Tetrahedron Letters No. 19, pp 1641 - 1644, 1978. 0040-4039/78/0501-1641. $02.00/0.

STEREOCHEMICALLY CONTROLLED SYNTHESIS OF 20-ISOCHOLESTEROL

Masato Koreeda* and Naoyuki Koizumi

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

(Received in USA 24 January 1978; received in UK for publication 23 March 1978)

Cholesterol (20R) is a precursor of pregnenolone in mammalian adrenal cortex.[1] The intermediacy of both (22R)-22-hydroxycholesterol and (20R,22R)-20,22-dihydroxycholesterol in this conversion is well established.[2] Our recent studies with various steroids using a highly purified steroid side chain cleaving enzyme have revealed that the enzyme appears to be more fastidious in its steric requirement at C-20 than at C-22.[3] Interestingly, 20-isocholesterol (20S) showed significant in vitro inhibitory activity in the conversion of cholesterol to pregnenolone.[3] For this purpose, we explored a novel, stereochemically controlled synthesis of 20-isocholesterol 10.

The synthesis of 20-isocholesterol employing regioselective catalytic hydrogenation of the 20,21-didehydrocholesterol has been reported.[4] This hydrogenation process, however, is not stereoselective providing a 1:1 mixture of the C-20 epimers of cholesterol. This communication describes a highly stereochemically controlled synthesis of 20-isocholesterol (20S) starting from pregnenolone tetrahydropyranyl (THP) ether 1. A novel stereospecific isomerization of the epoxide 2 to the 20-iso-21-aldehyde 3 accompanies the reaction of 2 with a Grignard reagent.

The key intermediate is the 20-iso-22-hydroxy compound 6, available from the 20R-epoxide 2.[5] Treatment of pregnenolone THP ether 1 with excess dimethylsulfoxonium methylide yielded exclusively the 20R-epoxide 2:[6] mp. 132-134°C; NMR: ^{1}H (δ ppm) 0.83 (s, 3H, 18-H), 1.38 (s, 3H, 20-CH_3), and 2.27 and 2.46 (AB quartet, J_{AB} = 5.0 Hz, 2H, 21-H), ^{13}C (δ ppm) 13.0 (18-C), 51.5 (21-C), and 56.1 (20-C).# The 20R-configuration of this epoxide was assigned on the basis of its conversion into the known (20S)-20-hydroxycholesterol 5.[8] Thus, the alkyldithiane adduct 4 [NMR: ^{1}H (δ ppm) 0.83 (s, 3H, 18-H) and 1.51 (s, 3H, 21-H), ^{13}C (δ ppm) 13.3 (18-C), 53.6 (23-C), and 76.3 (20-C)], obtained from the reaction of 2 with 2-lithio-2-isobutyl-1,3-dithiane, was reduced with Raney nickel to (20S)-20-hydroxycholesterol 5: mp. 133-134°C; $[\alpha]_D^{23}$ -56° (c 1.15, $CHCl_3$); NMR: ^{1}H (δ ppm) 0.86 (s, 3H, 18-H) and 1.27 (s, 3H, 21-H),[8] ^{13}C (δ ppm) 13.6 (18-C) and 75.3 (20-C). Alternative treatment of the epoxide 2 with excess isoamylmagnesium bromide in

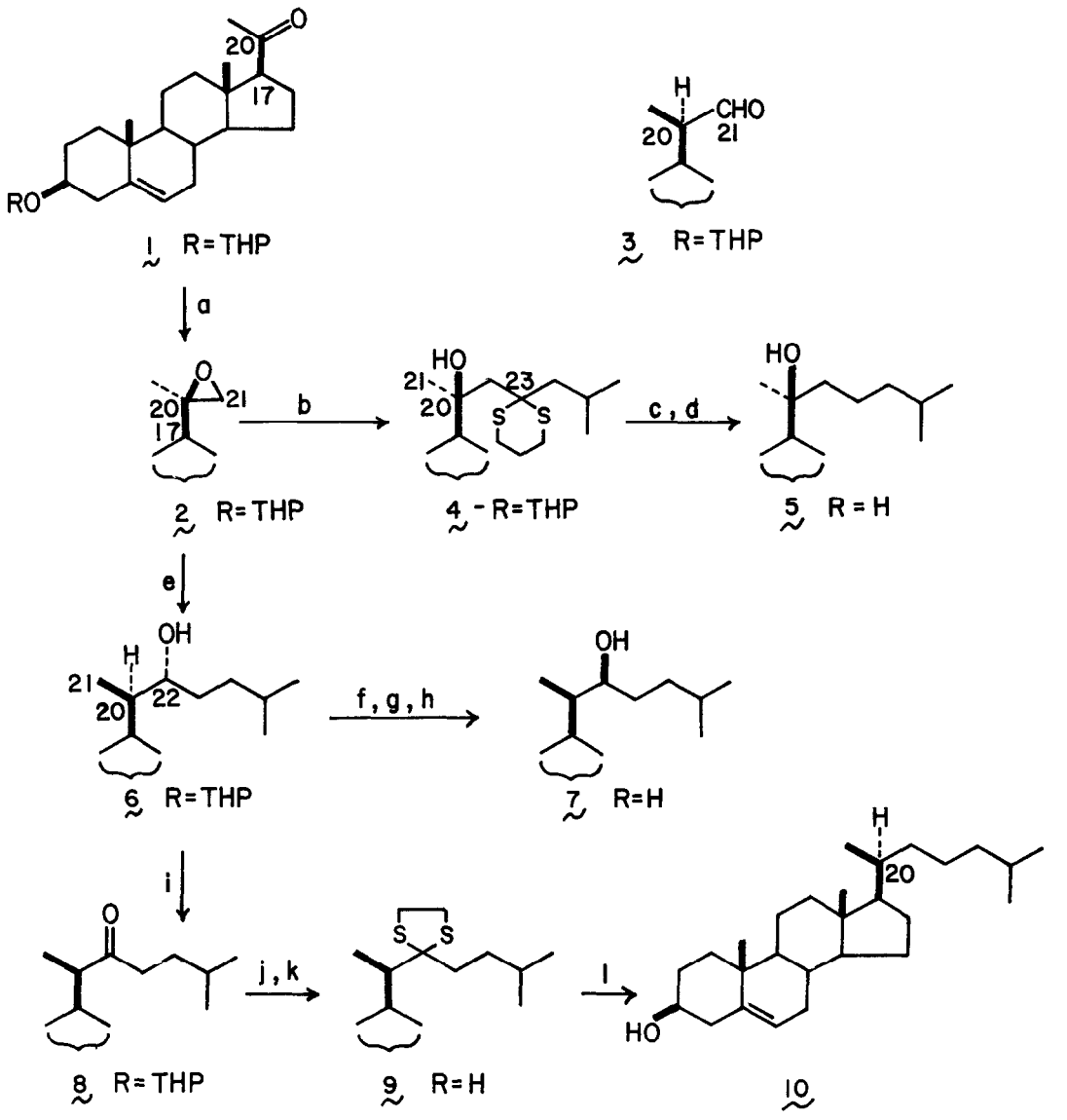
#NMR spectra were taken with a Jeol MH-100 (^{1}H) and a Varian CFT-20 (^{13}C) in $CDCl_3$.

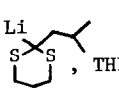
refluxing THF for 4 hours provided (20R,22R)-20-iso-22-hydroxycholesterol 3-THP ether 6 in 80% yield: mp. 131-133°C; NMR: ^{1}H (δ ppm) 0.69 (s, 3H, 18-H), 0.82 (d, J = 6.0 Hz, 3H, 21-H), and 3.82 (m, 1H, 22-H overlapped with the THP 3'-H's), ^{13}C (δ ppm) 11.3 (21-C), 12.2 (18-C), and 72.9 (22-C). This is in marked contrast with the results of Sydykov and Segal[9] who report obtaining the Grignard adduct at C-20, as well as, a dimeric epoxy steroid. The 20R,22R-stereochemistry of 6 was validated by its conversion to (20R,22S)-20-iso-22-hydroxycholesterol 7 [mp. 204-205°C; NMR: ^{1}H (δ ppm) 0.70 (s, 3H, 18-H), 0.83 (d, J = 6.0 Hz, 3H, 21-H), and 3.80 (m, 1H, 22-H)], which has also been obtained as one of the two products from the reaction of (E)-20,22-didehydrocholesterol with diborane followed by alkaline hydrogen peroxide treatment.[10] The Grignard reaction presumably proceeds via an initial Lewis acid-catalyzed, stereospecific isomerization of the epoxide 2 into the 20-iso-21-aldehyde 3[11] followed by the stereoselective reaction of the aldehyde with the Grignard reagent.

The conversion of 20-iso-22-hydroxycholesterol 6 into 20-isocholesterol 10 was accomplished as follows: Oxidation of 6 with pyridinium chlorochromate[12] gave the 20-iso-22-keto steroid 8 without affecting the stereochemistry at C-20: mp. 148-150°C; $\nu_{max}^{CHCl_3}$ 1718 cm^{-1}; NMR: ^{1}H (δ ppm) 0.67 (s, 3H, 18-H) and 1.03 (d, J = 6.0 Hz, 3H, 21-H), ^{13}C (δ ppm) 12.1 (18-C) and 215.6 (22-C). The deprotected 3-hydroxy steroid 8 (R = H) was converted into the thioketal 9 [NMR: ^{1}H (δ ppm) 0.68 (s, 3H, 18-H) and 1.08 (d, J = 7.0 Hz, 3H, 21-H), ^{13}C (δ ppm) 12.8 (18-C) and 80.0 (22-C)], which was then reduced with Raney nickel to the C-22 methylene, 20-isocholesterol 10. This reduction of the thioketal 9 is accompanied by the formation of traces of olefinic compounds which are readily removed during recrystallization. An alternative procedure for the removal of the 22-oxygen function employing the mesylation of 6 followed by super hydride treatment and removal of the 3-THP group produced considerable amounts of (E)- and (Z)-20,22-didehydrocholesterol (~50%), as well as, the desired 20-isocholesterol (~40%). Isolation of the latter from the product mixture proved to be too laborious.

The 20-isocholesterol thus obtained [10: mp. 152-154°C; $[\alpha]_D^{23}$ - 45° (C 0.101, $CHCl_3$); lit., mp. 152-154°C,[4] mp. 153-154°C;[13] $[\alpha]_D$ - 42° ($CHCl_3$)[4]] was identical with an authentic sample and had physico-chemical constants distinct from those of cholesterol. Among these, both ^{1}H NMR[13] and ^{13}C NMR are especially diagnostic for the differentiation of the two; *i.e.*, cholesterol: ^{1}H (δ ppm) 0.69 (s, 3H, 18-H) and 0.91 (d, J = 6.0 Hz, 3H, 21-H), ^{13}C (δ ppm) 11.8 (18-C); 20-isocholesterol: ^{1}H (δ ppm) 0.68 (s, 3H, 18-H) and 0.82 (d, J = 6.0 Hz, 3H, 21-H), ^{13}C (δ ppm) 12.1 (18-C).

SCHEME I. Synthesis of 20-Isocholesterol.



[a] $(CH_3)_3S(O)I$, room temperature, 4 days, 88%; [b]  , THF, 0°C, 18 hrs, 66%; [c] Raney nickel W-2, EtOH, reflux, 30 mins, 95%; [d] MeOH, trace of 3N HCl, room temperature, 2 hrs, 98%; [e] See text; [f] CH_3SO_2Cl, pyridine, 5°C, 5 hrs, 98%; [g] KO_2, 18-crown-6, DME/DMSO (1/2), room temperature, 12 hrs, 96%; [h] See *d*, 99%; [i] Pyridinium chlorochromate, NaOAc, CH_2Cl_2, room temperature, 2.5 hrs, 84%; [j] See *d*, 30 mins, 96%; [k] 1,2-Ethanedithiol, BF_3-etherate, AcOH, room temperature, 1 hr, 98%; [l] See *c*, 62%.

This constitutes a highly stereochemically controlled and efficient (34.5% overall yield from pregnenolone THP ether 1) synthesis of 20-isocholesterol 10.

Acknowledgment

This research was supported by U. S. Public Health Service Grant No. AI-12150 from the National Institutes of Health to whom we are very grateful.

References and Footnotes

1. a) S. Burstein and M. Gut, Recent Progr. Hormone Res., 27, 303 (1971); b) B. Luttrell, R. B. Hochberg, W. R. Dixon, P. D. McDonald, and S. Lieberman, J. Biol. Chem., 247, 1462 (1972).

2. S. Burstein and M. Gut, Steroids, 14, 207 (1969).

3. B. A. Teicher, N. Koizumi, M. Koreeda, M. Shikita, and P. Talalay, submitted.

4. F. Sondheimer and R. Mechoulam, J. Am. Chem. Soc., 80, 3087 (1958).

5. The 20-methyl-20,21-epoxides[6,7] have been prepared but their stereochemistry has never been assigned.

6. French Patent 1,359,646 (April 30, 1964) [See: Chem. Abst., 61, 13389f (1964)].

7. F. Bertini, P. Grasselli, and G. Zubiani, Tetrahedron, 27, 6109 (1971).

8. a) A. Mijares, D. I. Cargill, J. A. Glasel, and S. Lieberman, J. Org. Chem., 32, 810 (1967); b) T. A. Wittstruck, J. Org. Chem., 38, 1426 (1973).

9. Zh. S. Sydykov and G. M. Segal, Izv. Akad. Nauk SSSR, Ser. Khim., 1426 (1976) [See: Chem. Abst., 86, 16836p (1977)].

10. M. Koreeda and N. Koizumi, unpublished results.

11. A similar rearrangement using BF_3/benzene has recently been reported: Zh. S. Sydykov and G. M. Segal, Izv. Akad. Nauk SSSR, Ser. Khim., 2581 (1976) [See: Chem. Abst., 87, 23603j (1977)].

12. E. J. Corey and J. W. Suggs, Tetrahedron Lett., 2647 (1975).

13. W. R. Nes, T. E. Varkey, and K. Krevitz, J. Am. Chem. Soc., 99, 260 (1977).