A Concise Stereoselective Synthesis of Castasterone

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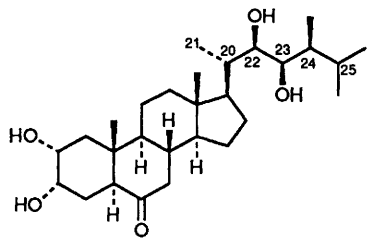
A stereoselective synthesis of a brassinosteroid, castasterone, has been achieved by employing a pyranone derivative as a side-chain precursor.

Brassinosteroids such as castasterone (**1**)[1] and brassinolide (**2**)[2] are plant growth-regulating substances. Because of their novel structural features and their attractive biological activities, much effort has been devoted to the development of methods and strategies for their synthesis.[3] Difficulties in their synthesis were usually encountered in the stereoselective construction of four contiguous acyclic chiral centres on the side chains, including a *syn*-diol system.

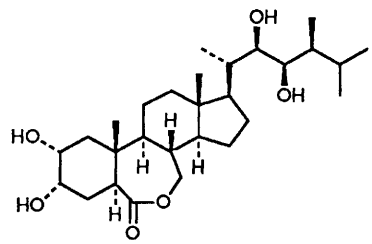
We have recently achieved the stereocontrolled syntheses of brassinolide and its congeners where the stereochemistry of the side chains was determined by the stereoselective reduction of oxygen-containing cyclic intermediates such as the tetronate (**3**)[3f,3h] and the pyranone (**4**)[3g] derivatives.

As an extension of the work on the synthesis of brassinosteroids, we have designed an alternative route for controlling the stereochemistry of the side chain, in which a stereoselective hydride reduction and subsequent 1,4-addition of the 24-methyl function to the pyranone derivative used as a side-chain precursor was involved as a key reaction, and here report its successful application to the synthesis of castasterone.

Treatment of the known aldehyde (**5**)[3d] with 2-lithio-4-methylfuran[4] in tetrahydrofuran (THF) afforded the Cram-adduct (**6**)† as a major product in 57.9% yield together with the anti-Cram-adduct (**7**) in 20.4% yield. The (22*R*)-compound (**6**) was then oxidised with *N*-bromosuccinimide (NBS)[5] in aqueous THF to give the lactol (**8**) which on exposure to pyridinium chlorochromate (PCC) provided the desired cyclic intermediate (**9**) in 81.2% overall yield from (**6**). Reduction of (**9**) with sodium borohydride–cerium(III) chloride[6] in methanol–methylene chloride furnished the

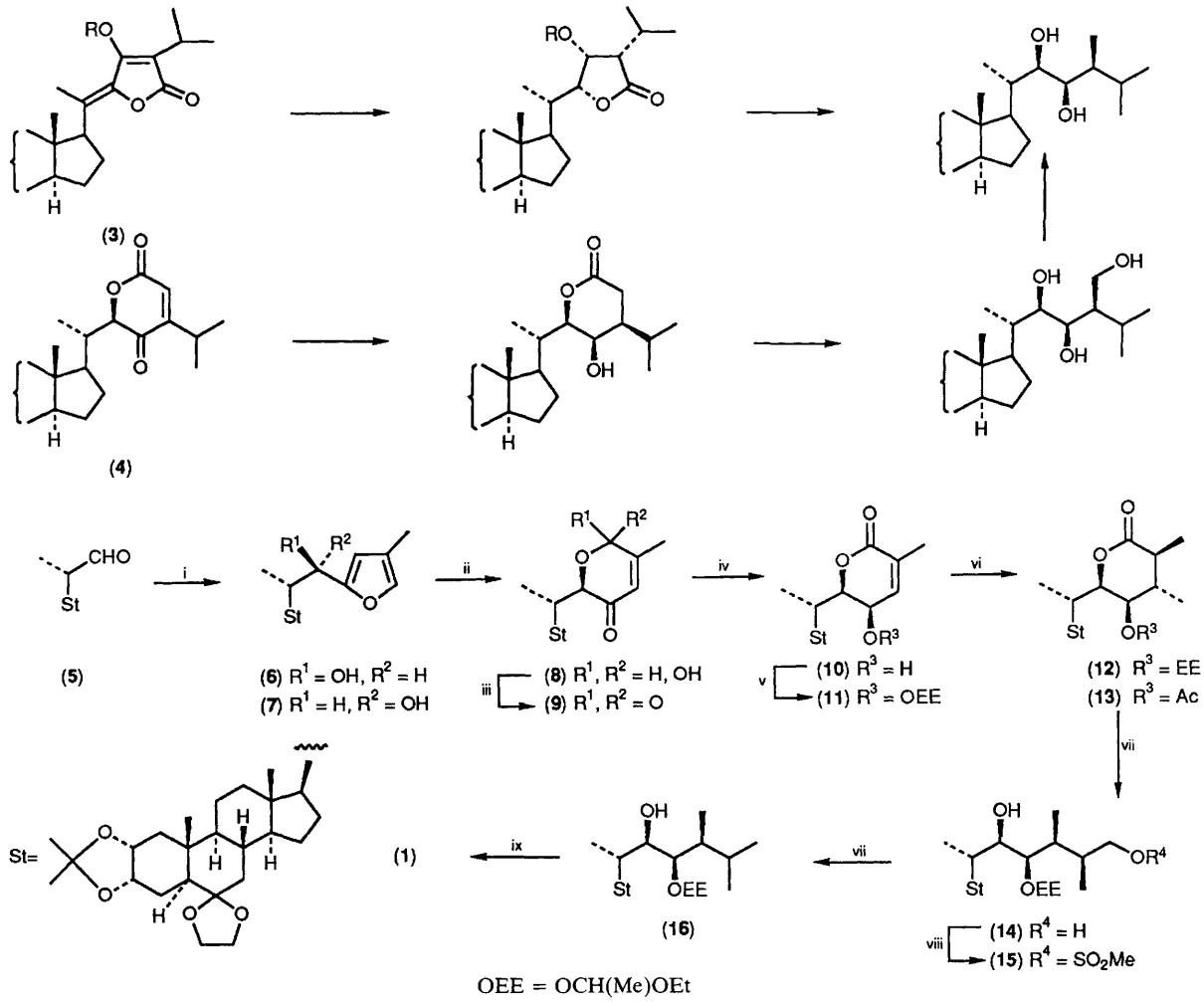


(**1**)



(**2**)

† Satisfactory analytical and spectral data were obtained for all new compounds.



Scheme 1. *Reagents and conditions:* i, 2-lithio-4-methylfuran, THF, −78 °C; ii, NBS, THF, H_2O; iii, PCC, AcONa, CH_2Cl_2; iv, $NaBH_4$, $CeCl_3·7H_2O$, MeOH, CH_2Cl_2; v, CH_2=CHOEt, PPTS, CH_2Cl_2; vi, Me_2CuLi, Et_2O, −10° C, 1 h; vii, $LiAlH_4$, Et_2O; viii, $MeSO_2Cl$, Et_3N, CH_2Cl_2; ix, 10% HCl, THF.

alcohol (**10**)‡ as the sole product in 97.1% yield, which was unambiguously assigned the (23*R*)-configuration on the basis of its NMR spectrum. The observed stereoselectivity can be rationalised by assuming that the hydride attack occurred exclusively from the less hindered side of the carbonyl group, because the steroidal nucleus was large enough to prevent hydride attack from the other side.

Since the *syn*-diol system with the desired stereochemistry was thus constructed, we turned our attention to the introduction of the 24-methyl group with the (*S*)-configuration.

Protection of the hydroxy group of (**10**) with ethyl vinyl ether and pyridinium toluene-*p*-sulphonate (PPTS) in methylene chloride yielded the ethoxyethyl ether (**11**),§ in 94.2% yield, which on treatment with lithium dimethylcuprate in ether afforded the lactone (**12**) in 84.6% yield. Again no compounds diastereoisomeric at the 24 and 25 positions were isolated in this 1,4-conjugate addition. The stereochemistry at the 23 and 24 positions of (**12**) was determined to be (*R*) and (*S*), respectively, based on the coupling constants in the NMR spectrum of the acetate (**13**),‡ derived from (**12**) by deprotection of the ethoxyethyl group on treatment with toluene-*p*-sulphonic acid followed by acetylation with acetic anhydride. Moreover, the stereochemistry at the 25 position of (**12**) was

‡ *Selected spectroscopic data* for (**10**): $\nu_{max.}$ ($CHCl_3$) 3350 and 1700 cm^{-1}; δ ($CDCl_3$) 0.72 (3H, s, 18-H_3), 0.83 (3H, s, 19-H_3), 1.25 (3H, d, *J* 6.7 Hz, 21-H_3), 1.32 and 1.48 (each 3H, each s, Me_2C), 1.95 (3H, d, *J* 1.2 Hz, 27-H_3), 3.72—3.95 (4H, m, OCH_2CH_2O), 4.08—4.13 (2H, m, 2-H and 23-H), 4.26 (1H, br d, *J* 4.3 Hz, 3-H), 4.29 (1H, d, *J* 1.8 Hz, 22-H), and 6.67 (1H, dd, *J* 1.2 and 6.1 Hz, 24-H).

(**13**): $\nu_{max.}$ ($CHCl_3$) 1730 cm^{-1}; δ ($CDCl_3$) 0.68 (3H, s, 18-H_3), 0.83 (3H, s, 19-H_3), 1.11 (3H, d, *J* 6.7 Hz, 21-H_3), 1.20 and 1.24 (each 3H, each d, *J* 6.7 Hz, 27- and 28-H_3), 1.33 and 1.48 (each 3H, each s, Me_2C), 2.07 (3H, s, COMe), 3.70—4.00 (4H, m, OCH_2CH_2O), 4.00—4.20 (1H, m, 2-H), 4.27 (2H, br s, 3-H and 22-H), and 4.81 (1H, t, *J* 1.8 Hz, 23-H).

(**14**): $\nu_{max.}$ ($CHCl_3$) 3400 cm^{-1}; δ ($CDCl_3$) 0.67 (3H, s, 18-H_3), 0.83 (3H, s, 19-H_3), 0.86 and 0.88 (each 1.5H, each d, *J* 6.7 Hz, 27- or 28-H_3), 0.89 and 0.91 (each 1.5H, each d, *J* 6.7 Hz, 27- or 28-H_3), 0.97 (3H, d, *J* 6.7 Hz, 21-H_3), 1.24 and 1.26 (each 1.5H, each d, *J* 6.7 Hz, CH_2*Me*), 1.33 and 1.48 (each 3H, each s, Me_2C), 1.34 and 1.36 (each 1.5H, each t, *J* 7.3 Hz, CH*Me*), 3.40—4.00 (10H, m, 22-H, 23-H, 26-H_2, OCH_2Me and OCH_2CH_2O), 4.03—4.20 (1H, m, 2-H), 4.27 (1H, br d, *J* 3.7 Hz, 3-H), and 4.58 and 4.88 (each 0.5H, each q, *J* 5.5 Hz, O*CH*Me).

§ The mixture of diastereoisomeric ethers, 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 a later step of the synthesis.

tentatively assigned as (*S*) from a molecular model study which adopted the stable all-*trans*-conformation for the δ-lactone ring. In order to complete the synthesis of castasterone, the lactone (**12**) was treated with lithium aluminium hydride in ether to give the primary alcohol (**14**),‡ which was further converted into (**16**) by reduction of its methanesulphonate (**15**) with lithium aluminium hydride in ether in 80.4% yield from (**12**). Finally, all the protecting groups in (**16**) were removed by acid treatment in one step to provide castasterone (**1**), m.p. 259—260 °C (lit. m.p. 259—261,[1] 252—255,[3b] and 258—260 °C[3d]), $[\alpha]_D^{25}$ +0.92° (*c* 1.46, $CHCl_3$–MeOH, 9 : 1) {lit.[3d] $[\alpha]_D^{24.5}$ +0.03° (*c* 1.17, $CHCl_3$–MeOH, 9 : 1)}, in 93.5% yield, whose spectroscopic data and TLC behaviour were identical with those of an authentic specimen.[3h]

Since the conversion of castasterone into brassinolide (**2**) has already been achieved,[3a—d] this synthesis constitutes its formal synthesis.

Thus, we have developed a new synthetic strategy for steroselective construction of the brassinolide side chain, in a procedure which should be widely applicable to the synthesis of other brassinosteroids.

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