oxide of **15** prepared by *m*-CPBA oxidation was treated with excess trifluoroacetic anhydride (TFAA) in CH_2Cl_2, and enamine ketone **16** was obtained as the sole product in 70% yield, which was apparently formed by isomerization of the initially generated iminium salt **4**. Compound **16** had been previously synthesized[6] by an alternative enamine alkylation of the so-called Dolby−Weinreb enamine,[1b] and it had been claimed[6] by Weinreb and Weinstein that cyclization to **2** (formally an endocyclic enamine annulation) could not be realized under various conditions, although Dolby et al. reported that acid-catalyzed

(16) Cf.: (a) Yasuda, S.; Yamada, T.; Hanaoka, M. *Tetrahedron Lett.* **1986**, *27*, 2023. (b) Yasuda, S.; Yamamoto, Y.; Yoshida, S.; Hanaoka, M. *Chem. Pharm. Bull.* **1988**, *36*, 4229.

(17) For example, see: Woodward, R. B. (work with Volpp, G.; Gougoutas, J. Z.) *The Harvey Lectures* **1963**, 31.

(18) We thank Professor Xiao-Tian Liang of Beijing Institute of Materia Medica for a gift of natural cephalotaxine.

(19) Cf. ref 1b, pp 219−220. See also: *Chem. Abstr.* **1995**, *122*, 56276.

(20) For an excellent review, see: Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 1007−1046.

(21) (a) Clemo, G. R.; Ramage, G. R. *J. Chem. Soc.* **1931**, 437. (b) Clemo, G. R.; Raper, R.; Vipond, H. J. *J. Chem. Soc.* **1949**, 2095.

(22) Prelog, V.; Seiwerth, R. *Chem. Ber.* **1939**, *72*, 1638.

(23) (a) Leonard, N. J.; Wildman, W. C. *J. Am. Chem. Soc.* **1949**, *71*, 3089. (b) Leonard, N. J.; Ruyle, W. V. *J. Am. Chem. Soc.* **1949**, *71*, 3094. (c) Leonard, N. J.; Barthel, E.; Jr. *J. Am. Chem. Soc.* **1949**, *71*, 3098. (d) Leonard, N. J.; Curry, J. W.; Sagura, J. J. *J. Am. Chem. Soc.* **1953**, *75*, 6249 and previous articles in this series. (e) Wilson, W. *Chem. Ind.* (*London*) **1955**, 200. (f) Brewster, J. H. *J. Am. Chem. Soc.* **1954**, *76*, 6364.

(24) Vedejs, E. *Org. React.* **1975**, *22*, 401.

(25) Studies along this line toward natural product synthesis are in progress and will be reported in due course.

(26) For a review, see: Leonard, N. J. *Rec. Chem. Prog.* **1956**, *17*, 243.

(27) Cf.: (a) Gaskell, A. J.; Joule, J. A. *Tetrahedron* **1968**, *24*, 5115. In contrast, see: (b) Noé, E.; Séraphin, D.; Zhang, Q.; Djaté, F.; Hénin, J.; Laronze, J.-Y.; Lévy, J. *Tetrahedron Lett.* **1996**, *37*, 5701. (c) Aït-Mohand, S.; Noé, E.; Hénin, J.; Laronze, J.-Y. *Eur. J. Org. Chem.* **1999**, 3429.

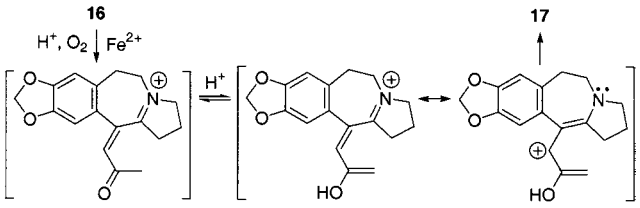
(28) For leading references, see: (a) Leonard, N. J.; Hay, A. S.; Fulmer, R. W.; Gash, V. W. *J. Am. Chem. Soc.* **1955**, *77*, 439. (b) Leonard, N. J.; Fulmer, R. W.; Hay, A. S. *J. Am. Chem. Soc.* **1956**, *78*, 3457.

(29) For a review, see: Grierson, D. S.; Husson, H.-P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp 910−947.

cyclization of **16** led to a rearranged product (saturated enone **3**) in low yield.[6a]

Although keto enamine **16** appeared not to be a promising intermediate,[6] a series of experiments on acidic treatment of **16** was examined. To our surprise, a hot mixture of 40% acetic acid and **16** in an open flask (exposure to air) generated gradually a sole isolable product in ca. 30% yield whose structure was verified as the pentacyclic enone **17** (spectroscopically).[30] Further experimentation improved the yield in this cyclization to 57% (glacial acetic acid as solvent, air, and a stoichiometric amount of $FeSO_4$). It is evident[31] that this cyclization is an acid-catalyzed O_2-dependent process, which we reasoned to be an unusual azo-Nazarov-type cyclization[32] (Scheme 5) initiated by an acid-catalyzed autoxidation.

Scheme 5. Oxidative Cyclization Pathway for **16** → **17**



Related acid-catalyzed, oxidative cyclizations can be found in Woodward's synthesis of chlorophyll-*a*[33] and in an oxy-Nazarov cyclization[5c] in Weinreb's pioneering CET synthesis.[6b] Since endocyclic enamine **16** is a direct enamine alkylation product, this unusual cyclization can be regarded as a novel *endocyclic enamine cyclopentenone annulation*.[34] Such processes could have broad applications to the synthesis of complex polycyclic natural alkaloids and other heterocycles.

(30) Dolby et al. had observed[6a] that, on treatment of keto enamine **16** with a hot mixture of HOAc−NaOAc, the formation of a *new* product with practically identical IR maxima absorptions with that of **17**, but did not further characterize its structure.

(31) Strict exclusion of O_2 from the reaction mixture led to *no* apparent reaction even after refluxing for 24 h. Oxidants other than O_2 can also be used, but they are much less efficient. Since the additive Fe^{2+} appears to accelerate the reaction with clean conversion, Fe^{2+} may act as a peroxide reductant. In contrast, for an alternative likely radical autoxidation of enamine catalyzed by Fe^{3+}, see: Malhotra, S. K.; Hostynek, J. J.; Lundin, A. F. *J. Am. Chem. Soc.* **1968**, *90*, 6565.

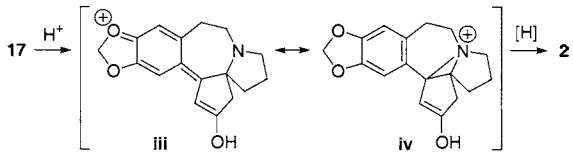
(32) Habermas, K. L.; Denmark, S. E. *Org. React.* **1994**, *45*, 1.

(33) Woodward, R. B.; Ayer, W. A.; Beaton, J. M.; Bickelhaupt, F.; Bonnett, R.; Buchschacher, P.; Closs, G. L.; Dutler, H.; Hannah, J.; Hauck, F. P.; Ito, S.; Langemann, A.; Le Goff, E.; Leimgruber, W.; Lwowski, W.; Sauer, J.; Valenta, Z.; Volz, H. *Tetrahedron* **1990**, *46*, 7599.

(34) For a review on enamine annulations, see: Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193.

Catalytic hydrogenation (H_2, 10% Pd−C, 10% HOAc-EtOH) of pentacyclic enone **17** gave the same pentacyclic ketone **2** described above in 76% yield. Interestingly, the action of zinc dust in hot HOAc produced smoothly ketone **2** (exclusively) without causing skeletal rearrangement (Scheme 6), which provides further support for our mechanistic rational (Scheme 2) for the transannular reductive rearrangement of enone **3** to pentacyclic ketone **2**. It is worthy to note that the isomeric resonance structures **i** vs **iv** and **ii** vs **iii** led to different reduction products as shown in Schemes 2 and 6, respectively.

Scheme 6. Zinc−Acid Reduction Pathway for **17** → **2**



In conclusion, a short, efficient, and practical total synthesis of CET has been developed based a conceptually novel strategy featuring transannular reductive rearrangements as key transformations for establishing the pentacyclic ring skeleton. The efficiency and practicality of the synthesis follow from its brevity (9 stages from diester **7**), the ready availability of starting materials, the operationally simple reactions with cheap reagent chemicals, and good overall yield. Finally, this synthesis of CET may be regarded as a biomimetic synthesis[35] in terms of pentacyclic ring construction.[7] Further work on the asymmetric synthesis of CET based on this strategy is underway in our laboratory.

Acknowledgment. This paper is dedicated to Professor E. J. Corey on the occasion of his 75th birthday. We thank the National Natural Science Foundation (Distinguished Youth Fund 29925204 and Fund 20021001), the Fok Ying Tung Education Foundation (Fund 71012), and the Ministry of National Education (Funds 99114 and 2000-66) for financial support. The Cheung Kong Scholars program is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data of compounds **2**, **3**, **5**, **7**, **9**−**11**, and **13**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(35) For attempted biomimetic synthesis, see: (a) Marino, J. P.; Samanen, J. M. *J. Org. Chem.* **1976**, *41*, 179. (b) Kupchan, S. M.; Dhingra, O. P.; Kim, C.-K. *J. Org. Chem.* **1978**, *43*, 4464.