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Synthesis of B-Ring-Modified Steroids through BF_3-Promoted Rearrangement/Substitution of 6β-Hydroxy-5,19-cyclosteroids

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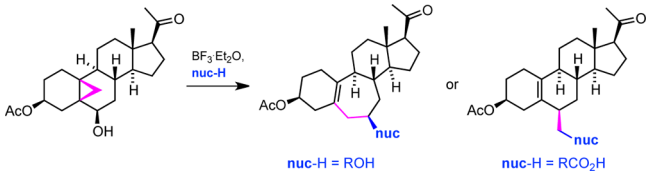
ABSTRACT



The $BF_3 \cdot Et_2O$-promoted reaction of 3β-acetoxy-5,19-cyclo-pregnan-6β-ol-20-one with different nucleophiles was investigated. B-*homo* steroids (3β-acetoxy-B-homo-6a-β-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 3β-acetoxy-6β-(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 unparallelled biological importance and structural diversity, steroids enjoy a continuing interest in biological and medicinal chemistry.[1] In recent years, unusual steroids with rearranged AB-ring systems such as the cyclocitrinols[2] or the cortistatins[3] 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[4] or as components of mixtures resulting from cationic rearrangement processes starting from 19-oxy steroids.[5] In the course of our interest in the synthesis of the cyclocitrinols,[2b] we recently discovered a high yielding access to the B-*homo* steroid **2** by BF_3-mediated acetylation/rearrangement of the 19,5-cyclosteroid **1** (Scheme 1).[6]

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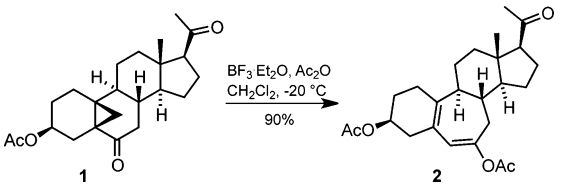
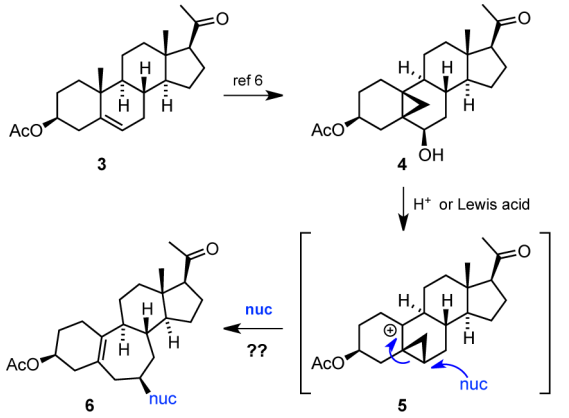
Scheme 1. Synthesis of the B-*homo* Steroid **2** according to Ref 6



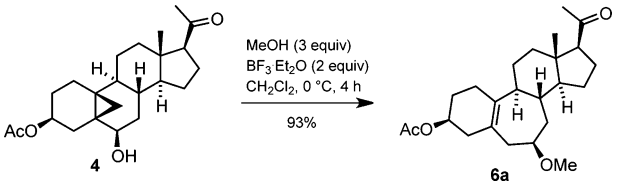
acid mediated transfomations.[7] In analogy to the mechanism proposed for the conversion of **1** to **2**[6] we envisioned that a rearranged cyclopropylmethyl cation[5a] of type **5** could possibly react with different nucleophiles to give rise to 6aβ-substituted B-*homo* steroids of type **6** in 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,[6,8] 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_2Cl_2 as a solvent and an excess of $BF_3 \cdot Et_2O$ 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 acetontrile, THF, or 2-methyl-THF were not effective (formation of complex mixtures). Best results were obtained in CH_2Cl_2 using 2 equiv of $BF_3 \cdot Et_2O$ and 3 equiv of MeOH. An excess of MeOH (in relation to $BF_3 \cdot Et_2O$) 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).

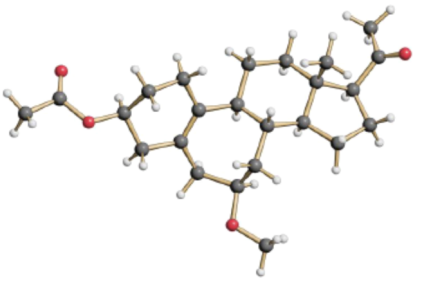


Figure 1. Structure of the B-*homo* steroid **6a** in the crystal.

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 (6a-β) 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 $BF_3 \cdot Et_2O$-mediated reaction of **4**.

In this case, the 6β-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 $BF_3 \cdot Et_2O$-mediated reaction of **4** under the standard conditions (Figure 4).

Treatment of **4** with $BF_3 \cdot Et_2O$ in the presence of some other nucleophilic reagents (allyl-TMS, KSCN, and TMS-N_3) 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.

(8) (a) Heusler, K.; Kalvoda, J. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 525–596. (b) Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501–526.

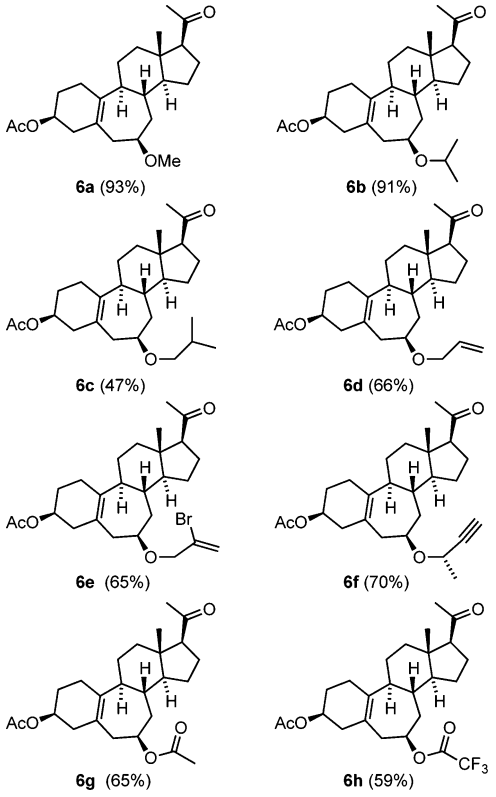
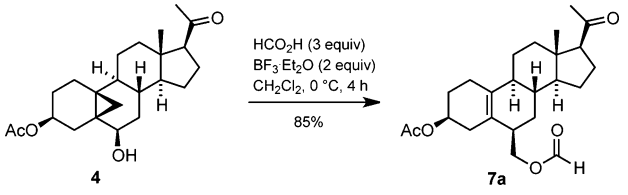


Figure 2. Preparation of B-*homo* steroids of type **6** by reaction of **4** with primary or secondary alcohols in the presence of BF_3 or by heating **4** in neat Ac_2O or $(TFAc)_2O$. Conditions: $BF_3 \cdot Et_2O$ (2 equiv), ROH or $(RCO)_2O$ (3 equiv), CH_2Cl_2, 0 °C, 2−3 h. Isolated yields given in parentheses. For **6e**, reaction performed at −78 °C (2 h) and −30 °C (30 min).

Scheme 4. Formation of the 6-Substituted 19-*nor* Steroid **7a** by 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).

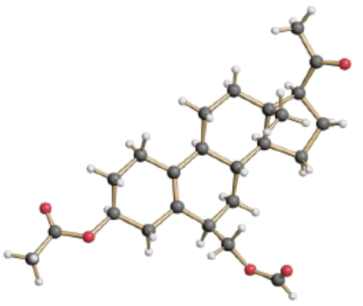


Figure 3. Structure of the 6β-formyloxymethyl-substituted 19-*nor* steroid **7a** in the crystalline state.

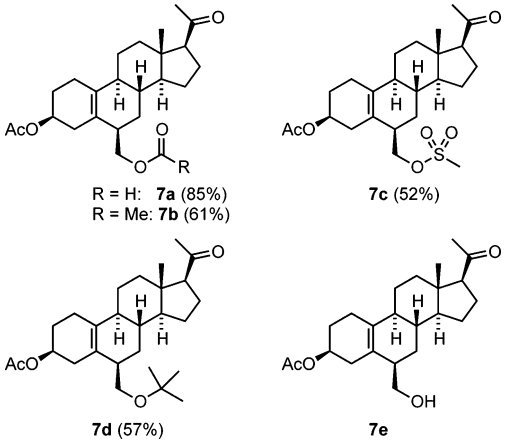
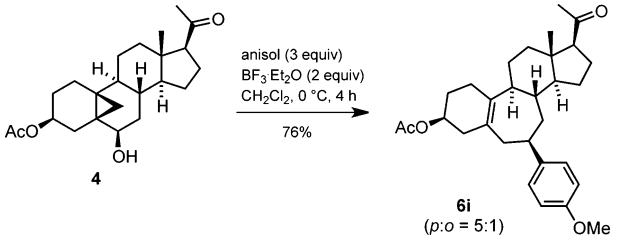


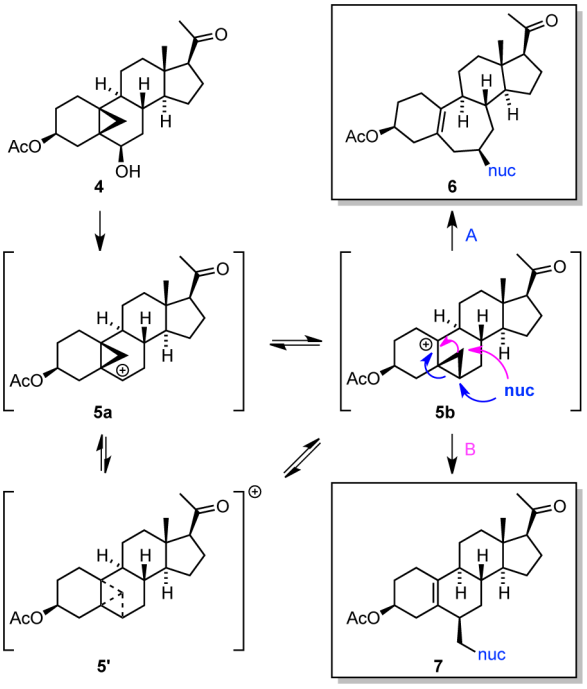
Figure 4. Preparation of 6β-oxymethyl-substituted 19-*nor* steroids of type **7** by reaction of **4** with HCO_2H, AcOH, $MeSO_3H$, or *tert*BuOH in the presence of BF_3. Conditions: $BF_3 \cdot Et_2O$ (2 equiv), ROH (3 equiv), CH_2Cl_2, 0 °C, 2−3 h. Isolated yields given in parentheses. **7e** was obtained (after aqueous workup) upon replacement of ROH by allyl-TMS (76%), KSCN (42%), or TMS-N_3 (35%).

Scheme 5. Formation of the Arylated B-*homo* Steroid **6i** by 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 (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[9] 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 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 BF_3 complexes) follows either pathway A or pathway B, in subtle dependence on the reaction conditions.[10] Of note, the rearrangement of the initial cation **5a** only takes place at −20 °C or above. At lower temperatures (−40 °C), treatment of **4** with MeOH in the presence of $BF_3 \cdot Et_2O$ (compare Scheme 3) afforded the corresponding methyl ether resulting from MeOH attack at the β-face of **5a**. Treatment of **6g** with $BF_3 \cdot Et_2O$ in CH_2Cl_2 in the presence of MeOH did not result in any conversion. This at least indicates that the (thermodynamically less stable)[11] 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.

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Supporting Information Available. Detailed experimental procedures, characterization data, and copies of ^1H and ^{13}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.

(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.

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

The authors declare no competing financial interest.