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# A NOVEL SYNTHETIC APPROACH TO THE ECDYSONE SIDE CHAIN VIA FURAN DERIVATIVES

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Summary A New type of synthesis of (22R)-22,25-dihydroxycholesterol and its 22S isomer from pregnenolone by using furan derivatives is reported.

The stereocontrolled introduction[1-6] of a cholesterol-type side chain has been investigated because of a major challenge in steroid chemistry by the importance of natural products containing modified side chains.[7-10] Since we have completed a stereocontrolled total synthesis of 2β,3β,-20β-triacetoxy-5α-pregnan-6-one which constituted a formal total synthesis of 20-hydroxyecdysone[11] we have studied a stereocontrolled transformation of pregnane-type to cholesterol-type steroids and here wish to report a new methodology for introduction of a cholesterol-type side chain by using furan derivatives.

As outlined in Scheme 1, $\Delta^{20(21)}$-furan derivative (2) [i.r. ($CHCl_3$) 1720; n.m.r. ($CCl_4$) 0.58 (3H, s, Me), 1.0 (3H, s, Me), 1.93 (3H, s, MeCO), 2.28 (3H, br s, aromatic Me), 4.9, 5.35, 5.55 (each 1H, each s, olefinic H), 5.85 (1H, m, aromatic H), 6.08 (1H, d, J = 3 Hz, aromatic H); m/e 422 ($M^+$)], prepared from pregnenolone acetate (1) by reaction with 2-lithio-5-methylfuran,[12] followed by exposure to silica gel effecting dehydration and then acetylation, was hydrogenated to give 20S compound (3), mp 179-180°C, [n.m.r. ($CCl_4$) 1.2 (3H, d, J = 7 Hz, Me); m/e 424 ($M^+$)] quantitatively as a single product in stereoselective manner. Ring opening reaction of furan ring in acidic medium and then acetylation afforded diketone (4) [i.r. ($CHCl_3$) 1720, 1710; n.m.r. ($CDCl_3$) 1.1 (3H, d, J = 7Hz, Me), 2.2 (3H, s, Me), 2.69 (4H, br s, 2 x $CH_2$]; m/e 442 ($M^+$)] which was reacted with methyllithium to give alcohol (5) as a single product selectively [i.r. ($CHCl_3$) 1718, 1725; n.m.r. ($CDCl_3$) 1.1 (3H, d, J = 7 Hz, Me), 1.2 (6H, s, 2 x Me)]. Finally, reduction of (5) was carried out under various conditions shown in Table 1 to yield a mixture of 22R (6) and 22S (7). Diacetates (8) and (9) obtained by acetylation of (6) and (7) were identical with the authentic sample derived from (22R)-22,25-dihydroxycholesterol and its 22S isomer[13] by acetylation ($Ac_2O$, pyridine) respectively.

Thus we have devised the simple methodology for transformation of pregnane-type to cholestane-type steroids by using furan derivatives. The remarkable feature of this synthesis is the stereoselective reduction of olefinic furan derivative (2) giving 20S compound (3) because hydrogenation of the double bond between C-20 and adjacent position is puzzling and sometimes lacks stereoselectivity.[2,14,15]

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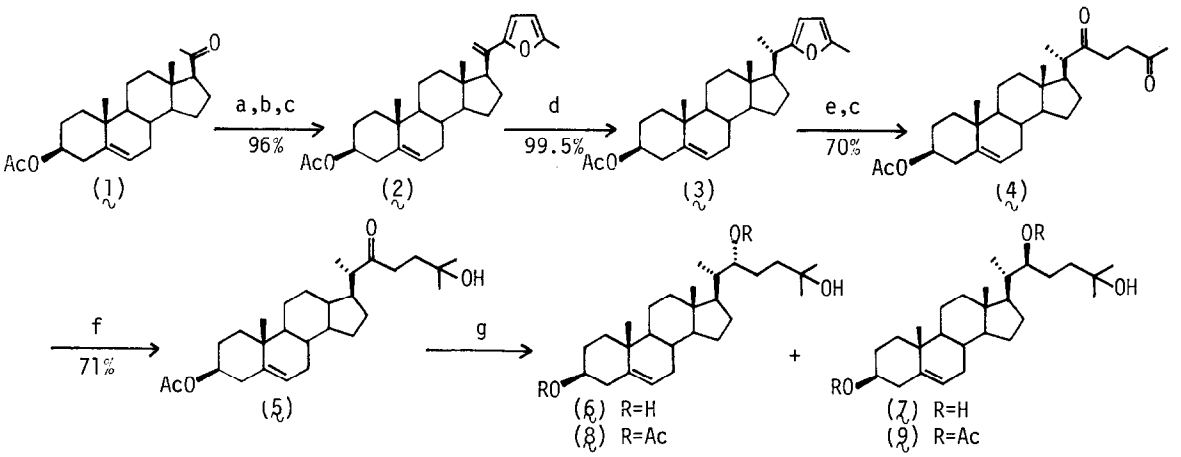
Scheme 1




Reagents a, 2-lithio-5-methlfuran, THF, -78°C. b, silica gel, $CH_2Cl_2$, R.T. c, $Ac_2O$, pyridine, d, $H_2$, 10%Pd-C, benzene, R.T. e, 10%$H_2SO_4$, AcOH, THF, 60°C. f, MeLi, THF, -20°C. g, see Table 1.

Table 1
Reduction of (5)[a]

| Reagent Solvent | Products | |
|---|---|---|
| | Ratio of 22R (8) and 22S (9) | Yield |
| $NaBH_4$-MeOH | 1 : 3 | 85 % |
| $LiAl^+Bu_3H$-THF | 1 : 5 | 80 % |
| $ZnBH_4$-$Et_2O$ | 1 : 2 | 75 % |

a: All the reactions were carried out at room temperature and the products obtained was successively acetylated ($Ac_2O$, pyridine)

References

(1) B. M. Trost and T. R. Verhoeven, J. Am. Chem. Soc., 100, 3435 (1978); (2) D. M. Piatak and J. Wicha, Chem. Rev., 78, 199 (1978); (3) M. Tanabe and K. Hayashi, J. Am. Chem. Soc., 102, 862 (1980); (4) Y.-W. Lee, E. Lee, and K. Nakanishi, Tetrahedron Lett., 21, 4323 (1980); (5) J. S. Temple and J. Schwartz, J. Am. Chem. Soc., 102, 7381 (1980); (6) M. Koreeda, Y. Tanaka, and A. Schwartz, J. Org. Chem., 45, 1172 (1980); (7) B. M. Trost, P. R. Bernstein, and P. C. Funfschilling, J. Am. Chem. Soc., 101, 4378 (1979); (8) P. A. Grieco, T. Takigawa, and D. R. Moore, ibid., 101, 4380 (1979); (9) S. R. Schow and T. C. McMorris, J. Org. Chem., 44, 3760 (1979); (10) M. F. Holick and H. F. DeLuca, Ann. Rev. Med., 25, 349 (1974); (11) T. Kametani, M. Tsubuki, and H. Nemoto. Tetrahedron Lett., 21, 4855 (1980); (12) G. Büchi and H. Wüest, J. Org. Chem., 31, 977 (1966); (13) B. M. Trost and Y. Matsumura, J. Org. Chem., 42, 2036 (1977); (14) E. N. Trachtenberg, C.-Y. Byon, and M. Gut, J. Am. Chem. Soc., 99, 6145 (1977); (15) W. R. Nes, J. Am. Chem. Soc., 100, 999 (1978).

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