JOC Article
pubs.acs.org/joc

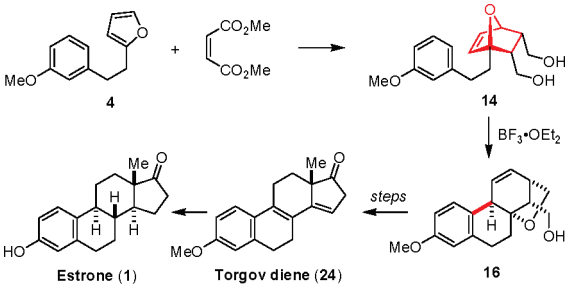
Formal Total Synthesis of (±)-Estrone via the Furano Diene Approach

Ya-Ping Xue[†] and Wei-Dong Z. Li*[,§,†,‡]

[†]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China, and [‡]State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

wdli@nankai.edu.cn

Received August 6, 2010



We present in this report the development and realization of a novel formal total synthesis of estrone (**1**) via the Torgov diene (**24**) by the furano diene approach, first attempted by Woodward in 1937. The core ring structure **16** was established by an acid-mediated regioselective and stereospecific cyclization of the *endo*-oxabicyclo[2.2.1]heptene derivative **14**, which is readily available from the $AlCl_3$-catalyzed Diels−Alder cycloaddition of 2-(3-methoxyphenethyl)furan (**4**) and dimethyl maleate. The mechanistic pathway of this S_N' type cyclization is discussed, and the earlier perspectives in our preliminary report (*Org. Lett.* **2004**, *6*, 1333) are corrected.

Introduction

Estrone (**1**) is a prominent female sex hormone that structurally represents a group of aromatized steroids. Estrone is one of the most popular synthetic targets due to its important physiological properties and characteristic steroidal skeleton.[1] Although numerous synthetic methods have been developed to date,[1a,2] the diene approach based on the Diels−Alder cycloaddition enjoys a privileged strategic choice in terms of convergence and stereo- and enantioselective control.[3] For example, Dane's diene (**2**), first introduced in 1939,[4] has been employed in recent asymmetric total

[§]Fax/Phone: 0086-(0)22-23494613

(1) For reviews, see: (a) Quinkert, G.; Stark, H. *Angew. Chem., Int. Ed.* **1983**, *22*, 637. (b) Groen, M. B.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 465. (c) Zeelen, F. J. *Nat. Prod. Rep.* **1994**, *11*, 607.

(2) For leading references on various recent synthetic approaches, see: (a) Hutchinson, J. H.; Money, T. *Tetrahedron Lett.* **1985**, *26*, 1819. (b) Posner, G. H.; Switzer, C. *J. Am. Chem. Soc.* **1986**, *108*, 1239. (c) Rao, G. S. R. S.; Devi, L. U.; Sheriff, U. J. *J. Chem. Soc., Perkin Trans. I* **1991**, 964. (d) Zoretic, P. A.; Ramchandani, M.; Caspar, M. L. *Synth. Commun.* **1991**, *21*, 923. (e) Mikami, K.; Takahashi, K.; Nakai, T.; Uchimaru, T. *J. Am. Chem. Soc.* **1994**, *116*, 10948. (f) Quinkert, G.; Grosso, M. D.; Döring, A.; Döring, W.; Schenkel, R. I.; Bauch, M.; Dambacher, G. T.; Bats, J. W.; Zimmermann, G.; Dürner, G. *Helv. Chim. Acta* **1995**, *78*, 1345. (g) Tietze, L. F.; Nobel, T.; Spescha, M. *J. Am. Chem. Soc.* **1998**, *120*, 8971. (h) Hanada, K.; Miyazawa, N.; Ogasawara, K. *Chem. Pharm. Bull.* **2003**, *51*, 104. (i) Braun, M.; Feischer, R.; Mai, B.; Schneider, M.-A.; Lachenicht, S. *Adv. Synth. Catal.* **2004**, *346*, 474. (j) Pattenden, G.; Gonzalez, M. A.; Mcculloch, S.; Walter, A.; Woodhead, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12024. (k) Soorukram, D.; Knochel, P. *Org. Lett.* **2007**, *9*, 1021. (l) Yeung, Y.-Y.; Chein, R.-J.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 10346. (m) Hermann, P.; Buděšínský, M.; Kotora, M. *J. Org. Chem.* **2008**, *73*, 6202. (n) Foucher, V.; Guizzardi, B.; Groen, M. B.; Light, M.; Linclau, B. *Org. Lett.* **2010**, *12*, 680. (o) Betík, R.; Herrmann, P.; Kotora, M. *Eur. J. Org. Chem.* **2010**, 646.

(3) For a recent review on the Diels−Alder route to steroids and related structures, see: (a) Ibrahim Ouali, M. *Steroids* **2009**, *74*, 133. For recent examples, see: (b) Vollhardt, K. P. C. *Pure Appl. Chem.* **1985**, *57*, 1819. (c) Sunder, N. M.; Patil, P. A.; Narasimhan, N. S. *J. Chem. Soc., Perkin Trans. I* **1990**, 1331. (c) Hakuba, H.; Kitagaki, S.; Mukai, C. *Tetrahedron* **2007**, *63*, 12639.

(4) (a) Dane, E.; Schmitt, J. *Liebigs Ann.* **1939**, *537*, 246. (b) Dane, E. *Angew. Chem.* **1939**, *52*, 655. (c) Ananchenko, S. N.; Torgov, I. V. *Tetrahedron Lett.* **1963**, *23*, 1553.

(5) For recent examples on the catalytic asymmetric estrone total synthesis from the Dane's diene (**2**), see: (a) Quinkert, G.; Grosso, M. D.; Bucher, A.; Bauch, M.; Döring, W.; Bats, J. W.; Dürner, G. *Tetrahedron Lett.* **1992**, *33*, 3617. (b) Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron Lett.* **1992**, *33*, 1909. (c) Sugahara, T.; Ogasawara, K. *Tetrahedron Lett.* **1996**, *37*, 7403. (d) Tanaka, K.; Nakashima, H.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 1915. (e) Hu, Q.-Y.; Rege, P. D.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 5984. (f) Canales, E.; Corey, E. J. *Org. Lett.* **2008**, *10*, 3271. (g) Weimar, M.; Dürner, G.; Bats, J. W.; Göbel, M. W. *J. Org. Chem.* **2010**, *75*, 2718. (h) Schotes, C.; Mezzetti, A. *J. Am. Chem. Soc.* **2010**, *132*, 3652. (i) Shibatomi, K.; Futatsugi, K.; Kobayashi, F.; Iwasa, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2010**, *132*, 5625.

DOI: 10.1021/jo1015486 Published on Web 12/06/2010

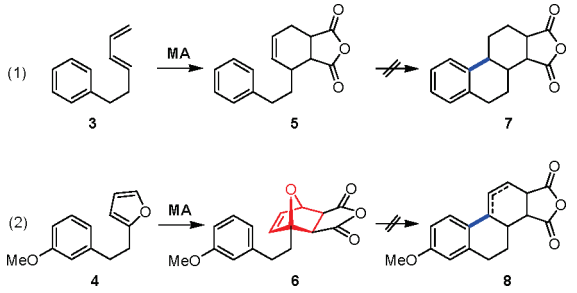
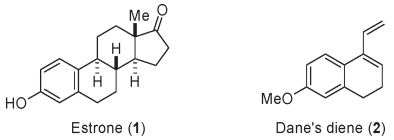


FIGURE 1. Attempted diene approaches by Cohen and Woodward.

synthesis of estrone via catalytic enantioselective Diels–Alder strategies.[5]



Historically, prior to the introduction of the Dane's diene (**2**), other diene partners have been explored by Cohen[6] and Woodward[7] as depicted in eqs 1 and 2, respectively, in Figure 1, in which acyclic diene **3** and 2-(3-methoxyphenethyl)furan (**4**) reacted with maleic anhydride (**MA**) to give the corresponding Diels–Alder adducts **5** and **6**, respectively. However, the attempted cyclizations of **5** and **6** to the typical steroidal structures **7** and **8**, respectively, under various acidic conditions were unsuccessful.[7b] The mechanistic explanation concerning the reluctant cyclization of the appealing oxabicyclo[2.2.1]heptene structure **6** has remained an intriguing question.[8]

We have recently developed in our laboratory a novel biomimetic strategy for the stereocontrolled total synthesis of eudesmane sesquiterpenoids based on the oxabicyclo-[2.2.1]heptane template assembly and the stereospecific cationic cyclization cascade (**9** → **10**, Figure 2), through which concise total syntheses of typical sesquiterpenoid natural products balanitol and gallicadiol were accomplished, respectively.[9] In connection with our interest in the development of novel synthetic strategies toward estrone and relevant natural steroids, we set out to explore and reinvestigate the Woodward furano diene approach[10] toward the synthesis of estrone to further extend the application of the oxabicyclo[2.2.1]heptane template[11] strategy for steroid synthesis.

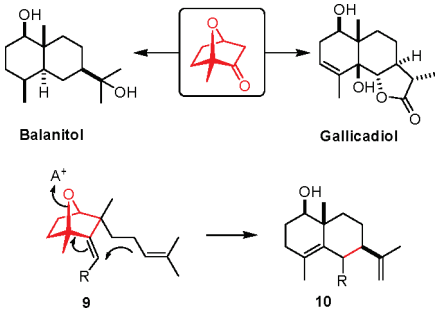
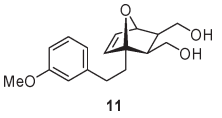


FIGURE 2. Biomimetic synthesis of eudesmane sesquiterpenoids.

Results and Discussion

Because the initial attempts to induce the anticipated cationic cyclization of the *exo*-oxabicyclic diol derivative **11**[12] under various protic or Lewis acid conditions resulted in either gradual decomposition of diol **11** or the formation of a complex product mixture from which no aryl-annulation structures were detectable, we decided to explore the cyclization of the corresponding diastereomeric *endo*-oxabicyclic diol **14** (Scheme 1).



As depicted in Scheme 1, the solvent-free Diels–Alder cycloaddition of 2-(3-methoxyphenethyl)furan (**4**)[7] with dimethyl maleate catalyzed by $AlCl_3$ (10 mol %)[13] at −10 °C afforded the readily separable *endo*-adduct **12** (65%) and minor *exo*-isomer **13** (17%).[14] Oxabicyclic diol **14** was obtained quantitatively by $LiAlH_4$ reduction of the *endo*-adduct **12** in THF. To our delight, the *endo*-cyclic diol **14** underwent smooth cyclization in the presence of BF_3 etherate or strong protic acid (i.e., CH_3SO_3H) to give the major tetracyclic products **16** (53%) and the minor regioisomer **17** in 70% overall yield. The tetracyclic structure and stereochemistry of products **16** and **17** were confirmed unambiguously by the X-ray crystallographic analysis of the corresponding hydrogenation derivatives **18** and **19**, respectively.[15] This effective cyclization was found to go through an initial intermediary bicyclic tetrahydrofuran derivative **15**, which can be isolated from the reaction mixture and fully characterized. Subjecting intermediate **15** to the above cyclization conditions (Scheme 1) afforded the cyclization products **16** and **17** in the same ratio of 53:17 and comparable yield.

Apparently, the facile cationic cyclization of diol **14** to tetracycles **16** and **17** was initiated by a regio- and stereospecific hydroxy-participated transannulative oxabicyclic

(6) (a) Cohen, A. *J. Chem. Soc.* **1935**, 429. (b) Cohen, A. *Nature* **1935**, 869. (c) Cohen, A.; Warren, F. L. *J. Chem. Soc.* **1937**, 1318.

(7) (a) Woodward, R. B. A Synthetic Attack on the Estrone Problem, Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 1937. (b) Woodward, R. B. *J. Am. Chem. Soc.* **1940**, *62*, 1478.

(8) For further stereochemical studies of the Diels–Alder cycloaddition of furan and **MA**, see: Woodward, R. B.; Baer, H. *J. Am. Chem. Soc.* **1948**, *70*, 1161. For a review on the intramolecular S_N' cyclization, see: Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383.

(9) (a) Zhang, Z.; Li, W.-D. Z.; Li, Y.-L. *Org. Lett.* **2001**, *3*, 2555. (b) Li, W.-D. Z.; Gao, Z.-H. *Org. Lett.* **2005**, *7*, 2917.

(10) For a general review on the furan Diels–Alder chemistry, see: Kappe, C. O.; Murphree, S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179.

(11) For recent reviews on the natural occurrence and synthetic utilities of the 7-oxabicyclo[2.2.1]heptane derivatives, see: (a) Vogel, P.; Cossy, J.; Plumet, J.; Arjona, O. *Tetrahedron* **1999**, *55*, 13521. (b) Schindler, C. S.; Carreira, E. M. *Chem. Soc. Rev.* **2009**, *38*, 3222.

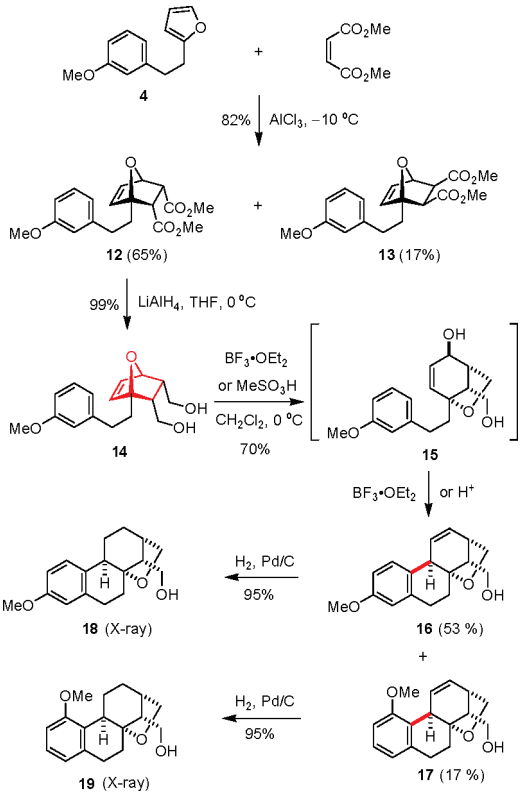
(12) Prepared by hydride reduction of the *exo*-cyclic adduct **6** [for analogous Diels–Alder adduct **13** (*vide infra*), see Supporting Information for details]. The structures of the cyclization precursor (diol **14** instead of **11**) and products were incorrectly assigned in our preliminary report: Li, W.-D. Z.; Wei, K. *Org. Lett.* **2004**, *6*, 1333. See footnotes 17 and 18 (*vide infra*) for detailed corrections.

(13) For a recent report on the $HfCl_4$-catalyzed diastereoselective furano-Diels–Alder cycloadditions, see: Hayashi, Y.; Nakamura, M.; Nakao, S.; Inoue, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4079.

(14) For the *endo*- and *exo*-stereochemical assignments according to ^1H NMR analysis, see: (a) Kotsuki, H.; Nishizawa, H.; Ochi, M.; Matsuoka, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 496. (b) Jarvest, R. L.; Readshaw, S. A. *Synthesis* **1992**, 962. (c) Leroy, J. *Tetrahedron Lett.* **1992**, *33*, 2969.

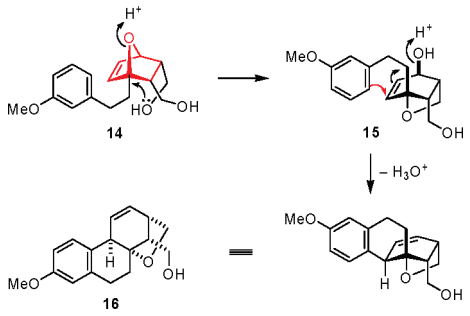
(15) See Supporting Information for detailed X-ray crystallographic data.

SCHEME 1. Stereospecific Cyclization of *endo*-Cyclic Diol 14



ring opening of **14** leading to the bicyclic allylic alcohol intermediate **15**, followed by an acid-mediated stereospecific Friedel−Crafts-type S_N' cyclization,[16] as illustrated in Scheme 2.[17] We reasoned that the *endo* hydroxy group of diol **14** contributed to release the acid-activated ring strain of the oxabicyclo[2.2.1]heptene system via the readily transannulative

SCHEME 2. Mechanistic Pathway of Cyclization 14 → 15 → 16

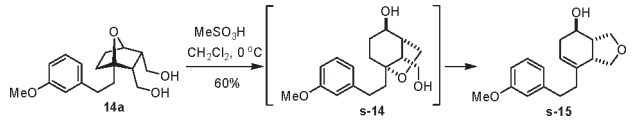


formation of **15**, which would adopt a favorable conformation as shown (Scheme 2) for the subsequent smooth S_N'-type carbocyclization. Thus, the earlier mechanistic perspectives in our preliminary report (*Org. Lett.* **2004**, *6*, 1333) based on the structural misinterpretation of the cyclization precursor (**14** instead of **11**) and products should be corrected as shown in Scheme 2.[18]

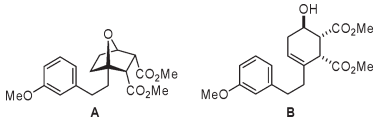
Toward the total synthesis of estrone, cyclization product **18** was oxidized with IBX in DMSO[19] to give the corresponding aldehyde (85%), which was homologated via the Horner−Emmons olefination (90%), then hydrogenated to afford the methyl ester **20** (Scheme 3). Acidolysis of **20** with *p*-TsOH and TFA in benzene[20] followed by methanolysis in the presence of K_2CO_3 gave the corresponding alcohol ester intermediate, which was oxidized (IBX, DMSO) to give ester **21** in good yield. After considerable experimentation, carbocyclization of **21** was achieved by exposure to a suspension of *tert*-BuOK in CH_2Cl_2 at 0 °C furnishing the tetracyclic ketone **22** in 65% yield.[21−23] Ketone **22** was dehydrogenated

(16) For a mechanistically interesting and relevant cationic cyclization and rearrangement case, see: (a) Doyle, T. J.; Hendrix, M.; Haseltine, J. *Tetrahedron Lett*. **1994**, *35*, 8295. (b) Doyle, T. J.; Hendrix, M.; Van Derveer, D.; Javanmard, S.; Haseltine, J. *Tetrahedron* **1997**, *53*, 11153. For recent examples of intramolecular S_N' cyclization, see: (c) Behenna, D. C.; Stockdill, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4077. (d) Stockdill, J. L.; Behenna, D. C.; Stoltz, B. M. *Tetrahedron Lett*. **2009**, *50*, 3182. For other related acid-mediated cyclizations, see: (e) Ma, S.; Zhang, J. *Tetrahedron Lett*. **2002**, *43*, 3435.

(17) Saturated derivative **14a** was found to produce under strong protic acid conditions the initial cyclization product **s-14** and eventually the furan derivative **s-15** as shown below:

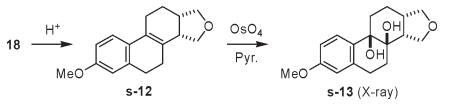


The chemical structures of **8a** and **9a** in our preliminary report (Li, W.-D. Z.; Wei, K. *Org. Lett*. **2004**, *6*, 1333) should be corrected to have structures **14a** and **s-15**, respectively. Accordingly, the chemical structures of **8b** and **9b** therein should be corrected as the following structures **A** and **B** respectively:



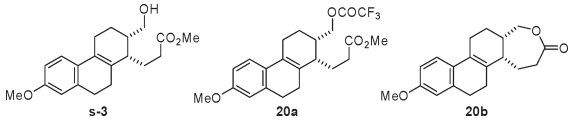
For similar corrections, see also: Wei, K.; Gao, H.-T.; Li, W.-D. Z. *J. Org. Chem*. **2009**, *74*, 8004.

(18) These corrections should be applied throughout our previous preliminary report (Li, W.-D. Z.; Wei, K. *Org. Lett*. **2004**, *6*, 1333). In addition, the furano structure of the acidolysis product **s-12** from **18** was unambiguously confirmed by the X-ray crystallographic analysis of the corresponding dihydroxylated derivative **s-13**:[15]



(19) (a) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem*. **1995**, *60*, 7272. (b) Allin, S. M.; Thoms, C. I.; Doyle, K.; Eisegood, M. R. J. *J. Org. Chem*. **2005**, *70*, 357.

(20) This acidolysis product mixture consists of the following hydrolytic derivatives:

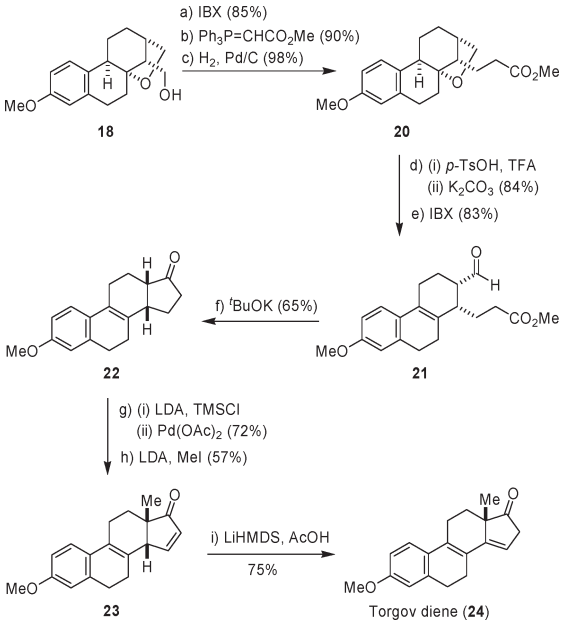


(21) This anionic cyclization was assumed to involve an initial Dieckmann-type condensation and a subsequent deformylation process. For relevant deformylation cases, see: (a) House, H. O.; Wasson, R. L. *J. Am. Chem. Soc*. **1957**, *79*, 1488. (b) Collins, D. J. *J. Chem. Soc*. **1959**, 3919. (c) Schultz, A. G.; Ravichandran, R. *J. Org. Chem*. **1980**, *45*, 5008. (d) Elings, J. A.; Lempers, H. E. B.; Sheldon, R. A. *Eur. J. Org. Chem*. **2000**, 1905.

(22) The *cis* ring fusion of product **22** was deduced according to the following: (a) House, H. O.; Rasmusson, G. H. *J. Org. Chem*. **1963**, *28*, 31. (b) Snider, B. B.; Marin, C. P. C. *J. Org. Chem*. **1984**, *49*, 1688.

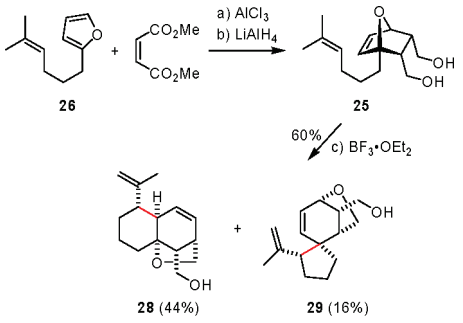
(23) For an example of an olefination reaction using a suspension of *tert*-BuOK in CH_2Cl_2, see: Angiolini, M.; Araneo, S.; Belvisi, L.; Cesarotti, E.; Checchia, A.; Crippa, L.; Manzoni, L.; Scolastico, C. *Eur. J. Org. Chem*. **2000**, 2571.

SCHEME 3. Formal Total Synthesis of Estrone (1) from 18[a]



[a]Reagents and conditions: (a) IBX, DMSO, 30 °C, 85%, 0.5 h; (b) $Ph_3P{=}CHCO_2Me$, benzene, 50 °C, 2 h, 90%; (c) H_2, Pd/C, EtOAc, 23 °C, overnight, 98%; (d) (1) *p*-TsOH, TFA, benzene, 50 °C, 1 h; (2) K_2CO_3, MeOH, 23 °C, 15 min, 84%; (e) IBX, DMSO, 30 °C, 0.5 h, 83%; (f) ^{t}BuOK, CH_2Cl_2, 0 °C, 10 min, 65%; (g) (1) LDA, TMSCl, THF, −78 °C, 0.5 h; (2) $Pd(AcO)_2$, MeCN, 23 °C, 2 h, 72%; (h) LDA, HMPA, MeI, THF, −78 °C, 2 h, 62%; (i) (1) LiHDMS, HMPA, THF, −78 °C, 20 min; (2) AcOH, −78 °C → 23 °C, 75%.

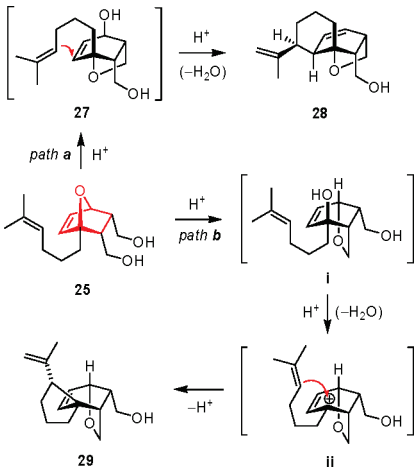
SCHEME 4. Cyclization of *endo*-Cyclic Diol 25[a]



[a]Reagents and conditions: (a) $AlCl_3$, −10 °C, 2 days, 75% (*endo*/*exo* 4:1); (b) $LiAlH_4$, THF, 0 °C, 96%; (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 60%.

(Saegusa oxidation)[24] via the corresponding enolsilane derivative and methylated[25] to give the desired unsaturated ketone **23**,[2f,5g,26] which was subjected to kinetic deconjugation via the corresponding lithium enolate to afford the well-known Torgov diene (**24**).[2f,4b,5e] Thus, the above synthetic sequence[27] constitutes the realization of the long-standing

SCHEME 5. Mechanistic Pathways of Cyclization 25 → 28, 29



Woodward furano diene approach to steroids and a formal total synthesis of (±)-estrone from furan **4** via the Torgov diene (**24**) in 12 steps and an overall yield of 4.5%.

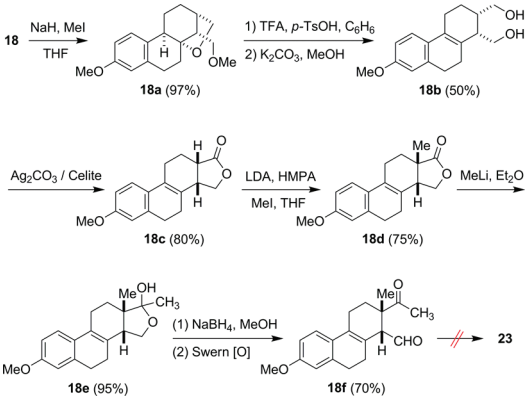
To further probe the cationic nature and stereospecificity of this mechanistically interesting cyclization pathway outlined in Scheme 2, bis-homoprenylated *endo*-oxabicyclic diol **25** was prepared by the above-described catalytic Diels–Alder cycloaddition of 2-(5-methylhex-4-enyl)furan (**26**)[28] and dimethyl maleate and subjected to the same acid-mediated cyclization conditions as described above (Scheme 4). A tricyclic structure **28** bearing the agarofuran ring skeleton was obtained as the major cyclization product (44%) along with an interesting spiro-tricyclic alcohol **29** as the minor product (16%). The carbocyclic and stereochemical structures of **28** and **29** were determined unambiguously by the X-ray crystallographic analysis of their corresponding hydrogenated carbamate derivatives.[29] Similarly, a bicyclic allylic alcohol intermediate **27** (Scheme 5) was also isolated from the initial cyclization reaction mixture and was identified as the precursor of the major cyclization product **28**.

(24) (a) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011. (b) Singh, V.; Vedantham, P.; Sahu, P. K. *Tetrahedron Lett.* **2002**, *43*, 519. (c) Singh, V.; Vedantham, P.; Sahu, P. K. *Tetrahedron* **2004**, *60*, 8161. (d) Asano, M.; Inoue, M.; Katoh, T. *Synlett* **2005**, 2599.

(25) (a) Paquette, L. A.; Geng, F. *J. Am. Chem. Soc.* **2002**, *124*, 9199. (b) Geng, F.; Liu, J.; Paquette, L. A. *Org. Lett.* **2002**, *4*, 71.

(26) All spectral data (IR, ^{1}H NMR, and ^{13}C NMR) of compound **23** are consistent with those of reported (refs 2f and 5g), see Supporting Information for details.

(27) Several other synthetic sequences from cyclization product **18** were explored but unsuccessfully, for instance (see Supporting Information for the corresponding spectroscopic data of intermediates **18a**–**f**):



(28) Readily prepared (see Supporting Information for details) from 2-(4-bromobutyl)furan according to: Rogers, C.; Keay, B. A. *Can. J. Chem.* **1992**, *70*, 2929.

(29) See Supporting Information for detailed experimental procedures and X-ray crystallographic data.

Thus, the major stereospecific cyclization pathway of **25** → **28** is operative via an analogous transannulative intermediate **27** as illustrated in Scheme 5 (path a). The unexpected spiro-annulation of **25** → **29** presumably involves the initial formation of an alternative transannulative intermediate **i** and a subsequent cationic spiro-cyclization via the corresponding cation species **ii** as depicted in Scheme 5 (path b). These results suggest that the transannulative ring strain releasing approach would provide a versatile activation strategy to harvest the unique reactivity of the rigid oxabicyclo[2.2.1]heptene system. It is worth noting that the geometric structure and electronic property of the distal annulating group would contribute to the product specificity of the corresponding cyclization. Interestingly, typical carbocyclic skeletons of natural sesquiterpenoids[30] relevant to the structures of **28** and **29** might be accessible with further synthetic methodological development.

Conclusion

In summary, a novel formal total synthesis of (±)-estrone (**1**) has been achieved from readily available 2-(3-methoxyphenethyl)furan (**4**) via a facile and stereospecific S_N' cyclization of the *endo*-oxabicyclo[2.2.1]heptene template assembly **14**. The realization of this classical diene approach for the estrone synthesis demonstrated the versatility and unique reactivities of the oxabicyclo[2.2.1]heptane template. This strategy could be applicable to the stereocontrolled synthesis of steroids[31,32] and relevant terpenoids in general with further development, which we are pursuing in our laboratories.

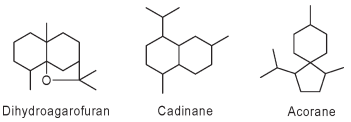
Experimental Section[33]

***endo*-Dimethyl 1-(3-Methoxyphenethyl)-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (12) and *exo*-Dimethyl 1-(3-Methoxyphenethyl)-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (13).** Neat dimethyl maleate (7.20 g, 52.50 mmol) was introduced into a flask containing powdered anhydrous $AlCl_3$ (667 mg, 5.00 mmol) at −10 °C under N_2. After the resulting mixture was stirred for 10 min, 2-(3-methoxyphenethyl)furan (**4**, 10.10 g, 50.00 mmol) was added neat via a syringe. The reaction mixture was stirred at −10 °C for 2 days and then extracted with ether. The organic layer was washed successively with water, brine, and dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (PET/EtOAc = 4:1) to give the *endo*-cyclic adduct **12** (11.0 g, 65%) as a colorless oil, and the *exo*-isomer **13** (3.20 g, 17%) as white plates. **12**: R_f = 0.45 (PET/EtOAc = 2:1); IR (film) ν_{max} 3002, 2952, 1741, 1604, 1490, 1436, 1259, 1163, 1044, 909, 789, 494 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, t, J = 7.6 Hz, ArH), 6.76 (3H, m, ArH), 6.52 (1H, d, J = 6.0 Hz, CH═), 6.45 (1H, d, J = 6.0 Hz, CH═), 5.11 (1H, d, J = 4.4 Hz, OCH), 3.80 (3H, s, OMe), 3.63 (3H, s, OMe), 3.60 (3H, s, OMe), 3.58 (1H, d, J = 4.8 Hz, CH), 3.13 (1H, d, J = 10.0 Hz, CH), 2.76 (2H, m, CH_2), 2.45 (1H, m, CH_2), 2.15 (1H, m, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.6, 159.6, 143.1, 136.9, 135.2, 129.3, 120.5, 113.9, 111.2, 91.2, 79.4, 55.0, 51.7, 51.7, 51.4, 50.5, 33.5, 30.90 ppm; HRMS (ESI) m/z calcd for $C_{19}H_{26}O_6N$ 364.1755, found for $[M + NH_4]^+$ 364.1754. **13**: R_f = 0.20 (PET/EtOAc = 2:1); mp 109−110 °C; IR (film) ν_{max} 2949, 2844, 1743, 1601, 1436, 1261, 1215, 1159, 1039, 922, 786, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, t, J = 7.6 Hz, ArH), 6.76 (3H, m, ArH), 6.47 (1H, d, J = 5.6 Hz, CH═), 6.30 (1H, d, J = 5.6 Hz, CH═), 5.44 (1H, s, OCH), 3.80 (3H, s, OMe), 3.69 (3H, s, OMe), 3.67 (3H, s, OMe), 2.97 (1H, d, J = 9.2 Hz, CH), 2.84 (1H, d, J = 9.2 Hz, CH), 2.83−2.80 (1H, m, CH_2), 2.74−2.70 (1H, m, CH_2), 2.21−2.13 (2H, m, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 171.4, 159.5, 143.0, 137.9, 137.4, 129.3, 120.6, 113.9, 111.2, 91.2, 79.1, 54.9, 52.1, 51.9, 50.0, 49.8, 31.5, 31.4 ppm. HRMS (ESI) m/z calcd for $C_{19}H_{26}O_6N$ 364.1755, found for $[M + NH_4]^+$ 364.1748.

***endo*-(1-(3-Methoxyphenethyl)-7-oxabicyclo[2.2.1]hept-5-ene-2, 3-diyl)dimethanol (14).** To a suspension of powdered $LiAlH_4$ (1.70 g, 45.00 mmol) in 40 mL of dry THF at 0 °C was added a solution of compound **12** (14.20 g, 41.00 mmol) in dry THF (20 mL) under N_2. After being stirred for 10 min at 0 °C, the reaction mixture was quenched with 5 mL of water and extracted with ether, and the organic layer was washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (PET/EtOAc = 1:2) to give compound **14** (11.90 g, 99%) as a colorless oil. **14**: R_f = 0.15 (PET/EtOAc = 1:2); IR (film) ν_{max} 3359, 2934, 1603, 1490, 1456, 1316, 1258, 1155, 1039, 912, 782, 727, 698, 574 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, t, J = 7.6 Hz, ArH), 6.76 (3H, m, ArH), 6.30 (1H, d, J = 5.6 Hz, CH═), 6.11 (1H, d, J = 5.6 Hz, CH═), 4.80 (1H, d, J = 3.6 Hz, OCH), 4.30 (2H, s, br., OH), 3.79 (3H, s, OMe), 3.55 (2H, d, J = 10.8 Hz, OCH_2), 3.35 (2H, m, OCH_2), 2.78 (2H, m, CH_2), 2.64 (1H, m, CH_2), 2.42−2.25 (2H, m, CH), 2.11 (1H, m, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 143.4, 136.5, 135.1, 129.3, 120.5, 113.9, 111.1, 90.5, 79.2, 60.8, 60.5, 55.0, 48.4, 46.7, 33.8, 30.9 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{26}O_4N$ 308.1856, found for $[M + NH_4]^+$ 308.1864.

8-(Hydroxymethyl)-5-(3-methoxyphenethyl)-6-oxabicyclo[3.2.1]-oct-3-en-2-ol (15), (9-Methoxy-3,6,7,11b-tetrahydro-4*H*-3,5a-methanonaphtho[2,1-*b*]oxepin-12-yl)methanol (16), and (11-Methoxy-3,6,7,11b-tetrahydro-4*H*-3,5a-methanonaphtho[2,1-*b*]oxepin-12-yl)-methanol (17). To a stirred solution of compound **14** (2.90 g, 10.00 mmol) in dry CH_2Cl_2 (20 mL) was added freshly distilled $BF_3 \cdot OEt_2$ (1.26 mL, 10.00 mmol) at 0 °C under N_2. TLC monitoring of the reaction indicated that intermediary product **15** was produced solely after 0.5 h, which could be isolated and characterized after usual workup and purification procedures, or was transformed gradually into the eventual carbocyclization products **16** and **17** after 1 h. The reaction mixture was quenched with H_2O and extracted with ether, and the organic layer was washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (PET/EtOAc = 5:1) to give **16** (1.430 g, 53%) as a colorless oil and **17** (0.476 g, 17%) as a colorless oil. **15**: IR (film) ν_{max} 3367, 2943, 2880, 1603, 1490, 1458, 1260, 1154, 1038, 908, 783, 733, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (1H, t, J = 7.6 Hz, ArH), 6.80 (1H, d, J = 7.6 Hz, ArH), 6.75 (2H, m, ArH),

(30) For recent reviews, see: (a) Fraga, B. M. *Nat. Prod. Rep.* **2004**, *21*, 669. (b) Gao, J.-M.; Wu, W.-J.; Zhang, J.-W.; Konishi, Y. *Nat. Prod. Rep.* **2007**, *24*, 1153. Relevant carbocyclic skeletons of natural sesquiterpenoids include:



(31) For a review, see: Wiechert, R. *Angew. Chem., Int. Ed.* **1970**, *9*, 321.

(32) Asymmetric synthesis could be achievable in view of recent advances on the catalytic enantioselective furan Diels−Alder cycloaddition to 7-oxabicyclo[2.2.1]heptene derivatives, see: (a) Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979. (b) Evans, D. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 57. (c) Ryu, D. H.; Kim, K. H.; Sim, J. Y.; Corey, E. J. *Tetrahedron Lett.* **2007**, *48*, 5735. (d) Mukherjee, S.; Scopton, A. P.; Corey, E. J. *Org. Lett.* **2010**, *12*, 1836.

(33) For general information, complete experimental procedures, and detailed spectroscopic data of all numbered compounds, see Supporting Information.

6.03 (1H, d, J = 9.6 Hz, CH═), 5.87 (1H, dd, J_1 = 9.2 Hz, J_2 = 2.4 Hz, CH═), 4.20 (1H, s, OCH), 4.04 (1H, m, OCH_2), 3.82 (4H, m, OMe and OCH_2), 3.56 (1H, m, OCH_2), 3.38 (1H, d, J = 9.2 Hz, OCH_2), 2.66 (3H, m), 2.32 (2H, m), 2.00 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 143.2, 136.2, 129.4, 129.4, 120.5, 114.0, 111.1, 81.3, 70.5, 66.1, 60.6, 60.4, 55.1, 44.0, 43.6, 34.9, 30.7 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{26}O_4N$ 308.1856, found for $[M + NH_4]^+$ 308.1860. **16**: IR (film) ν_{max} 3415, 2931, 2872, 1608, 1500, 1462, 1236, 1042, 958, 851 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (1H, d, J = 8.4 Hz, ArH), 6.72 (1H, dd, J_1 = 9.6 Hz, J_2 = 2.4 Hz, ArH), 6.63 (1H, d, J = 2.4 Hz, ArH), 6.20 (1H, m, CH═), 6.07 (1H, dd, J_1 = 9.6 Hz, J_2 = 3.2 Hz, CH═), 4.04 (1H, m, OCH_2), 3.93, (2H, m, OCH_2), 3.78 (3H, s, OMe), 3.55 (1H, t, J = 10.0 Hz, OCH_2), 3.39 (1H, br s, CH), 2.98−2.81(3H, m, CH and CH_2), 2.08−1.98(3H, m, CH and CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 136.4, 132.8, 130.8, 127.7, 127.6, 113.1, 112.3, 83.3, 74.6, 60.4, 55.2, 49.7, 45.7, 38.1, 29.7, 28.9 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{21}O_3$ 273.1485, found for $[M + H]^+$ 273.1488. **17**: IR (film) ν_{max} 3420, 2931, 2874, 1579, 1464, 1438, 1249, 1094, 1039, 962, 907, 856 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (1H, t, J = 8.0 Hz, ArH), 6.70 (2H, m, ArH), 6.50 (1H, dd, J_1 = 9.6 Hz, J_2 = 3.2 Hz, CH═), 6.20 (1H, m, CH═), 4.08 (1H, m, OCH_2), 3.95 (2H, m, OCH_2), 3.82 (3H, s, OMe), 3.53 (2H, m, CH and OCH_2), 3.00 (1H, m, CH), 2.76 (2H, m, CH_2), 2.05 (1H, m, CH), 1.96 (2H, m, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 137.3, 133.2, 128.1, 126.8, 126.5, 121.2, 108.3, 83.7, 75.0, 60.5, 55.0, 49.7, 46.9, 36.8, 29.5, 29.4 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{21}O_3$ 273.1485, found for $[M + H]^+$ 273.1481.

(9-Methoxy-1,3,4,6,7,11b-hexahydro-2*H*-3,5a-methanonaphtho-[2,1-*b*]oxepin-12-yl)methanol (18). To a solution of compound **16** (1.36 g, 5.00 mmol) in EtOAc (20 mL) was added 10% Pd/C (136 mg) at room temperature. The reaction flask was evacuated and recharged with H_2 three times by a H_2 balloon. After being stirred for 5 h under H_2 atmosphere, the suspension was filtered through Celite and washed with EtOAc. The resulting filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (PET/EtOAc = 2:1) to give hydrogenation product **18** (1.30 g, 95%) as colorless solids. R_f = 0.31 (PET/EtOAc = 1:2); mp 152−153 °C; IR (film) ν_{max} 3400, 2928, 2858, 1607, 1492, 1420, 1267, 1247, 1070, 1048, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (1H, d, J = 8.4 Hz, ArH), 6.70 (1H, d, J = 8.4 Hz, ArH), 6.65 (1H, s, ArH), 4.00 (1H, m, OCH_2), 3.91 (1H, d, J = 8.0 Hz, OCH_2), 3.78 (4H, m), 3.43 (1H, m, OCH_2), 3.00 (2H, m, CH_2), 2.85 (1H, d, J = 6.4 Hz, CH), 2.48 (1H, s, CH), 2.24 (1H, m, CH_2), 2.15 (1H, m, CH), 2.06 (1H, m, CH_2), 1.96 (2H, m, CH_2), 1.80 (1H, m, CH_2), 1.60 (1H, m, CH_2), 1.48 (1H, m, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 137.4, 130.7, 125.5, 113.8, 111.4, 84.5, 70.0, 61.0, 55.1, 47.6, 46.0, 37.8, 29.2, 28.7, 27.5, 20.3 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{26}O_3N$ 292.1907, found for $[M + NH_4]^+$ 292.1902.

Methyl 3-(9-Methoxy-1,3,4,6,7,11b-hexahydro-2*H*-3,5a-methanonaphtho[2,1-*b*]oxepin-12-yl)propanoate (20). A mixture of **18** (1.37 g, 4.15 mmol) in DMSO (10 mL) was treated with IBX (1.28 g, 4.60 mmol) at 30 °C, and the resulting mixture was stirred for 30 min and extracted with ether, and the organic layer was washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (PET/EtOAc = 10:1) to give the corresponding aldehyde derivative **s-1** (1.15 g, 85%)[33] as white plates (mp 113−115 °C). To a mixture of the above aldehyde intermediate **s-1** (680 mg, 2.50 mmol) in 15 mL of benzene was added powdered ylide Ph_3P═$CHCO_2Me$ (1.67 g, 5.00 mmol) in one portion. The reaction mixture was brought to 50 °C, stirred for 2 h, cooled to room temperature, and extracted with ether. The organic layer was washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (PET/EtOAc = 3:1) to give the corresponding olefination product **s-2** (738 mg, 90%)[33] as white plates (mp 127−129 °C). To a solution of the above prepared methyl ester derivative **s-2** (1.38 g, 4.20 mmol) in EtOAc (20 mL) was added 10% Pd/C (130 mg) at room temperature. The reaction flask was evacuated and recharged with H_2 three times by a H_2 balloon. After being stirred for 20 h under H_2 atmosphere, the suspension was filtered through Celite and washed with EtOAc. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (PET/EtOAc = 5:1) to give the hydrogenation product **20** (1.35 g, 98%) as white plates. R_f = 0.43 (PET/EtOAc = 3:1); mp 105−106 °C; IR (film) ν_{max} 2937, 2877, 1734, 1611, 1497, 1461, 1437, 1367, 1269, 1163, 1070, 1050, 975, 790, 582 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.15 (1H, d, J = 8.4 Hz, ArH), 6.66 (2H, m, ArH), 4.00 (1H, m, OCH_2), 3.90 (1H, d, J = 8.4 Hz, OCH_2), 3.78 (3H, s, OMe), 3.60 (3H, s, OMe), 2.96 (2H, m, CH_2), 2.90 (1H, d, J = 6.0 Hz, CH), 2.34−2.30 (1H, m, CH), 2.24−2.12 (5H, m, CH_2 and CH), 1.97−1.84 (2H, m, CH_2), 1.61−1.42 (4H, m, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 157.4, 137.5, 130.8, 125.4, 113.7, 113.3, 85.0, 69.7, 54.9, 51.3, 45.9, 44.6, 38.5, 31.7, 29.2, 28.5, 27.8, 22.2, 20.3 ppm; HRMS (ESI) m/z calcd for $C_{20}H_{27}O_4$ 331.1904, found for $[M + H]^+$ 331.1906.

Methyl 3-(2-formyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthren-1-yl)propanoate (21). A solution of **20** (330 mg, 1.00 mmol) in 10 mL of benzene was treated with TFA (0.5 mL) and *p*-toluenesulfonic acid (60 mg, 0.20 mmol). The reaction mixture was brought to 50 °C, stirred for 1 h, and cooled to room temperature. The reaction mixture was quenched by 2 mL of saturated aqueous $NaHCO_3$ and extracted with ether, and the organic layer was washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo to give the crude acidolysis product mixture, which was used directly in the following step. The above crude product mixture was taken up in absolute MeOH (5 mL), to which K_2CO_3 (207 mg, 1.50 mmol) was added in one portion at room temperature, and the resulting mixture was stirred for 10 min. The reaction mixture was extracted with ether, and the organic layer was washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (PET/EtOAc = 5:1) to give the corresponding methyl ester derivative **s-3** (280 mg, 84%)[33] as a colorless oil. A mixture of the above prepared methyl ester intermediate **s-3** (700 mg, 2.12 mmol) in DMSO (10 mL) was treated with powdered IBX (650 mg, 2.33 mmol) at 30 °C, stirred for 30 min, and extracted with ether, and the organic layer was washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (PET/EtOAc = 10:1) to give the desired ester aldehyde product **21** (580 mg, 83%) as white plates. R_f = 0.60 (PET/EtOAc = 2:1); mp 104−105 °C; IR (film) ν_{max} 2926, 2831, 1733, 1713, 1606, 1497, 1433, 1245, 1198, 1154, 1039, 980, 803 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (1H, s, CHO), 7.11 (1H, d, J = 8.4 Hz, ArH), 6.69 (2H, m, ArH), 3.78 (3H, s, OMe), 3.66 (3H, s, OMe), 2.73 (2H, t, J = 8.0 Hz), 2.67−2.62 (2H, m), 2.56−2.52 (1H, m), 2.44−2.30 (4H, m), 2.30−2.09 (2H, m), 1.90−1.83 (3H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 173.2, 158.0, 137.1, 132.9, 128.4, 127.0, 122.9, 113.1, 110.7, 54.9, 51.4, 51.0, 38.6, 32.9, 28.7, 28.2, 26.1, 24.2, 18.1 ppm; HRMS (ESI) m/z calcd for $C_{20}H_{24}O_4Na$ 351.1567, found for $[M + Na]^+$ 351.1571.

3-Methoxy-6,7,12,13,15,16-hexahydro-11*H*-cyclopenta[*a*]-phenanthren-17(14*H*)-one (22). To a suspension of powdered *t*-BuOK (103 mg, 0.92 mmol) in 5 mL of dry CH_2Cl_2 at 0 °C was added a solution of ester aldehyde **21** (75 mg, 0.23 mmol) in dry CH_2Cl_2 (1 mL) under N_2. After being stirred vigorously for ca. 1 min at 0 °C, the reaction mixture was quenched by saturated aqueous NH_4Cl and extracted with ether. The organic layer was washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column

chromatography (PET/EtOAc = 15:1) to give the desired tetracyclic ketone **22** (36 mg, 65%) as colorless solids. R_f = 0.44 (PET/EtOAc = 5:1); mp 129−130 °C; IR (film) ν_{max} 2927, 2881, 1736, 1607, 1498, 1430, 1251, 1143, 1041, 812 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (1H, d, J = 8.0 Hz, ArH), 6.69 (2H, m, ArH), 3.79 (3H, s, OMe), 2.97 (1H, s, CH), 2.81−2.69 (2H, m, CH_2), 2.47−2.10 (8H, m, CH and CH_2), 2.02−1.92 (2H, m, CH_2), 1.86−1.80 (1H, m, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.4, 158.1, 137.0, 131.3, 129.1, 128.3, 123.1, 113.3, 110.8, 55.2, 47.4, 41.0, 36.9, 28.7, 26.9, 26.0, 23.1, 20.7 ppm; HRMS (ESI) m/z calcd for $C_{18}H_{21}O_2$ 269.1536, found for $[M + H]^+$ 269.1543.

3-Methoxy-13-methyl-6,7,12,13-tetrahydro-11*H*-cyclopenta[*a*]-phenanthren-17(14*H*)-one (23). To a stirred solution of diisopropylamine (0.07 mL) in dry THF (1 mL) was added *n*-BuLi (1.6 M in hexane, 0.25 mL) dropwise at 0 °C under N_2, and the mixture was stirred for 30 min. The resulting LDA solution was cooled to −78 °C, and then a solution of **22** (35 mg, 0.13 mmol) in dry THF (1 mL) was added dropwise via a syringe, and the mixture was stirred for 10 min. A solution of TMSCl (0.07 mL) in THF (1 mL) was added, and the reaction mixture was stirred for 10 min and monitored by TLC. The solvent was evaporated, and the resulting suspension was filtered through alumina (1.00 g, PET/EtOAc = 4:1). After the solvent was removed, the resulting crude silyl ether derivative was taken up in dry acetonitrile (1 mL), to which powdered $Pd(OAc)_2$ (30 mg) was added. The resulting mixture was stirred for 2 h at room temperature and filtered through Celite. The filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (PET/EtOAc = 10:1) to give the corresponding dehydrogenated product **s-4** (25 mg, 72%)[33] as colorless solids (mp 111−112 °C). To a stirred solution of diisopropylamine (0.26 mL) in dry THF (1 mL) was added *n*-BuLi (1.6 M in hexane, 0.90 mL) dropwise at 0 °C under N_2, and the mixture was stirred for 10 min. The resulting LDA solution was cooled to −78 °C, to which a mixture of the above prepared dehydrogenated product **s-4** (20 mg, 0.075 mmol) and HMPA (0.2 mL) in dry THF (1 mL) was added dropwise via a syringe. After being stirred for 30 min, the reaction mixture was treated with MeI (0.2 mL, excess) at −78 °C. The resulting reaction mixture was allowed to warm to room temperature gradually over a period of 2 h and monitored by TLC. The reaction was quenched by 0.5 mL of saturated aqueous NH_4Cl, and extracted with ether, and the organic layer was washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography to give the methylated product **23** (13 mg, 62%) as colorless solids. R_f = 0.32 (PET/EtOAc = 5:1); mp 113−114 °C; IR (film) ν_{max} 2923, 2851, 1707, 1607, 1499, 1250, 1158, 1039, 812 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (1H, d, J = 8.0 Hz, CH═), 7.08 (1H, d, J = 8.0 Hz, ArH), 6.71 (2H, m, ArH), 6.11 (1H, dd, J_1 = 5.6, J_2 = 2.8 Hz, CH═), 3.80 (3H, s, OMe), 3.15 (1H, s, CH), 2.85−2.75 (2H, m, CH_2), 2.45−2.39 (2H, m, CH_2), 2.32−2.12 (2H, m, CH_2), 1.94−1.89 (1H, m, CH_2), 1.62−1.58 (1H, m, CH_2), 1.20 (3H, s, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.5, 162.6, 158.3, 136.7, 130.6, 129.6, 128.6, 128.4, 123.4, 113.6, 111.0, 55.5, 46.9, 31.5, 29.7, 28.7, 27.5, 22.5, 22.3 ppm; HRMS (ESI) m/z calcd for $C_{19}H_{21}O_2$ 281.1536, found for $[M + H]^+$ 281.1536.

3-Methoxy-13-methyl-6,7,12,13-tetrahydro-11*H*-cyclopenta[*a*]-phenanthren-17(16*H*)-one (Torgov diene, 24). To a stirred mixture of hexamethyldisilylamine (0.05 mL,) and HMPA (0.5 mL) in dry THF (1 mL) was added *n*-BuLi (1.6 M in hexane, 0.17 mL) dropwise at −78 °C under N_2, and the mixture was stirred for 15 min. A solution of compound **23** (8 mg, 0.03 mmol) in dry THF (1 mL) was added dropwise to the above reaction mixture via a syringe. After being stirred for 20 min at −78 °C, the reaction mixture was treated with glacial acetic acid (0.5 mL) and warmed to room temperature gradually. The mixture was poured into a solution of aqueous HCl (1 M, 5 mL) and extracted with ether, and the organic layer was washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (PET/EtOAc = 15:1) to give known Torgov ketone **24** (6 mg, 75%) as colorless solids. R_f = 0.48 (PET/EtOAc = 5:1); mp 106−107 °C; [lit.[5b] mp 115−116 °C (MeOH); lit.[5c] mp 108−109 °C (MeOH)]; IR (film) ν_{max} 2922, 2852, 1744, 1601, 1461, 1248, 1160, 1041, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (1H, s, ArH), 6.73 (2H, m, ArH), 5.87 (1H, s, CH═), 3.82 (3H, s, OMe), 3.33 (1H, dd, J_1 = 23.2 Hz, J_2 = 2.8 Hz, CH_2), 2.93 (1H, dd, J_1 = 23.2 Hz, J_2 = 2.8 Hz, CH_2), 2.81 (2H, m, CH_2), 2.66−2.59 (3H, m, CH_2), 2.33−2.29 (1H, m, CH_2), 2.07−2.02 (1H, m, CH_2), 1.63−1.59 (1H, m, CH_2), 1.14 (3H, s, Me) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.1, 158.7, 146.9, 138.2, 129.9, 128.6, 125.3, 124.1, 114.7, 113.6, 111.1, 55.3, 49.1, 42.0, 29.7, 28.4, 27.3, 23.0, 20.6 ppm; HRMS (ESI) m/z calcd for $C_{19}H_{21}O_2$ 281.1536, found for $[M + H]^+$ 281.1543.

***endo*-(1-(5-Methylhex-4-enyl)-7-oxa-bicyclo[2.2.1]hept-5-ene-2,3-diyl)dimethanol (25).** Neat dimethyl maleate (792 mg, 5.50 mmol) was introduced into a flask containing powdered $AlCl_3$ (135 mg, 1.00 mmol) at −10 °C under N_2. The resulting mixture was stirred for 10 min, to which compound **26** (802 mg, 5.0 mmol)[28] was added via a syringe. The reaction mixture was stirred at −10 °C for 2 days and extracted with ether, and the organic layer was washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (PET/EtOAc = 5:1) to give the *endo*-cycloadduct **s-6** (951 mg, 60%)[33] as a colorless oil and the exoisomer **s-7** (230 mg, 15%)[33] as white plates (mp 83−84 °C). To a suspension of powdered $LiAlH_4$ (76 mg, 2.00 mmol) in 10 mL of dry THF at 0 °C was added a solution of the above prepared *endo*-cycloadduct **s-6** (616 mg, 2.00 mmol) in dry THF (5 mL) under N_2. After being stirred for 10 min at 0 °C, the reaction mixture was quenched with 5 mL of water and extracted with ether, and the organic layer was washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (PET/EtOAc = 1:2) to give the *endo*-cyclic diol **25** (490 mg, 96%) as a colorless oil. R_f = 0.20 (PET/EtOAc = 1:2); IR (film) ν_{max} 3374, 2923, 2856, 1442, 1380, 1037, 935, 725, 468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.26 (1H, d, J = 5.2 Hz, CH═), 6.11 (1H, d, J = 6.0 Hz, CH═), 5.11 (1H, t, J = 7.2 Hz, CH═), 4.77 (1H, dd, J_1 = 4.4, J_2 = 1.6 Hz, OCH), 4.02 (2H, s, br., OH), 3.60 (2H, dd, J_1 = 10.8, J_2 = 3.2 Hz, OCH_2), 3.25 (2H, m, OCH_2), 2.77 (1H, m, CH), 2.36 (1H, m, CH), 2.04 (2H, m, CH_2), 1.97 (1H, m, CH_2), 1.81 (1H, m, CH_2), 1.69 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.56−1.42 (2H, m, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 134.9, 131.8, 124.1, 90.9, 79.1, 61.0, 60.7, 48.5, 46.9, 31.4, 28.2, 25.7, 24.9, 17.7 ppm; HRMS (ESI) m/z calcd for $C_{15}H_{28}NO_3$ 270.2064, found for $[M + NH_4]^+$ 270.2059.

8-(Hydroxymethyl)-5-(5-methylhex-4-enyl)-6-oxabicyclo[3.2.1]-oct-3-en-2-ol (27), [(3α,5aα,6α,9aα,10α)-6-Isopropenyl-3,5a,6,7,8,9-hexahydro-2*H*-3,9a-methano-1-benzoxepin-10-yl]methanol (28), and [(1α,2α,2′α,5α,8α)-2′-Isopropenyl-6-oxaspiro[bicyclo[3.2.1]-octane-2,1′-cyclopentane]-3-en-8-yl]methanol (29). To a solution of compound **25** (180 mg, 0.71 mmol) in dry CH_2Cl_2 (4 mL) was added $BF_3 \cdot OEt_2$ (0.09 mL, 0.70 mmol) at 0 °C under N_2. Monitoring of the reaction by TLC indicated that the major intermediary product **27** was formed after 10 min, which was transformed into the eventual cyclization products **28** and **29** after 30 min. The reaction mixture was quenched with 1 mL of H_2O and extracted with ether, and the organic layer was washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (PET/EtOAc = 5:1) to give the cyclization products **28** (72 mg, 44%) as a colorless oil and **29** (26 mg, 16%) as a colorless oil. **27**: R_f = 0.15 (PET/EtOAc = 1:2); IR (film) ν_{max} 3351, 2927, 2874, 1741, 1531, 1032, 914, 841, 763, 713, 666, 615, 526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (1H, d, J = 9.2 Hz, CH═), 5.78 (1H, br

s, CH═), 5.08 (1H, br s, CH═), 4.13 (1H, br s, OH), 4.00 (1H, m, OCH), 3.78 (3H, br, OCH_2 and OH), 3.34 (2H, m, OCH_2), 2.72 (1H, br s, CH), 2.26 (1H, br s, CH), 2.02 (2H, d, J = 6.8 Hz, CH_2), 1.69 (3H, s, CH_3), 1.57 (5H, m), 1.35 (2H, m, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 132.2, 129.0, 123.8, 81.5, 70.5, 66.1, 60.3, 43.8, 43.3, 32.8, 28.3, 25.6, 24.7, 17.7 ppm; HRMS (ESI) m/z calcd for $C_{15}H_{24}O_3Na$ 275.1618, found for $[M + Na]^+$ 275.1612. **28**: R_f = 0.58 (PET/EtOAc = 1:2); IR (film) ν_{max} 3405, 2930, 2863, 1644, 1448, 1380, 1054, 1027, 960, 889, 852, 726, 571 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.05 (1H, m, CH═), 5.45 (1H, dd, J_1 = 9.6, J_2 = 3.2 Hz, CH═), 4.75 (1H, s, CH_2═), 4.71 (1H, s, CH_2═), 3.95 (1H, m, OCH_2), 3.85 (1H, m, OCH_2), 3.79 (1H, d, J = 3.2 Hz, OCH_2), 3.51 (1H, t, J = 10.0 Hz, OCH_2), 2.74 (1H, m), 2.30 (1H, t, J = 10.0 Hz), 2.04 (1H, m), 1.95 (1H, m), 1.80 (2H, m), 1.69 (3H, s), 1.60 (3H, m), 1.42−1.31 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 131.7, 128.7, 111.5, 84.5, 73.6, 60.5, 52.2, 50.9, 45.0, 38.8, 32.7, 31.9, 24.0, 19.1 ppm; HRMS (ESI) m/z calcd for $C_{15}H_{26}O_2N$ 252.1958, found for $[M + NH_4]^+$ 252.1952. **29:** R_f = 0.56 (PET/AcOEt = 1:2); IR (film) ν_{max} 3380, 2952, 2878, 1710, 1450, 1374, 1222, 1049, 888, 731, 574, 520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (1H, m, CH═), 5.60 (1H, d, J = 7.6 Hz, CH═), 4.80 (1H, s, CH_2═), 4.77 (1H, s, CH_2═), 4.22 (1H, d, J = 5.6 Hz, OCH), 3.70−3.50 (4H, m, OCH_2), 2.58−2.51 (2H, m), 2.10−1.59 (12H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 136.2, 128.1, 112.4, 72.3, 67.7, 63.1, 57.1, 55.0, 46.8, 46.7, 36.9, 30.3, 22.4, 21.5 ppm; HRMS (ESI) m/z calcd for $C_{15}H_{23}O_2$ 235.1693, found for $[M + H]^+$ 235.1689.

Acknowledgment. We are grateful to Mr. Hai-Tao Gao (Lanzhou University) for kind technical assistance during the earlier stage of this research. We thank the National Natural Science Foundation (Grant QT 20572047) for financial support. The Cheung Kong Scholars program and the Outstanding Scholars program of Nankai University are gratefully acknowledged.

Supporting Information Available: Complete experimental procedures, spectroscopic data, copies of ^1H NMR and ^{13}C NMR spectra, and CIF files for compounds **18**, **19**, **s-9**, **s-11**, and **s-13**. This material is available free of charge via the Internet at http://pubs.acs.org.