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New Approach to the Progesterone BCD-Ring System by Utilizing a Tandem Transannular Radical Cyclization

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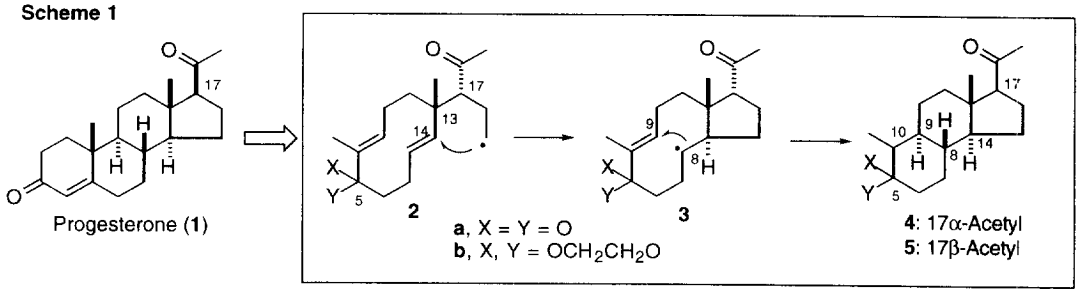
***Abstract**: The synthesis of the progesterone BCD-ring system utilizing a tandem transannular radical cyclization and its diastereoselectivity based on MM2 transition state model calculations (flexible model) are described.*

Keywords: Radicals and radical reactions; Transannular reactions; Molecular modelling/mechanics; Steroids and sterols

Due to the remarkable structural features of medium- and large-membered ring systems, macrocyclic reactions have attracted much attention in synthetic organic chemistry.[1] In particular, transannular carbon-carbon bond formation is a useful method for the stereoselective synthesis of polycyclic compounds such as the steroid skeleton in a single chemical step. Previously, we have reported the efficient transannular Diels-Alder reaction of a 14-membered triene to construct the steroid ABC-ring skeleton.[2,3] Now we report an efficient synthesis of the steroid BCD-ring system **5**, a partial structure of progesterone (**1**), using a tandem transannular radical cyclization. Radical cyclization is a powerful method for the synthesis of polycyclic compounds and their regio- and stereoselectivities are well studied in acyclic systems.[4,5] However, it is not easy to predict regio- and stereoselectivities quantitatively[6] in transannular radical cyclization of medium- and large-membered ring systems.[7] To provide a solution to this problem, MM2 transition structure models can bring significant information in this regard.

Scheme 1



In our synthetic plan (Scheme 1), the free radical **2** is a key intermediate for tandem transannular radical cyclization in the one-pot synthesis of the BCD ring system **4**. Addition of the radical **2** to the C14 position in a *5-exo-trig* cyclization produces a new radical **3** at the C8 position, which should undergo transannular addition to C9 in a *6-exo-trig/6-endo-trig* manner, generating B, C, and D rings and three consecutive stereogenic

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centers at the C9, C8, and C14 positions. The stereochemistry at the C17 position of the cyclized product **4** may epimerize to the more stable 17β-acetyl derivative **5** under basic conditions.[5,8] In order to design a suitable synthetic intermediate for the cyclization, MM2 transition structure model calculations of **2a** and **2b** were performed.[9] Interestingly, the calculations suggested that the functional group at the C5 position will control the newly formed stereogenic centers. We assumed that the initial conformations of the 10-membered ring compound **2** are held during the tandem radical cyclization, because the reaction sites between the C8 and C9 positions of a ten-membered intermediate **3**, formed by the first cyclization, will be close enough to undergo immediate transannular cyclization. The various initial coordinates of **2a** generated by the Monte Carlo (MC) random search, were minimized by MACROMODEL[10] using the extended force field for radical additions to alkenes developed by Houk *et al.*[11] We found 17 optimized transition structure models within 3.0 kcal/mol of the global minimum, where it is suggested that the five-membered D-ring rather than a 6-membered ring should be formed in the first proposed cyclization reaction and the reaction sites between the C8 and C9 positions on the 10-membered ring are very close (ca. 2.9 Å), presumably providing the B- and C-rings smoothly via the subsequent transannular cyclization.

Figure 1 MM2 Transition Structure Models of Tandem Radical Cyclization of **2a**

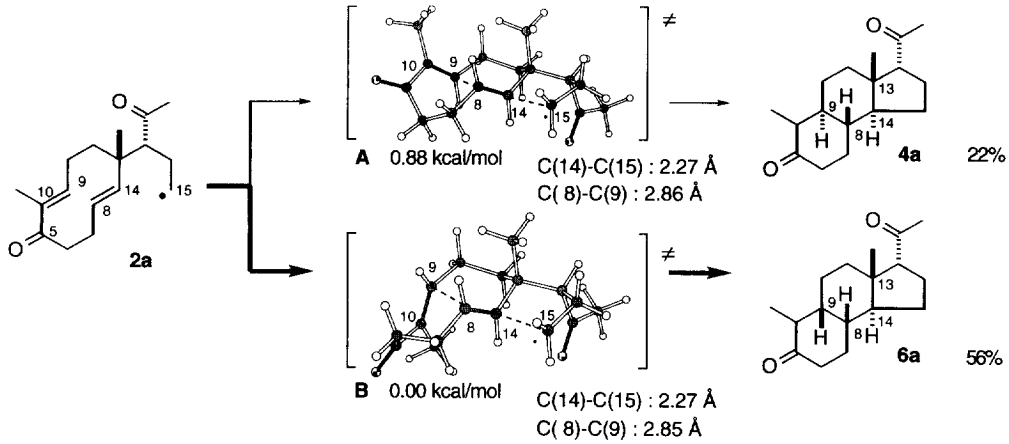


Figure 2 MM2 Transition Structure Models of Tandem Radical Cyclization of **2b**

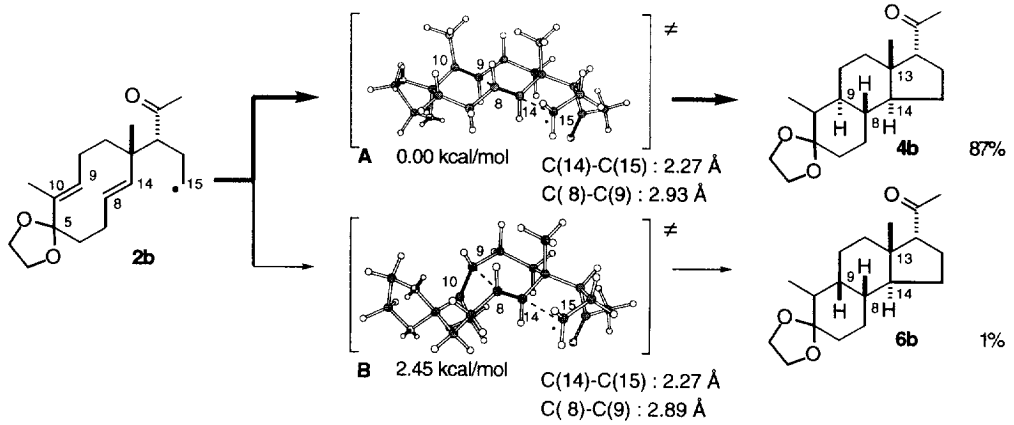
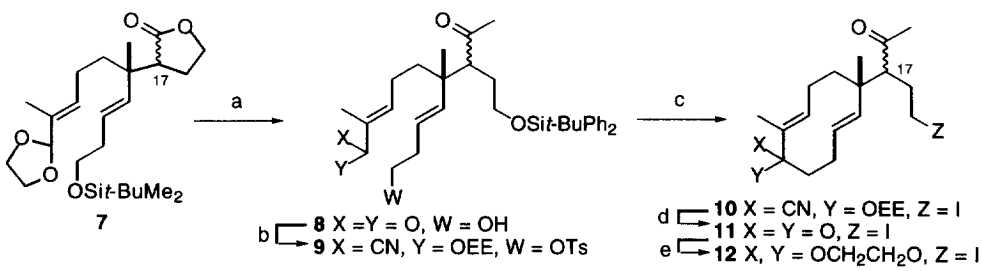


Figure 1 shows the lowest energy transition structure **A**$^{\neq}$ and **B**$^{\neq}$ leading to **4a** and **6a**, respectively. According to these calculations and a Boltzmann distribution at 353 K based on the energy difference among these transition structure models, it is predicted that the ratio of **4a**, **6a**, and the cis-isomer (13-Me/14-H) would be 22:56:22 and that the anticipated major product should be **6a** having the undesired ***cis-anti-trans*** (B/C/D) system. On the other hand, similar calculations for the ketal derivative **2b** (15 unique transition structure models found within 3.0 kcal/mol of the global minimum), predicted that the ratio of the **4b**, **6b**, and cis-isomer (13-Me/14-H) would be 87:1:12 (Figure 2). Thus, the acetal group at the C5 position in **2b** is a prerequisite to obtain the desired **4b** with ***trans-anti-trans*** (B/C/D) relative stereochemistries.

The key intermediate **2b** was prepared in the following manner (Scheme 2). A diastereomeric mixture of γ-lactones **7** (75 : 25 mixture of the 17α- and 17β-epimers) was prepared from readily available geranyl acetate following our previously reported procedure.[5b] Addition of methyllithium to lactone **7**, followed by protection of the resulting alcohol with *t*-butyldiphenylsilyl chloride afforded the protected methyl ketone, whose *t*-butyldimethylsilyl group and acetal were hydrolyzed with acid providing enal **8** in 78% overall yield. Tosylation of the primary alcohol was followed by the conversion of aldehyde into the corresponding cyanohydrin ether **9** in 3 steps (96% overall yield). Intramolecular alkylation of **9** was performed using $LiN(TMS)_2$ in dioxane at 100 °C (71%). Deprotection of the *t*-butyldiphenylsilyl group, followed by iodination afforded the iodide **10**. Acid treatment of the cyanohydrin ether **10**, followed by base treatment of the resulting cyanohydrin provided diketone **11** in 76% overall yield. Selective acetal formation of the cyclic ketone (ethylene glycol/2-methoxy-1,3-dioxolane/benzene) furnished a 60 : 40 mixture of the 17α- and 17β-epimers **12** in 50% yield.[12]

Scheme 2



a) MeLi, THF, -78 °C; *t*-$BuPh_2SiCl$, imidazole, DMF, r.t.; AcOH / THF / H_2O = 4 / 1 / 1, r.t., 78% from **7**. b) TsCl, pyridine, $CHCl_3$, 99%; TMS(CN), cat. DC-18-crown-6 KCN; 1 M HCl, THF; ethyl vinyl ether, cat. TsOH, PhH, 96%. c) $LiN(TMS)_2$, dioxane, 100 °C, 71%; TBAF, THF, 83%; I_2, PPh_3, PhH; 1 M HCl, THF; 10% NaOH aq., 76%. d) ethylene glycol, 2-methoxy-1,3-dioxolane, PhH, 50%

After the separation of the diastereomers, the tandem radical cyclization of the 17α-acetyl isomer of iodide **12** was carried out in the following way. Treatment of 17α-**12** with tributyltin hydride in the presence of a catalytic amount of AIBN in refluxing benzene provided a BCD-ring cyclized product **4b** in 74% isolated yield.[12] The HPLC analysis of crude products revealed that the tandem radical cyclization of **2b** afforded the desired ***trans-anti-trans*** (B/C/D) relative stereochemistries with 95% stereoselectivity.[13] These experimental results are in good agreement with the calculations based on the MM2 transition structure models shown in Figure 2.[14] The stereochemistry of **4b** was determined by single-crystal X-ray analysis of 10α-methyl **5b** that was obtained by base catalyzed isomerization of **4b** (K_2CO_3, MeOH, r.t., 70%; **5b** : **4b** = 90 : 10).[15] In the same manner, the radical cyclization of 17β-acetyl isomer of **12** provided the disired **5b** in 94% yield with

>95% stereoselectivity.

In conclusion, we have accomplished an efficient synthesis of the progesterone BCD-ring via tandem transannular radical cyclization of both isomers of **12** in a one-pot operation, and achieved the quantitative prediction of the stereochemistry of the product by utilizing MM2 transition structure models.

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12. Spectrum data of **12** (17α-acetyl isomer) : ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.47 (br d, *J* = 11.9 Hz, 1H), 5.32 (d, *J* = 15.8 Hz, 1H), 4.95 (ddd, *J* = 15.8, 10.6, 3.3 Hz, 1H), 3.99-3.68 (m, 4H), 3.17 (ddd, *J* = 9.9, 6.9, 4.3 Hz, 1H), 2.85 (ddd, *J* = 9.9, 9.9, 6.3 Hz, 1H), 2.69 (dd, *J* = 11.1, 2.5 Hz, 1H), 2.48-1.39 (m, 10H), 2.16 (s, 3H), 1.50 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 211.9, 139.1, 131.1, 130.6, 124.3, 110.9, 64.5, 63.0, 62.2, 42.3, 38.0, 35.3, 31.3, 30.6, 29.7, 24.0, 17.3, 13.8, 5.6; IR (neat): 2940, 1702, 1167, 1105, 1051 cm^{-1}; Spectrum data of **4b** (10α-methyl isomer) : ^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.00-3.86 (m, 4H), 2.79 (dd, *J* = 8.3, 2.6 Hz, 1H), 2.11 (s, 3H), 1.98-0.94 (m, 16H), 0.92 (s, 3H), 0.82 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 212.5, 110.8, 65.0, 64.9, 61.3, 49.0, 45.9, 45.8, 44.4, 40.7, 35.3, 34.9, 32.7, 28.4, 26.5, 25.7, 24.2, 20.9, 10.7; IR (neat): 2928, 2872, 1700, 1104 cm^{-1}.
13. Cyclized Product **4b** was obtained with an 88 : 12 mixture of the 10α- and 10β-methyl group. Neither **6b** and cis-isomer (13-Me/14-H) was detected (less than 5%).
14. The radical cyclization of 17α-**11** gave a 43 : 57 mixture of **4a** and **6a** in 94% combined yield. The **6a** isomerized to 17β-isomer, which was identical with the synthetic material previously reported; Uskokovic, M.; Iacobelli, J.; Philion, R.; Williams, T. *J. Am. Chem. Soc.* **1966**, *88*, 4538-4539; Uskokovic, M. R.; Williams, T. H. U.S. **Patent** 3,956,316, 1973 to Hoffmann-La Roche Inc.
15. The authors have deposited atomic coordinates for the 10α-methyl **5b** with the Cambridge Crystallographic Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.