Total Synthesis of (−)-Paeoniflorin

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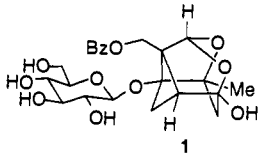
Received October 19, 1993

Paeoniflorin (**1**),[2] a monoterpene glycoside, was isolated by Shibata and co-workers[3] in 1963 as the major physiologically active principle from Paeoniae Radix (Shakuyaku in Japanese), the root of *Paeonia albiflora* Pallas. The crude drag has been



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used extensively in oriental medicine as an analgesic, an antispasmodic, an astringent, and a sedative for the treatment of a variety of painful afflictions.[4] Recently, it was found that Toki-Shakuyaku-San, a representative herbal medicine prepared from Paeoniae Radix, diminishes cognitive disruption caused by central cholinergic dysfunction, thus showing therapeutic potential in Alzheimer's disease.[5] Our interest in paeoniflorin (**1**) arose from its biological activity,[4,6] which is responsible for the pharmacological action of Paeoniae Radix, and also from its highly oxygenated cagelike pinane skeleton. Herein, we report a novel total synthesis of paeoniflorin (**1**) in its naturally occurring form.[7,8]

Retrosynthetic analysis of **1** led to tricyclic ketone **13** as a synthetic precursor (Scheme 1). The strategy we have employed to construct the oxatricyclo[4.3.0.0^{4,7}]nonane core of **13** relies on intramolecular photochemical [2 + 2] cycloaddition[9] of enone **8** having a suitably disposed diene functionality. The key enone **8** was prepared by taking advantage of the chemistry of (allenylmethyl)trimethylsilanes which we have recently developed.[10] Thus, aldehyde **2** was allowed to react with alkenyllithium **3**,[11] prepared from the corresponding alkenyl bromide by the action of *tert*-butyllithium, to give alcohol **4**.[12,13] Upon sequential pivaloylation, acidic methanolysis, oxidation, and esterification, **4** gave ester **5** in good overall yield. Addition of (allenylmethyl)-trimethylsilane **6**[10] to **5** in the presence of a catalytic amount of trimethylsilyl triflate proceeded smoothly at −20 °C in acetonitrile to give diene **7** as a 5:1 diastereoisomeric mixture. Without separation, **7** was successively subjected to hydrolysis, esterification, and Swern oxidation to afford the required enone **8** as the sole product. The crucial intramolecular [2 + 2] photocycloaddition of **8** was effected by irradiating a diluted *n*-hexane solution of **8** at 350 nm using a Rayonet photoreactor. The cycloaddition was shown to occur with complete regioselectivity as in **9** to yield tricyclic compound **10** as the only isolable product. No other isomeric adducts were produced. Stereoselective reduction of **10**, followed by esterification of the resulting alcohol **11** with (*R*)-*O*-methylmandelic acid in the presence of dicyclohexylcarbodiimide, yielded enantiomerically pure mandelate **12**[14] after chromatographic separation. The resolved mandelate **12** was then converted into ketone **13** by sequential reduction, benzoylation, and Swern oxidation.

Elaboration of the protected aglycon of **1** was accomplished from **13** using two radical reactions and oxidative degradation of the isopropenyl group as follows (Scheme 2). The ketone **13** was first converted[15] to cyanohydrin **14** in a completely stereoselective manner. Without purification, **14** was treated[16] with phenyliodine(III) diacetate and iodine under irradiation using a tungsten lamp which brought about instantaneous cyclization of the generated oxy radical to produce nitrile **15** in essentially quantitative yield. Acid hydrolysis of **15** provided carboxylic acid **16**, which was converted directly into bisketal **18** by decarboxylative radical oxygenation *via* **17** according to the method of Barton and co-workers.[17,18] After protection of the hydroxyl group of **18**, ozonolysis of **19** followed by *p*-nitrobenzoylation caused Criegee rearrangement[19] of the resulting peroxy ester to afford **20** together with the corresponding methyl ketone (10%).[20]

With the required aglycon **20** in hand, we then investigated the final attachment of glucose. After many discouraging results, we eventually found that, upon treatment[21] of **20** with imidate **21**[22] using a large excess of $BF_3{\cdot}Et_2O$ (18 equiv) in toluene at −78 °C, glycosylation took place with complete stereoselectivity to give β-glycoside **22**. No α-glycoside was formed.[23] Finally, hydrogenolytic removal of all benzyl ether protecting groups in **22** furnished (−)-paeoniflorin (**1**) quantitatively. The synthetic substance, $[\alpha]^{29}_D$ −11.5° (*c* 0.13, MeOH), was identical with natural paeoniflorin (**1**), $[\alpha]^{16}_D$ −12.8° (*c* 4.6, MeOH),[3] by spectroscopic (^{1}H and ^{13}C NMR, IR, MS) and chromatographic (TLC, HPLC) comparison.[24] Furthermore, the corresponding

(1) Present address: Faculty of Pharmaceutical Sciences, Nagasaki University, Bunkyo-Machi, Nagasaki 852, Japan.

(2) Structure: Kaneda, M.; Iitaka, Y.; Shibata, S. *Tetrahedron* **1972**, *28*, 4309–4317.

(3) Shibata, S.; Nakahara, M. *Chem. Pharm. Bull.* **1963**, *11*, 372–378.

(4) Hikino, H. In *Economic and Medicinal Plant Research*; Wagner, H., Hikino, H., Farnsworth, N. R., Eds.; Academic Press, Inc.: London, 1985; pp 55–85.

(5) Fujiwara, M. *Jpn. J. Neuropsychopharmacol.* **1990**, *12*, 217–226.

(6) Harada, M. *J. Tradit. Sino-Jpn. Med.* **1985**, *6*, 45–50 and references cited therein.

(7) For a synthetic study toward paeoniflorin, see: Hatakeyama, S.; Kawamura, M.; Shimanuki, E.; Saijo, K.; Takano, S. *Synlett* **1992**, 114–116.

(8) Recently, the first total synthesis of paeoniflorin has been accomplished by Corey and Wu: Corey, E. J.; Wu, Y.-J. *J. Am. Chem. Soc.* **1993**, *115*, 8871–8872.

(9) For a review of intramolecular enone–olefin photocycloadditions, see: Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453–1473.

(10) For the chemistry of (allenylmethyl)trimethylsilanes, see: Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1993**, 125–127 and earlier papers.

(11) Danishefsky, S. J.; Mantlo, N. *J. Am. Chem. Soc.* **1988**, *110*, 8129–8133.

(12) New compounds exhibited satisfactory spectral and analytical (high-resolution mass or combustion) data.

(13) Compounds **4**, **5**, **7**, **8**, **10**, and **11** are racemic.

(14) The absolute structure and optical purity were determined by ^{1}H NMR (500 MHz) analysis of the corresponding MTPA esters, which were derived from **12** and its diastereoisomer by $LiAlH_4$ reduction, benzoylation, and esterification using (*R*)- or (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride: cf. Kusumi, T. *J. Synth. Org. Chem. Jpn.* **1993**, *50*, 462–470.

(15) Evans, D. A.; Truesdale, L. K. *Tetrahedron Lett.* **1973**, 4929–4932.

(16) Dorta, R. L.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Chem. Res. (S)* **1990**, 240–241.

(17) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901–3924.

(18) Barton and co-workers suggest[17] that addition of *tert*-butyl mercaptan as a hydrogen donor to the reaction mixture suppresses side reactions caused by the intermediate hydroperoxyl radical. However, in our particular case, addition of the mercaptan resulted in capture of the carbon radical generated from **17** by a hydrogen atom to produce the corresponding decarboxylated compound as the major product.

(19) Schreiber, S. L.; Liew, W. F. *Tetrahedron Lett.* **1983**, *24*, 2363–2366.

(20) In this case, the alcohol **20** was obtained directly; the corresponding acetate was not formed under these conditions.

(21) Schmidt, R. R. *Pure Appl. Chem.* **1989**, *61*, 1257–1270.

(22) Schmidt, R. R.; Michel, J. *Tetrahedron Lett.* **1984**, *25*, 821–824.

(23) When a catalytic amount of $BF_3{\cdot}Et_2O$ (0.1 equiv) was employed, no reaction occurred at −78 °C. However, a reaction took place at −40 °C to give **22** and its α-isomer in a ratio of 9:1 in 20% yield together with unreacted **20** (79%). It is interesting to note that this glycosylation using 3 equiv of $BF_3{\cdot}Et_2O$ at −40 °C proceeded with opposite stereoselectivity to produce **22** and its α-isomer in a ratio of 1:2 in 64% yield.

(24) Both synthetic and natural paeoniflorin showed additional but similar minor peaks in their ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra in CD_3COCD_3, C_5D_5N, or CD_3OD: see the supplementary material. From these observations, we believe that paeoniflorin exists partially as its open form under the conditions of the NMR measurement. This supposition is supported by the fact that acetylation of paeoniflorin (Ac_2O, Et_3N, DMAP, CH_2Cl_2) gave the pentaacetate of **1** (49%) along with two epimeric pentaacetates derived from the corresponding keto-hemiacetals (36%).

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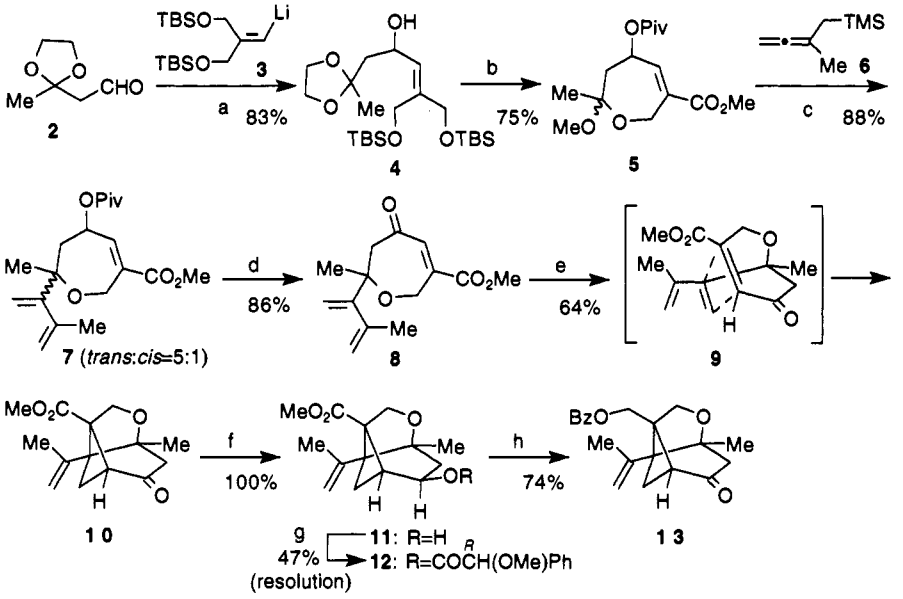
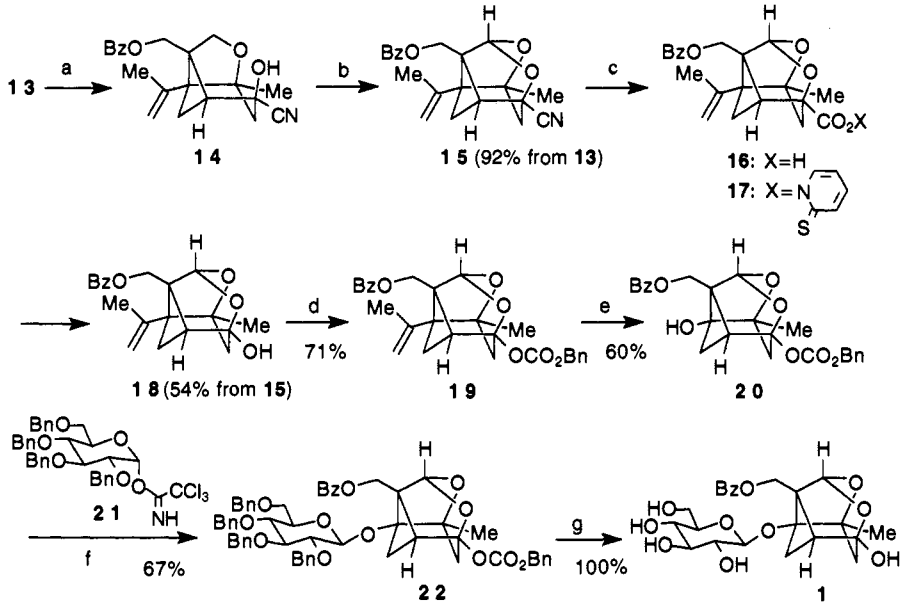
Scheme 1[a]



[a] (a) $(TBSOCH_2)_2C{=}CHBr$, *t*-BuLi, Et_2O, −78 °C; (b) (i) *t*-BuCOCl, Et_3N–DMAP (catalyst), CH_2Cl_2, (ii) *p*-TsOH (catalyst), MeOH; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C and then Et_3N, (iv) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH–H_2O (4:1), (v) CH_2N_2, Et_2O; (c) **6** (2.2 equiv), TMSOTf (catalyst), MeCN, −20 °C; (d) (i) 1 M NaOH, MeOH, reflux, (ii) CH_2N_2, Et_2O, (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C and then Et_3N; (e) *hν* (350 nm), hexane (4×10^{-3} M); (f) $NaBH_4$, MeOH, −20 °C; (g) (*R*)-*O*-methylmandelic acid, DCC–DMAP (catalyst), CH_2Cl_2 and then separation by column chromatography; (h) (i) $LiAlH_4$, THF; (ii) PhCOCl, Et_3N, CH_2Cl_2, (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C and then Et_3N.

Scheme 2[a]



[a] (a) (i) TMSCN, KCN, 18-crown-6·MeCN complex (catalyst), MeCN, (ii) 0.1 M HCl, THF; (b) $PhI(OAc)_2$ (1.5 equiv), I_2 (1.0 equiv), benzene, *hν*; (c) (i) concentrated HCl–dioxane (1:4), 40 °C, (ii) $(COCl)_2$, DMF (catalyst), benzene, (iii) *N*-hydroxythiopyridone, pyridine–DMAP (catalyst), toluene, introduce O_2 at 80 °C then $(MeO)_3P$; (d) $PhCH_2OCOCl$, Et_3N–DMAP (catalyst), CH_2Cl_2; (e) (i) O_3, MeOH, CH_2Cl_2 (4:1), −78 °C, (ii) *p*-NO_2-C_6H_4COCl, Et_3N–DMAP (catalyst), CH_2Cl_2; (f) **21** (6.0 equiv), $BF_3{\cdot}Et_2O$ (18 equiv), toluene, −78 °C; (g) H_2, $Pd(OH)_2$, MeOH–AcOEt–H_2O (10:10:1).

pentaacetate, mp 160.5–162.5 °C (lit.[8] mp 159–160 °C), exhibited spectroscopic properties (^1H and ^{13}C NMR, IR, MS) and chromatographic behavior (TLC) in accord with those of an authentic sample prepared from natural paeoniflorin.

Acknowledgment. We thank professor M. Nishizawa and Dr. H. Yamada (Tokushima Bunri University) for helpful discussions on the final glycosylation.

Supplementary Material Available: IR, ^1H NMR, and ^{13}C NMR spectra of **1** and its pentaacetate, IR and ^1H NMR spectra of **8**, **10**–**13**, **15**, **18**–**20**, and **22**, and optical rotations of **12**, **13**, **15**, **18**–**20**, and **22** (30 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.