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The synthesis of brassinosteroid

Wei-Shan Zhou

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Lu, Shanghai, China

Abstract: The methods of A,B ring functionalization and side chain construction of brassinolide, using hyodeoxycholic acid as starting material are described. For A,B ring functionalization, a high regioselective formation of steroidal 7-oxa-lactone ring via ozone oxidation of enol silyl ether was developed. For side chain construction, several efficient stereoselective synthetic routes were carried out by us. In the meantime, (22S,23S)-typhasterol, natural typhasterol and brassinolide were synthesized.

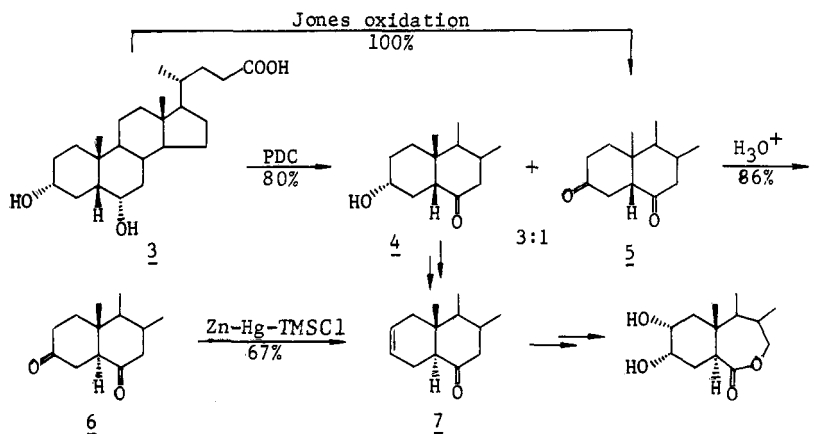
INTRODUCTION

Brassinolide (1), (22R,23R,24S)-2α,3α,22,23-tetrahydroxy-24-methyl-B-homo-7-oxa-5α-cholestan-6-one isolated from the pollen of rape (Brassica napus) is a plant growth promoting steroid having a seven-membered B-ring lactone and four successive chiral centers in the side chain(ref.1). Synthesis of brassinolide requires a suitable steroid as starting material for introduction of characteristic structural feature in the A,B ring system and stereoselective building of dihydroxyl side chain with (22R,23R and 24S)-configuration. The stigmasterol or ergosterol has been used as starting material for both purposes(ref.2). The hyodeoxycholic acid (3) is also a suitable starting material(ref.3).

A, B RING FUNCTIONALIZATION

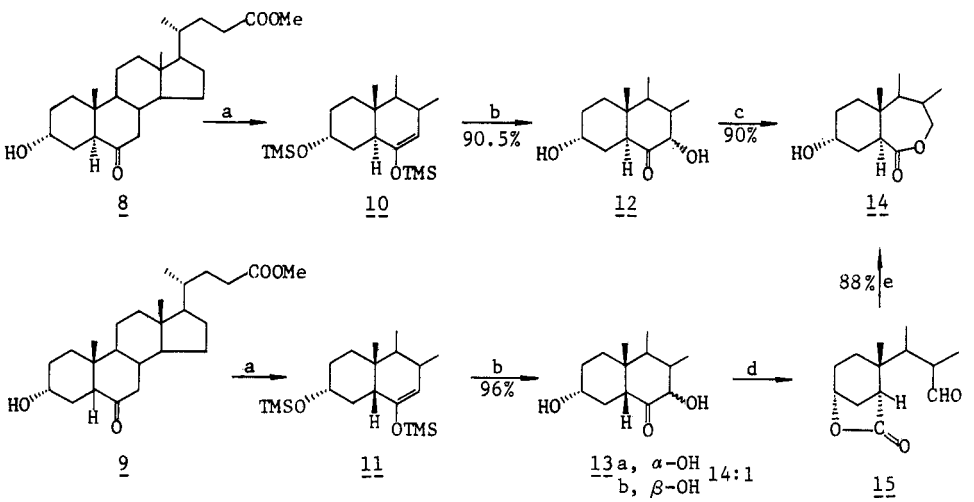
Some known methods for construction of the A,B-ring structure unit consist of that the stigmasterol or ergosterol is first converted to Δ^2-6-keto steroid which is then converted to 2α,3α-dihydroxy-7-oxalactone by hydroxylation with OsO_4-NMMNO and Baeyer-Villiger oxidation. The Δ^2 -6-keto-steroid (see 7) also could be more conveniently obtained from hyodeoxycholic acid (3) (Scheme 1).

Scheme 1



The Baeyer-Villiger oxidation for the construction of 7-oxalactone from 2,3-dihydroxy-6-keto moiety has been successively used (see Scheme 1). However, in the case of 3α(β)-hydroxy-5α(β)-steroid-6-one, only a mixture of 6-oxa- and 7-oxalactone in the ratio of ca. 1:2(ref.4) or 3:2(ref.5) was obtained. On this account a regioselective preparation of the 7-oxa-lactone 14 from methyl 3α-hydroxy-5α-6-keto cholanate (8) and methyl-3α-hydroxy-5β-6-keto cholanate (9) obtained from hyodeoxycholic acid (3) by the oxidation of an enol silyl ether with ozone was carried out by us(ref.6)(Scheme 2).

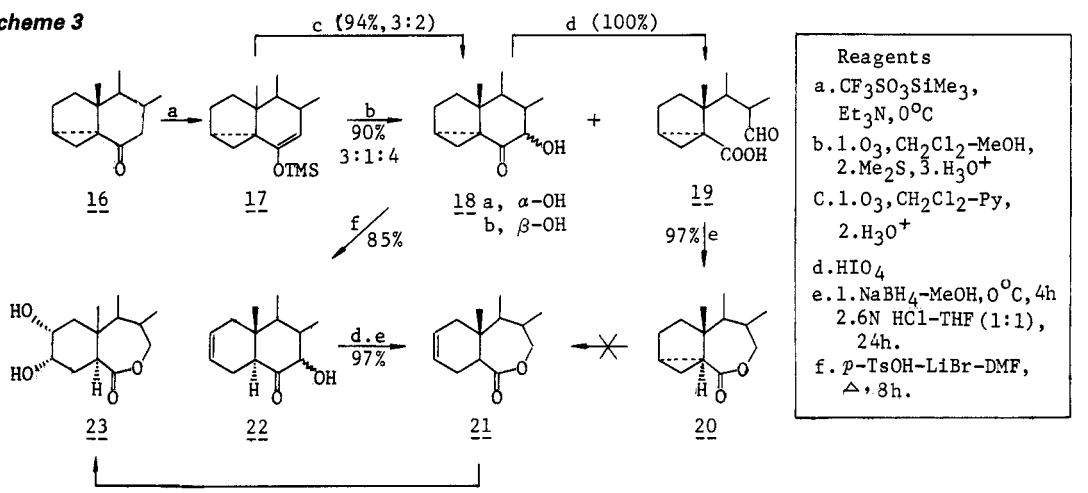
Scheme 2



Reagents: a. TMSCl, LDA, Et_3N, -78°C, b. 1.O_3, CH_2Cl_2, Py, 2.H_3O^+, c. 1.HIO_4, 2.$NaBH_4$, 3.H_3O^+, d. HIO_4, e. 1.$NaBH_4$ $2.OH^-$ 3.H_3O^+, 4.CH_2N_2.

Similarly, the trimethylsilyl enol ether 17 obtained from i-cholestanone 16 was ozonized in CH_2Cl_2-MeOH followed by reduction with Me_2S and acidification gave a mixture of 18a,b and 19 in 90% yield in a ratio of 3:1:4. When 17 was ozonized in CH_2Cl_2 in the presence of a small amount of pyridine(ref.7), only 18a,b was obtained in 3:2 ratio in 94% yield. All attempts of opening the cyclopropane ring of 20 to form compound 21 were without success, however, the cyclopropane ring of 18 could be smoothly opened to give Δ^2-ketol 22 in 85% yield. 21 could be converted to the known compound 23 (ref.8)(Scheme 3). This highly regioselective formation of 7-oxalactone ring by ozone oxidation of enolsilyl ether is a complement of the Baeyer-Villiger oxidation.

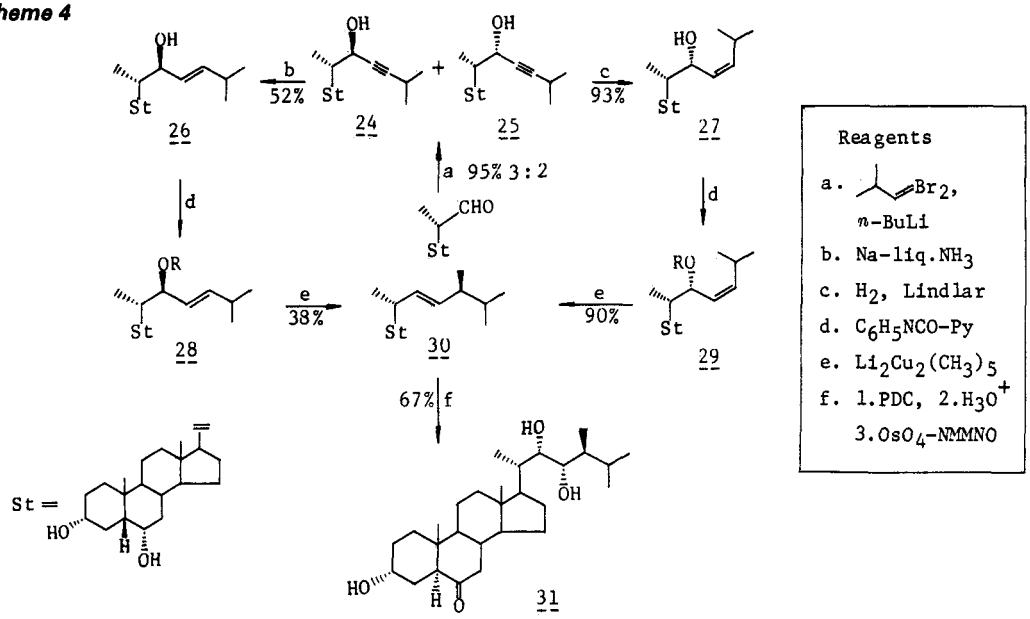
Scheme 3



SIDE CHAIN BUILDING

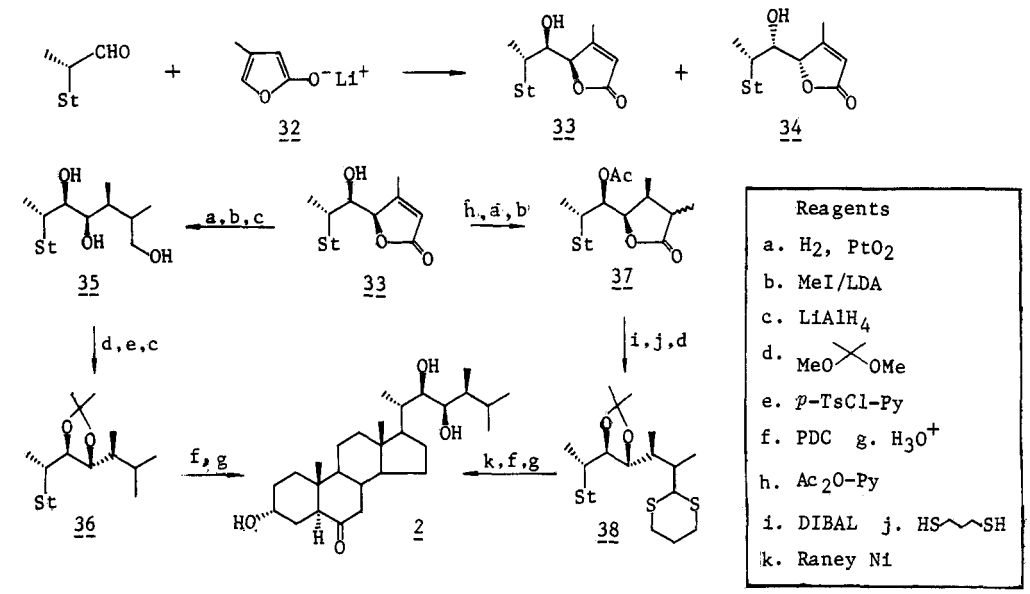
Because the method via metal acetylide produces a mixture of the Cram and anti-Cram isomers with low diastereoselectivity(ref 9), we planned to utilize the both isomer in combination of the 1,3-chiral transfer process (S_N2' reaction) for the construction of the side chain portion of brassinolide. But hydroxylation of unsaturated side chain with OsO_4-NMMNO gave the (22S, 23S) -typhasterol(ref.10)(Scheme 4).

Scheme 4



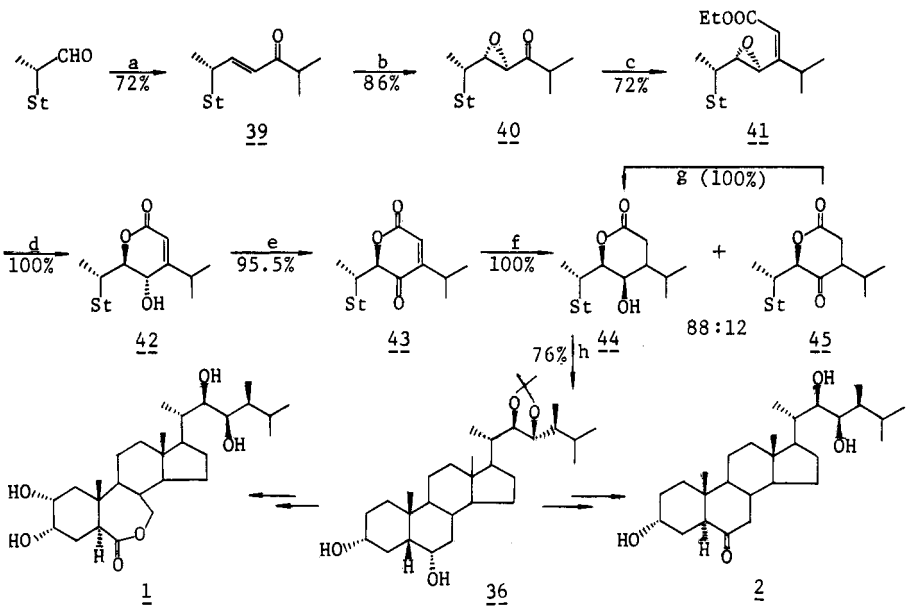
Construction of side chain was accomplished by the reaction of streoidal aldehyde with the anion of 3-methylbutenolide 32 (ref.11). Thus, the aldol reaction of aldehyde with the anion from 3-methylbutenolide 32 gave a mixture of the Cram 33 and anti-Cram 34 isomers in 99% yield in a ratio of 70:30 (ref. 12). The natural typhasterol (2) was obtained from 33 as shown in Scheme 5.

Scheme 5



A method for construction of the brassinolide side chain has been achieved on the basis of lactonization of 41 under acidic condition to form an α,β-unsa-turated-δ-lactone 42 with the inversion of the configuration at C_{22} (ref.13) (Scheme 6).

Scheme 6



Reagents: a. $MeCH_2C(O)CH=AsPh_3$; b. 1. H_2O_2-4N NaOH, 2. Ac_2O-Py c. $(MeO)_2P(O)CH_2COOEt$; d. 30%$HClO_4$-MeOH; e. PDC-CH_2Cl_2; f. H_2-PtO_2; g. KBH_4-MeOH-CH_2Cl_2; h. 1.DIBAL, 2.p-TsOH, $Me_2C(OMe)_2$, 3.$(Ph_3P)_3RhCl$.

REFERENCES

1. M.D.Grove, G.F.Spencer, W.F.Rohwedder, N.Mandava, J.F.Worley, J.D.Jr. Warthen, J.L.Flippen-Anderson, and J.C.Jr.Cook, Nature(London) 281, 216(1979).
2. W.S.Tian, Youji Huaxue, 259(1984).
3. a, W.S.Zhou, W.S.Tian, Acta Chemica Sinica, 42, 1173(1984).
   b, W.S.Tian, W.S.Zhou, Acta Chemica Sinica, to be published.
4. W.S.Zhou, B.Jiang, X.F.Pan, to be published.
5. S.Tahatsuto, N.Ikekawa, Tetrahedron Lett., 24, 917(1983).
6. W.S.Zhou, B.Jiang, X.F.Pan, to be published.
7. M.Anastasia, P.Alleni, P.Ciuffneda, A.Fiechi, A.Scala, J.Chem.Soc. Perkin Trans. I, 2117(1986).
8. M.T. Thompson, W.T.Meudt, S.R.Dutky, W.R.Lusby, D.N.Spanlding, Steroids, 39, 2894(1982).
9. M.Ishiguro, S.Takatsuto, M.Morisaki, N.Ikekawa, Chem. Commun., 962(1980).
10. W.S.Zhou, W.S.Tian, Acta Chimica Sinica, 43, 1060(1985).
11. W.S.Zhou, W.S.Tian, Tetrahedron, 43, 3705 (1987).
12. W.S.Zhou, W.S.Tian, H.Zheng, X.Y.Zhao, Acta Chimica Sinica, to be published.
13. W.S.Zhou, B.Jiang, X.F.Pan, to be published.