Synthesis of New Naturally Occurring 6-Deoxo Brassinosteroids

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Suguru Takatsuto,*[a] Tsuyoshi Watanabe,[b] Shozo Fujioka[c] and Akira Sakurai[c]

[a]*Department of Chemistry, Joetsu University of Education, Joetsu-shi, Niigata 943, Japan*
[b]*Tama Biochemical Co. Ltd., 2-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 163, Japan*
[c]*The Institute of Physical and Chemical Research (RIKEN), Wako-shi, Saitama 351-01, Japan*

New natural 6-deoxo brassinosteroids, 6-deoxoteasterone **1**, 3-dehydro-6-deoxoteasterone **2** and 6-deoxotyphasterol **3**, as well as 6-deoxocastasterone **4**, are synthesized from (20*S*)-20-formyl-6β-methoxy-3α,5-cyclo-5α-pregnane **5**.

The occurrence of new 6-deoxo brassinosteroids (BRs), 6-deoxoteasterone **1**, 3-dehydro-6-deoxoteasterone **2** and 6-deoxotyphasterol **3**, along with 6-deoxocastasterone **4** (Fig. 1) in plants, has been demonstrated.[3,4,6] Recently, we have identified 6-deoxotyphasterol **3**, 6-deoxocastasterone **4**, typhasterol and castasterone in a wild type of *Arabidopsis thaliana*, suggesting the possibility that both the late and early C6-oxidation pathways[4] of the BR biosynthesis are operating in *A. thaliana*.[9] In order to establish the involvement of the late C6-oxidation pathway of the brassinolide biosynthesis in *A. thaliana*, the 6-deoxo BRs (**1**, **2**, **3** and **4**) are required as authentic specimens. It is also necessary to evaluate their biological activities. Because of the scarcity of the natural products, we now describe the synthesis of these 6-deoxo BRs.

The side chain of these 6-deoxo BRs was constructed in six steps (Scheme 1) in 26% overall yield from the known C-22-aldehyde **5**.[12] The key reactions for the construction of the (22*R*,23*R*,24*S*)-side chain of these C_{28} BRs are the reaction of the C-22-aldehyde **5** with the Grignard reagent derived from (*Z*)-1-bromoprop-1-ene, orthoester Claisen rearrangement[13] of the resulting (22*S*,23*Z*)-allylic alcohol, and the asymmetric dihydroxylation[10] of the crinosterol side chain. As the transformation of the diol **9** into brassinolide is

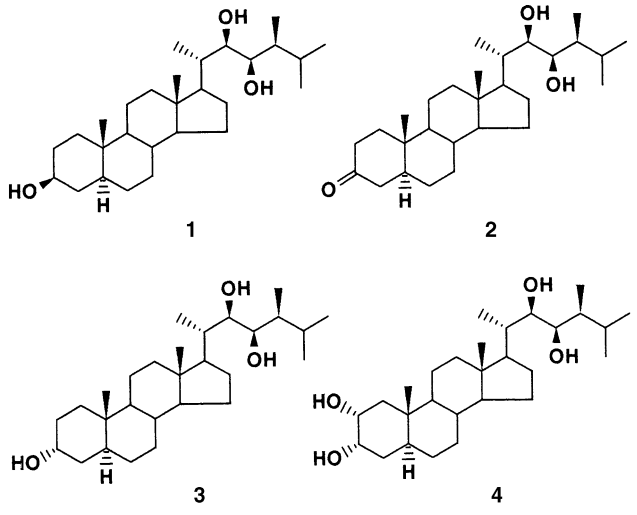
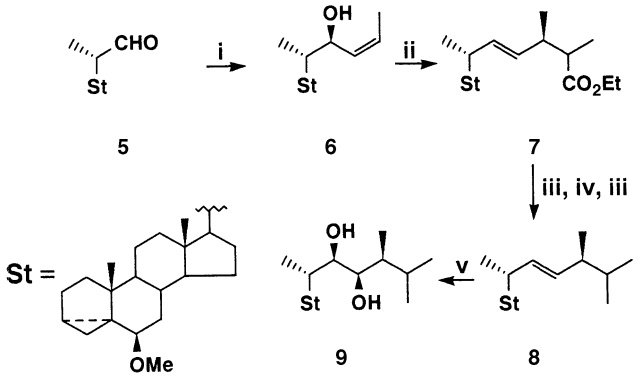
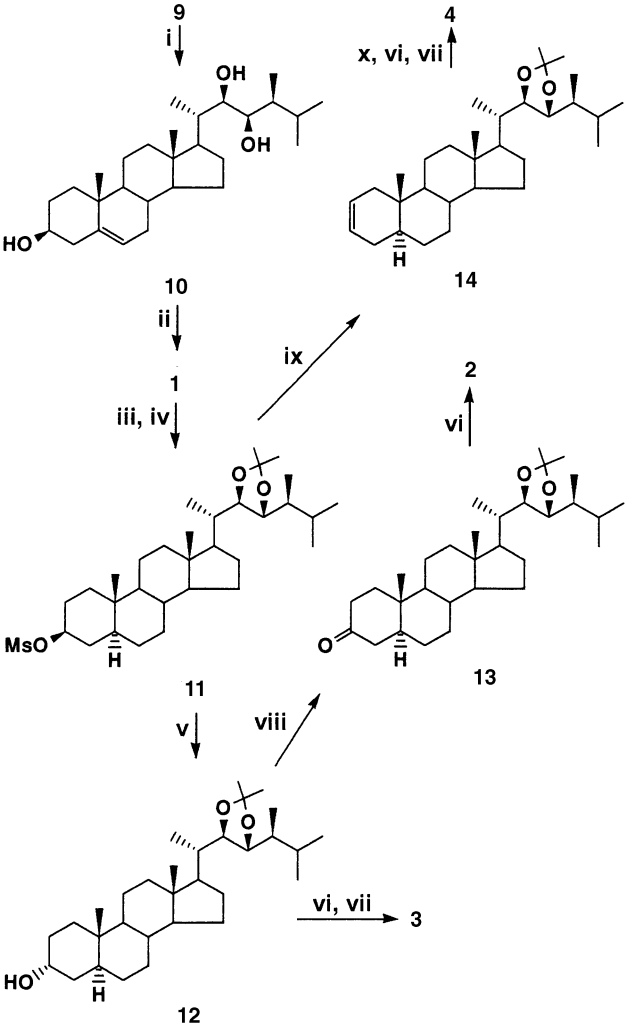


Fig. 1 Structure of 6-deoxo brassinosteroids **1–4**



Scheme 1 *Reagent and conditions:* i, BrMgCH=CHCH$_3$, THF, 0 °C to room temp., 1 h; ii, Et(OEt)$_3$, propionic acid, xylene, reflux, 2 h; iii, LiAlH$_4$, THF, reflux, 2 h; iv, MeSO$_2$Cl, Et$_3$N, toluene, room temp., 2 h; v, OsO$_4$, K$_3$[Fe(CN)$_6$], dihydroquinidine *p*-chlorobenzoate, K$_2$CO$_3$, methanesulfonamide, Bu^{t}OH–H$_2$O, room temp., 15 d



Scheme 2 *Reagent and conditions:* i, TsOH, aq. dioxane, reflux, 4 h; ii, H$_2$/Pd–C, EtOH, 40 °C, 2 h; iii, TsOH, acetone, room temp., 1 h; iv, MeSO$_2$Cl, pyridine, room temp., 1 h; v, KO$_2$, 18-crown-6, DMSO–DMF, room temp., 2 h; vi, 70% aq. AcOH, 100 °C, 4 h; vii, 5% KOH–MeOH, room temp., 1 h; viii, PCC, CH$_2$Cl$_2$, room temp., 1 h; ix, Li$_2$CO$_3$, DMF, 170 °C, 1 h; x, OsO$_4$, NMO, aq. THF, room temp., 4 h

*To receive any correspondence.

known,[18] the formal synthesis of brassinolide was achieved.

We next modified the A/B ring of the diol **9** for the target 6-deoxo BRs (Scheme 2). Regeneration of a 5-en-3β-ol system followed by hydrogenation provided 6-deoxoteasterone **1** quantitatively, which was converted to the sulfonate **11**. Introduction of the 3α-hydroxy and 2-ene functionality was achieved in 66 and 71% yield, respectively. The 3α-alcohol **12** was deprotected to afford 6-deoxotyphasterol **3**. The alcohol **12** was oxidized to give, after deprotection, 3-dehydro-6-deoxoteasterone **2** in 83% yield. Introduction of the 2α,3α-diol group into the 2-ene **14** followed by deprotection afforded 6-deoxocastasterone **4** in 72% yield.

In conclusion, we have developed a convenient method to construct the (22*R*,23*R*,24*S*) side chain of natural C_{28} BRs and synthesized three new 6-deoxo BRs (**1**, **2** and **3**) and also 6-deoxocastasterone **4**. The method is also suitable for the preparation of biosynthetically important 6-oxo BRs such as teasterone, 3-dehydroteasterone, typhasterol and castasterone.

Techniques used: ^{1}H and ^{13}C NMR, EI-MS, EI-HR-MS, FAB-MS

References: 38

Figure: 1

Schemes: 2

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