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SYNTHESIS OF AN OPTICALLY ACTIVE 13ß-METHYL 14ß-HYDROXY STEROID VIA BASE-CATALYZED REACTIONS

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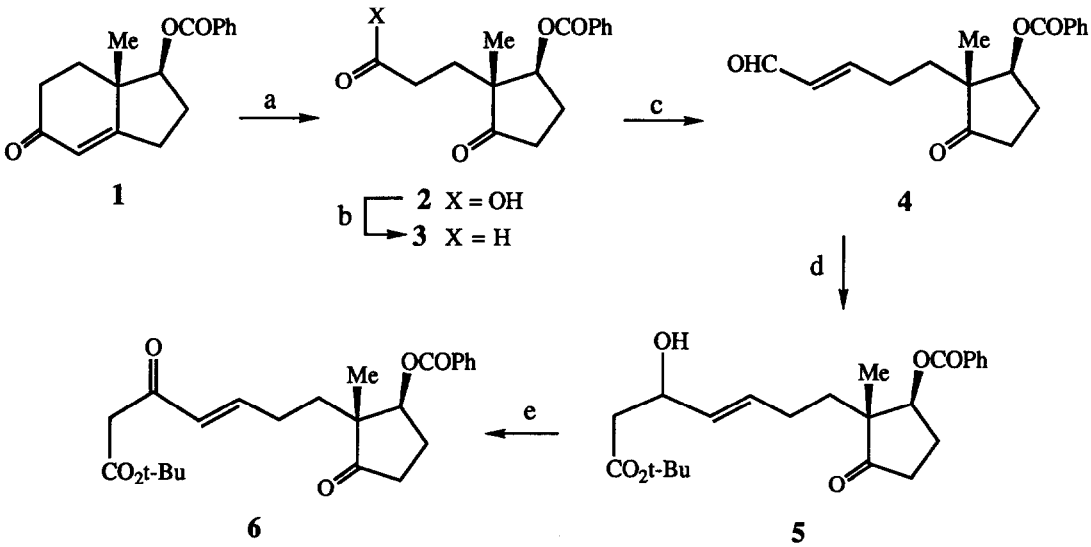
ABSTRACT: The synthesis of optically active 14ß-hydroxy steroid 9 is reported. This steroid is obtained in only two steps from chiral precursors 6 and 7 via anionic cycloaddition followed by base-catalyzed aldol reaction of triketone 8.

We have previously reported the one-step stereocontrolled synthesis of a 13α-methyl 14α-hydroxy steroid via a new anionic polycyclization method.[1] The configuration of the C_{13} and C_{14} carbon centers in this steroid was opposite to the 13ß-methyl 14ß-hydroxy arrangement normally found in cardioactive steroids.[2] Further investigation led us to conceive a very short synthesis of a steroid bearing the correct C_{13} and C_{14} stereocenters. We now wish to report this work, namely, the preparation of (+)-13ß-methyl 14ß-hydroxy steroid **9** (Scheme 2). This compound was obtained from aldol condensation of **8** which was produced from the base-catalyzed cycloaddition[3] of chiral precursors **6** and **7**.

The substituted Nazarov reagent **6** was obtained by the sequence described in Scheme 1. Ozonolysis of the known chiral bicyclic enone **1**[4] gave the keto acid **2**[5] according to the procedure reported by Mori and collaborators.[6] Selective borane reduction of acid **2** followed by PCC[7] oxydation led to the aldehyde **3** ($[\alpha]_D$ +43.1°(c 4)). This aldehyde was treated with (formylmethylene)triphenylphosphorane[8] to give *trans* unsaturated aldehyde **4** ($[\alpha]_D$ +65.9° (c 1)). Treatment of aldehyde **4** with the Reformatsky reagent of *t*-butylbromoacetate gave *trans* diastereomeric allylic alcohols **5** (1:1) which were converted into the desired substituted Nazarov reagent **6** with manganese dioxide.

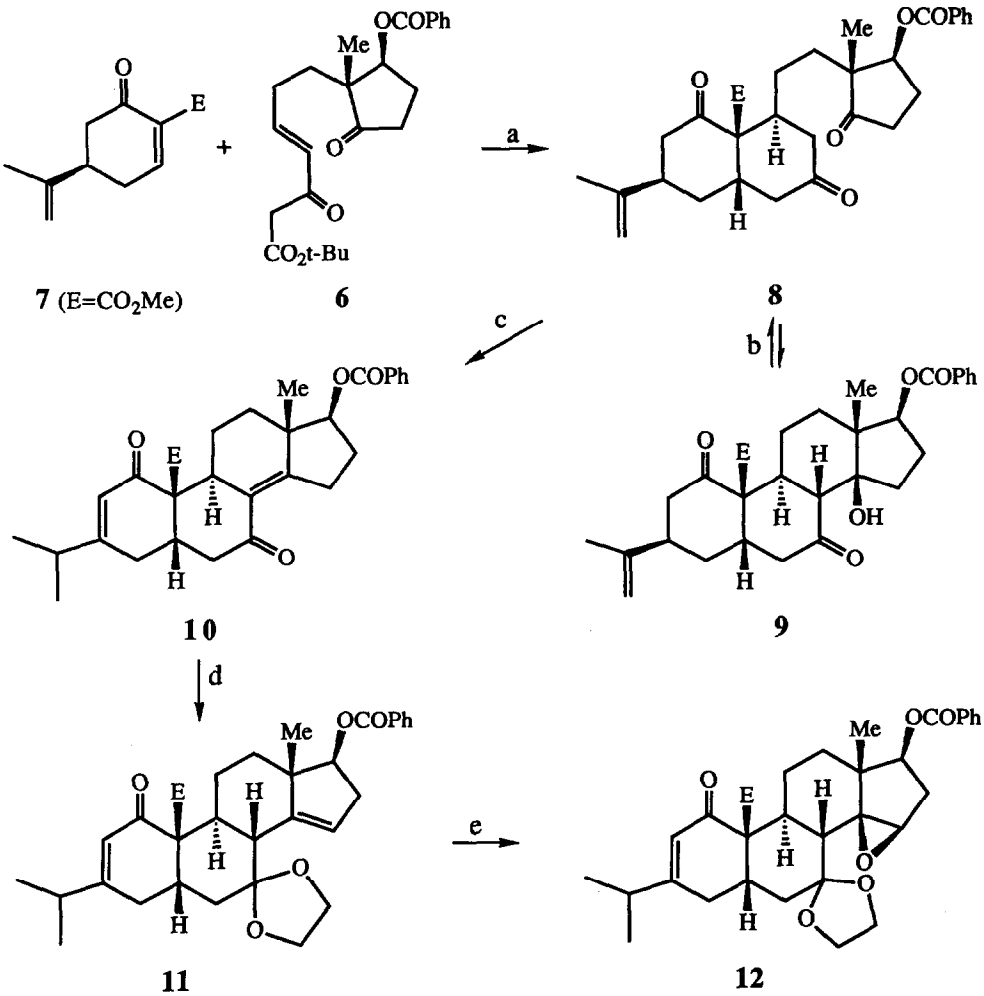
The triketone compound **8** was then obtained from selective decarboxylation of the cycloaddition product resulting from the reaction of precursors **6** and **7**[9] with cesium carbonate in chloroform. As in our preceding model study,[9] the cycloaddition (70% yield) led to a (85:15) diastereomeric mixture in which the major compound **8** ($[\alpha]_D$ +83.6° (c 1)) was easily separated. The cesium carbonate-catalyzed aldol condensation was then carried out in acetonitrile and produced the steroid derivative **9** as the



SCHEME 1: (a) O_3, MeOH, -78°C;
(b) i) BH_3-THF, THF, 0°C,
ii) PCC, CH_2Cl_2 (50% from **1**);
(c) $Ph_3PCHCHO$, PhH, reflux;
(d) Zn, $BrCH_2CO_2t$-Bu, THF, reflux; then add **4** in THF, 0°C;
(e) MnO_2, AcOEt, r.t. (51% from **3**).

sole product although in low yield (32%). When the purified steroid **9** was re-submitted to the same conditions (Cs_2CO_3, CH_3CN, reflux), a (1:1) mixture of **8** and **9** was obtained. This result clearly indicated the reversibility of the aldol reaction. The general structure and the *cis-anti-trans-syn-cis* ring junction stereochemistry of 14β-hydroxy steroid **9** were rigorously established by X-ray analysis.[10]

When a benzene solution of triketone **8** was heated in the presence of *p*-toluenesulfonic acid (PTSA), the *bis*-enone **10** ($[\alpha]_D$ -106.4° (c 1)) was produced in 77% yield. Thus, not only did dehydration of the ß-hydroxy ketone occur, but the initial C_3-isopropenyl substituent was also transformed into the 2-cyclohexene-1-one unit in **10**. Interestingly, selective protection of the C_7 carbonyl group was achieved on *bis*-enone **10**. Thus, when treated with excess ethylene glycol and PTSA, **10** was converted to ketal **11** ($[\alpha]_D$ +17.0° (c 2)) in 71% yield. Importantly, this protection step allowed the expected[11] isomerization of the C_8-C_{14} double bond to the C_{14}-C_{15} position. Furthermore, the C_2-C_3 and C_{14}-C_{15} double bonds were then differentiated. The latter was in fact selectively oxidized with *m*-CPBA to give epoxide **12** ($[\alpha]_D$ +11.6° (c 1)) in 81% yield.



SCHEME 2: (a) i) 7 in $CHCl_3$ was added to **6** and Cs_2CO_3 in $CHCl_3$, r.t., ii) TFA, PhH, reflux (60%); (b) Cs_2CO_3, CH_3CN, reflux (32%; 47% based on recovered **8**); (c) PTSA, PhH, reflux (77%); (d) $(CH_2OH)_2$, PTSA, PhH, reflux (71%); (e) *m*-CPBA, CH_2Cl_2 (81%).

In conclusion, we are reporting a very simple synthesis of an optically active 14ß-hydroxy steroid as well as other steroid derivatives. The absolute stereochemistry of the C/D ring junction in **9** is exactly that found in natural 14-hydroxy steroids. We are currently trying to find simple ways to shift the equilibrium aldol reaction (**8** → **9**) in order to improve the so far modest yield. Work directed toward the synthesis of optically active steroids bearing the general C/D *trans* ring junction has also been undertaken in our laboratory.[12]

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(9) For the cycloadditon of the (-)-carvone derived (-)-**7** and a methyl substituted Nazarov reagent see: R.Ruel, K.T. Hogan, and P. Deslongchamps. *Tetrahedron Lett.* Submitted.

(10) X-ray analysis was carried out by M. Drouin and Dr A.G. Michel, Département de chimie, Université de Sherbrooke; m.p. 156-157°C; exact mass calculated for $C_{30}H_{36}O_7$: 508.2461; found: 508.2472; $[\alpha]_D$ +61.5° (c 1); ^1H nmr ($CDCl_3$, 250 MHz) δ ppm: 8.08, 7.53, 7.42 (5H, 3 m, C_6H_5), 5.01 (1H, m, 17α-H), 4.84, 4.73 (2H, 2 s, H olefin), 4.01 (1H, s, OH), 3.81 (3H, s, COOMe), 3.19 (1H, m, 5ß-H), 2.79 (1H, d, J=13.6 Hz, 8ß-H), 2.64-1.35 (16H, m), 1.72 (3H, s, Me), 1.07 (3H, s, 13ß-Me); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ ppm: 214.8, 206.3, 171.5, 166.5, 146.0, 132.7, 129.6, 128.3, 111.1, 84.1, 82.9, 82.3, 62.8, 52.7, 52.4, 50.5, 45.2, 42.5, 40.8, 36.6, 35.1, 34.1, 32.6, 28.9, 28.0, 23.5, 20.7, 13.2.

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