Practical Synthesis of Lespedezol A_1

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A practical formal synthesis of lespedezol A_1 (**1**) was accomplished in 33% yield for four steps starting from formation of the substituted chalcone. Of particular note is a useful protocol for reduction of the 2-ene bond in the isoflavone intermediate. A significant improvement in the final ring closure when water was scavenged from the reaction is also noteworthy. The ready availability of lespedezol A_1 will provide material for further pharmacological evaluation and for exploration of the pterocarpene nucleus as a potential entry into various 6a-hydroxypterocarpans.

The 6a-hydroxypterocarpans are isoflavonoid phytoalexins that display selective estrogen receptor modulating (SERM) properties and marked antioxidant and anticancer activity.[1–3] The glyceollins, represented by glyceollin I (**2** in Figure 1), are particularly interesting members of this class of compounds. Although **2** can be elicited from the common soybean *Glycine max* by various insults, it is typically obtained as a complex mixture in only very small quantities.[4–6] This situation has prompted explorations directed toward the production of **2** by chemical synthesis.[7,8] Like others,[9] we regard the stereospecific introduction of the 6a-hydroxy group to be the most challenging step in these types of synthetic strategies. Noting that certain pterocarpanoids like lespedezol A_1 (**1** in Figure 1) possess a 6a,11a-double bond that might be amenable to the addition of a water molecule, we decided to prepare **1** as a model to investigate such an approach toward producing various 6a-hydroxypterocarpan systems.

Lespedezol A_1 and several related family members were first isolated by Miyase et al. from a methanolic extract of *Lespedeza homoloba* stems.[10] Some of these compounds demonstrate significant antioxidant and antiallergic activity, while other members from the broader family show promise as SERMs, anticancer agents, and antifungals.[11–13] Although a formal synthesis of **1** has not been reported, its synthesis was traversed by Prasad et al. during their unambiguous structural proof of the prenylated relative shown in Figure 1 as compound **3**.[14,15]

Our synthesis of **1** paralleled the biosynthetic pathway for these types of compounds by going through an isoflavone followed by conversion to an isoflavonone prior to final cyclization.[16] There are several methods reported for the preparation of isoflavones.[17–20] We decided to first examine a Suzuki coupling approach. Using commercially available 3-bromochromone as a model, coupling reactions with the appropriate boronic acid partner were attempted under various conditions.[17,18] In all cases, however, only vey low yields of the desired isoflavone were obtained. Alternatively, we observed immediate success with the chalcone route depicted in Scheme 1 wherein the requisite intermediate **4** was first obtained via a well-behaved Claisen−Schmidt condensation.[19] The latter was performed in anhydrous MeOH using piperidine as base,[20] a combination that afforded crystalline chalcone **4** directly from the reaction medium upon standing at room temperature after refluxing for 4 h. After filtration, concentration of the anhydrous MeOH and refluxing for another 4 h, a second crop was obtained for which the combined yield became 80%. The latter was nearly double that previously reported by Prasad et al., who deployed aqueous NaOH

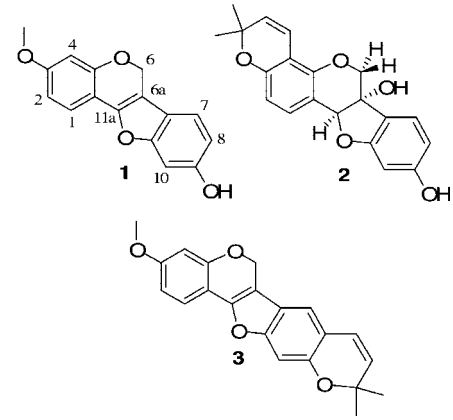

Figure 1. Structure **1** is lespedezol A_1, a representative member of the anhydropterocarpanoids also shown with its numbering system. Structure **2** is glyceollin I, a representative member of the 6a-hydroxypterocarpans. Structure **3** is a prenylated relative of **1** that has previously undergone total synthesis.

in EtOH to effect this reaction.[14] The next step involved oxidative rearrangement of chalcone **4** to the acetal intermediate **5** followed by closure to the isoflavone **6**. Use of thallium(III) nitrate for the rearrangement followed by treatment with acid for the ring closure constitutes a well-trodden path to a variety of isoflavones.[21] We also attempted this sequence by using newer methodology that deployed Koser's hypervalent iodine reagent to form the acetal under conditions that we felt might eventually be developed into much greener chemistry overall.[22,23] In this case, model chemistry with commercially available 2′-hydroxychalcone, protected as its benzyl ether, proceeded quite favorably. When attempted on **4**, however, a complex mixture of products was obtained that appeared to reflect other rearrangement possibilities in addition to the one that did lead to at least small amounts of desired material. The more traditional path, "b(i)" and "b(ii)" in Scheme 1, proceeded in a favorable manner to produce the protected isoflavone **6** in approximately 75% yield, which was comparable to the previous literature.[14,21]

The next step of the synthesis involved simultaneous removal of the two benzyl-protecting groups and reduction of the isoflavone nucleus to the isoflavanone **7**. Not unexpectedly, when this conversion was undertaken at 15 psi hydrogen over 10% Pd−C, a mixture was obtained that consisted of debenzylated isoflavone, a small amount of desired product, and some cyclized product in the form of a pterocarpan, which was not useful because it lacked the 6a,11a-double bond.[14] Alternatively, using ammonium formate as a source of hydrogen atoms[24–26] resulted in a much cleaner reaction wherein the degree of reduction could be controlled by the choice

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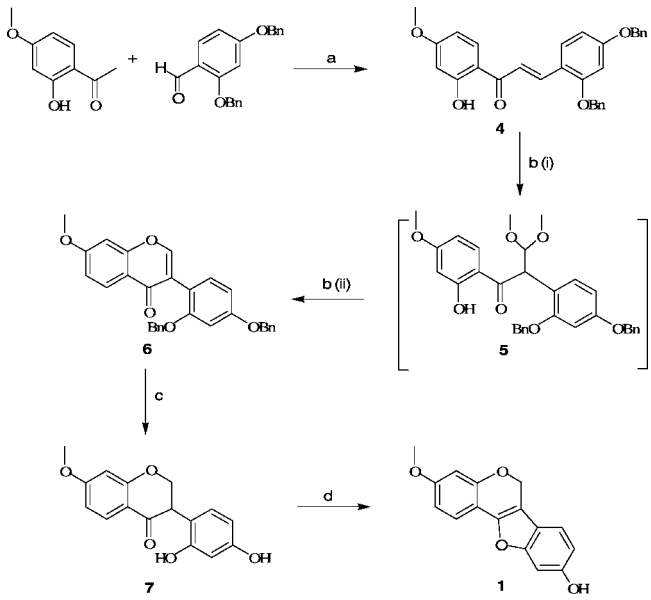
Scheme 1. Synthesis of Lespedezol A_1 (**1**)[a]



[a] (a) MeOH, piperidine (2 equiv), reflux (80%); (b-i) $Tl(NO_3)\cdot 3H_2O$ (1.5 equiv), CH_2Cl_2/MeOH (1:12), rt; (b-ii) 1 N HCl, MeOH, reflux (75%); (c) 10% Pd−C, ammonium formate (8 equiv), acetone/MeOH (10:1), rt (78%); (d) cat. HCl, 3 A molecular sieves, MeOH/trimethyl orthoformate (1:1), reflux (71%).

of solvent, reaction temperature, and the number of reagent equivalents so as to produce various products in high yield and purity. For example, when **6** was refluxed in MeOH with 15 equiv of ammonium formate over 10% Pd−C for 12 h, not only did debenzylation and reduction of the 2-ene bond occur, but the keto group was also reduced to an alcohol. Alternatively, stirring **6** in acetone at room temperature for 12 h and using only 8 equiv of ammonium formate provided the desired isoflavanone **7** as a white solid in nearly 80% yield. This represented a considerable improvement over the previous method, which produced an oil in about 10% yield after a tedious separation.[14]

The final ring closure to form **1** (step "d") requires considerable thermal energy even when catalyzed by acid. The previously reported yield for this reaction was only about 30%.[15] It is likely that the keto group first forms a hemiacetal with MeOH, which then collapses to a five-membered cyclic ether upon acid-catalyzed, intramolecular nucleophilic attack by the neighboring *othro*-hydroxy group. Subsequent dehydration then produces the highly conjugated pterocarpene nucleus. Accordingly, the driver for the overall pathway is the loss of water, leading to formation of the highly stabilized, conjugated double bond that embeds a fully aromatic benzofuran system within the pterocarpene nucleus. On the basis of this mechanism, we imagined that the addition of molecular sieves and, in particular, equimolar quantities of trimethyl orthoformate[27] to scavenge water might serve to both facilitate this reaction and lead to higher yields. To this end, **7** was gently refluxed in anhydrous MeOH/trimethyl orthoformate over molecular sieves with a catalytic amount of concentrated HCl for 4 h. After removing the sieves and evaporating solvent, the residue was extracted with water and EtOAc. The organic phase was dried and chromatographed through silica gel to provide the desired product **1** as a solid in approximately 70% yield. Thus, this modified reaction was accomplished at lower temperature and in a significantly higher yield.

The overall yield for the entire synthesis of lespedezol A_1, **1**, was 33% starting from formation of the substituted chalcone. This represents a considerable improvement over the 1% yield that can be calculated across the analogous steps associated with its prior synthesis by Prasad et al. while on route to **3**.[14,15] Requiring only routine separation and purification methods, the present synthesis is very practical and should be amenable to further scale-up. Of particular note is a useful protocol for reduction of the 2-ene bond in the isoflavone to produce the penultimate intermediate required for cyclization to the pterocarpene nucleus. Likewise, a significant improvement was observed for the final ring closure when water was scavenged from the reaction. The pterocarpenes and homopterocarpans are of interest for their potential therapeutic properties. The availability of lespedezol A_1 via the practical synthesis described herein will allow for further synthetic explorations directed toward producing 6a-hydroxypterocarpans, as well as allowing for a more thorough characterization of its distinct pharmacologic profile.

Experimental Section

General Experimental Procedures. Chemical reactions were conducted under nitrogen in anhydrous solvents unless stated otherwise. Reagents obtained from commercial suppliers were used without further purification. Acetone was dried over 4 Å molecular sieves. Tetrahydrofuran (THF) was distilled under nitrogen over sodium-benzophenone. Thin-layer chromatography (TLC) was done on 250 μm fluorescent plates and visualized by using UV light or iodine vapor. Normal-phase flash column chromatography was performed using silica gel (200–425 mesh 60 Å pore size) and ACS grade solvents. Melting points (mps) are uncorrected. NMR spectra were recorded on either a 600 MHz or a 400 MHz instrument. Peak locations were referenced using either tetramethylsilane (TMS) or residual nondeuterated solvent as an internal standard. Proton coupling constants are expressed in hertz. In some cases, overlapping signals occurred in the ^{13}C NMR spectra. Spectroscopic data are in agreement with all known compounds.

2,4-Dibenzyloxy-2′-hydroxy-4′-methoxychalcone (4). 2,4-Dibenzyloxybenzaldehyde[28] (3.18 g, 10 mmol) and 2-hydroxy-4-methoxyacetophenone (1.66 g, 10 mmol) were dissolved in 100 mL of MeOH, followed by addition of piperidine (2 mL, 20 mmol). The mixture was refluxed for 4 h and cooled to ambient temperature. A yellowish solid was produced that was filtered and washed with 100 mL of MeOH. The filtrate was reduced to ca. 50 mL and refluxed for another 4 h, after which it provided additional product upon cooling to ambient temperature. The combined yield of solid **4** was 3.71 g (80%): mp 156–157 °C [lit.,[14] 157–164 °C]; TLC R_f 0.23 in hexanes/EtOAc (5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, 1H, J = 15.6 Hz, CH═), 7.75 (d, 1H, J = 15.6 Hz, CH═), 7.54–7.36 (m, 11H, 2 × C_6H_6/Ar-H6), 7.24 (d, 1H, J = 9 Hz, Ar-H6′), 6.68 (d, 1H, ^3J = 2.4 Hz, Ar-H3) 6.53 (dd, 1H, ^2J = 8.4 Hz, ^3J = 2.4 Hz, Ar-H5), 6.41 (d, 1H, ^3J = 2.4 Hz, Ar-H3′), 6.24 (dd, 1H, ^2J = 9 Hz, ^3J = 2.4 Hz, Ar-H5′), 5.12 (s, 2H, O-CH_2), 5.11 (s, 2H, O-CH_2), 3.83 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 166.8, 165.8, 162.2, 160.2, 141.2, 136.4, 136.2, 134.4, 131.4, 129.1, 128.9, 128.7, 128.6, 128.5, 127.8, 119.8, 117.6, 114.5, 107.7, 106.6, 100.8, 100.6, 70.9, 70.5, 55.7.

2′,4′-Dibenzyloxy-7-methoxyisoflavone (6). Chalcone **4** (0.467 g, 1 mmol) was dissolved in 2 mL of DCM and 25 mL of MeOH was added, followed by addition of thallium nitrate trihydrate (0.666 g, 1.5 mmol). Upon stirring this suspension for 2 h at room temperature, it became a clear solution with white thallium(I) nitrate precipitating. After stirring for an additional 4 h, the TLC showed complete disappearance of chalcone. Solvents were evaporated to reduce the volume to ca. one-third, and then 20 mL of CH_2Cl_2 was added, followed by the addition of 0.2 g of sodium bisulfite. After stirring for 1 h, the entire solid was filtered, solvent evaporated, and the resulting residue passed through a short column of silica with hexanes/EtOAc (10:1) as eluant. The eluting solvents were evaporated to provide a yellowish, oily acetal, which was used directly in the next step without further purification. Crude acetal (ca. 0.5 g) was dissolved in 10 mL of MeOH and refluxed with 2 mL of 1 N HCl for ca. 12 h. After disappearance of acetal (TLC), the reaction mixture was poured into ice–water (100 mL). A white solid precipitated. The precipitate was filtered and recrystallized from MeOH/DCM (ca. 20:5 mL) to provide 0.348 g (75%) of **6** as a white solid: mp 138–140 °C [lit.,[14] 139 °C]; TLC R_f 0.14 in hexanes/THF (5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, 1H, J = 9 Hz, Ar-H5), 7.89 (s, 1H, OCH═), 7.42–7.22 (m, 10 + 2H, 2 × C_6H_5/Ar-H6′/Ar-H3′), 6.97 (dd, 1H, ^2J = 9 Hz, ^3J = 2.4 Hz, Ar-H6), 6.82 (d, 1H, J = 1.8 Hz, Ar-H8), 6.64 (dd, 1H, ^2J = 8.4 Hz, ^3J = 1.8 Hz, Ar-H5′), 5.05 (s, 2H, Ph-CH_2), 5.03 (s, 2H, Ph-CH_2), 3.89 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 164.0, 160.4, 158.2, 157.8, 154.0, 137.2,

137.1, 132.5, 128.9, 128.7, 128.3, 128.0, 127.9, 127.8, 127.4, 122.4, 118.7, 114.5, 106.2, 101.7, 70.8, 70.4, 56.0.

2′,4′-Dihydroxy-7-methoxyisoflavanone (7). 10% Pd−C (0.3 g) was added to a solution of isoflavone **6** (0.464 g, 1 mmol) in 20 mL of acetone and 2 mL of MeOH at 0 °C, followed by addition of ammonium formate (0.504 g, 8 mmol). The reaction mixture was stirred for ca. 8 h at room temperature. Catalyst was filtered through a pad of Celite, solvent evaporated, and the residue extracted with EtOAc/water (40 mL; 1:1). The organic layer was dried over sodium sulfate and evaporated to give a reddish solid. The solid was dissolved in EtOAc and chromatographed over silica using hexanes/EtOAc (3:1) as eluant. The organic fractions were evaporated to provide 0.224 g (78%) of **7** as a white solid: mp 168–170 °C [lit.,[14] oil]; TLC R_f 0.23 in hexanes/EtOAc (3:2); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.51 (s, 1H, OH), 8.2 (s, 1H, OH), 7.80 (d, 1H, J = 9 Hz, Ar-H5) 6.91 (d, 1H, J = 7.8 Hz, Ar-H6′), 6.64 (dd, 1H, ^2J = 8.4 Hz, ^3J = 2.4 Hz, Ar-H6), 6.5 (d, 1H, J = 2.4 Hz, Ar-H7), 6.42 (d, 1H, J = 1.8 Hz, Ar-H3′), 6.30 (dd, 1H, ^2J = 8.4 Hz, ^3J = 2.4 Hz, Ar-H5′), 4.67 (t, 1H, J = 11.4 Hz, H3), 4.55 (dd, 1H, ^2J = 11.4 Hz, ^3J = 5.4 Hz, H-2ax), 4.14 (dd, 1H, ^2J = 11.4 Hz, ^3J = 5.4 Hz, H-2eq), 3.87 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 191.5, 166.5, 164.4, 158.5, 156.7, 131.1, 129.4, 115.9, 114.2, 110.3, 107.5, 103.5, 101.2, 71.5, 55.9, 47.5; *anal*. calcd for $C_{16}H_{14}O_5 \cdot 0.25H_2O$, C 66.08, H 5.02; found, C 66.29, H 4.83.

Lespedezol (A_1) or 3-Methoxy-6*H*-benzo[4,5]furo[3,2-*c*]chromen-9-ol (1). To a solution of **7** (0.141 g, 0.5 mmol) in 50 mL of MeOH/trimethyl orthoformate (1:1) was added two drops of concentrated HCl and ca. 5 g of 3 Å molecular sieves, after which the solution was gently refluxed for 4 h. A solid was filtered and the solvent evaporated at 20 °C. The resulting residue was extracted with EtOAc/water (2 × 100 mL; 1:1). The organic layers were combined, dried over sodium sulfate, and evaporated. The residue was chromatographed over silica using hexanes/EtOAc (5:1) as eluant. The organic fractions were evaporated to provide 0.95 g (71%) of **1** as a white solid with slight yellow tinge: decomposes at 130–140 °C [lit.,[15] 134 °C]; TLC R_f 0.52 in hexanes/EtOAc (3:2); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.57 (s, 1H, OH), 7.35 (d, 1H, J = 8.4 Hz, Ar-H1), 7.31 (d, 1H, J = 8.4 Hz, Ar-H7), 7.01 (d, 1H, J = 2.4 Hz, Ar-H10), 6.82 (dd, 1H, ^2J = 8.4 Hz, ^3J = 1.8 Hz, Ar-H8), 6.58 (dd, 1H, ^2J = 8.4 Hz, ^3J = 2.4 Hz, Ar-H2), 6.49 (d, 1H, J = 2.4 Hz, Ar-H4), 5.57 (s, 2H, H6), 3.8 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 161.7, 157.1, 156.3, 155.8, 147.0, 121.3, 119.8, 118.9, 112.9, 110.4, 107.7, 106.9, 103.0, 98.9, 65.9, 55.5; *anal*. calcd for $C_{16}H_{12}O_4$. 0.25 H_2O, C 70.46, H 4.62; found, C 70.33, H 4.42.

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Supporting Information Available: (S1) Model chemistry associated with an attempted Suzuki coupling route to an isoflavone; (S2) model chemistry associated with use of Koser's hypervalent iodine reagent including preparation of 2′-benzyloxychalcone and its related isoflavone; (S3) preparation of 2,4-dibenzyloxybenzaldehyde in 90% yield from commercially available starting material, and additional reference citations pertaining to S1, S2, and S3; (S4) proposed mechanism for the cyclization of an isoflavanone to the pterocarpene nucleus in methanolic HCl; and (S5 to S17) copies of proton and carbon NMR spectra for lespedezol A_1 and synthetic intermediates **4**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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