ORGANIC LETTERS

2004
Vol. 6, No. 8
1333−1335

Intramolecular Alkylative Arylation of Oxabicylic Alkene: A Potential Diene Approach for the Synthesis of Estrone and Analogous Steroid Structures†

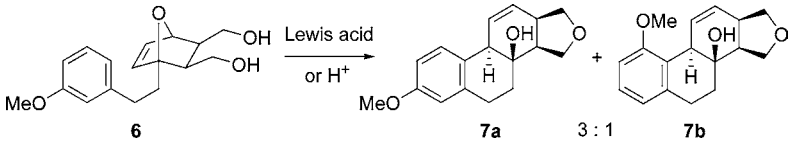
Wei-Dong Z. Li*,‡ and Kun Wei

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

wdli@fas.harvard.edu

Received March 1, 2004

ABSTRACT



Regioselective and stereospecific intramolecular alkylative arylation of unsaturated oxabicyclic diol 6, mediated by Lewis acid or strong protic acid to give the tetracyclic products 7a and 7b, as shown above, represents the first example of an electrophilic (cationic in character) ring-opening–cyclization of oxabicyclic alkene. This constitutes the key cyclization step for a long-standing and potentially useful diene approach for the synthesis of estrone and analogous steroid structures.

Estrone (**1**) and analogous steroids are physiologically highly active compounds, and thus a variety of synthetic strategies

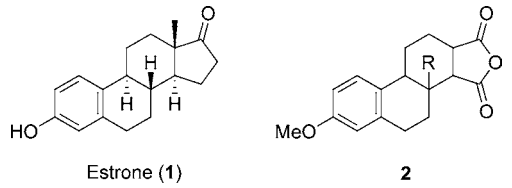
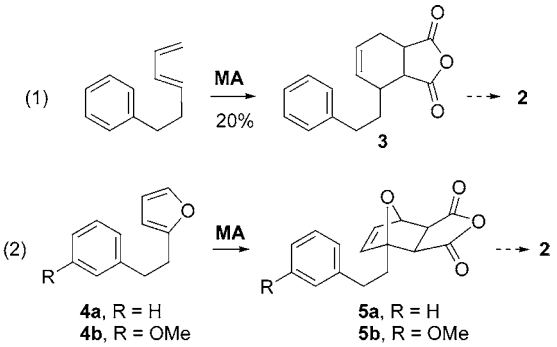


Figure 1.

and methods have been developed for this important class of substances,[1] among which the diene cycloaddition approaches are the most extensively studied.[2]



An interesting early synthetic approach explored by Cohen[3] in 1935 is shown in eq 1, in which the attempted

† In memory of the late R. B. Woodward.

‡ Current address: Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, MA 02138.

(1) For reviews, see: (a) Groen, M. B.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 465. (b) Zeelen, F. J. *Nat. Prod. Rep.* **1994**, *11*, 607.

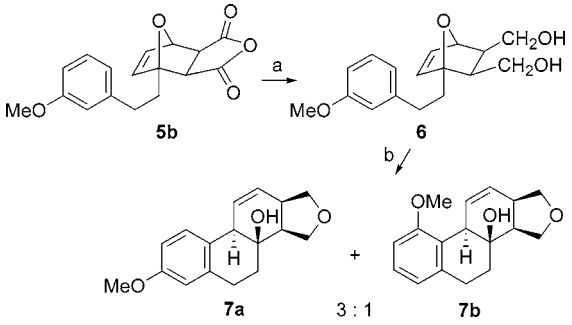
(2) For recent examples, see: (a) Tsogoeva, S. B.; Dürner, G.; Bolte, M.; Göbel, M. W. *Eur. J. Org. Chem.* **2003**, 1661. (b) Schuster, T.; Kurz, M.; Göbel, M. W. *J. Org. Chem.* **2000**, *65*, 1697. (c) Quinkert, G.; Grosso, M. D.; Döring, A.; Döring, W.; Schenkel, R. I.; Bauch, M.; Dambacher, G. T.; Bats, J. W.; Zimmermann, G.; Dürner, G. *Helv. Chim. Acta.* **1995**, *78*, 1345. (d) Quinkert, G.; del Grosso, M.; Bucher, A.; Bauch, M.; Döring, W.; Bats, J. W.; Dürner, G. *Tetrahedron Lett.* **1992**, *33*, 3617. (e) Tanaka, K.; Nakashima, H.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 1915. (f) Sugahara, T.; Ogasawara, K. *Tetrahedron Lett.* **1996**, *37*, 7403. (g) Rigby, J. H.; Warshakoon, N. C.; Payen, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 8237.

10.1021/ol049618u CCC: $27.50
Published on Web 03/19/2004

intramolecular cyclization of a diene-maleic anhydride (MA) adduct **3** to an analogous structure **2** was unsuccessful. Woodward had investigated[4] this approach in 1940 at MIT, in which furan derivatives **4a** and **4b** were employed as the dienes[5] for the Diels−Alder cycloaddition with MA (eq 2). However, due to some difficulties in the catalytic hydrogenation of cycloadducts **5a** and **5b**,[6] the subsequent assumed acid-mediated isomerization−cyclization[7] of the postulated dihydro derivatives of **5a** and **5b** to establish estrone analogue **2** or related structures was left unverified, due presumably to the ready dissociation of cycloadducts **5a** and **5b** via retro-Diels−Alder process.[4,8]

In connection with our general program on the development of novel strategy for stereocontrolled terpenoid synthesis based on the cationic ring-opening−cyclization of oxabicyclic alkenes,[9] we report here a successful realization of the aforementioned strategic approach to estrone-like steroid structures attempted by Cohen and Woodward many decades ago, via a novel electrophilic cyclization of the unsaturated oxabicyclic intermediate.[10] To prevent the ready dissociation of the Diels−Alder cycloadduct **5**, the labile adduct **5b**[11] was directly reduced by $LiAlH_4$ in THF to give the corresponding oxabicyclic diol **6** (Scheme 1). The

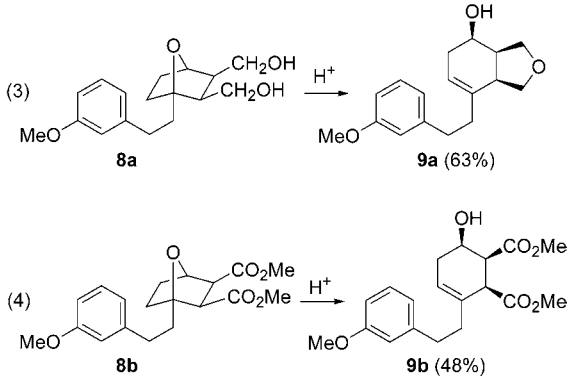
Scheme 1[a]



[a] Conditions: (a) $LiAlH_4$, THF, 0 °C to rt, 40% from **4b**. (b) Lewis acid or protic acid (see text).

designated acid-mediated cyclization reaction of **6** was examined next.

To our delight, common strong Lewis acids such as TMSOTf, $BF_3{\cdot}(OEt_2)$, $TiCl_4$, or $SnCl_4$ and strong protic acids (i.e., $MeSO_3H$ or CF_3SO_3H) were found to be effective to promote the intramolecular alkylative arylation of unsaturated oxabicycle **6** to give dehydrated tetracyclic products **7a** (more polar) and **7b** in a ratio of ca. 3:1 (para vs ortho cyclization)[12] and in an overall yield of 70%, while relatively weaker Lewis acids such as $EtAlCl_2$, MgI_2, or ZnI_2, as well as weaker protic acids (i.e., CH_3CO_2H, HCO_2H, or CF_3CO_2H), resulted in no apparent reaction (starting material was recovered). The reactions are generally carried out in a dilute (<0.1 M) solution of CH_2Cl_2 at 0 °C to ambient temperature with 30 mol % acid catalyst.[13] In contrast, the saturated oxabicycles **8a** and **8b**[14] did not yield any intramolecular arylation product under a variety of acidic conditions, and underwent instead epoxy ring-opening to give cyclohexene derivatives **9a** and **9b**, respectively, on treatment with strong protic acids (i.e., CF_3SO_3H or $MeSO_3H$) in moderate yields (eqs 3 and 4). These results indicated that the previously assumed[4a,7] acid-mediated isomerization−cyclization of analogous precursors (vide supra) leading to a steroid skeleton would not take place readily even under strongly acidic conditions.



It is apparent that the presence of the olefinic function in the unsaturated oxabicyclic ring system is crucial for the observed cyclization reaction. It is important to note that the trans-fused BC ring system was formed exclusively in this intramolecular cationic cyclization, presumably via a concerted pathway of exo-S_N2' type as illustrated in eq 5, which involves consecutive epoxy ring-opening, olefinic double-bond transposition, and para-selective alkylative arylation,[15]

(3) (a) Cohen, A. *J. Chem. Soc.* **1935**, 429. (b) Cohen, A. *Nature* **1935**, 869. (c) Cohen, A.; Warren, F. L. *J. Chem. Soc.* **1937**, 1315.

(4) (a) Woodward, R. B. *J. Am. Chem. Soc.* **1940**, *62*, 1478. (b) Woodward, R. B. A Synthetic Attack on the Oestrone Problem. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 1937. (c) Woodward, R. B. Preliminary Studies in the Synthesis of the Polynuclear Hydroaromatic Ring Systems. B.S. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 1936.

(5) Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1931**, *490*, 243.

(6) Catalytic hydrogenation (over Pd−C) of analogous intermediates can be carried out smoothly in alcoholic solvent (vide infra); see also footnote 12 in ref 4.

(7) Cf.: (a) Cook, J. W.; Hewett, C. L. *J. Chem. Soc.* **1933**, 1098. (b) Cook, J. W.; Hewett, C. L. *J. Chem. Soc.* **1934**, 365. (c) Cook, J. W.; Hewett, C. L.; Girard, A. *J. Chem. Soc.* **1934**, 653.

(8) Woodward, R. B.; Baer, H. *J. Am. Chem. Soc.* **1948**, *70*, 1161.

(9) Zhang, Z.; Li, W.-D. Z.; Li, Y. *Org. Lett.* **2001**, *3*, 2555.

(10) For a recent account on the transition metal-catalyzed nucleophilic alkylative ring-opening of oxabicyclic alkenes and synthetic applications, see: Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48. For an excellent review on *Using Ring-Opening Reactions of Oxabicyclic Compounds as a Strategy in Organic Synthesis*, see: Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1−85. For some recent examples, see also: (a) Nakamura, M.; Matsuo, K.; Inoue, T.; Nakamura, E. *Org. Lett.* **2003**, *5*, 1373. (b) Arrayas, R. G.; Cabrera, S.; Carretero, J. C. *Org. Lett.* **2003**, *5*, 1333. (c) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437.

(11) Obtained as a crude exo-isomeric (>50:1) adduct; see also ref 8.

(12) For an earlier similar regioselective cationic intramolecular arylation, see: (a) Bartlett, P. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 7501. (b) Bartlett, P. A.; Brauman, J. I.; Johnson, W. S.; Volkmann, R. A. *J. Am. Chem. Soc.* **1973**, *95*, 7502. (c) Groen, M. B.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 239 and earlier papers in this series.

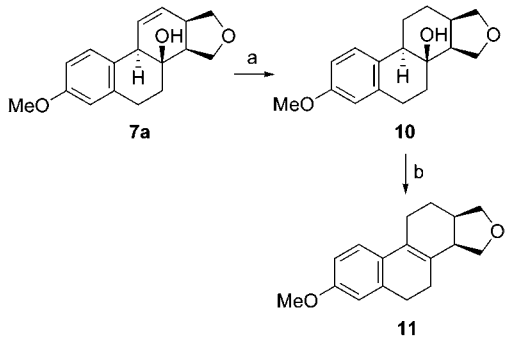
(13) No apparent reaction occurred at lower temperature; see Supporting Information for a typical experimental procedure.

(14) Prepared from the corresponding unsaturated precursors (i.e., **6**) by catalytic hydrogenation in MeOH over 10% Pd−C at ambient temperature.

(15) For a recent example of acid-catalyzed intramolecular arylation, see: Harrowven, D. C.; Tyte, M. J. *Tetrahedron Lett.* **2004**, *45*, 2089.

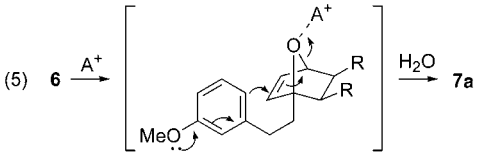
along with the facile dehydrative tetrahydrofuran ring formation. The structures of the tetracycles **7a** and **7b** were fully characterized by extensive spectroscopic analysis (including NOE and two-dimensional NMR) and confirmed furthermore by the following chemical transformations (Scheme 2): (1)

Scheme 2[a]



[a] Conditions: (a) H_2, 10% Pd−C, MeOH, 96%. (b) Cat. *p*-TsOH·H_2O, benzene, reflux, 80%.

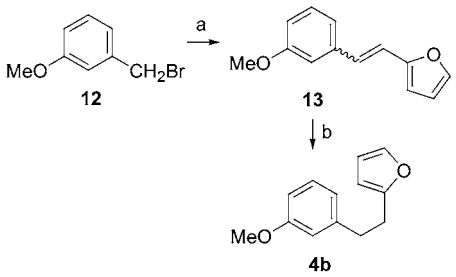
catalytic hydrogenation of **7a** gave the corresponding dihydro derivative **10** (mp 144−145 °C), and (2) ready dehydration on treatment with *p*-TsOH in refluxing benzene produced the sole elimination product **11** in 80% yield. The chemical structures of both **10** and **11** were verified by spectroscopic methods.



To the best of our knowledge, this is the first example of an acid-mediated cationic intramolecular alkylative cyclization[16] of an oxabicyclic alkene initiated by the epoxy ring-opening, although various catalytic nucleophilic ring-opening reactions of oxabicyclic alkenes have been studied extensively.[10] Since the tetracyclic product **7a** is of great potential for further elaboration to the analogous steroid structures,[17] the synthetic method demonstrated herein represents a novel diene cycloaddition approach for steroids.

Although Woodward had described the synthesis of furano diene precursors **4a** and **4b** in some detail in 1940,[4] we found that it is more convenient to reduce the olefination product **13** by magnesium in absolute methanol to give **4b** in nearly quantitative yield (Scheme 3). [18]

Scheme 3[a]



[a] Conditions: (a) (i) Ph_3P, benzene; (ii) ^{t}BuOK, THF, then furfural, 0 °C to rt, 82%. (b) Mg, MeOH, reflux, 98%.

In summary, the key cyclization step of a long-standing strategic diene approach[19] directed toward the synthesis of estrone and analogous steroid structures was realized via a novel acid-catalyzed regioselective and stereospecific intramolecular alkylative arylation of oxabicyclic alkene intermediates. The success of the electrophilic (cationic) cyclization of unsaturated oxabicyclics initiated by acid-mediated 1,4-epoxy ring-opening[20] should provoke the investigation of cyclization of substrates bearing other π-nucleophiles (i.e., olefinic or electron-rich systems) and implies further application of oxabicyclic alkene as a stereocontrolling template[21] for natural product synthesis. Studies along these lines are under way in our laboratory.

Acknowledgment. We thank the National Natural Science Foundation of China (Distinguished Youth Fund 29925204; Funds 20021001 and 20172022) and Ministry of National Education of China (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 **4b**, **6**, **7a**, **7b**, **9a**, **9b**, **10**, **11**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049618U

(16) For the only example of intramolecular *anionic* alkylative ring-opening−cyclization of oxabicyclic alkenes, see: Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.* **1995**, *117*, 1954.

(17) Cf., synthesis of equilin and equilenin: (a) Zderic, J. A.; Carpio, H.; Bowers, A.; Djerassi, C. *Steroids* **1963**, *1*, 233. (b) Stein, R. P.; Buzby, G. C., Jr.; Smith, H. *Tetrahedron Lett.* **1966**, *7*, 5015.

(18) Cabares, J.; Mavoungou-Gomes, L. *Bull. Soc. Chim. Fr.* **1986**, 401.

(19) Introduction of the angular methyl on the steroid framework by this approach would be possible by employing citraconic anhydride as a dienophile in the furano Diels−Alder cycloaddition stage; cf. ref 4c and see also: Corey, E. J. The Condensation of Citraconic and Maleic Anhydrides with Chloroprene and Ethoxyprene. B.S. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 1948.

(20) This mode of initiation could be regarded as a novel type of initiating method for cationic π-cyclization, compared with other well-known methods based on other oxy-functional units (i.e., epoxide, allylic alcohol, acetal). Cf.: ref 9 for an earlier example.

(21) An asymmetric furano Diels−Alder cycloaddition to optically pure oxabicycle **6** or analogue would ensure an enantiocontrolled synthesis based on this strategy.