

# Synthesis of B-Ring-Modified Steroids through $\text{BF}_3$ -Promoted Rearrangement/Substitution of 6 $\beta$ -Hydroxy-5,19-cyclosteroids

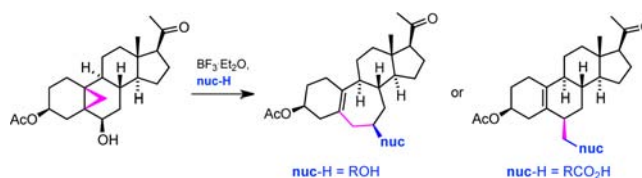
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Received June 4, 2012

## ABSTRACT



The  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -promoted reaction of 3 $\beta$ -acetoxy-5,19-cyclo-pregnan-6 $\beta$ -ol-20-one with different nucleophiles was investigated. B-homo steroids (3 $\beta$ -acetoxy-B-homo-6 $\alpha$ - $\beta$ -alkoxy-pregna-5(10)-en-20-ones) were obtained with primary and secondary alcohols, while the reaction with common carboxylic acids selectively afforded the corresponding 3 $\beta$ -acetoxy-6 $\beta$ -(acyloxymethyl)-pregna-5(10)-en-20-ones. The transformations are supposed to proceed via the rearrangement of a cyclopropyl-methyl cation (bicyclobutonium) intermediate, which is regioselectively opened in dependence on the nucleophile employed. The method represents an efficient, diversity-oriented entry to new B-ring-modified steroids, which are of potential pharmaceutical relevance.

As a consequence of their unparalleled biological importance and structural diversity, steroids enjoy a continuing interest in biological and medicinal chemistry.<sup>1</sup> In recent years, unusual steroids with rearranged AB-ring systems such as the cyclocitrinols<sup>2</sup> or the cortistatins<sup>3</sup> have revitalized the interest of chemists in the synthesis of B-homo steroids, only a few of which had been prepared

in the past either by target-oriented synthesis<sup>4</sup> or as components of mixtures resulting from cationic rearrangement processes starting from 19-oxy steroids.<sup>5</sup> In the course of our interest in the synthesis of the cyclocitrinols,<sup>2b</sup> we recently discovered a high yielding access to the B-homo steroid **2** by  $\text{BF}_3$ -mediated acetylation/rearrangement of the 19,5-cyclosteroid **1** (Scheme 1).<sup>6</sup>

The unprecedented efficiency of the formation of **2** now prompted us to also explore the use of the cyclopropylcarbinol **4** as an alternative substrate in related acid or Lewis

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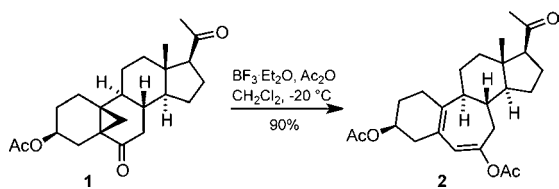
(4) (a) Ringold, H. J. *J. Am. Chem. Soc.* **1960**, *82*, 961–963. (b) Galantay, E.; Weber, H. P. *Experientia* **1969**, *25*, 571–572. (c) Kupchan, S. M.; Findlay, J. W. A.; Hackett, T.; Kennedy, R. M. *J. Org. Chem.* **1972**, *37*, 2523–2525. (d) Groen, M. B.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 169–173.

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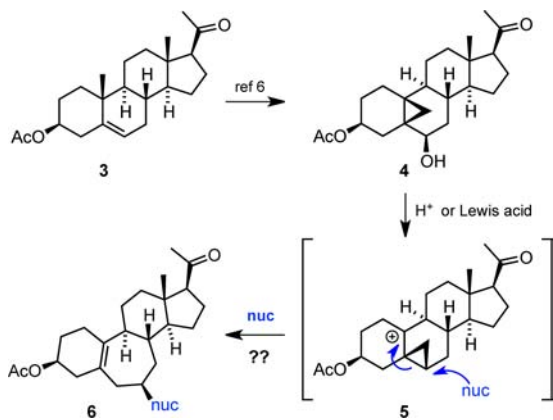
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**Scheme 1.** Synthesis of the *B-homo* Steroid **2** according to Ref 6



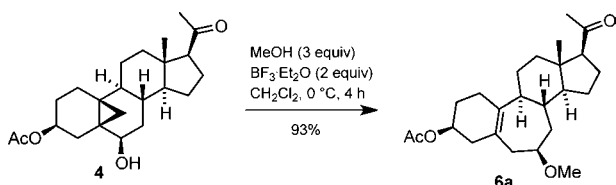
acid mediated transformations.<sup>7</sup> In analogy to the mechanism proposed for the conversion of **1** to **2**<sup>6</sup> we envisioned that a rearranged cyclopropylmethyl cation<sup>5a</sup> of type **5** could possibly react with different nucleophiles to give rise to 6 $\beta$ -substituted *B-homo* steroids of type **6** in a diversity-oriented manner (Scheme 2).

**Scheme 2.** Projected Conversion of the 19,5-Cyclosteroid **4** into *B-homo* Steroids of Type **6**

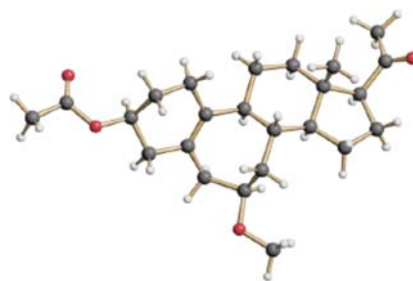


Following the procedures disclosed before,<sup>6,8</sup> the cyclosteroid **4** was synthesized in four steps (25% overall yield) starting from commercially available pregnenolone acetate (**3**). In a first set of experiments we then investigated the reaction of **4** with methanol as a nucleophile. Using CH<sub>2</sub>Cl<sub>2</sub> as a solvent and an excess of BF<sub>3</sub>·Et<sub>2</sub>O as a Lewis acid, we were pleased to find that the envisioned reaction indeed proceeded smoothly at 0 °C to give the methoxy-substituted product **6a** in 93% yield with virtually complete stereoselectivity (Scheme 3).

**Scheme 3.** Conversion of **4** into the *B-homo* Steroid **6a**



Other solvents such as acetonitrile, THF, or 2-methyl-THF were not effective (formation of complex mixtures). Best results were obtained in CH<sub>2</sub>Cl<sub>2</sub> using 2 equiv of BF<sub>3</sub>·Et<sub>2</sub>O and 3 equiv of MeOH. An excess of MeOH (in relation to BF<sub>3</sub>·Et<sub>2</sub>O) proved to be beneficial to avoid the formation of unseparable mixtures. The structure (constitution and relative configuration) of **6a** was unambiguously confirmed by X-ray crystal structure analysis (Figure 1).



**Figure 1.** Structure of the *B-homo* steroid **6a** in the crystal.

Having identified efficient and reliable conditions for the preparation of the methoxy derivative **6a** we next probed the scope of the method employing a set of different nucleophiles (always using **4** as the substrate). The results shown in Figure 2 reveal the formation of the expected products (of type **6**) with a seven-membered ring B in moderate to high yields. Related products (i.e., the esters **6g** and **6h**) were also obtained when acetic or trifluoroacetic anhydride were used instead of an alcohol. In all cases a single diastereomer was observed, and the similarity of the NMR spectra suggested all products belong to the same configurational series (6 $\alpha$ - $\beta$ ) as **6a**.

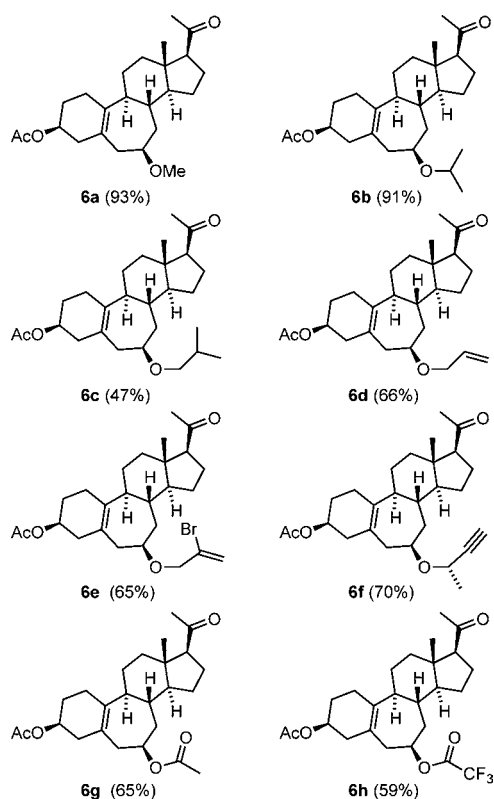
Having so far observed a seemingly general transformation pattern (Figure 2), we were surprised to find that the reaction outcome was completely different when formic acid was used instead of an alcohol in the BF<sub>3</sub>·Et<sub>2</sub>O-mediated reaction of **4**.

In this case, the 6 $\beta$ -formyloxymethyl-substituted 19-nor-steroid **7a** was isolated in 85% isolated yield (Scheme 4). Again, the NMR-based structural assignments were confirmed by X-ray crystallography (Figure 3).

Besides formic acid, acetic acid, methanesulfonic acid, and *tert*-BuOH also gave rise to the corresponding 6-substituted 19-nor-steroids of type **7** in the BF<sub>3</sub>·Et<sub>2</sub>O-mediated reaction of **4** under the standard conditions (Figure 4).

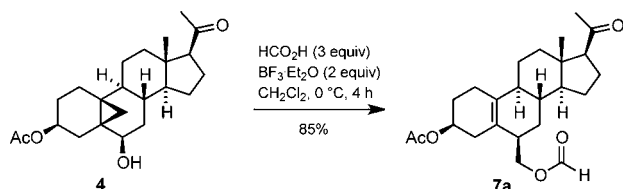
Treatment of **4** with BF<sub>3</sub>·Et<sub>2</sub>O in the presence of some other nucleophilic reagents (allyl-TMS, KSCN, and TMS-N<sub>3</sub>) afforded the rearranged alcohol **7e** (in up to 76% isolated yield) as the sole major product after quenching the reaction mixture with water. Attempts to react **4** with amines, phthalimide, diethyl malonate, or ferrocene only led to the formation of unseparable mixtures.

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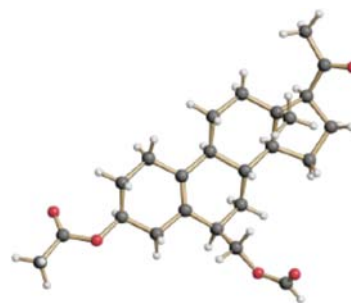
**Figure 2.** Preparation of *B-homo* steroids of type **6** by reaction of **4** with primary or secondary alcohols in the presence of  $\text{BF}_3$  or by heating **4** in neat  $\text{Ac}_2\text{O}$  or  $(\text{TfAc})_2\text{O}$ . Conditions:  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (2 equiv), ROH or  $(\text{RCO})_2\text{O}$  (3 equiv),  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 2–3 h. Isolated yields given in parentheses. For **6e**, reaction performed at  $-78^\circ\text{C}$  (2 h) and  $-30^\circ\text{C}$  (30 min).

**Scheme 4.** Formation of the 6-Substituted 19-*nor* Steroid **7a** by  $\text{BF}_3$ -Mediated Reaction of **4** with Formic Acid

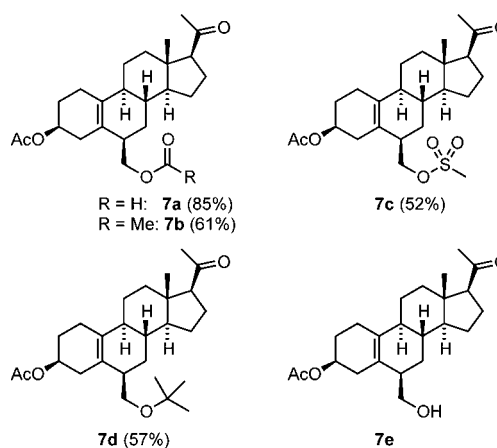


Besides a variety of *O*-nucleophiles, which reliably afforded rearranged steroids of type **6** or **7**, respectively, in a highly regio- and stereoselective manner under the Lewis acid mediated conditions (Figures 2 and 4), we identified anisole as a suitable *C*-nucleophile giving rise to the arylated *B-homo* steroid **6i** in good yield as a 1:5 mixture of *ortho/para*-isomers (Scheme 5). Of note, the use of phenol resulted in the formation of a mixture of *C*- and of *O*-substituted products (of type **6**).

The mechanistic rationalization of the observed selectivities remains, at least in part, speculative (Scheme 6).

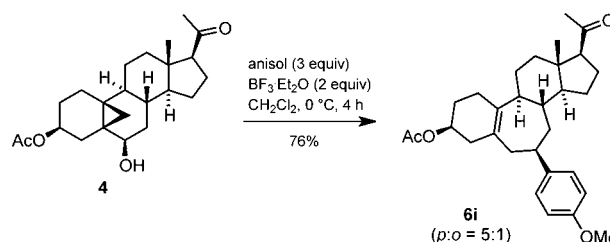


**Figure 3.** Structure of the  $6\beta$ -formyloxymethyl-substituted 19-*nor* steroid **7a** in the crystalline state.



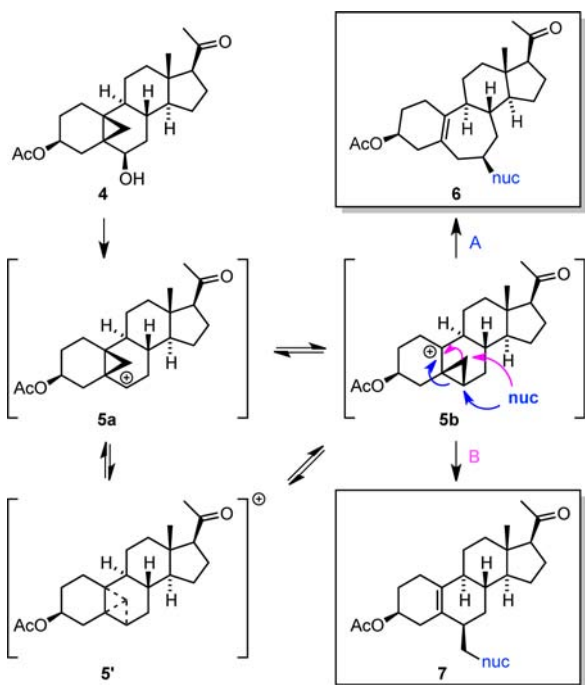
**Figure 4.** Preparation of  $6\beta$ -oxymethyl-substituted 19-*nor* steroids of type **7** by reaction of **4** with  $\text{HCO}_2\text{H}$ ,  $\text{AcOH}$ ,  $\text{MeSO}_3\text{H}$ , or *tert*BuOH in the presence of  $\text{BF}_3$ . Conditions:  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (2 equiv), ROH (3 equiv),  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 2–3 h. Isolated yields given in parentheses. **7e** was obtained (after aqueous workup) upon replacement of ROH by allyl-TMS (76%), KSCN (42%), or TMS- $\text{N}_3$  (35%).

**Scheme 5.** Formation of the Arylated *B-homo* Steroid **6i** by  $\text{BF}_3$ -Mediated Reaction of **4** with Anisole



We assume the transformation of **4** to products of type **6** or **7** being initiated by the ( $\text{BF}_3$ -induced) formation of a cationic intermediate (**5a**) which is in equilibrium with

**Scheme 6.** Proposed Mechanistic Pathway



the rearranged cation **5b** probably through a bicyclobutonium-type<sup>9</sup> intermediate **5'**. While the formation of *B*-*homo* steroids of type **6** through attack of the nucleophile according to pathway A (Scheme 6) was in accordance with our expectations, the change of the reaction pathway in certain cases (to give compounds of type **7** according

(9) See, for instance: Olah, G. K.; Prakash, S.; Rasul, G. *J. Am. Chem. Soc.* **2008**, *130*, 9168–9172 and references cited therein.

(10) In some experiments, especially in the presence of traces of water, the reaction of **4** with acetic acid (Figure 4) afforded **6g** instead of **7b** (for unknown reasons). However, the reaction of **4** with formic acid to give **7a** proved to be fully reproducible.

to pathway B) deserves notice. The latter pathway seems to be preferred in the case of sterically more hindered nucleophiles (e.g., *tert*-butanol). However, we have no explanation for why the nucleophilic attack of the carboxylate (and mesylate) anions (or their  $\text{BF}_3$  complexes) follows either pathway A or pathway B, in subtle dependence on the reaction conditions.<sup>10</sup> Of note, the rearrangement of the initial cation **5a** only takes place at  $-20\text{ }^\circ\text{C}$  or above. At lower temperatures ( $-40\text{ }^\circ\text{C}$ ), treatment of **4** with MeOH in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (compare Scheme 3) afforded the corresponding methyl ether resulting from MeOH attack at the  $\beta$ -face of **5a**. Treatment of **6g** with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in  $\text{CH}_2\text{Cl}_2$  in the presence of MeOH did not result in any conversion. This at least indicates that the (thermodynamically less stable)<sup>11</sup> product **6g** is not reconverted into a cationic species under the reaction conditions.

In conclusion, we have developed efficient protocols for the synthesis of new ring-B-modified steroids starting from **4** as a readily available precursor. Due to the operational simplicity the method might find future exploitation in the preparation of compound libraries in the context of pharmaceutical research.

**Acknowledgment.** This work was supported by the Universität zu Köln and the Fond der Chemischen Industrie. We thank Dr. Niels Schlörner, University of Cologne, for his help concerning NOESY NMR spectra.

**Supporting Information Available.** Detailed experimental procedures, characterization data, and copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of all new compounds. X-ray crystallographic data for **6a** and **7a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(11) According to MM3 calculations (Maestro), **6** is by  $43\text{ kJ mol}^{-1}$  less stable than its isomer **7** (for nuc = OMe).

The authors declare no competing financial interest.