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STEREOCONTROLLED SYNTHESIS OF THE BRASSINOLIDE SIDE CHAIN VIA A PYRANONE DERIVATIVE

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Abstract: *A new method for assembling the brassinolide side chain from 20-carboxaldehyde* **2** *was developed via the stereoselective construction of the pyranone moiety as key steps.*

Brassinolide 1,[1] isolated from rape pollen (*Brassica napus* L.), is known to exhibit plant growth regulating activity. One of the most challenging aspects of the synthesis of the important steroid is the stereocontrolled synthesis of the side chain having contiguous four chiral centers.[2] In connection with the synthesis of physiologically active steroids, we have been interested in the stereocontrolled synthesis of polyhydroxylated steroid side chains employing pyranone derivatives as versatile intermediates,[3] and here report a stereocontrolled synthesis of the brassinolide side chain.

Addition of 2-lithiofuran to the (20S)-20-carboxaldehyde **2**[4] produced the furylcarbinols **3** and **4** in a ratio of 3 : 7 in 96% yield.[5] Conversion of **3** into **4** was achieved employing oxidation of **3** with pyridinium chlorochromate followed by reduction of the ketone. Oxidation of the furan **4** with *N*-bromosuccinimide afforded the lactol **5** as an inseparable mixture of two anomers, which were converted into the α - and β -ethoxyethyl ethers[6] **6** and **7** in a ratio of 1 : 3 in 96% yield.[7] Deprotection of ethoxyethyl moiety of **6** on treatment with 10 % HCl gave **5** , which was again subjected to the protection to afford **6** and **7** in the same ratio. Thus, the minor β -anomer **6** could be recycled practically.

With the requisite pyranone derivative in hand, elaboration for the stereocontrolled construction of the brassinolide side chain was carried out as follows. Conjugate addition of lithium dimethylcuprate to **7** afforded the ketone **8** (90 % yield), whose treatment with lithium diisopropylamide and methyl iodide gave the bis methylated compound **9** in 84% yield. These reactions would occur smoothly from the opposite side of the adjacent groups as expected on the basis of results appeared in the literatures.[8] The ^{1}H NMR spectrum[9] of **9** shows protons at δ 2.26 (dq,J=6.1 and 6.7 Hz,H-24) and 4.95(d,J=6.1Hz,H-26), suggesting Fig. A as its conformation. Reduction of the ketone **9** with sodium borohydride afforded the desired alcohol **10** in 92% yield. The stereochemistry at C(23) is deduced by the ^{1}H NMR spectrum[9] of the acetate **11** which shows the protons at δ 3.94 (d,J=4.9Hz,H-22) and 4.74(dd,J=4.9 and 6.7 Hz,H-23), clearly indicative of an axial hydrogen at C(23).

Treatment of **10** with 10% HCl afforded the lactol, which was reduced with lithium aluminum hydride to give the triol **12** in 82% overall yield. Compound **12** was heated in acetic acid to give the acetate (96%), whose treatment with *p*-TsOH in acetone furnished the acetonide **13** in 90% yield. This compound was finally converted into the known acetate **14**[10] by the successive treatment with methanesulfonyl chloride and pyridine, reduction with lithium aluminum hydride, and acetylation with acetic anhydride. Conversion of **14** into brassinolide 1 was already achieved,[10] therefore this constitutes a formal synthesis of brassinolide.

Thus, we could develop a new method for construction of the brassinolide side chain employing the pyranone as a useful intermediate.

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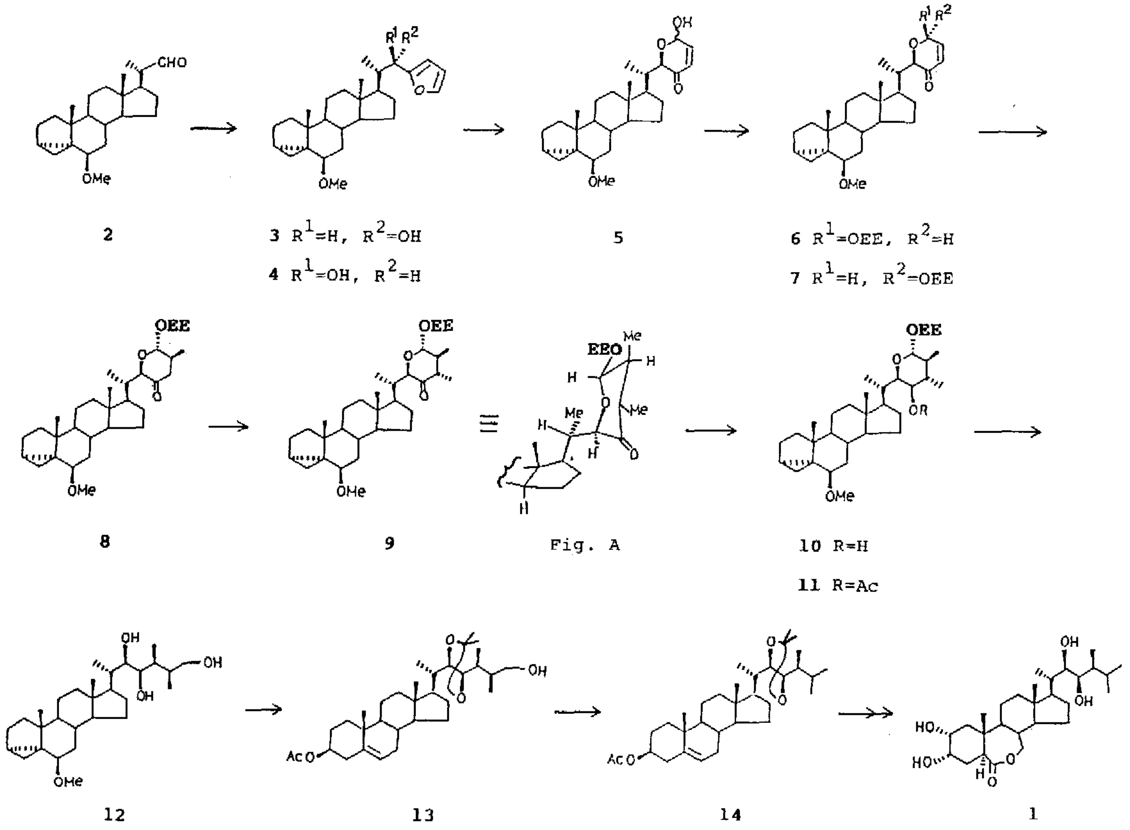

2

3 R^1=H, R^2=OH

4 R^1=OH, R^2=H

5

6 R^1=OEE, R^2=H

7 R^1=H, R^2=OEE

8

9

Fig. A

10 R=H

11 R=Ac

12

13

14

1

References and Notes

1)M.D.Grove, G.F.Spencer, W.K.Rohwedder, N.Mandava, J.F.Worley, J.D.Warthen, G.L.Steffens, J.L. Flippen-Anderson, and J.C.Cook, *Nature(London)*,**281**, 216(1979). 2) T.Kametani, T.Katoh, M.Tsubuki, and T.Honda, *J.Am.Chem.Soc.*, **108**, 7055(1986) and references cited therein. 3)a) T.Kametani, M.Tsubuki, H.Furuyama, and T.Honda, *J.Chem.Soc.,Chem.Commun.*,**1984**, 375; b) T.Kametani, M.Tsubuki, K.Higurashi, and T.Honda, *J.Org.Chem.*,**51**, 2932(1086); c) T.Kametani, M.Kigawa, M.Tsubuki, and T.Honda, *J.Chem.Soc., Perkin Trans.1*,**1988**, 1503. 4)a) J.A.Steel and E.J.Mosettig, *J.Org.Chem.*,**28**, 571(1963); b) J.J.Pappas, W.P.Keaveney, E.Gancher, and M.Berger, *Tetrahedron Lett.*,**1966**, 4273. 5) Selected ^{1}H NMR (270 MHz,$CDCl_3$) data are included here for reference purpose. 3 δ 4.81(1H,d,J=3.7Hz,H-22), 7.35(1H,d,J=1.8Hz,H-26). 4 δ 4.86(1H,bs,H-22),7.35(1H,d,J=1.8Hz,H-26). 6) The structure of the ethoxyethyl ethers **6** and **7** , diastereomers at the anomeric position, were easily determined based on their NMR spectra indicating the characteristic anomeric protons as follows. **6** δ 4.04(1H,bs,H-22), 5.52(0.5H,d,J=1.8Hz,H-26), 5.57(0.5H,d,J=1.8Hz,H-26). 7 δ 4.41 (0.5H,d,J=1.2Hz,H-22), 4.47(0.5H,d,J=1.2Hz,H-22), 5.56(0.5H,d,J=3.7Hz,H-26), 5.58(0.5H,d,J=3.7Hz,H-26). 7) The mixture of diastereoisomeric pyranones, which was epimeric at the acetal carbon of the ethoxyethyl group, was used without separation in the following reactions since the ethoxyethyl group was removed in the later step of the synthesis. 8)a) M.B.Yunker, D.E.Plaumann, and B.Fraser-Reid, *Can.J.Chem.*,**55**, 4002(1977); b) N.L.Holder, *Chem.Rev.*,**82**, 287(1982); c) S.F.Martin and D.E.Guinn, *J.Org.Chem.*,**52**, 5588(1987). 9) One of the diastereoisomers at the acetal carbon of the ethoxyethyl group was reported. 10) S.Takatsuto, N.Yazawa, M.Ishiguro, M.Morisaki, and N.Ikekawa, *J.Chem.Soc.,Perkin Trans.1*,**1984**, 139.

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