Total Synthesis of (±)-Paeoniflorigenin and Paeoniflorin

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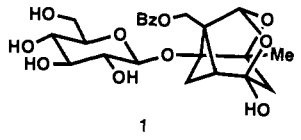
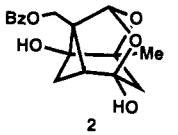
Paeoniflorin (**1**),[1] the β-glucoside of paeoniflorigenin (**2**), is a novel complex terpenoid from the roots of the Chinese paeony (*Paeonia lactiflora*), which is widely used in traditional Chinese medicine. Interesting anticoagulant, sedative, antiinflamatory, and neuromuscular activities have been reported.[2] The chemical synthesis of **1** and of (±)-**2**, a prominent unsolved problem for almost three decades,[3] is reported herein.



1

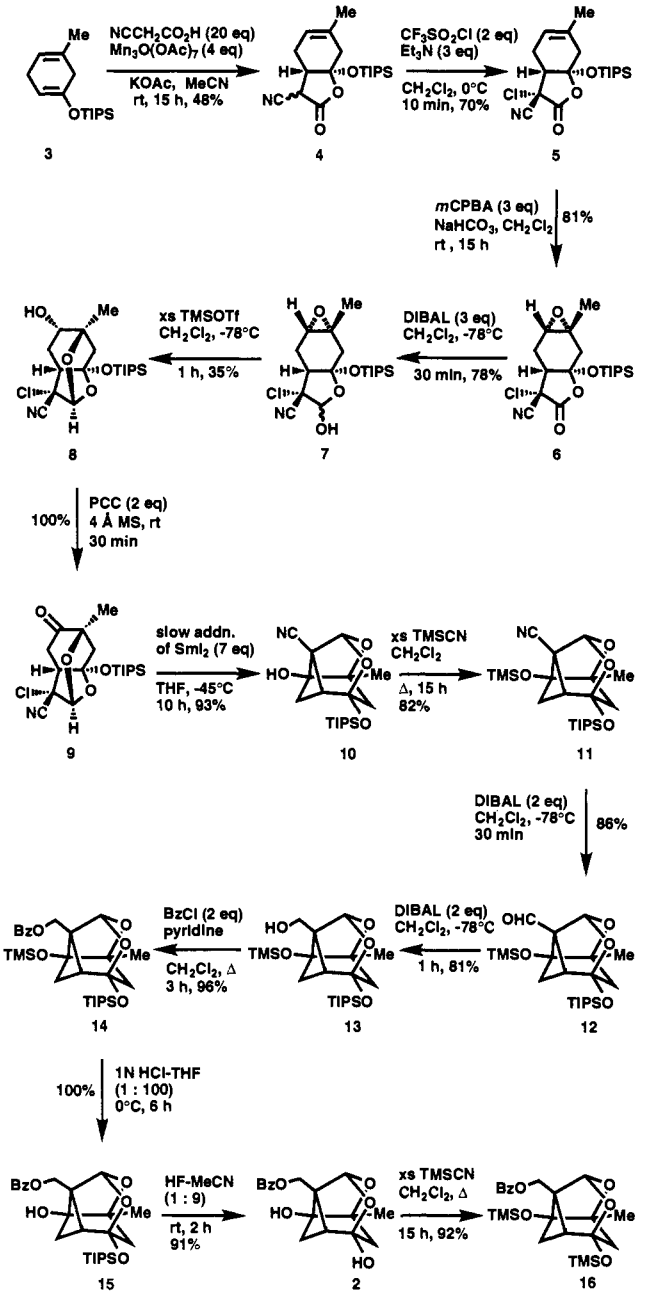


2

Mn(III)-promoted annulation of the dihydro-*m*-cresol triisopropylsilyl (TIPS) ether (**3**)[4] with cyanoacetic acid[5] provided **4**, which contains all 10 carbons of the terpenoid part of **1** or **2** (Scheme I). The major side reaction in this step is the aromatization of **3** to the TIPS ether of *m*-cresol. The chlorination of **4** under the indicated conditions afforded the α-chloronitrile **5** stereospecifically. Epoxidation of **5** by peracid was also stereospecific and resulted in selective formation of **6**. Reduction of **6** by diisobutylaluminum hydride gave a mixture of epimeric lactols **7**. These lactols were extremely sensitive to base or silica gel and decomposed by a pathway involving deprotonation of the lactol hydroxyl, lactol ring cleavage, and irreversible loss of the (triisopropylsilyl)oxy group to form an unstable keto aldehyde. The epimeric lactols **7** could neither be separated nor interconverted, but one of the lactols in the mixture was converted to the hydroxy tricyclic ether **8** using trimethylsilyl triflate at low temperature. Pyridinium chlorochromate effected selective oxidation of the secondary hydroxyl group of **8** to form the tricyclic ketone **9**.

The novel SmI_2-induced cyclization of **9** to **10**, corresponding to a normally unfavorable aldol cyclization, proceeded in excellent yield to give the core substructure of paeoniflorin (Scheme I). In the presence of bases such as triethylamine, the β-hydroxynitrile **10** suffers rapid retro aldol cleavage of the cyclobutane ring, and for this reason, silylation of the bridgehead hydroxyl group of **10** could not be effected under the usual conditions (TMSCl and tertiary amine bases). However, trimethylsilylcyanide (without base) cleanly transformed **10** to the bridgehead silyl ether **11**. The cyano group of **11** was reduced via the aldehyde **12** to yield the corresponding primary alcohol **13**, which upon benzoylation afforded the benzoate **14** in excellent yield. Both of the silyl protecting groups were removed upon exposure of **14** to 1:9 50% aqueous hydrofluoric acid–acetonitrile at 23 °C to form the very sensitive paeoniflorigenin (**2**), which was isolated as the bis TMS derivative **16** for comparison with a naturally derived specimen.

Scheme I



Under milder conditions, the TMS ether was selectively cleaved to form the bridgehead alcohol **15**, a key intermediate for the synthesis of paeoniflorin. Totally synthetic (±)-**15** and (±)-**16** and naturally derived **15** and **16** were identical by 500-MHz ^1H NMR, ^{13}C NMR, IR, mass spectral, and chromatographic comparison.

Naturally derived **15** and **16** were obtained from **1**[6] by the following sequence (Scheme II): (1) selective silylation of the primary hydroxyl of **1** to form **17** (*tert*-butyldimethylsilyl chloride–Et_3N–4-(dimethylamino)pyridine–CH_2Cl_2, 23 °C, 48 h, 91%);

(1) (a) Shibata, S.; Aimi, N.; Watanabe, M. *Tetrahedron Lett.* **1964**, 1991. (b) Aimi, N.; Inaba, M.; Watanabe, M.; Shibata, S. *Tetrahedron* **1969**, *25*, 1825.

(2) Kimura, M.; Kimwia, I.; Nojima, H.; Takahashi, K.; Hayashi, T.; Shimizu, M.; Morita, N. *Jpn. J. Pharmacol.* **1984**, *35*, 61 and refs cited therein.

(3) For synthetic efforts by other groups, see: Hatakeyama, S.; Kawamura, M.; Shimanuki, E.; Saijo, K.; Takano, S. *Synlett.* **1992**, 114.

(4) Synthesized from the TIPS ether of *m*-cresol by Birch reduction with 4.7 equiv of Li in liquid NH_3 and EtOH as proton source.

(5) For methodology, see: (a) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1985**, *26*, 4291. (b) Corey, E. J.; Ghosh, A. *Chem. Lett.* **1987**, 223.

(6) We are indebted to Professor Shoji Shibata of Tokyo University and Professor Xiao Tian Liang of the Beijing Institute of Materia Medica for authentic samples of **1**. Additional quantities of **1** were obtained by us from *P. lactiflora* by the following process. The ground roots were extracted with hot methanol for 48 h, and the resulting extract was concentrated to a residue which was dissolved in a little water and extracted several times with 1-butanol. The red oil obtained upon concentration of the 1-butanol-soluble fraction was extracted with acetone, and the extracts were concentrated and purified by chromatography on silica gel (9:1 $CHCl_3$–MeOH) to give paeoniflorin in *ca.* 2% yield.

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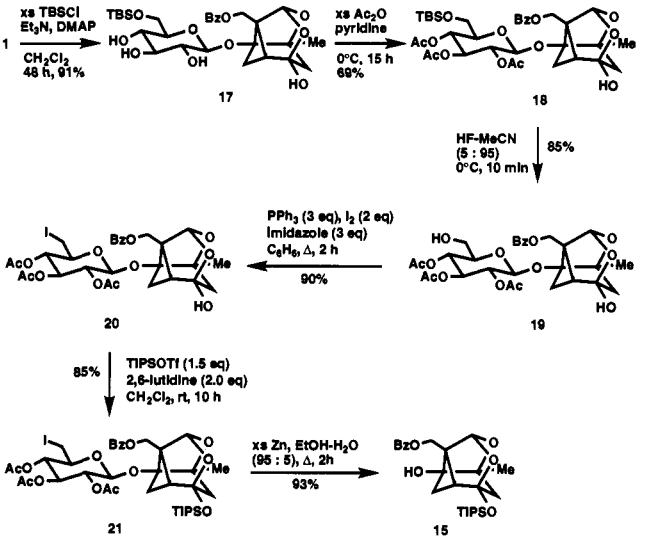
Scheme II

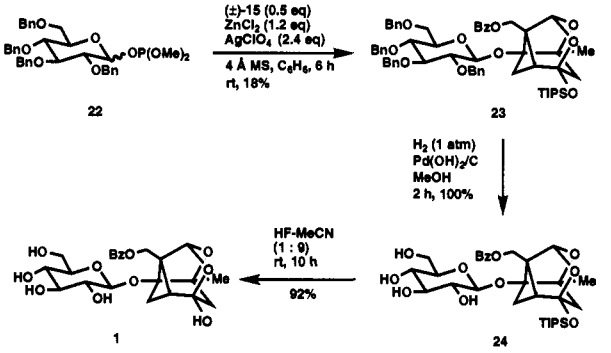


(2) acetylation to **18** (Ac_2O–py, 0 °C, 15 h, 69%); (3) desilylation to **19** (5% aqueous HF–MeCN, 0 °C, 10 min, 85%); (4) iodination (Ph_3P, I_2, imidazole, C_6H_6, at reflux for 2 h, 90%) to give iodo sugar **20**; (5) silylation of **20** to give **21** (TIPSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C, 10 h, 85%); and (6) reductive cleavage of **21** (excess Zn dust, 20 : 1 EtOH–H_2O, reflux, 2 h, 93%) to form **15**, which was transformed into **2** and **16** as shown in Scheme II.

The synthesis of paeoniflorin from the synthetic mono TIPS ether **15** was successfully carried out using the method of Watanabe *et al.*[7,8] The 1-dimethylphosphite derivative of the tetrabenzyl ether of 1-glucose underwent coupling with (±)-**15** in the presence of $ZnCl_2$–$AgClO_4$ in benzene to form a mixture of **23** and its α-anomer (1:1) and the corresponding 1:1 α,β-anomeric mixture from the enantiomer of **15** in 71% total yield (78% based on recovery of starting material **15**). Preparative thin-layer chromatography on silica gel plates followed by HPLC using a preparative Daicel OD column separated this mixture of four components and afforded pure **23**. Debenzylation of **23** gave **24**, which was cleanly disilylated to give synthetic **1** (Scheme III). Synthetic **1** and its pentaacetate were compared with

(7) Watanabe, Y.; Nakamoto, C.; Ozaki, S. *Synlett* **1993**, 115.

Scheme III



authentic samples provided by Prof. Shoji Shibata (500-MHz ^1H NMR, 100-MHz ^{13}C NMR, IR, TLC, optical rotation[9]) and were found to be indistinguishable. The inefficiency of the conversion of **15** to paeoniflorin **1** underscores the need for improved methodology for β-glycosylation of tertiary or very hindered alcohols (studies toward this end are currently underway) despite the noteworthy general advances recently reported.[8]

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Supplementary Material Available: Characterization data for new compounds (8 pages). Ordering information is given on any current masthead page.

(8) A number of other processes for β-glycosylation were evaluated using model tertiary alcohols such as 1-adamantanol or the synthetic mono-TIPS ether **15** but did not seem promising. Included among these methods [for a recent review, see: Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503] were the following procedures using various tetraacetyl glucose derivatives: (1) Koenigs-Knorr coupling on the 1-bromide; (2) Mukaiyama method, $Ph_3C^+ClO_4^-$ on the 1-acetate; (3) Kahn method, Tf_2O or TMSOTf on the 1-phenylsulfinyl derivative; (4) Fraser-Reid method, *N*-iodosuccinimide–TMSOTf on the 1-thiomethyl derivative; (5) Wong method, TMSOTf on the 1-dibenzylphosphite; and (6) the Schmidt trichloroimidate process using $BF_3 \cdot Et_2O$ or TMSOTf. The use of 1-fluoroglucose tetrabenzyl ether with Cp_2HfCl_2–$AgClO_4$ (Suzuki), $SnCl_2$–$AgClO_4$ (Mukaiyama), or 1,2-α-oxidoglucose tribenzylether (Danishefsky) did not result in formation of the desired glycoside.

(9) The rotation of the pentaacetate of **1** was found to be $[\alpha]^{23}_D$ +1.33° (c = 0.9, MeOH) for both synthetic and reference samples rather than +13.5° as reported in ref 1. Mp and mixture mp of synthetic and naturally derived **1** pentaacetate were identical (mp 159–160 °C).