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A FACILE PREPARATION OF ECDYSONE SIDE CHAIN BY UTILIZING FURAN DERIVATIVE

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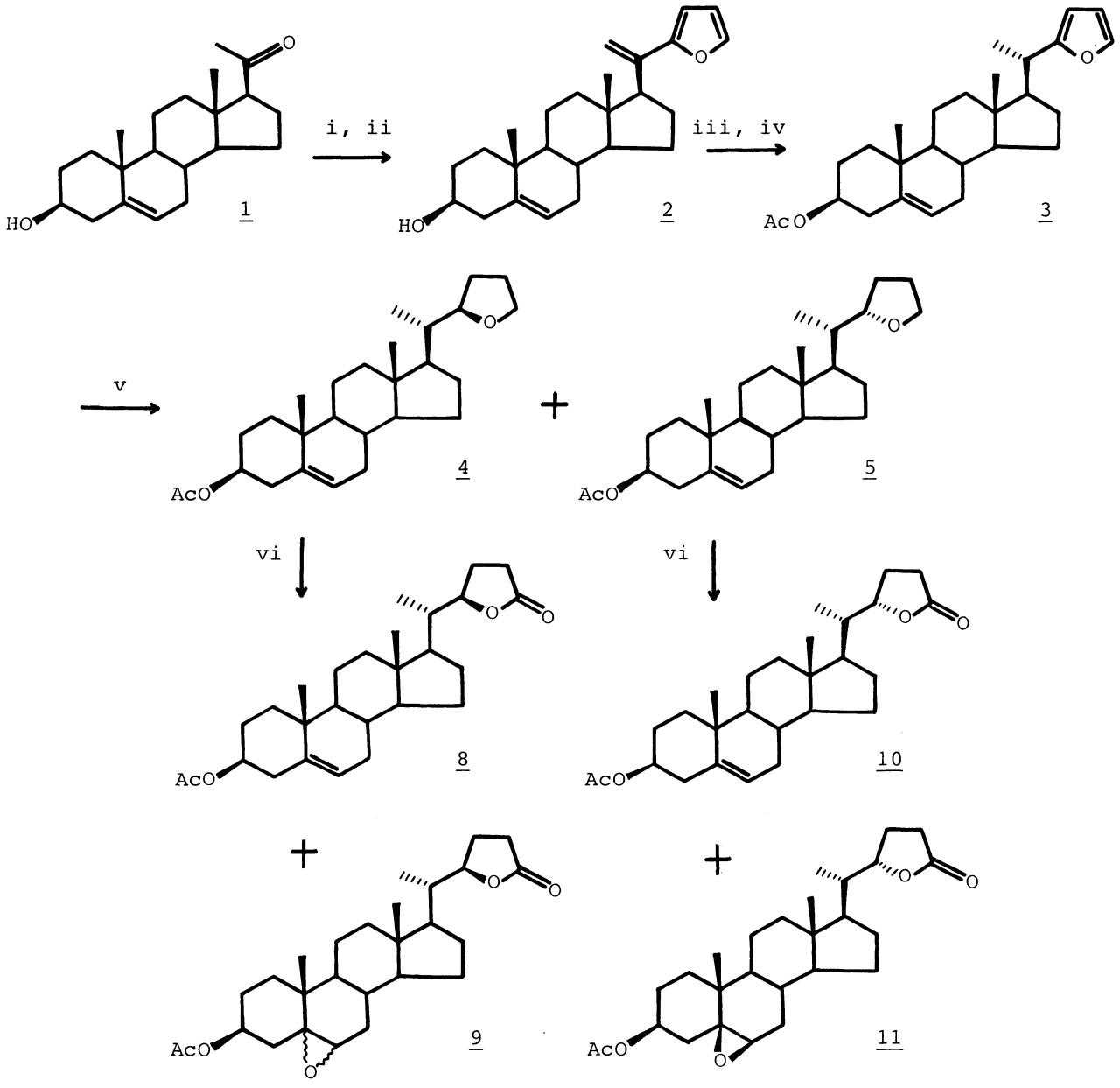
Construction of the ecdysone side chain starting from pregnenolone was achieved *via* a furan derivative. Reduction of the olefinic-furan over palladium-carbon afforded the hydrogenated furan derivative with the desired stereochemistry at C-20, exclusively, whose subsequent reduction over rhodium-alumina, followed by ruthenium tetroxide oxidation, gave the lactones in a ratio of ca. 1:1. Grignard reaction of both lactones with methylmagnesium bromide led to the synthesis of the triols having ecdysone-type side chains, respectively.

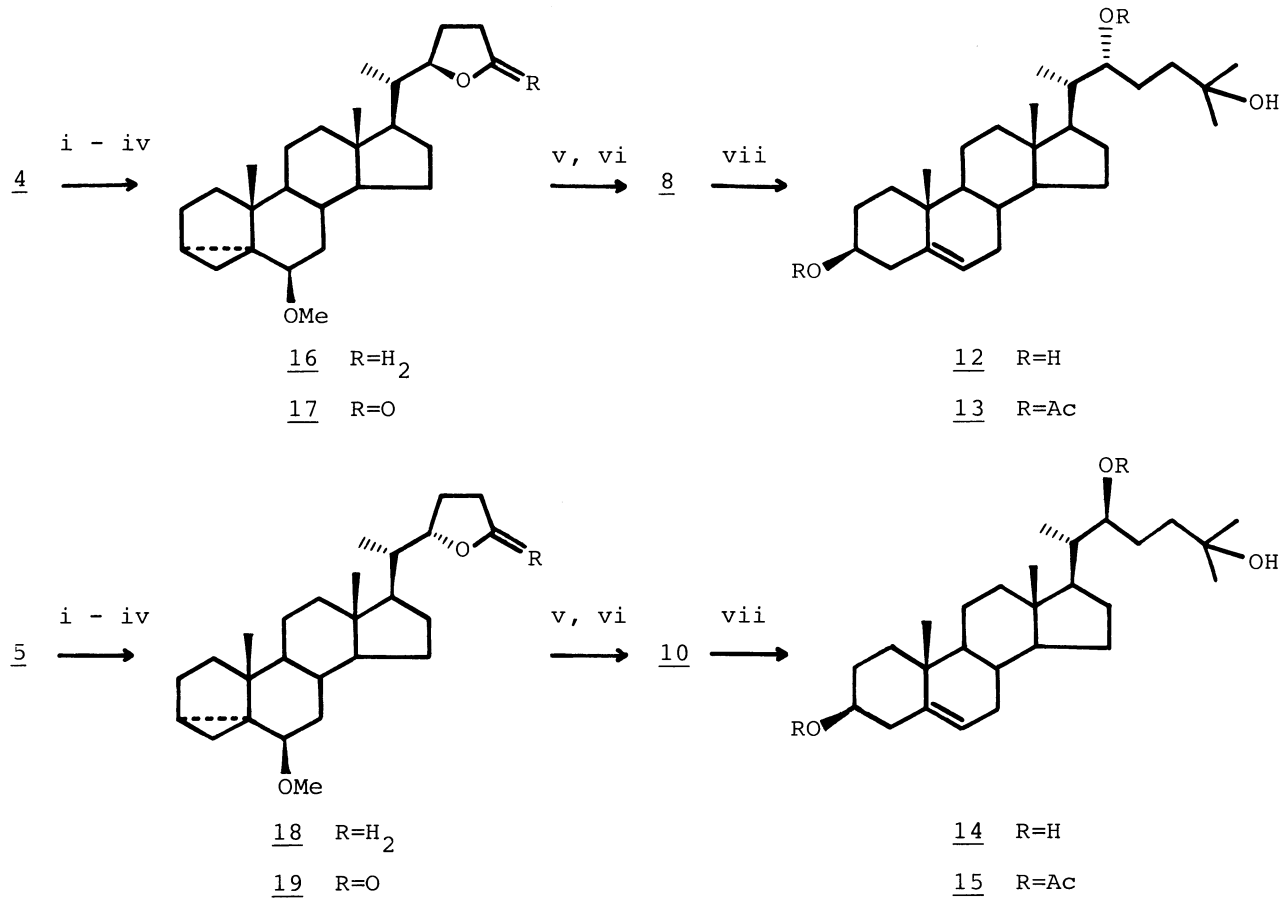
As a part of our continuing exploration of the synthesis[1] and reactions[2] of furan derivatives, we have investigated a facile construction of ecdysone side chain starting from pregnenolone, and here wish to report a simple synthetic route to 12 utilizing a furan derivative as a key intermediate.

The reaction of pregnenolone (1) with 2-lithiofuran, followed by dehydration of the resulting alcohol with p-toluenesulfonic acid afforded the olefinic-furan (2), whose catalytic reduction over palladium-carbon followed by acetylation with acetic anhydride and pyridine yielded the furan derivative (3)[3] with the desired stereochemistry at the C-20 position, exclusively, in 97% yield from 1. The furan ring of 3 was further reduced over rhodium on alumina in ethyl acetate for 1 h under medium pressure (4.2 atm) of hydrogen to give the tetrahydrofuran derivatives (4 and 5) in 50% and 46% yields, respectively. Whereas, the longer reaction time (6 h) in the above reduction led to the formation of the saturated compounds (6 and 7) in 49% and 45% yields, respectively. The conversion of an ether to a corresponding lactone has been known[4] to be achieved by utilization of ruthenium tetroxide oxidation efficiently. Therefore, 4 was subjected to the oxidation to give the desired lactone (8)[5] in 12% yield, together with the epoxide (9) in 48% yield. The same treatment of the ether (5) also afforded the lactone (10)[6] and the epoxide (11) in 10% and 49% yields, respectively. In order to confirm the stereochemistry at the C-22 position of the lactones, the less polar lactone (8) was treated with methylmagnesium bromide to furnish the triol (12) in 85% yield, whose diacetate (13) was identical with an authentic specimen.[7] Therefore, the stereochemistry of the less



i) 2-lithiofuran ii) p-TsOH iii) Pd/C, H_2
iv) Ac_2O, Py v) Rh/Al_2O_3, H_2, 4.2 atm vi) RuO_4

polar lactone (8) was unambiguously determined to have 22-R configuration. On the same treatment as above, the more polar lactone (10) was converted into the triol (14), in 83% yield, whose diacetate (15) was also identical with an authentic sample.[7] However, a ruthenium tetroxide oxidation of the tetrahydrofuran derivatives (4 and 5), which gave the corresponding 5,6-epoxides preferentially, was found to be a crucial step in the above synthesis of ecdysone side chain from pregnenolone although this type of oxidation is a synthetically interesting reaction.[8]



16 R=H_2
17 R=O
12 R=H
13 R=Ac
18 R=H_2
19 R=O
14 R=H
15 R=Ac

i) 10 % KOH ii) p-TsCl, Py iii) MeOH, Py
iv) RuO_4 v) p-TsOH vi) Ac_2O, Py vii) MeMgBr

Thus, 4 was converted into the cyclopropane derivative (16) by a usual manner,[9] whose oxidation with ruthenium tetroxide, followed by acid treatment[10] of the resulting lactone (17), afforded the desired lactone (8) in 69% yield from 4. Similarly, 5 was also converted to 10 via 18 and 19.

Moreover, the saturated steroids (6 and 7), whose stereochemistry at C-22 was deduced by the reduction of the corresponding $\Delta^{5,6}$-derivatives (4 and 5), were also transformed into the ecdysone-type analogues (22[11] and 23[12]), via 20 and 21, in good yields, respectively.

Thus, we could achieve a facile introduction of an ecdysone side chain into 20-keto steroid by using a furan derivative as a key compound.

Further experiments aimed at increasing a stereoselectivity at C-22 are in progress.

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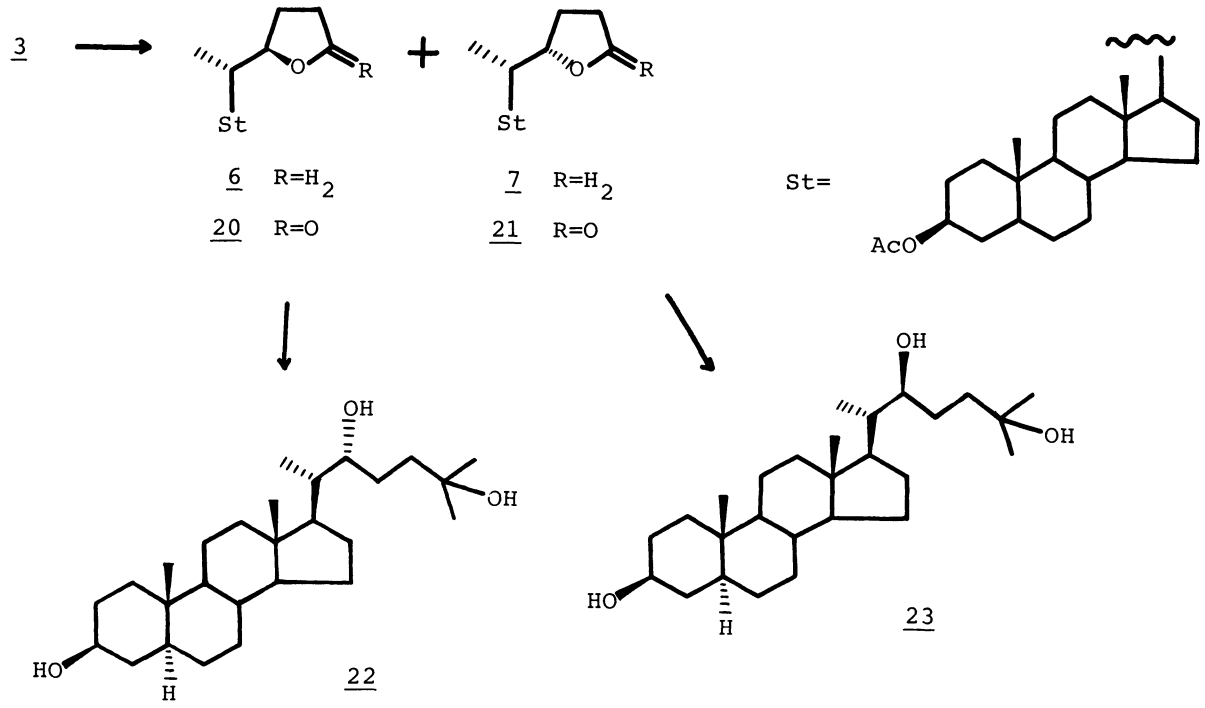

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3) Mp 180 - 181°C (from benzene-hexane); IR ($CHCl_3$), 1730 cm^{-1}; NMR ($CDCl_3$), δ 0.74 (3H, s), 1.03 (3H, s), 1.25 (3H, d, J=7 Hz), 2.02 (3H, s).

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5) Mp 262 - 263°C (from benzene-hexane); IR ($CHCl_3$), 1770, 1730 cm^{-1}; NMR ($CDCl_3$), δ 0.70 (3H, s), 0.84 (3H, s), 0.90 (3H, d, J=7 Hz), 2.02 (3H, s).

6) Mp 245 - 246°C (from benzene-hexane); IR ($CHCl_3$), 1770, 1730 cm^{-1}; NMR ($CDCl_3$), δ 0.66 (3H, s), 0.82 (3H, s), 0.94 (3H, d, J=7 Hz), 2.02 (3H, s).

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11) This compound was characterized as its acetate; IR ($CHCl_3$), 1720 cm^{-1}; NMR ($CDCl_3$), δ 0.67 (3H, s), 0.83 (3H, s), 0.90 (3H, d, J=7 Hz), 1.43 (6H, s), 2.30 (9H, s); $[\alpha]_D$ = +16.0° (c 1.90, $CHCl_3$).

12) IR ($CHCl_3$), 3400 cm^{-1}; NMR ($CDCl_3$), δ 0.66 (3H, s), 0.80 (3H, s), 0.90 (3H, d, J=7 Hz), 1.26 (6H, s); $[\alpha]_D$ = +23.6° (c 0.57, $CHCl_3$).

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