Tetrahedron Letters,Vol.24,No.8,pp 773-776,1983 0040-4039/83/080773-04$03.00/0
Printed in Great Britain

STEREOSELECTIVE SYNTHESIS OF PLANT GROWTH-PROMOTING STEROIDS, DOLICHOLIDE AND 28-NORBRASSINOLIDE

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Abstract: Stereoselective introduction of (22R,23R)-vicinal diol function at C-22, C-23 position of the steroidal side chain was achieved using the method of chelation control, leading to the stereoselective synthesis of dolicholide(4) and 28-norbrassinolide(2).

Stereoselective introduction of (22R,23R)-vicinal diol function at C-22, C-23 position of the steroidal side chain is a crucial step to synthesize natural plant growth hormone, brassinolide(1)[1] and its related compounds, since direct cis hydroxylation of the 22E olefins of the steroidal side chains with osmium tetroxide provided the unnatural (22S,23S)-vicinal diols exclusively.[2,3,4,5,6] Furthermore, investigation into structure-activity relationship of brassinosteroids indicated that (22R,23R)-brassinosteroids were most active among four possible stereoisomers of 22,23-diols in many bioassay systems.[4,6] In our previous papers we developed stereoselective introduction of (22R,23R)-vicinal diol function into the steroidal side chain using hydroxy-directing epoxidation and synthesized brassinolide(1)[7] and 28-norbrassinolide(2)[2], stereoselectively. We report herein alternative stereoselective introduction method of (22R,23R)-vicinal diol function at the C-22, C-23 position by the chelation controlled Grignard reaction[8], leading to stereoselective synthesis of dolicholide(4) and 28-norbrassinolide(2), which were recently isolated and identified as plant growth-promoting steroids in higher plants.[9,10]

The key intermediate, 2α,3α,22-triacetoxy-6-ketone(7) was obtained from the known 22-ene(5), which was used for our synthesis of (22R,23R)-28-homobrassinolide(3) and its analogues,[3] by five steps in 60% overall yield as follows. Ozonolysis of the 22-ene(5) after protection of the carbonyl group at C-6 as an ethylene ketal and reduction of the resulting ozonide with sodium borohydride gave the 22-alcohol(6). This was acetylated and deketallized to provide the triacetate(7), mp 212-213°C.

Baeyer-Villiger oxidation of the 6-oxosteroid(7) with two equivalent of CF_3CO_3H in CH_2Cl_2 in the presence of Na_2HPO_4 at 0°C for 2h afforded, after chromatographic purification, the 7-oxalactone(8), mp 240-241°C, ^{1}H-NMR($CDCl_3$) δ3.00 (1H, dd, J= 6 and 13 Hz, 5α-H), 4.10 (2H, m, 7-H_2), in 83% yield[11]. This was subjected to saponification and acetonide formation to provide the 22-alcohol(9), mp 193-195°C, in 95 % yield. Oxidation of the alcohol(9) with pyridinium chlorochromate in the presence of sodium acetate gave the 22-aldehyde (10), oil, ^{1}H-NMR($CDCl_3$) δ 9.55 (1H, d, J = 4 Hz, 22-H), in 75 % yield. The aldehyde(10) was reacted with lithium salt of 1,3-dithiane at -20°C in THF, followed by treatment with chloromethyl methyl ether and cyclohexyldiethylamine in dioxane to afford the oily (22R)-dithiane(11) in 85 % yield as a major product. The configuration at C-22 was tentatively assigned from the stereochemistry well-known for the reaction of C-22 aldehydes with nucleophiles[12] and this was finally confirmed by conversion of (11) into dolicholide(4). Dethioketallization of the dithiane(11) with red mercuric oxide and boron trifluoride etherate in aqueous THF gave the 23-aldehyde(12), oil, ^{1}H-NMR($CDCl_3$) δ 9.70 (1H, s, 23-H), quantitatively, without epimerization at C-22 position.

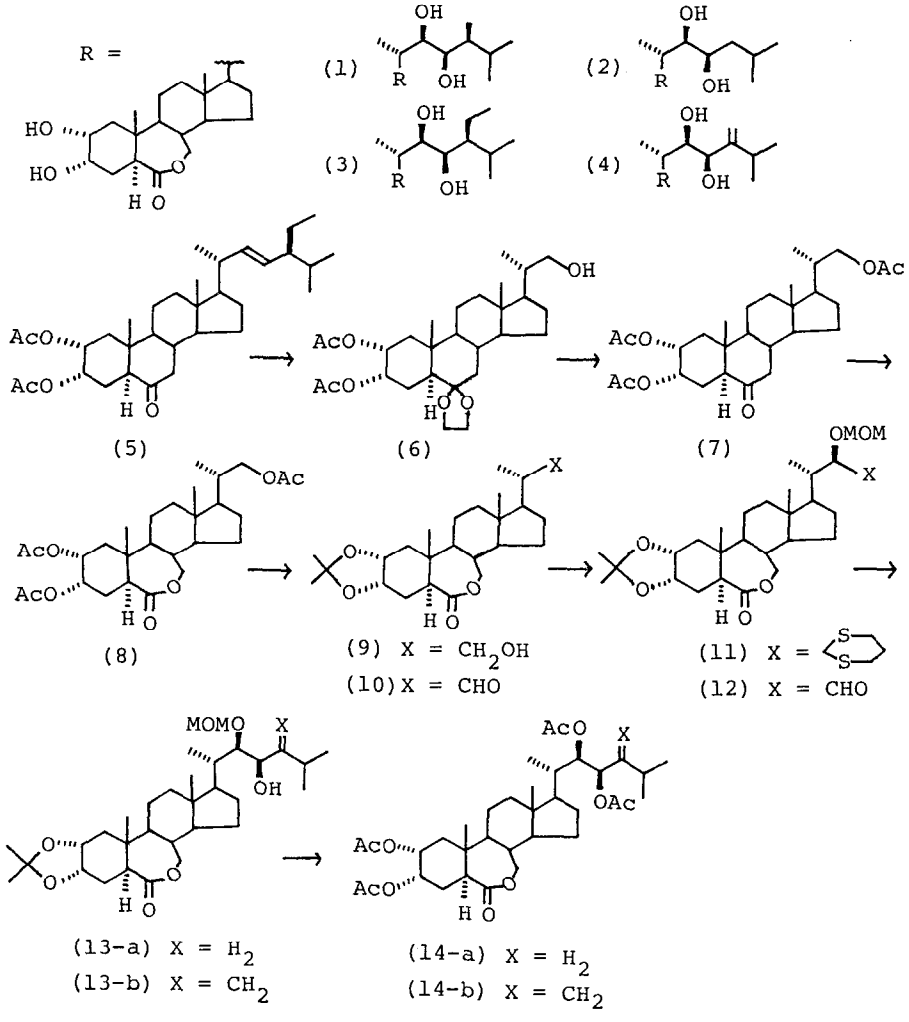
Chelation controlled coupling reaction of the (22R)-23-aldehyde(12) with the Grignard reagent derived from 2-bromo-3-methyl-1-butene[13] in THF at -78°C afforded, exclusively, the (22R,23R)-22,23-vicinal diol 22-methoxymethyl ether (13-a), oil, in 73 % yield, whose C-23R stereochemistry was assigned from the prediction reported by Still[8]. Acetylation of the 23-alcohol(13-a), removal of acetonide(AcOH-H_2O, 5 : 1, reflux) and methoxymethyl group(6M HCl, MeOH-THF, 1 : 1, at 60°C), and acetylation at 60°C overnight provided the tetra-acetate (14-a), oil, in 80 % yield, after chromatographic purification. The acetate (14-a) was saponified with 5 % KOH/MeOH under reflux and subsequently acidified with 6M HCl to afford dolicholide(4), mp 238-242°C (lit[9] mp 234-238°C), in 93 % yield. The ^{1}H-NMR(400 MHz) and high resolution EI-MS of the synthetic dolicholide(4) are in complete agreement with those reported for natural dolicholide (4)[9].

Similarly, the 23-aldehyde(12) was reacted with isobutylmagnesium bromide to give the (22R,23R)-22,23-vicinal diol 22-methoxymethyl ether(13-b), oil, in 80 % yield. This was converted into (22R,23R)-28-norbrassinolide(2), mp 257-260°C (lit[2] mp 256-259°C), in 72 % overall yield, via the tetra-acetate(14-b), as described for dolicholide(4).

This method to introduce (22R,23R)-vicinal diol function at C-22, C-23 position of the steroidal side chain seems to be useful to synthesize (22R,23R)-brassinosteroids with modified side chain[14]. In addition, tritium labelled brassinolide and its 6-ketone analogue can be prepared from the corresponding 24-methylenebrassinosteroids. These are now in progress in our laboratory. Detailed plant growth-promoting activities of the synthetic dolicholide(4) are

now investigated and will be reported in due course.

Acknowledgement: The authors are grateful to Miss S. Miki, Central Research Laboratories, Meiji Seika Kaisha, Ltd., for the measurement of mass spectra, Dr. J. Uzawa, the Institute of Physical and Chemical Research, for the measure ment of ^{1}H-NMR(400 MHz), and Prof. N. Takahashi, the University of Tokyo, for the information on dolicholide. This work was supported in part by Grant-in-Aid from the Ministry of Education, Science and Culture, Japan.



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(Received in Japan 8 November 1982)