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STEREOSELECTIVE REDUCTION OF THE STEROIDAL 23-EN-22-ONE: A ROUTE TO THE SIDE CHAIN OF THE PLANT GROWTH PROMOTER BRASSINOLIDE.

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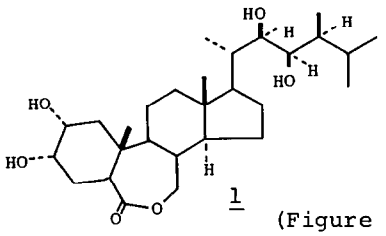
Summary: The side chain of brassinolide (**1**) was stereoselectively synthesized, in which the 20(S)- and the 22(R)-configurations were introduced by the alkylation (S_N2) of the 20(R)-tosyloxy steroid **7** with the protected cyanohydrin **8** followed by the stereoselective reduction of the 23-en-22-one **10** with Dibal-H.

With the recent discoveries of new steroids possessing various kinds of side chain, there is a compelling need to develop an efficient method for the construction of the basic steroid nucleus.[1)] Furthermore, syntheses of side chain of the plant growth promoter brassinolide (**1**)[2)] and the insect moulting hormone α-ecdysone (**2**) (Figure 1) require the stereoselective introduction of the 22α(R)- and 22β(R)-hydroxy group. Reductions of C(22)-ketone with various kinds of hydride reagents or additions of alkyl Grignards to C(22)-aldehyde were well studied[1a)]. However these stereoselectivities were not high and gave the 22α-OH isomer as the major product.



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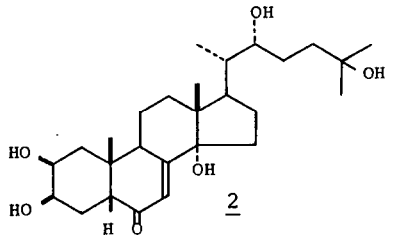

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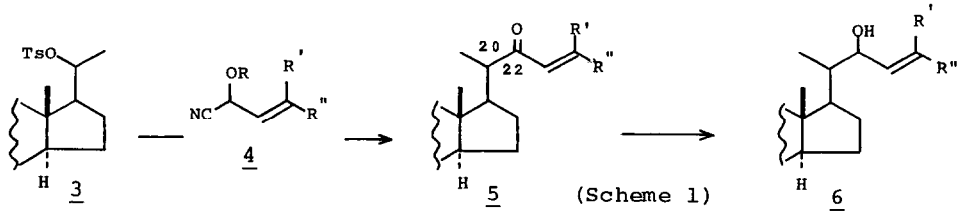
(Figure 1)

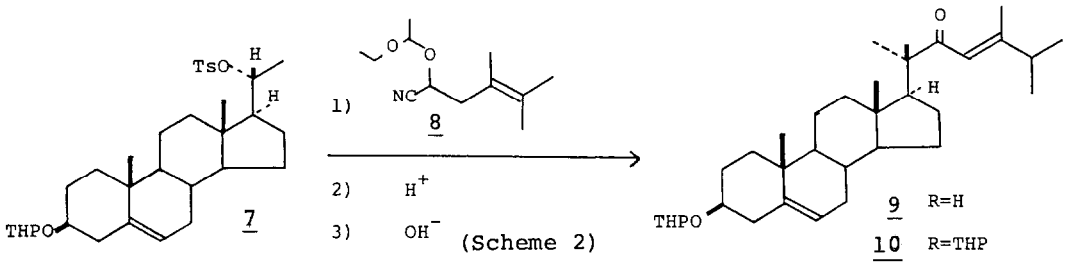
We have tested here the stereoselectivity in the reduction of 23-en-22-one **5** which was derived by the alkylation[3)] of 20β(R)-tosylate **3**, prepared from pregnenolone, with the acyl carbanion **4** (Scheme 1). The reduction of **5** with Dibal-H gave the 22α(R)-allylic alcohol **6**, while the reduction with L-selectride gave the 22β(S)-**6**. Thus these overall transformations can afford complex steroid side chain.



3 **4** **5** **6**

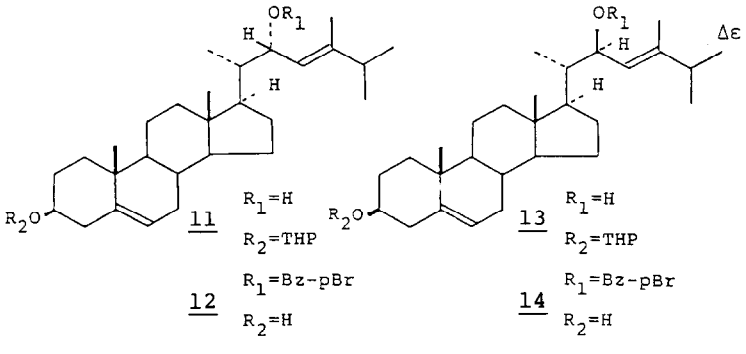
(Scheme 1)

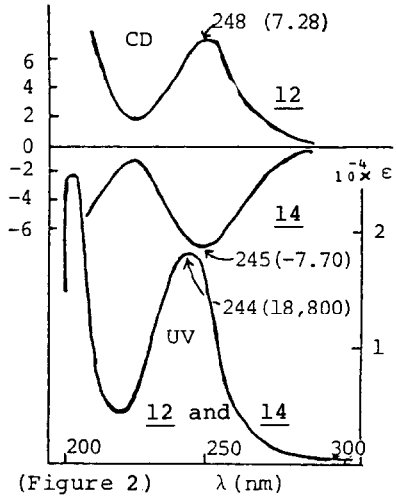
The 20β(R)-tosylate **7** was prepared from 3-tetrahydropyranyl ether of pregnenolone [$LiAlH_4$ in THF at 0 °C; 20β(R)-alcohol (66% yield), 20α(S)-alcohol (10% yield): p-TsCl in pyridine at room temp. (91% yield)]. Alkylation of the protected cyanohydrin **8** with the tosylate **7** and the conversion of the alkylated product to the enone **9** were carried out by the following reaction sequence (Scheme 2). A mixture of the tosylate **7** (0.8 mmol) and three equiv. of the protected cyanohydrin **8** in dry benzene was added to a solution of sodium bis(trimethylsilyl)amide in dry benzene at 80 °C. The acid treatment of the alkylated product [p-TsOH/MeOH at 0 °C for 1 h] and followed by base treatment of the resultant cyanohydrin with 2% aq. NaOH at 0 °C for 10 min gave the corresponding enone **9**[4] in 83% overall yield without C(20)-epimerization.



(Scheme 2)

The hydride reduction of 22-keto steroids with $NaBH_4$ and $LiAlH_4$ is well known[5] to give the 22β(R)-OH (Cram product) and 22α(S)-OH (anti-Cram product) in a 1 : 3 ratio. We investigated the reduction of 23-en-22-one **10**, derived from the enone **9** (dihydropyran and p-TsOH in CH_2Cl_2; 90%), with diisobutylaluminum hydride (Dibal-H) and lithium tri-sec-butylborohydride (L-selectride). The reduction of the enone **10** with L-selectride in THF at -78 °C gave the Cram product 22β(S)-OH **11**[6] in a ratio of 93 :7 (72% yield), while the reduction with Dibal-H in THF at -78 °C gave an anti-Cram product 22α(R)-OH **13**[6] in a ratio of 97 : 3 (85% yield). To determine the absolute configuration of the resultant allylic alcohols **11** and **13**, they were converted, to the corresponding

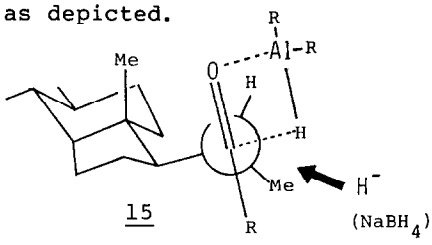




(Figure 2)

benzoates **12** and **14** [p-bromobenzoyl chloride and pyridine in CH_2Cl_2 for 15 h; the removal of THP (PPTS/MeOH)]. The exciton-split CD curves[7] (Fig. 2) of the benzoates **12** and **14** exhibit the strong positive and negative first Cotton effects in the region of the $\pi-\pi^*$ transition around 248 nm, respectively, as is predicted by "exciton chirality method" developed by Harada and Nakanishi.[8]

This peculiarity observed in the reduction of 23-en-22-one, comparing with the reduction of the 22-keto-steroids, can be explained as follows. The stereochemistry of hydride additions ($NaBH_4$ or $LiAlH_4$) to 22-keto steroids has been postulated by Ourisson[1a,5a] to occur from the conformation **15** rather than **16** due to nonbonding interaction between C(23)methylene and C(13)methyl groups in **16** to result in an anti-Cram situation. While the preferred conformation for the L-selectride reduction of 23-en-22-one **10** would be as shown by **16**, according to Felkin model,[9] and addition of a nucleophile would take place from the smallest group to give the Cram-product **11**. In the two most likely conformations **15** and **16** of the transition state for the Dibal-H reduction of the enone **10**, the conformation **15** would be more favored owing to the increased steric repulsion of C(20)methyl with alkyl groups on aluminum in the case of **16**, if the Dibal-H reduction of the carbonyl group was initiated by the complex formation as depicted.



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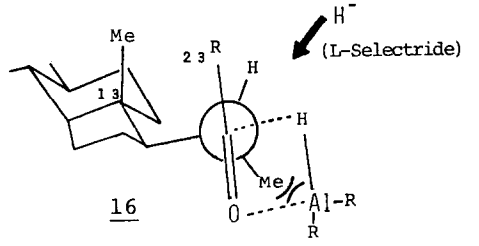
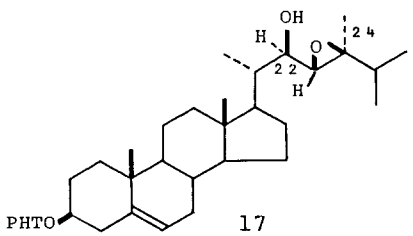


16

Then construction of the side chain was carried out from the allylic alcohol **13** by appling the Siddall's method.[2a] The stereoselective allylic epoxidation of **13** using the Sharpless method[10] [$^tBuOOH/VO(acac)_2$ in benzene at room temp. for 1 h] gave the desired epoxide **17** in 79% yield along with its isomer in 7% yield. They were easily separated by chromatography on silica gel. The stereo- and regioselective opening of the epoxide **17** with inversion at C(24) [AlH_3, freshly prepared from $LiAlH_4$ and $AlCl_3$ in ether; at room temp.] gave the 22α(R),23α(R)-dihydroxy product **18** in 64% yield and the 22(R),24-dihydroxy product was formed in 17% yield. Hydrolysis of 3-tetrahydropyranyl ether of **18** with p-toluenesulfonic acid in methanol gave the triol **19** in 82%



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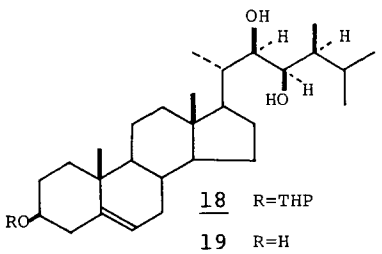

18 R=THP

19 R=H

yield [m.p. 219-220 °C, (lit.[2a] m.p. 205-208 °C); $[\alpha]_D$ -33° (c=0.21, EtOH); Ms m/e=432(M^+); ^{1}H-NMR (200 MHz, C_5D_5N) 0.82 (3H, s, C(13)-Me), 1.04 (3H, d, J=7.0), 1.06 (3H, s, C(10)-Me), 1.11 (3H, d, J=6.6), 1.17 (3H, d, J=6.8), 1.28 (3H, d, J=6.6)]. The ^{1}H-NMR spectrum of our synthetic triol **19** was identical with an authentic spectrum kindly supplied to us by Prof. N. Ikekawa.[2b] The conversion of the 3-hydroxy-5-en moiety of the triol **19** to the lactone portion of the brassinolide (**1**) is known.[2a]

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(4) mp 147.5-149 °C (acetone); $[\alpha]_D$ = -66.7° (c=0.75, $CHCl_3$); ^{1}H-NMR (90 MHz) 1.07 (6H, d, J=6.8, C(25)-Me), 1.12 (3H, d, J=6.6, C(20)-Me), 2.07 (3H, d, J=1.1, C(24)-Me); EI-MS, 412(M^+).

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(6) HPLC; **11** Rt=10-11.5 min, **13** Rt=8-9.8 min, (Silicagel-60-5 μm, 2 mL/min, 0.5% isopropyl alcohol in hexane). This behavior of polarities is reverse to the previous result reported by Siddall; see ref. (2)-a).

(7) For the determination of the configuration of 22-OH groups, the usually observed polarities of epimeric pairs of 22-OH groups were used in earlier works; J.R.Wiersig, N.Waespe-Sarcevic, C.Djerassi, J.Org.Chem., **44**, 3374 (1979). Recently M.Anastasia has attempted to support the configuration of 22-OH groups by application of the 2-nitrobenzoate chirality rule, without success and eventurally used the behavior of polarlities; M.Anastasia, A.Fiecchi, J.Org.Chem., **46**, 1726 (1981).

(8) N.Harada, K.Nakanishi, "Circular Dichromic Spectroscopy-Exciton Coupling in Organic Stereochemistry", University Science Books, California (1983).

(9) 22-Keto steroids have nonbonding interaction between C(23) methylene and C(13) methyl groups, while 23-en-22-ones have no such an interaction, thereby the preferred conformation would be **16** according to ordinary Felkin model.

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