Synthesis of Fern Sesquiterpene Pterosin Z via a Novel Palladium-Catalyzed Route

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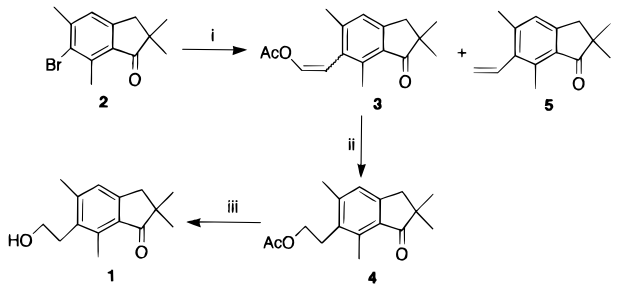
A novel palladium-catalyzed synthesis of the fern sesquiterpenoid metabolites pterosin Z (**1**) and acetylpterosin Z (**4**) is reported.

It is unusual to find secondary metabolites with the same complex structures occurring in plant families at very different evolutionary levels of development. Such compounds are of considerable biogenetic and taxonomic interest. One group of compounds that spans this evolutionary divide is the pterosins, a large group of naturally occurring sesquiterpene indanones. Initially isolated from bracken fern, *Pteridium aquilinum*,[1] pterosins have since been found to have a widespread distribution in the Pteridophyta (ferns).[2] Surprisingly, similar compounds have also been found to occur in members of the Basidiomycotina family of fungi, in particular in *Cyathus* species.[3] The pterosins isolated from these sources have the same basic carbon skeleton but differ in their oxygenation pattern. Several pterosin compounds have been shown to possess pharmacological activity, for example, the smooth muscle relaxants onitin and onitinsin derived from the fern *Onychium siliculosum*.[4,5] A number of synthetic analogues of pterosin Z (**1**), isolated from the fern *P. aquilinum*, have been shown to possess very potent smooth muscle relaxant activity.[6] Pterosin Z (**1**) has also been shown to have mild cytotoxic activity.[7]

Several multistep approaches to the synthesis of pterosins have been reported in the literature.[8−12] Recently, our group has reported an alternative, though low-yielding route to the synthesis of the pterosins.[6] In this route the 6-bromoindan-1-one (**2**) was identified as a key synthetic intermediate. The bromine at position 6 was substituted by a two-carbon side chain via a Grignard reagent.

Because of our ongoing interest in the synthesis and pharmacological activity of the pterosins and their analogues, we now report a novel approach to the synthesis of pterosin Z (**1**). This approach has also been applied successfully to the synthesis of unnatural pterosin analogues.[13] In our synthesis of **1** a palladium-catalyzed coupling of **2** with vinyl acetate was achieved using the methodology established by Heck[14] for vinylic substitution reactions. The coupling of vinyl acetate with bromoindanone **2** yielded a mixture of *E* and *Z* isomers (**3**), which was reduced via a rhodium-catalyzed hydrogenation. The reduced product, acetylpterosin Z (**4**), was converted to pterosin Z (**1**) by deacylation (Scheme 1). A 6-vinyl indanone (**5**) is produced as a byproduct of this coupling reaction with yields of **5** increasing with reaction temperature. Byproduct **5** can also be converted to pterosin Z (**1**) via protection of the carbonyl group followed by hydroboration.[9]

Scheme 1. Synthesis of Pterosin Z (**1**)[a]



[a] Key: (i) vinyl acetate, $Pd(OAc)_2$, PPh_3, Et_3N; (ii) $[RhCl(PPh_3)_3]$, H_2, EtOH; (iii) 2 M NaOH, 50% EtOH.

The use of palladium-catalyzed coupling reactions in the synthesis of pterosins and their analogues has been successful. This synthetic approach can be applied to the preparation of C-6-substituted pterosins and allows access to significant quantities of this large group of natural sesquiterpenes for pharmacological screening. Optimization of the coupling conditions is ongoing, with couplings in excess of 50% achieved using the bromoindanone substrate. Couplings with an iodoindanone will now be investigated and are expected to give higher yields.

Experimental Section

General Experimental Procedures. Melting points were determined on a hot stage apparatus and an Electrothermal apparatus and are uncorrected. Spectra were obtained on the following instruments: IR, Nicolet 205 FT-IR; UV, Varian CARY 3E UV−vis spectrometer; ^{1}H NMR, Bruker MSL 300, 300.13 MHz; ^{13}C NMR, Bruker MSL 300, 75.47 MHz; DEPT 135, Bruker MSL 300. All NMR spectra were analyzed with Bruker WIN-NMR software. The NMR spectra were obtained in $CDCl_3$ (except where indicated). Peak positions were assigned relative to the $CHCl_3$ resonances at 7.25 ppm for ^{1}H NMR and at 78.16, 76.90, and 75.62 ppm for ^{13}C NMR. MS were obtained from the Department of Pure and Applied Chemistry, University of Strathclyde. Column chromatography was carried out with Si gel 60 (230−400 mesh) and TLC with Si gel 60 F-245 precoated plates (E. Merck Laboratories).

***(E,Z)*-6-(2′-Acetoxyethenyl)-2,2,5,7-tetramethylindan-1-one (3).** A solution of **2** (synthesized as per Sheridan *et al.* [6]) (2.4 mmol, 640 mg) in Et_3N (10 mL) was added to palladium acetate (0.13 mmol, 30 mg), triphenylphosphine (0.27 mmol, 70 mg), and vinyl acetate (5 mmol, 430 mg) in a 25-mL glass ampule. The ampule was sealed and shaken until the mixture was homogenous. The mixture was then heated in an oven

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at 100 °C for 48 h. After cooling, the reaction mixture was poured on ice and dilute HCl, extracted with EtOAc (100 mL), dried over sodium sulfate, and evaporated under vacuum, leaving a residue that was purified by column chromatography (eluent: petroleum ether-EtOAc, 9:1) to yield two compounds. The most polar compound was a waxy oil, which did not crystallize from EtOH, MeOH, or *n*-hexane and was identified as **3** (*E* and *Z* isomers, 1:1) (190 mg, 28.9%): IR υ_{max} (film) 2925, 1762, 1705, 1337, 1209, 1056 cm^{-1}; UV (50% EtOH) λ_{max} 220 nm (log ϵ 5.24), λ 236 nm (log ϵ 5.15), λ 261 nm (log ϵ 5.09), λ 305 nm (log ϵ 4.35); ^{1}H NMR ($CDCl_3$, 300 MHz), δ_H 1.20 (12H, s, 4 × CH_3), 2.08 (6H, s, OCOCH_3), 2.21 (3H, s, ArCH_3), 2.29 (3H, s, ArCH_3), 2.38 (2H, s, H-3), 2.60 (3H, s, ArCH_3), 2.65 (3H, s, ArCH_3), 2.78 (2H, s, H-3), 5.76 (1H, d, J = 7 Hz, (*E*)H-2′), 6.42 (1H, d, J = 13 Hz, (*Z*)H-2′), 6.99 (2H, s, H-4), 7.35 (1H, d, J = 7 Hz, (*Z*)H-1′), 7.54 (1H, d, J = 13 Hz, (*E*)H-1′); ^{13}C NMR ($CDCl_3$, 75.37 MHz), δ_C 14.03 (Ar*C*H$_3$), 17.95 (Ar*C*H$_3$), 20.38 (Ar*C*H$_3$), 20.72 (Ar*C*H$_3$), 20.96 (OCO*C*H$_3$), 22.59 (OCO*C*H$_3$), 25.45 (4 × CH$_3$), 42.11 (C-3), 42.98 (C-3), 45.35 (C-2), 108.13 (C-1′), 110.44 (C-1′), 127.97 (ArC), 128.31 (ArC), 128.74 (C-4), 130.79 (C-4), 131.34 (C-2′), 134.98 (C-2′), 137.95 (ArC), 138.17 (ArC), 138.76 (2 × ArC), 142.69 (ArC), 143.03 (ArC), 151.2 (ArC), 152.09 (ArC), 167.36 (O−C=O), 211.83 (C-1); EIMS *m*/*z* 272.1418 (48, $C_{17}H_{20}O_3$ requires 272.1413, M^+), 231 (19, $M^+ - C_2HO$), 230 (100, $M^+ - C_2H_2O$), 215 (33, $M^+ - C_3H_5O$), 172 (35, $M^+ - C_5H_8O_2$), 144 (20, $M^+ - C_6H_8O_3$).

6-Ethenyl-2,2,5,7-tetramethyl-indan-1-one. The nonpolar product was identified as 6-ethenyl-2,2,5,7-tetramethylindan-1-one (**%**) (**5**) (150 mg, 29.2%): UV (50% EtOH) λ_{max} 200 nm (end abs, log ϵ 3.44), λ 236 nm (log ϵ 3.28); IR υ_{max} (film) 2958, 1703.6, 1629, 1601, 1571, 1378 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz), δ_H 1.20 (6H, s, 2 × CH_3), 2.38 (3H, s, ArCH_3), 2.59 (3H, s, ArCH_3), 2.95 (2H, s, H-3), 5.45 (1H, dd, J = 1.5, 17.9 Hz, H-2′, M of AMX), 5.56 (1H, dd, J = 1.5, 11.7 Hz, H-2′, A of AMX), 6.74 (1H, dd, J = 11.7, 17.9 Hz, H-1′, X of AMX), 6.98 (1H, s, H-4); ^{13}C NMR ($CDCl_3$, 75.37 MHz), δ_C 18.00 (Ar*C*H$_3$), 20.70 (Ar*C*H$_3$), 25.46 (2 × *C*H$_3$), 42.74 (C-3), 45.39 (C-2), 119.23 (C-2′), 130.90 (ArC), 131.94 (C-4), 132.52 (ArC), 132.61 (C-1′), 137.85 (ArC), 142.33 (ArC), 151.14 (ArC), 212.01 (C-1); EIMS *m*/*z* 214.1355 (97.1, $C_{15}H_{18}O$ requires 214.1357, M^+), 200 (16.2, $M^+ - CH_2$), 199 (100, $M^+ - CH_3$), 173 (22, $M^+ - C_3H_5$), 171 (45.2, $M^+ - C_2H_3O$), 156 (23.4, $M^+ - C_3H_6O$), 144 (18.3), 129 (18.3), 85 (31.6), 71 (44.6).

6-[2′-Acetoxyethyl]-2,2,5,7-tetramethylindan-1-one (Acetyl pterosin Z) (4). A solution of **3** (150 mg, 0.55 mmol) in EtOH (10 mL) was stirred under H_2 with Wilkinson's catalyst [$RhCl(PPh_3)_3$] (90 mg, 0.1 mmol) at room temperature for 24 h. On completion, the EtOH was evaporated off under vacuum. The residue was purified by column chromatography (eluent:petroleum ether-EtOAc, 7:3), yielding **4** (130 mg, 85.6%) as a white crystalline solid (from *n*-hexane): mp 61−62 °C (lit.[2] oil); IR υ_{max} (KBr): 2958,1743, 1703, 1582, 1379, 1239 cm^{-1}; UV (50% EtOH) λ_{max} 215 nm (log ϵ 3.72), λ 261 nm (log ϵ 3.41); ^{1}H NMR ($CDCl_3$, 300 MHz), δ_H 1.21 (6H, s, 2 × CH_3), 2.04 (3H, s, OCOCH_3), 2.39 (3H, s, ArCH_3), 2.57 (3H, s, ArCH_3), 2.92 (2H, s, H-3), 2.97 (2H, t, J 7.3 Hz, H-1′), 4.18 (2H, t, J = 7.3 Hz, H-2′), 6.96 (H-4); ^{13}C NMR ($CDCl_3$, 75.37 MHz), δ_C 17.83 (Ar*C*H$_3$), 19.50 (Ar*C*H$_3$), 20.88 (OCO*C*H$_3$), 25.50 (2 × *C*H$_3$), 28.00 (C-1′), 41.40 (C-3), 45.40 (C-2), 62.80 (C-2′), 130.30 (ArC), 130.86 (ArC), 132.06 (C-4), 137.54 (ArC), 143.32 (ArC), 152.44 (ArC), 170.86 (O−*C*=O), 211.91 (C-1); EIMS *m*/*z* 274.1576 (72, $C_{17}H_{22}O_3$ requires 274.1569, M^+), 231 (5, $M^+ - C_2H_3O$), 214 (100, $M^+ - C_2H_4O_2$), 199 (98, $M^+ - C_3H_7O_2$), 172 (24, $M^+ - C_5H_{10}O_2$), 156 (11).

6-[2′-Hydroxyethyl]-2,2,5,7-tetramethylindan-1-one (Pterosin Z) (1). A solution of **4** (150 mg, 0.54 mmol) in EtOH (10 mL) and 2 M NaOH (5 mL) was stirred at room temperature for 1 h. The reaction mixture was neutralized with dilute HCl and the EtOH evaporated off under vacuum. The residue crystallized from Et_2O−hexane to yield **1** (115 mg, 92%) as white needles: mp 89−91 °C (lit.[2] mp 86−88 °C, lit.[10] mp 89−90 °C, lit.[11] mp 90−91 °C) ; IR υ_{max} (KBr): 3430 (br), 2958, 2924, 1686, 1579, 1458, 1379, 1044 cm^{-1} ; UV (50% EtOH) λ_{max} 216 nm (log ϵ 4.76), λ 263 nm (log ϵ 4.52), λ 301 nm (log ϵ 3.78); ^{1}H NMR ($(CD_3)_2CO$) 300 MHz), δ_H 1.14 (6H, s, 2 × CH_3), 2.38 (3H, s, ArCH_3), 2.50 (3H, s, ArCH_3), 2.89 (2H, t, J = 7 Hz, H-1′), 2.96 (2H, s, H-3), 3.70 (2H, td, J = 7, 3 Hz, CH_2OH), 3.82 (1H, t, J = 3 Hz, O*H*), 6.98 (1H, s, H-4); ^{13}C NMR ($CDCl_3$, 75.37 MHz), δ_C 17.81 (Ar-*C*H$_3$), 19.67 (Ar-*C*H$_3$), 25.50 (2 × *C*H$_3$), 31.91 (C-1′), 41.56 (C-3), 45.41 (C-2), 61.57 (C-2′), 131.07 (ArC), 132.05 (C-4), 137.27 (ArC), 143.39 (ArC), 147.02 (ArC), 152.53 (ArC), 218.11 (C-1); EIMS *m*/*z* 232.1452 (64, $C_{15}H_{20}O_2$ requires 232.1463, M^+), 217 (40, $M^+ - CH_3$), 201 (100, $M^+ - CH_3O$), 199 (11, $M^+ - CH_5O$), 159 (9, $M^+ - C_3H_5O_2$), 143 (11, $M^+ - C_4H_9O_2$), 128 (10).

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