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Synthesis of 28-Norbrassinolide[1)]

28-Norbrassinolide (2α,3α,22*R*,23*R*-tetrahydroxy-B-homo-7-oxa-5α-cholestan-6-one), which is an analog of the plant growth promoting steroidal lactone, brassinolide, was synthesized *via* 22*R*,23*R*-dihydroxycholesterol. Syntheses of the other C-22, 23 stereoisomers of 22,23-dihydroxycholesterol were also described.

Keywords——brassinolide; plant growth promoter; 22,23-dihydroxycholesterol; 22-dehydrocholesterol; Baeyer–Villiger oxidation

Brassinolide (**1**) isolated from rape pollen is a steroidal lactone producing a novel plant growth-promoting effect.[2)] The remarkable biological activity[2,3)] and the novel structural features made **1** an enticing synthetic target. We[4)] and others[5)] have recently completed synthesis of **1**. Syntheses of the analogs, 24-epibrassinolide **2**[6)] and homo-brassinolide **3**[7)] were also reported. It is interesting to note that **2** and **3** showed potent but a little weaker biological activity, compared to **1**.[3,6)] To have a further insight into the C-24 substituent effect on biological activity and the stereochemical importance of the vicinal glycol moiety, we have now aimed to synthesize all the four C-22, 23 stereoisomers of 28-nor-brassinolide. Described here are syntheses of the synthetic progenitors, 22,23-dihydroxycholesterols (**6**—**9**) and transformation of one of the stereoisomers **6** into 28-norbrassinolide (**20**).

Apparently, the precursors of the vicinal glycols (**6**—**9**) are (22*E*)- and (22*Z*)-dehydrocholesterol (**4** and **5**). The *Z* olefin **5**, mp 137—139°, was easily prepared according to the published method.[8)] The *E* isomer **4**, mp 130—132°, was obtained in 68% overall yield from the previously described[9)] ester **14** in four steps: (i) LAH/THF; (ii) MsCl/pyridine; (iii) LAH/THF; (iv) a trace of HCl–MeOH. Oxidation of the *E* olefin **4** with a catalytic amount of OsO_4 and N-methylmorpholine N-oxide in *t*BuOH–THF–H_2O (10: 6: 1)[10)] gave a mixture (75% yield) of the more polar triol **6**, mp 187—191°, and the less polar triol **7**, mp 182—183° (2: 5). Since the *Z* olefin **5** was more reluctant to react in the same conditions, this was treated with OsO_4 in Et_2O for 10 days to give a mixture (69% yield) of the less polar triol

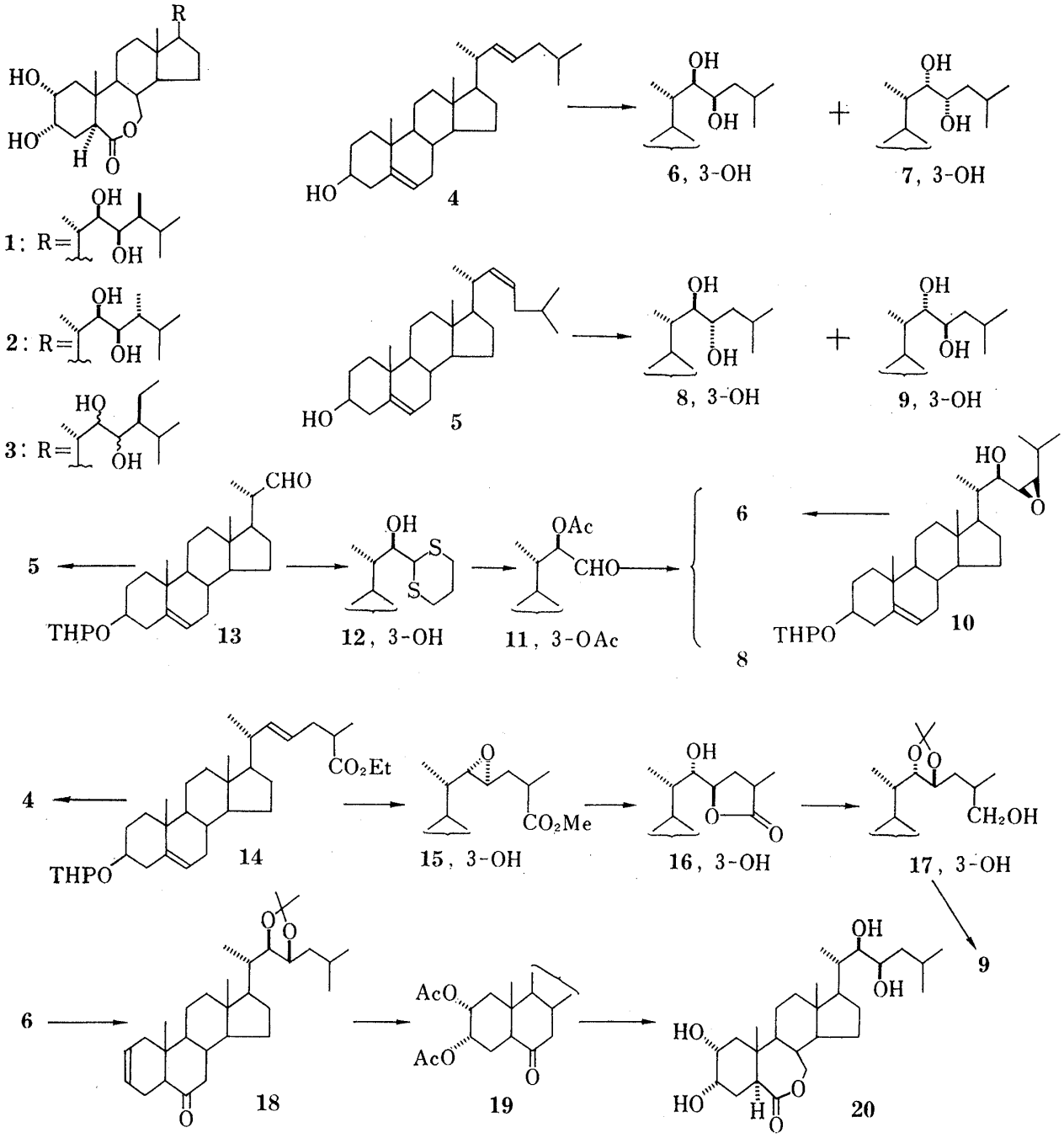

Chart 1

8, mp 189—190° and the more polar triol **9**, mp 192—194° (7 : 1). Configurational assignment of the triol **6** as 22*R*, 23*R* came from the interrelation to the (22*R*,23*R*)-epoxide **10**, which was used as an intermediate of our brassinolide synthesis.[4] Thus, the THP ether of **10** was treated with LAH in THF at reflux to yield, after deprotection (a trace of HCl in MeOH–THF), the triol **6** identified by thin-layer chromatography (TLC), nuclear magnetic resonance (NMR) and mixed mp. The same triol **6** was alternatively prepared by Grignard reaction (isoBuMgBr/THF) of the (22*R*)-aldehyde **11**, mp 142—146°, which in turn was synthesized from the 20-formyl compound **13**[11] *via* the 1,3-dithian derivative **12**, mp 199—202° in 4 steps (46% overall yield): (i) 1,3-dithiane–BuLi/THF; (ii) HCl/C_6H_6–THF–MeOH; (iii) Ac_2O/pyridine; (iv) BF_3-etherate–HgO/THF–H_2O. The Grignard reaction followed by saponi-

fication afforded, besides the triol **6** (46%), the isomeric triol **8** (22%) identical with the major product of the above-mentioned OsO_4 oxidation of **5**. Therefore, the stere ochemistry of **8** was determined as 22*R*, 23*S*. From the known mechanism (*cis*-addition) of OsO_4 oxidation and the established geometry of the olefins (**4** and **5**), the other triols **7** and **9** should have the configurations of 22*S*, 23*S*, and 22*S*, 23*R*, respectively. Confirmation of the stereochemistry of **9** was rested on its alternative synthesis. Thus, the (22*S*,23*S*)-epoxide **15**, mp 124—125°, derived[9] from the ester **14** was lactonized (70% $HClO_4$/THF) to give **16**, mp 206—209° in 90% yield, with inversion of the configuration at C-23. Reduction of **16** (LAH–THF) followed by acetonide formation (Me_2CO– *p*-TsOH) gave the alcohol **17**, mp 197—199° (94%), which on partial tosylation (*p*-TsCl/pyridine), reduction (LAH/THF) and deprotection (80% aq. AcOH, 90°) yielded **9** in 22% overall yield.

Transformation of the (22*R*,23*R*)-triol **6** into 28-nor-brassinolide (**20**) was achieved with the similar procedures as described for **1**.[4] The enone **18**, mp 186—188°, was obtained in 41% overall yield from **6** by the sequences: (i) acetonide formation (Me_2CO, *p*-TsOH); (ii) mesylation (MsCl/pyridine); (iii) hydroboration-oxidation (BH_3-THF complex and then 2 N NaOH–30% H_2O_2); (iv) oxidation (pyridinium chlorochromate/CH_2Cl_2; (v) elimination of MsOH (LiBr/DMF, reflux). Oxidation of **18** (a trace of OsO_4-N-methylmorpholine–N-oxide/THF–*t*BuOH–H_2O (10:6:1)[10]), followed by acetylation (Ac_2O–4-dimethylamino-pyridine/pyridine) afforded the diacetate **19**, mp 177—180° in 87% yield. Baeyer–Villiger oxidation of **19** (CF_3CO_3H–Na_2HPO_4/CH_2Cl_2, 0°) and the subsequent base treatment (4% KOH/MeOH–THF) furnished, in 56% yield, 28-norbrassinolide (**20**) [mp 256—259° (dec.), $[\alpha]_D^{14}$ +32° (*c*=1.15, MeOH), *m/e*: 394 ($M-4H_2O$), 379 (C-22, 23 fission) and 361 ($379-H_2O$)]. Conversion of the other triols (**7**—**9**) to the corresponding 28-norbrassinolide isomers are in progress.

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