New Approach to the Steroid BCD-Ring System Using Tandem Radical Cyclization

Takashi Takahashi,* Satoshi Tomida, Yasuharu Sakamoto, and Haruo Yamada

Department of Chemical Engineering, Tokyo Institute of Technology, 2-12-1 Ookayama, Meguro, Tokyo 152, Japan

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Syntheses of polycyclic skeletons, such as steroids and terpenes, have a central place in the development of regio- and stereochemically controlled synthetic methodology.[1] The elaboration of ring-fused carbocycles based upon "tandem cyclizations" such as cation cyclization,[2] radical cyclization,[3] and tandem Heck cyclization[4] offer efficient methods for the rapid and stereocontrolled synthesis of polycyclic skeletons. We have developed efficient approaches to the steroid CD ring based upon the double Michael reaction,[5] sequential Claisen rearrangement,[6] and Pd-catalyzed cyclization.[7] We have also described a unique synthesis of the steroid ABC ring system using a transannular Diels−Alder reaction.[8] Recently, a tandem radical cyclization using an acyl radical intermediate to synthesize the steroid skeleton (A → B → C → D) has been reported.[9] We report here an alternative approach (D → C → B) to the steroid BCD-ring **4** using a "tandem radical cyclization",[10] with a view toward the syntheses of progesterone (**1**), 11α-hydroxyprogesterone (**2**), a key intermediate for hydrocortisone, and Proscar (**3**),[11] an inhibitor of enzyme human prostatic 5α-reductase (Figure 1).

In our synthetic plan (Figure 1), acyclic iodide **7** is the key intermediate for the tandem radical cyclization, which involves the first cyclization to generate the D-ring via a 5-*exo*-*trig* closure (**7** → **6**) and the subsequent second cyclization to provide the C-ring via a 6-*exo*-*trig* closure (**6** → **5**). Cyclization of the B ring in **5** using an acyl anion, followed by a base-induced isomerization of the resulting cyclized product, should provide the stable 10α,17*β*-BCD ring **4**.[12,13] It is well known that 5-*exo*-*trig* cyclizations are generally preferred over 6-*endo*-*trig* closures, and introduction of an activating group on the alkene terminus accelerates 6-*exo*-*trig* cyclization.[3d,14] Thus, the regiochemical outcome of the cyclization would be directed to give the desired steroid CD ring system. However, it is still difficult to predict the stereochemical outcome of the acyclic radical cyclizations of **7** because of the many conformational possibilities and relative stereochemistry between the C(13)-methyl and C(17) methyl ketone. For the quantitative modeling of the radical cyclization of **7**, the MM2 transition-state model[15] (*flexible reactant model*) was applied to the tandem radical cyclizations of 17*β*-**8** and 17α-**8** (*t*-BuMe$_2$SiO group is replaced by a hydrogen; see Figure 2). On the basis of the assumption of a stepwise process for this tandem radical cyclization, we constructed MM2 transition-state structures for all possible ring closures by using Monte Carlo (MC) random-search[16] to find the initial structures. The extended MM2* force field[17] and Houk's radical cyclization parameters[18] were applied to minimize the energies. MM2 calculations and a Boltzmann dis-

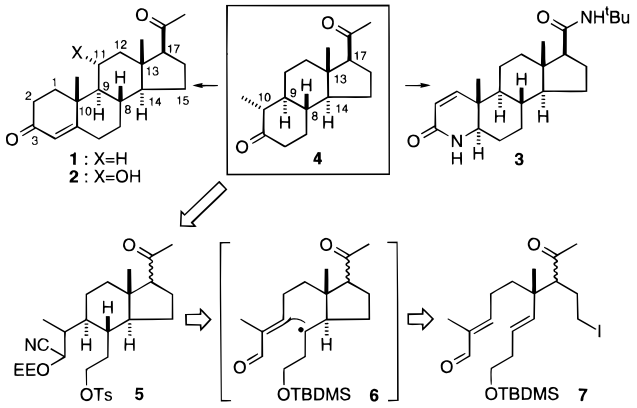

Figure 1. Retrosynthesis of **4** and tandem radical cyclization giving **5**.

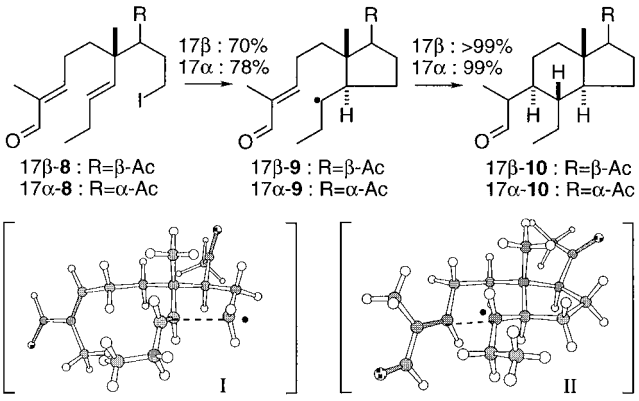

Figure 2. Flexible reactant models of the tandem radical cyclization.

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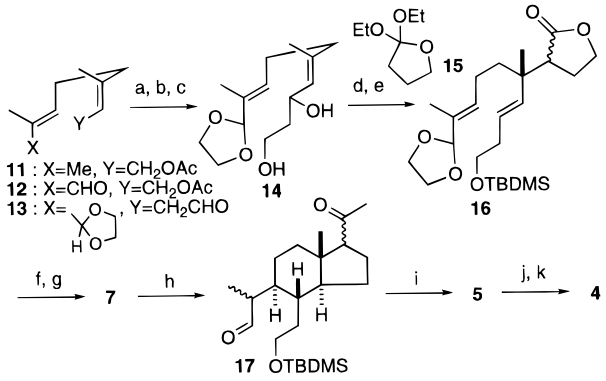
Scheme 1[a]



[a] Synthesis of **4**: (a) SeO_2, TBHP, salicyclic acid, CH_2Cl_2 then Me_2S, AcOH; MnO_2, benzene/CH_2Cl_2, 36%; (b) ethylene glycol, triethyl orthoformate, *p*-TsOH, benzene; K_2CO_3, MeOH; MnO_2, benzene, 62%; (c) LDA, ethyl acetate, THF, −78 °C; $NaBH_4$, LiCl, MeOH, 90%; (d) *t*-BuMe_2SiCl, Et_3N, CH_2Cl_2, 69%; (e) **15**, heptanoic acid, xylene, 140 °C, 80%; (f) MeLi, THF, −78 °C, 85%; (g) I_2, PPh_3, imidazole, benzene; THF/AcOH/H_2O = 4:1:1, 0 °C, 57%; (h) AIBN (0.33 equiv), *n*-Bu_3SnH (1.9 equiv), benzene, reflux, 93%; (i) Me_3SiCN, ZnI_2; 1 MHCl, THF; TsCl, pyridine, CH_2Cl_2; ethyl vinyl ether, PPTS, benzene, 41%; (j) $LiN(TMS)_2$, THF, 68 °C, 98%; (k) PPTS, MeOH; 2% NaOH (aq), THF; K_2CO_3, MeOH, 85%.

tribution of the transition-state structures of 17β-methyl ketone **8** suggest that the first cyclization of 17β-**8** should give a 70:28 mixture of the 17β-*trans*-**9** and its *cis*-isomer and that the 6-*endo*-*trig* closure products would be formed in less than 2% yield. On the basis of this analysis, the second 6-*exo*-*trig* cyclization of the major radical intermediate 17β-**9** was examined. These calculations and a Boltzmann distribution suggest that the second cyclization of 17β-**9** should provide the exclusive formation (>99%) of 17β-**10** with the *trans*-*anti*-*trans* (B/C/D) relative stereochemistry. In a similar manner, the analysis of tandem radical cyclization of the 17α-methyl ketone **8** was conducted. The first cyclization of 17α-**8** should give a 78:13:9 mixture of the 17α-*trans*-**9** and its *cis*-isomer and 6-*endo*-*trig* products, and the subsequent cyclization via the major radical intermediate 17α-**9** should provide exclusively (99%) the CD-ring 17α-**10** having the *trans*-*anti*-*trans* (B/C/D) relative stereochemistry. Overall, the MM2 transition-state calculations suggest that the initial radical cyclizations of both the 17β- and 17α-form of **7** introduce the D-ring of **5** with the correct *trans*-stereochemistry between the C(13)-methyl (18-methyl) and C(14)-hydrogen and the subsequent cyclizations provide the C-ring of **5** with the desired *trans*-*anti*-*trans* (B/C/D) relative stereochemistry.

The key intermediate **7** was prepared in the following way (Scheme 1). Two-step oxidation (SeO_2 then MnO_2) of the terminal methyl group in geranyl acetate (**11**) gave the α,β-unsaturated aldehyde **12** in 36% yield. Protection of the aldehyde **12** with ethylene glycol, methanolysis of the acetyl group, and MnO_2 oxidation of the resulting allylic alcohol afforded the α,β-unsaturated aldehyde **13** in 62% overall yield. 1,2-Addition of the lithium enolate of ethyl acetate at −78 °C, and reduction of the resulting ester provided diol **14** in 90% overall yield. Selective protection of the primary alcohol with *t*-BuMe_2SiCl (69% yield) and Claisen rearrangement of the resulting secondary alcohol with the cyclic orthoester **15**[19] afforded a 75:25 mixture of the 17α- and 17β-epimers **16** in 80% yield. Without separation of these epimers, γ-lactone **16** was transformed to γ-iodo ketone **7** in three steps: (1) addition of methyllithium (85% yield), (2) conversion of the resulting alcohol into the iodide,[20] and (3) deprotection of the acetal (57% yield for two steps). In these transformations, isomerization of the 17-acetyl group did not take place and HPLC analysis showed a 75:25 mixture of the 17α- and 17β-methyl ketone **7**.

Without separation of the 17α- and 17β-epimers, the tandem radical cyclization of iodide **7** was carried out in the following way.[21] Treatment of **7** with tributyltin hydride (1.9 equiv) in the presence of AIBN (0.33 equiv) at benzene reflux gave in 93% yield the CD-ring **17** with the desired *trans*-*anti*-*trans* (B/C/D) relative stereochemistry. In this cyclization, none of the *cis* ring-fused bicycles were detected by HPLC and NMR analyses. Selective cyanohydrin formation of the aldehyde in **17**, deprotection of the trimethyl- and *tert*-butyldimethylsilyl groups, tosylation of the primary alcohol, and reprotection of the cyanohydrin with ethyl vinyl ether gave the protected cyanohydrin **5** in 41% overall yield. Cyclization of **5** (98% yield) and acid treatment of the cyclized product, followed by base treatment of the resulting cyanohydrin (10% NaOH (aq) and then K_2CO_3/MeOH) gave an 80:20 mixture of the BCD-ring **4** and its 17α-isomer in 85% combined yield. The structure of **4** was established by X-ray crystallographic analysis.[22] None of the 10β-methyl derivatives were detected in a crude mixture by HPLC and NMR analyses.

An efficient synthesis of the steroid BCD-ring system having a 17β-methyl ketone was accomplished using a tandem radical cyclization and subsequent cyanohydrin alkylation. Moreover, conformational analysis utilizing the "MM2 transition-state model" predicts the stereoselectivity in the radical cyclization, and in general, considerations of stereochemical control based upon *ab initio* and MM2 calculations might have predictive value in the design of key synthetic intermediates.

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Supporting Information Available: Experimental details for the synthesis of the BCD-ring system **4**, the transition-state modeling of the radical cyclization of iodide **8**, and X-ray crystallographic data for **4** (27 pages).

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(21) After separation of the 17α- and 17β-epimers of **7**, their tandem radical cyclizations were also examined. The 17β-methyl ketone **7** provided **17** having 17β-acetyl group and the *trans*-*anti*-*trans* relative stereochemistry in the C-ring with more than 74% stereoselectivity, and the 17α-methyl ketone **7** afforded **17** having a 17α-acetyl group and the *trans*-*anti*-*trans* relative stereochemistry in the C-ring with more than 78% stereoselectivity.

(22) The authors have deposited atomic coordinates for the BCD-ring system **4** 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.