Tetrahedron Letters,Vol.26,No.41,pp 5021-5024,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

STEREOSPECIFIC SYNTHESIS OF (25R)-26-HYDROXYCHOLESTEROL VIA [2,3] SIGMATROPIC REARRANGEMENT. A NEW STEREOSELECTIVE TWO-CARBON HOMOLOGATION OF 20-KETO STEROIDS TO THE 23-ALDEHYDE.

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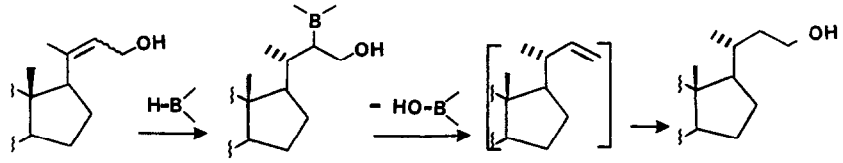
Abstract: Pregnenolone was stereoselectively converted into (25R)-26-hydroxycholesterol using a stereoselective hydroboration, asymmetric reduction and a stereospecific [2,3] sigmatropic rearrangement as key steps.

(25R)-26-Hydroxycholesterol is known to be an important intermediate in the biosynthesis of bile acid. It is also reported as a potent inhibitor of cholesterol synthesis in vitro.[1] Ready availability of (25R)-26-hydroxycholesterol is essential to the studies on atherosclerosis and metabolism of cholesterol.[2] Furthermore, the recent discovery of the steroid shark repellents, pavoninins, whose side chain is identical to that of (25R)-26-hydroxycholesterol, has reinforced the importance of the stereocontrolled synthesis of such side chains.[3]

(25R)-26-Hydroxycholesterol has been synthesized from kryptogenin and diosgenen,[2,4] by asymmetric hydroboration of cholesta-5,25-diene-3-ol,[5] by coupling of a chiral moiety with a 23-steroid tosylate,[6] by microbial oxidation of cholesterol[5] and by microsomal oxidation of cholesterol.[7] These methods often give mixtures of components which are difficult to separate. Herein, we report a stereospecific synthesis of (25R)-26-hydroxycholesterol from readily available pregnenolone, controlling the stereochemistry at C-20 and C-25 via stereoselective hydroboration of an alkenyl ester, asymmetric reduction of an alkynyl ketone and stereospecific [2,3] sigmatropic rearrangement of an organostannylmethyl ether of an allylic alcohol. The first sequence of

these reactions represents a new synthetic route to (20R)-23-steroid aldehydes and alcohols, which can be elaborated to other important steroid side chains.[6,8] The synthesis is outlined in Scheme I.

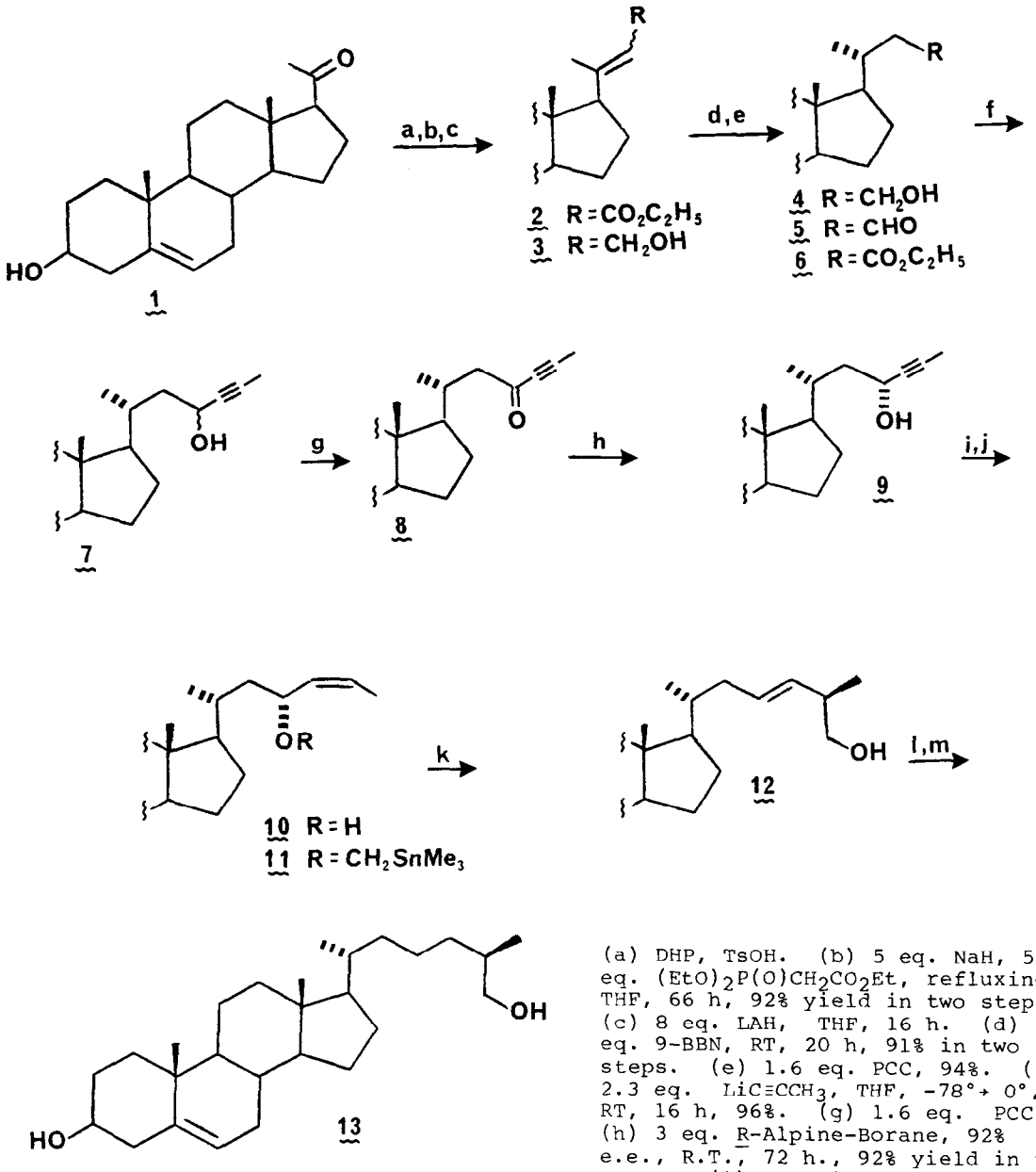
Pregnenolone **1** was protected with the tetrahydropyranyl (THP) group and subjected to a Wadsworth-Emmons reaction affording the α,β-unsaturated ester **2** (1.3:1/E:Z mixture). It was hoped that stereoselective[9] hydroboration of the 20(22) double bond would provide either the ester b (from hydrolysis of the α-boron ester) or the alcohol **4** (from reduction of the ester followed by β-elimination of the borane-alcohol and hydroboration of the terminal olefin[10]). In practice,



the best results were obtained when the ester was reduced to the alcohol prior to hydroboration. Hydroboration with 3.4 equivalents of 9-borabicyclo[3.3.1]nonane (9-BBN) provided the desired 20R alcohol in a 95:5 ratio ((20R):(20S), HPLC). The more polar 20R isomer **4** was isolated by chromatography. The 23-aldehyde was obtained by pyridinium chlorochromate (PCC) oxidation.

Addition of propynyl lithium to **5** afforded a 1:1 diastereomeric mixture of a propargyl alcohol **7** which was subsequently oxidized to alkynyl ketone **8**. Asymmetric reduction of **8** with R-Alpine-Borane[11] (from 92% e.e. (+)-α-pinene) gave predominantly the less polar (23R)-epimer (**9**) ((23R):(23S) = 96:4). Partial hydrogenation of **9** with Lindlar catalyst afforded **10**, which was subsequently deprotonated with NaH and treated with ICH_2SnMe_3 to give the trimethylstannylmethyl ester **11**.[12] Treatment of **11** with n-butyllithium at -78° followed by warming to 0° afforded a homoallylic alcohol **12**. Studies on [2,3] sigmatropic rearrangements of anions derived from trialkylstannylmethyl allylic ethers have revealed that essentially complete chirality transfer occurs (>120:1) in these systems.[13] The 23(24)-double bond of **12** was preferentially hydrogenated on 5% Pd/C in the presence of the 5(6)-double bond. Deprotection of the THP group provided the desired product (25R)-26-hydroxycholesterol (**13**). ^1H and ^{13}C NMR spectra of **13** were identical with an authentic sample.[14] m.p.

Scheme I



(a) DHP, TsOH. (b) 5 eq. NaH, 5 eq. $(EtO)_2P(O)CH_2CO_2Et$, refluxing THF, 66 h, 92% yield in two steps. (c) 8 eq. LAH, THF, 16 h. (d) 3.4 eq. 9-BBN, RT, 20 h, 91% in two steps. (e) 1.6 eq. PCC, 94%. (f) 2.3 eq. $LiC{\equiv}CCH_3$, THF, -78°→ 0°, RT, 16 h, 96%. (g) 1.6 eq. PCC. (h) 3 eq. R-Alpine-Borane, 92% e.e., R.T., 72 h., 92% yield in two steps. (i) H_2, Lindlar catalyst. (j) 2.5 eq. NaH, 2.5 eq. ICH_2SnMe_3, 40°, 20 h, 62%. (k) 2.3 eq. n-BuLi, THF, -78°→0°, 80%. (l) H_2, 5% Pd/C. (m) HOAc-THF-H_2O (4:2:1), 40~50°, 4 h, RT 16 h., 98% in two steps.

176-178°C (lit.[4b] 177-178°C), $[\alpha]_D$-30.8° (c 0.50, $CHCl_3$) (lit.[4b] $[\alpha]_D$ - 30° (c 1, $CHCl_3$); lit.[5] $[\alpha]_D$ - 33.5±1.3° (c 1.5, $CHCl_3$).

Acknowledgment. We wish to thank the National Institutes of Health (GM30081) for financial support.

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14. We thank A.F. Kluge for providing an authentic sample of (25R)-26-hydroxycholesterol and a preprint of ref. 2.

(Received in USA 27 June 1985)