Total Synthesis of (\pm) -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 (\pm) -2, a prominent unsolved problem for almost three decades,³ is reported herein.



Mn(III)-promoted annulation of the dihydro-m-cresol triisopropylsilyl (TIPS) ether $(3)^4$ with cyanoacetic acid⁵ 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, silvlation 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 silvl 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 silvl 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 (\pm) -15 and (\pm) -16 and naturally derived 15 and 16 were identical by 500-MHz ¹H NMR, ¹³C NMR, IR, mass spectral, and chromatographic comparison.

Naturally derived 15 and 16 were obtained from 16 by the following sequence (Scheme II): (1) selective silvlation of the primary hydroxyl of 1 to form 17 (tert-butyldimethylsilyl chloride-Et₃N-4-(dimethylamino)pyridine-CH₂Cl₂, 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,

⁽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 NH₃ 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 CHCl3-MeOH) to give paeoniflorin in ca. 2% vield.

Scheme II



(2) acetylation to **18** (Ac₂O-py, 0 °C, 15 h, 69%); (3) desilylation to **19** (5% aqueous HF-MeCN, 0 °C, 10 min, 85%); (4) iodination (Ph₃P, I₂, imidazole, C₆H₆, at reflux for 2 h, 90%) to give iodo sugar **20**; (5) silylation of **20** to give **21** (TIPSOTf, 2,6-lutidine, CH₂Cl₂, 23 °C, 10 h, 85%); and (6) reductive cleavage of **21** (excess Zn dust, 20 : 1 EtOH-H₂O, 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 (\pm) -15 in the presence of ZnCl₂-AgClO₄ 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 ¹³C NMR, IR, TLC, optical rotation⁹) 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, Ph₃C+ClO₄ on the 1-acetate; (3) Kahn method, Tf₂O 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 BF₃: Et₂O or TMSOTf. The use of 1-fluoroglucose tetrabenzyl ether with Cp₂HfCl₂-AgClO₄ (Suzuki), SnCl₂-AgClO₄ (Mukaiyama), or 1,2-a-oxidoglucose tribenzylether (Danishefsky) did not result in formation of the desired glycoside.

⁽⁹⁾ The rotation of the pentaacetate of 1 was found to be $[\alpha]^{23}_D + 1.33^\circ$ (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).