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A CONCISE TOTAL SYNTHESIS OF C(14)-C(15) METHYLENE-BRIDGED EQUILENIN DERIVATIVES

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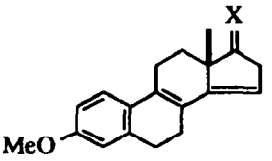
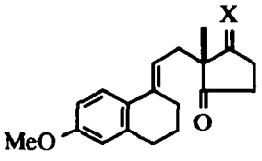
Summary. A five-step reaction sequence including hydroxyl group-assisted cyclopropanation, C(17)-oxidation, B-ring aromatization, C(17)-reduction, and methyl ether cleavage has been devised to convert **2** into **12**. The synthesis of **19** took advantage of a facile isomerization of vinyl(benzyl)cyclopropane derivatives **6-11** into the corresponding β-bridged analogues **13-18** over molecular sieves.

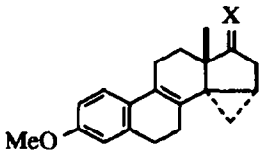
Continuing work in these laboratories devoted to the discovery of novel D-ring modified steroid hormone analogues[1] with therapeutic potential has led us to consider C(14)-C(15) methylene-bridged derivatives as promising target structures. The purpose of this communication is to describe a short stereocontrolled approach to C(14)α-C(15)α methylene-bridged equilenin-type steroids, together with a novel vinyl(benzyl)cyclopropane-vinyl(benzyl)cyclopropane isomerization reaction by which C(14)β-C(15)β methylene-bridged derivatives are accessible from the corresponding α-bridged congeners.



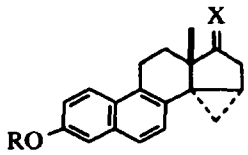
1 X= α-H, β-OH
2 X= β-H, α-OH



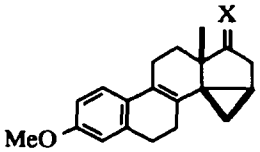
3 X= O
4 X= α-H, β-OH
5 X= β-H, α-OH



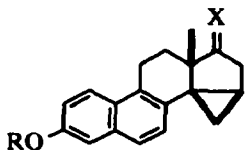
6 X= β-H, α-OH
7 X= O
8 X= α-H, β-OH



9 R= Me; X= O
10 R= Me; X= α-H, β-OH
11 R= Me; X= β-H, α-OH
12 R= H; X= α-H, β-OH



13 X= α-H, β-OH
14 X= β-H, α-OH
15 X= O



16 R= Me; X= O
17 R= Me; X= α-H, β-OH
18 R= Me; X= β-H, α-OH
19 R= H; X= α-H, β-OH

During the planning stage, previously reported C(17)-epimeric alcohols **1** and **2** were recognized as particularly attractive intermediates[2] for the synthetic problem at hand. Implementation of enantio- and diastereoselective enzymatic carbonyl group reduction steps (**3**→**4**, **3**→**5**) into the classic Torgov protocol provided enantiomerically pure, epimeric starting materials **4** and **5** in analogy to literature precedent.[2] Guided by the characterization of 14,15α-methylenestra-1,3,5(10)-triene-3,17β-diol as a most interesting steroid derivative with estrogenic activity when administered orally,[3] we first embarked on a set of transformations in the 17α-series.

Fortunately enough, cyclization of the secosteroid **5** delivered a crude product **2** sufficiently pure for direct use in the crucial cyclopropanation step. In practice, hydroxyl group-directed methylenation proceeded gratifyingly well upon exposure of **2** to a Simmons-Smith reagent prepared in dimethoxyethane according to the protocol of LeGoff.[4] After purification by chromatography on silica gel (hexane/ethyl acetate, 3:2, gradient elution), the pentacyclic key intermediate **6** was obtained in 71% overall yield for the two steps. Storage over an extended period of time or attempted purification by chromatography on silica gel of the cyclization product **2** furnished **6** in less satisfactory overall yields. At this point, our synthetic scheme called for hydroxyl group inversion at C(17). Toward this end, **6** was oxidized utilizing methodology (DMSO, NEt_3, $Py{\cdot}SO_3$, 22°C; 88%) developed by Parikh and Doering.[5] Reduction (MeOH, THF, $CeCl_3{\cdot}7H_2O$, $NaBH_4$, -30°C) of the resulting carbonyl derivative **7** gave rise to a mixture of C(17)-epimeric alcohols **6** and **8** in a ratio of 1:1.6, which was readily separated by chromatography on silica gel (hexane/ethyl acetate, 3:2, gradient elution). In an effort to arrive at B-ring aromatic derivatives, a solution of ketone **7** in toluene was treated with DDQ at room temperature for 2.5 hours. From the purified dehydrogenation product **9** (92%), two epimeric alcohols **10** (59%) and **11** (37%) became available by standard hydride reduction (MeOH, THF, $CeCl_3{\cdot}7H_2O$, $NaBH_4$, -25°C). The final deprotection (toluene, DIBAH, 120°C, 4h) occurred without complication to afford **12** in 77% yield. Contrary to the smooth methylenation observed for **2**, the epimeric cyclization product **1** was reluctant to undergo hydroxyl group-assisted cyclopropanation in a synthetically acceptable manner, apparently as a consequence of a prohibitively large distance between the C(14)-C(15) π-system and a quasi-equatorially C(17)-anchored Simmons-Smith reagent. Since various complementary methylenation procedures were equally unrewarding, the need arose for a conceptually different entry into this class of compounds. To our delight, unidirectional isomerization[6] of trans CD-ring fused products **6-11** into the elusive, less strained β-bridged diastereoisomers **13-18** proved to be feasible in yields ranging from 70-87%. Thus, complete conversion of **7**, for example, in dichloromethane over activated molecular sieves (4Å, Merck) took place during 48 hours at room temperature to give **15** in 87% yield. Although molecular sieves also promoted the transformation of **12** into **19**, the recovery of **19** was poor. This difficulty was circumvented by postponing methyl ether cleavage to the isomerization step, **10**→**17**→**19**.[7]

References and Notes

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7. Physical data for selected steroids are as follows. **6**: mp 167-168°C (ether/pentane); $[\alpha]_D^{22}$ -82.5° (c 0.52, CH_2Cl_2). **7**: mp 146-148°C (acetone/hexane); $[\alpha]_D^{22}$ -102.7° (c 0.51, CH_2Cl_2). **10**: mp 137-138°C (acetone/hexane); $[\alpha]_D^{22}$ -57.6 (c 0.51, CH_2Cl_2). **12**: mp 199-200°C (acetone/hexane); $[\alpha]_D^{22}$ -34.3° (c 0.52, CH_3OH). **19**: mp 208-210°C (acetone/hexane); $[\alpha]_D^{22}$ +45.5° (c 0.50, CH_3OH).

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