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A CYCLOADDITION ROUTE TO 14-HYDROXYSTEROIDS

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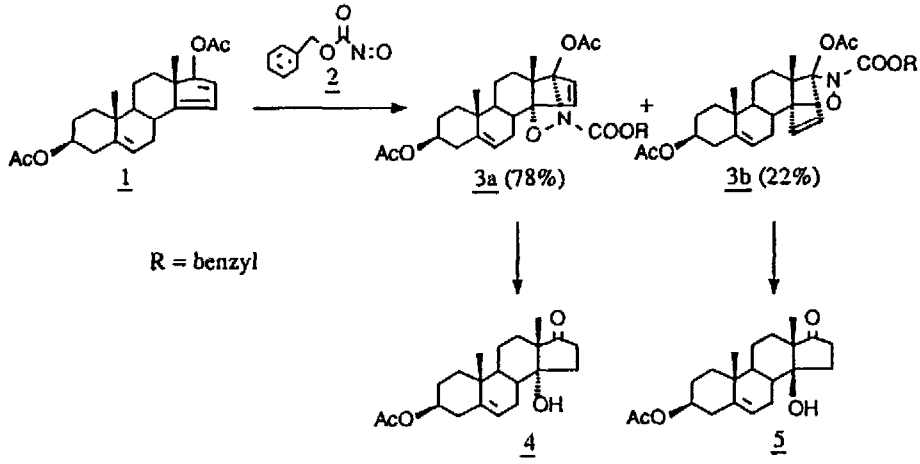
SUMMARY: Steroidal 14,16-dienolacetates are stereoselectively converted to either 14ß- or 14α-hydroxy steroids by a reaction sequence based on [4+2] cycloaddition with benzyl nitrosoformate.

Although chemical[1] and microbiological[2] procedures exist to introduce a 14-hydroxy group into the steroid skeleton, there is an obvious need for more general methodology and for a better control of stereoselectivity.

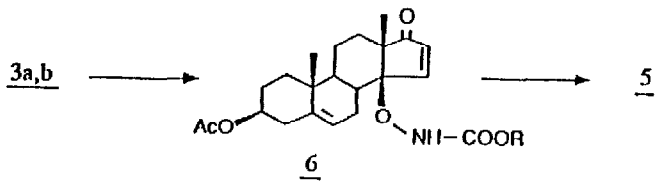
Benzyl nitrosoformate **2** generated *in situ* by tetrabutyl ammonium periodate oxidation of benzyl-*N*-hydroxycarbamate[3] regioselectively added to dienolacetate **1** with formation of two stereoisomeric cycloadducts **3a,b**. Surprisingly, α-adduct **3a**[5] turned out to be the major component - a result in marked contrast to the exclusive formation of ß-face adducts from type **1** dienes and various other dienophiles[4].



Obviously, chromatographic separation of **3a,b** and hydrogenation would lead to 14α-hydroxy androstane **4** and, in a less economic fashion, to 14ß-hydroxy isomer **5**. However, the nonstereoselective cycloaddition step made this approach unattractive.

The procedure became noteworthy after we found experimental conditions to transform the total isomeric mixture **3a,b** to either 14ß-hydroxy derivative **5** or to 14α-hydroxy epimer **4**.

Upon heating the crude reaction product **3a,b** in methanol (10 h, reflux) both isomers underwent conversion to 14ß-oximino substituted enone **6**[5] whic by palladium-catalyzed hydrogenation was transformed to 14ß-hydroxy androstane **5** in an excellent overall yield (87 % based on **1**).



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As a next step, we separated **3a,b** by silicagel chromatography in order to subject both isomers individually to solvolytic conditions.

α-Adduct **3a** reacted very sluggishly in methanol requiring a 10 hour reflux period for full transformation to enone **6**. Pure ß-adduct **3b**[5] rapidly (methanol, reflux, 20 min) underwent conversion to a mixture of **6** and α-adduct **3a**

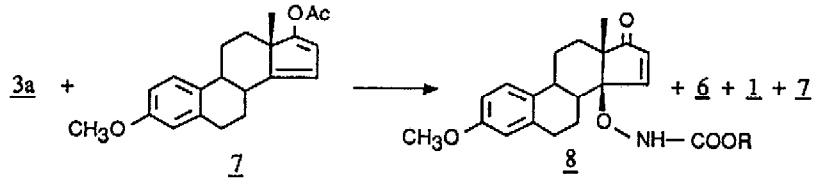
There are two conclusions to be drawn from these experiments:

a. chemoselectivity: α-adduct **3a** is remarkably stable towards methanolysis whereas ß-adduct **3b** is readily solvolyzed with formation of enone **6**. The formation of **6** from α-adduct **3a** is explained by a retro Diels-Alder process and recycloaddition to give an equilibrium mixture **3a,b** from which **3b** is removed by methanolysis.

b. thermodynamic stability: the observation of products **6** and **3a** after short methanol treatment of pure **3b** clearly demonstrates that ß-face adduct **3b**, besides being rapidly solvolyzed, isomerizes with formation of α-adduct **3a**. In order to exclude the solvolytic process, we heated isomer **3b** in toluene (20 min, 80 °C) obtaining a mixture **3a,b** in a ratio of 9:1 in favor of the α-isomer **3a**.

With these results in mind it became quite obvious how to proceed experimentally in order to obtain either isomer in almost quantitative yield. As described above, methanolysis of a cycloadduct mixture **3a,b** will lead to 14ß-hydroxy derivative **5** via intermediate **6**, irrespective of the ratio **3a:3b**. Alternatively, 14α-hydroxyandrostane **4** is obtained by a normal work-up of cycloaddition product **3a,b** crystallization of which from diisopropyl ether giving a first crop (60 %) of pure α-adduct **3a**. The mother liquor is concentrated and heated shortly in toluene (20 min, 80 °C) to allow equilibration. Subsequent crystallization and chromatography yield another 29 % of **3a** which by palladium-catalyzed hydrogenation in ethanol is smoothly converted into 14α-hydroxy androstane **4**.

In order to make sure that the formation of 14ß-oximino substituted enone **6** from α-adduct **3a** was not the result of an unknown intramolecular rearrangement, we repeated the process of methanolysis with **3a** in the presence of a competing diene **7**. The detection of enone **8**[5] in the product mixture clearly supports the mechanistic interpretation given above.



(molar ratio 3a : 7 = 1 : 1)

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5. All compounds were characterized by nmr (300 MHz), ir, uv and mass spectra.

   3a: m.p. 145-147°C (from ethyl acetate/diisopropyl ether), $[\alpha]_D^{20}$ -60.9° ($CHCl_3$, c = 0.505). nmr ($CDCl_3$): δ = 0.95 ppm (s, 3H, H-18), 1.01 (s, 3H, H-19), 1.96 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 4.59 (m, 1H, H-3), 5.07 (d, J = 11 Hz, 1H, benzylic), 5.16 (d, J = 11 Hz, 1H, benzylic), 5.43 (m, 1H, H-6), 6.22 (d, J = 5.5 Hz, 1H, H-16), 6.90 (d, J = 5.5 Hz, 1H, H-15), 7.34 (m, 5H, aromatic).

   3b: oil, nmr ($CDCl_3$): δ = 1.03 ppm (s, 3H, H-19), 1.17 (s, 3H, H-18), 3.03 (s, 6H, $COCH_3$), 4.59 (m, 1H, H-3), 5.14 (s, 2H, benzylic), 5.43 (m, 1H, H-6), 6.31 (d, J = 5.5 Hz, 1H, H-16), 6.68 (d, J = 5.5 Hz, 1H, H-15), 7.33 (m, 5H, aromatic).

   6: m.p. 183-184°C (from ethyl acetate/diisopropyl ether), $[\alpha]_D^{20}$ -47.3° ($CHCl_3$, c = 0.505). nmr ($CDCl_3$): δ = 1.00 ppm (s, 3H, H-19), 1.12 (s, 3H, H-18), 2.03 (s, 3H, $COCH_3$), 4.58 (m, 1H, H-3), 5.04 (d, J = 11 Hz, 1H, benzylic), 5.13 (d, J = 11 Hz, 1H, benzylic), 5.46 (m, 1H, H-6), 6.31 (d, J = 5.5 Hz, 1H, H-16), 6.78 (s, 1H, NH), 7.34 (m, 5H, aromatic), 7.49 (d, J = 5.5 Hz, 1H, H-15).

   8: m.p. 178-179°C (from methanol), $[\alpha]_D^{20}$ +86.6° ($CHCl_3$, c = 0.51), nmr ($CDCl_3$): δ = 1.14 ppm (s, 3H, H-18), 3.77 (s, 3H, OCH_3), 5.09 (d, J = 11 Hz, 1H, benzylic), 5.18 (d, J = 11 Hz, 1H, benzylic), 6.31 (d, J = 4 Hz, 1H, H-16), 6.62 (m, 1H, H-4), 6.71 (m, 1H, H-2), 6.92 (s, 1H, NH), 7.10 (d, J = 4 Hz, 1H, H-1), 7.33 (m, 6H, aromatic and H-15).

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