Total Syntheses of Racemic and Natural Glycinol

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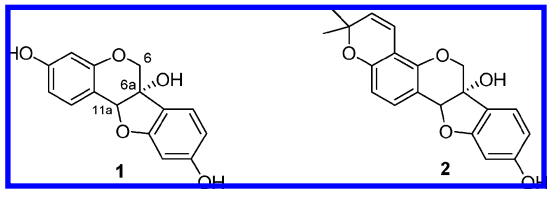
Received August 17, 2009

Total syntheses of racemic and (−)-glycinol (**1**) are described. A Wittig reaction produced the isoflav-3-ene from which a Sharpless dihydroxylation introduced either the racemic or enantiomeric 6a-hydroxy group. A 5.5% overall yield of racemic material was obtained after 12 steps. A method was devised for a one-pot switch of protecting groups masking a sensitive resorcinolic *para*-functionality, and conditions were optimized to prompt spontaneous closure of the pterocarpanolic dihydrofuran upon subsequent exposure of its *ortho*-functionality. These improvements eliminated two steps and increased the overall yield to 9.8% during production of the natural enantiomer.

Glycinol (**1**) is a key intermediate in the biosynthetic pathway leading to the glyceollin family of natural products.[1] These 6a-hydroxypterocarpans are phytoalexins[2] that become elicited in low amounts when soybeans are subjected to specific types of stress.[3] Our collaborators have shown that the most prevalent member of this family, glyceollin I (**2**), is also the most prominent in exhibiting antiestrogenic (antagonist) properties that may be useful to prevent or treat breast cancer.[4] Alternatively, in recent studies they have demonstrated that **1** exhibits potent estrogenic (agonist) activity,[5] thus confirming an earlier hypothesis[6] and, in turn, suggesting that this particular member may instead be useful as a selective estrogen receptor modulating agent, or SERM, during hormone replacement therapy.[5,7] Corresponding efforts in our laboratory have been directed toward synthesizing the various glyceollin family members and their analogues in quantities conducive to further structure−activity relationship studies.[8]



First identified by Lyne and Mulheirn in 1978 as a minor constituent in $CuCl_2$-treated soybean cotyledons,[9] **1** was given its trivial name in 1984 by Weinstein et al., who used bacteria and ultraviolet light to elicit the compound and then studied its activity against a variety of microorganisms.[10] Owing in part to the low amounts of material, further characterization of **1**'s biological properties has lagged. This situation, coupled with the recent demonstration of its interesting SERM activity,[5] prompted our production of **1** by total synthesis from commercially available materials. Our route is shown in Scheme 1, where the longer path that includes all steps is analogous to the synthesis of glyceollin I, which we previously elaborated from **13** in two steps (dotted lines).[8g] This path was followed to prepare racemic materials for use as chiral chromatography standards while also conducting process chemistry enhancements. The latter resulted in the shorter route depicted in Scheme 1, which deploys two one-pot reactions (steps g and k). With these two modifications and other process improvements, the shorter route nearly doubled the overall yield when it was applied toward preparing (−)-**1**.

The steps leading to **8** were conducted as before except that we found it beneficial to add triphenylphosphine hydrobromide ($Ph_3P\cdot HBr$) in five, 0.2 molar equiv portions so as to better preserve the MOM protecting group during the course of the internal Wittig reaction (step d). In the next two steps (e and f) leading to **10**, we were able to devise a one-pot procedure for the exchange of MOM with TBDMS as opposed to our previous purification of intermediate **9**, which is susceptible to spontaneous decomposition during workup. Thus, after taking advantage of our novel deprotection method that utilizes $Ph_3P\cdot HBr$ in dichloromethane to gently remove MOM within the course of a few hours (TLC showing disappearance of **8**),[8g] Et_3N followed by TBDMSCl was added to the same reaction flask, which was then allowed to stir overnight. In addition to providing for a more facile process, the yield from **8** to **10** was increased by nearly 15%.

While the non-asymmetric conversion of **10** to **11** can be accomplished by deploying only catalytic amounts of osmium tetroxide (OsO_4) without chiral catalyst, a nearly equal stoichiometry of OsO_4, substrate, and $(DHQD)_2PHAL$ is required in order to thoroughly establish the (6a*S*, 11a*S*) stereochemistry present in this family's natural enantiomers.[8g,11,12] During our asymmetric synthesis we found that commercial supplies of this chiral catalyst had become limited. This prompted us to prepare our own catalyst. The latter followed literature procedures,[13] which proceeded uneventfully in high yield from readily available starting materials and, ultimately, resulted in a fortuitous reduction in overall cost. Intermediate **11** exhibited greater than 98% enantiomeric excess (ee) when determined by chiral HPLC.[14] The excellent separation of these enantiomers, as well as those for **1**, and the distinctly diagnostic peaks obtained from the latter's forced decomposition are noteworthy. These methods can serve as useful analytical tools during future syntheses in this arena (specific results and analytical details are provided in the Supporting Information).

Although we previously found it more convenient to isolate **12** while on route to **13** from **11**,[8g] we further investigated the possibility of allowing the ring closure to occur spontaneously upon debenzylation of the resorcinolic *ortho*-hydroxy group. This maneuver has been successful in the hands of others when preparing different pterocarpanoid natural products,[12d,15] and we were able to establish conditions that optimized this one-pot transformation relative to **13**. Thus, by changing the reaction solvent during hydrogenolysis from acetone to anhydrous EtOH and by increasing the hydrogen pressure from 15 to 35 psi so as to allow equivalent reaction times, at least 85% yields of cyclized material **13** can be obtained rather than high yields of **12**. This remarkable solvent effect may be due to enhanced solvation of the polar transition state during nucleophilic attack by the resorcinolic *ortho*-hydroxy-oxygen atom on the proposed quinone-methide formed as a transient species prior to cyclization.[8g] Alternatively, anhydrous ethanol may better sequester the water byproduct and thus serve to drive the cyclization

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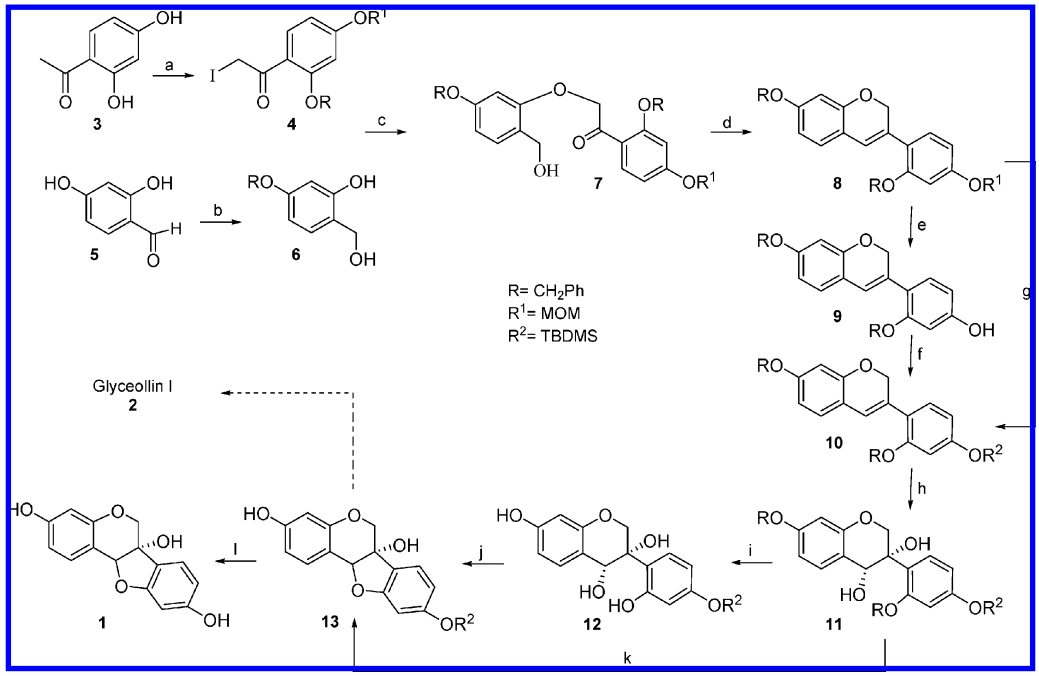
10.1021/np900509f CCC: $40.75
Published on Web 11/04/2009

Scheme 1. Synthetic Routes Used to Prepare Racemic and Natural **1**[a]



[a] (a) (i) MOMCl, K_2CO_3, Me_2CO, rt, (ii) BnBr, K_2CO_3, Me_2CO, reflux, (iii) I_2, Selectfluor, MeOH, rt, 50% over three steps; (b) (i) BnBr, $NaHCO_3$, CH_3CN, 60 °C, (ii) $NaBH_4$, MeOH, rt, 61% over two steps; (c) K_2CO_3, Me_2CO, reflux, 72%; (d) (i) $PPh_3 \cdot HBr$ (added in portions), CH_3CN, rt, (ii) t-BuONa, MeOH, reflux, 70% over two steps; (e) $PPh_3 \cdot HBr$, CH_3CN, water, reflux, 78%; (f) TBDMSCl, Et_3N, CH_2Cl_2, rt, 69%; (g) $PPh_3 \cdot HBr$, CH_2Cl_2, rt, then Et_3N, TBDMSCl, rt, 70%; (h) OsO_4, $(DHQD)_2PHAL$, CH_2Cl_2, −20 °C, 86%; (i) 10% Pd−C, H_2, Me_2CO, 15 psi, rt, 89%; (j) polymeric base, 4 Å MS, EtOH, 80 °C, 60%; (k) 10% Pd−C, H_2, EtOH, 35 psi, rt, 85%; (l) $Et_3N \cdot 3HF$, pyridine, pH 5−6, CH_2Cl_2/MeOH (5:1), rt, 78%.

further toward completion, an aspect we also found to be useful previously when going from isolated **12** to **13** via step j.[8g]

The final conversion of **13** to **1** (step l) was accomplished in a manner analogous to how we previously effected this deprotection to liberate **2** except that pyridine was utilized as the buffering system rather than $Et_3N \cdot 3HF$.[8g] The amorphous solids obtained after evaporation of eluents from preparative TLC and column chromatography, or after manipulating other types of solutions of the final product, tend to entrain traces of solvent that are difficult to completely remove by either drying or lyophilization. The integrity of our final product was confirmed by melting point, optical rotation, TLC, chiral HPLC, NMR (^1H and ^{13}C), HREIMS, and elemental analysis. Because **1** readily can lose water to form the 6a−11a double bond and can undergo oxidation to various other degradation products, small portions of our final product were also forced in each of these directions so as to provide fingerprints of such materials for use during our chromatography studies. This information is summarized in Tables 1 and 2 in the Supporting Information. Experimental details for all new or significantly modified synthetic procedures are provided below, namely, steps d, g, k, and l, along with that for h, wherein we deployed the chiral catalyst that was prepared in-house.

In summary, a 10-step total synthesis of glycinol from commercially available starting materials is described. Providing product having at least 98% ee in nearly 10% overall yield, this convenient procedure can be used to supply quantities of material needed to further characterize the promising SERM and other novel biological properties of this distinct 6a-hydroxypterocarpan phytoalexin. Chiral HPLC methods are also reported that can be used to provide ready assessment of ee for the key enantiomeric intermediate **11**, as well as for the final product.

Experimental Section

General Experimental Procedures. Chemical reactions were conducted under N_2 in anhydrous solvents unless stated otherwise. Reagents obtained from commercial suppliers were used without 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 SiO_2 TLC plates and visualized by using UV light or iodine vapor. Normal-phase flash CC was performed using silica gel (200−425 mesh 60 Å pore size) and ACS grade solvents. Melting points (mp's) are uncorrected. NMR spectra were recorded on either a 600 or 400 MHz instrument. Peak locations were referenced using either 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 were in agreement with all known intermediates **4** to **13**.

2′,7-(Dibenzyloxy)-4′-(methoxymethyloxy)isoflav-3-ene (8). To a suspension of **7**[8g] (5.03 g, 9.8 mmol) in anhydrous CH_3CN (150 mL) was added $PPh_3 \cdot HBr$ (3.36 g, 9.8 mmol) in five portions of ca. 0.7 g each at intervals of ca. 15−20 min. By the last addition, the reaction mixture became a clear solution. The progress of the reaction was checked by TLC [CH_2Cl_2/MeOH (15:1)]. The reaction was complete in 1−2 h. Solvents were then evaporated to dryness under vacuum at rt to obtain an off-white residue. The crude material was used in the next step without further purification.

To the solution of the crude material in anhydrous MeOH (ca. 400 mL) was added potassium *tert*-butoxide (2.2 g, 19.6 mmol) with stirring. The reaction mixture was refluxed for ca. 18−24 h. Reaction progress was monitored by TLC. After completion, the mixture was cooled to rt and filtered. The precipitate was dissolved in CH_2Cl_2 (ca. 100 mL) after washing with a small amount of cold MeOH (ca. 5−10 mL). The organic layer was partitioned with water (ca. 50 mL), separated, and dried over anhydrous Na_2SO_4. Solvents were evaporated to obtain **8** (3.3 g, 6.8 mmol) as an off-white solid in ca. 70% yield over the two steps: mp 126−131 °C (lit.[8g] 115−118 °C); TLC R_f 0.39 [hexanes/EtOAc (5:1)].

2′,7-Dibenzyloxy-4′-(*tert*-butyldimethylsilyloxy)isoflav-3-ene (10). After addition of $PPh_3 \cdot HBr$ salt (0.74 g, 2.2 mmol) to a solution of **8** (1.0 g, 2.0 mmol) in anhydrous CH_2Cl_2 (10 mL), the reaction mixture was allowed to stir at rt and followed by TLC [hexanes/EtOAc (2:1)]. The reaction was complete in 1−2 h, after which Et_3N (0.5 mL, 3.6 mmol) followed by TBDMS-Cl (0.35 g, 2.3 mmol) were added. The reaction was again monitored by TLC. After completion in ca. 12 h,

the reaction solvents were evaporated under vacuum at 30 °C. The solid residue was dissolved in ca. 100 mL of CH_2Cl_2, and 15 g of silica reagent[17] ($NaHSO_4/SiO_2$) preactivated (120 °C for 48 h) was added. The mixture was stirred vigorously for ca. 1 h. Solids were filtered, and the filtrate was passed through a pad of silica (3 cm thick × 9 mm dia.). The solvents were evaporated under vacuum, and the crude residue was recrystallized from CH_2Cl_2/MeOH (1:5) to obtain **10** (0.77 g, 1.4 mmol) as white crystals in 70% yield: mp 104−106 °C [lit.,[8g] 106−107 °C]; TLC R_f 0.42 [hexanes/EtOAc (2:1)].

(+)-4′-*tert*-Butyldimethylsilyloxy-2′,7-(dibenzyloxy)isoflavan-3,4-diol (11). A solution (2.5 mL) of OsO_4 (0.25 g, 0.98 mmol) in toluene was added to a solution of chiral ligand $(DHQD)_2PHAL$ (0.86 g, 1.1 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for ca. 1 h at −20 °C. A solution of **10** (0.48 g, 0.87 mmol) dissolved in CH_2Cl_2 (10 mL) was then added slowly over 10−15 min, and the mixture stirred for ca. 18 h at −20 °C. Reaction progress was monitored by TLC. After completion, the reaction was allowed to warm to rt, and 15 mL of 10% sodium sulfite (pH ∼9.0) was added followed by 15 mL of 10% sodium bisulfite (pH ∼4). The resulting deep brown mixture was allowed to stir for ca. 2 h at rt, after which 10 mL of THF and 40 mL of EtOAc were added.

The reaction mixture was stirred for 3−4 h at 55 °C (external oil bath temp). After cooling, the mixture was filtered through a filter paper and the filtrate passed through a pad of Celite (ca. 1 g). The pad was washed with water (2 × 10 mL) and EtOAc (2 × 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and filtered. The filtrate was applied to a quick silica pad filtration (1−2 cm thick and 9 cm dia.), followed by evaporation of solvents under vacuum. The crude product was purified using CC [silica gel ca. 60 g with hexanes/EtOAc (3:1)] to obtain **11** (0.44 g, 0.75 mmol) as a white solid in 86% yield and >98% ee: mp 75−77 °C; $[\alpha]^{25}_D$ +6.7 (*c* 1.6, MeOH); TLC R_f 0.28 [hexanes/EtOAc (3:1)]; *anal*. (%) calcd for $C_{35}H_{40}O_6Si$, C 71.89, H 6.89, found C 71.83, H 6.92.

(−)-9-(-*tert*-Butyl dimethylsilyloxy)glycinol (13). Palladium on carbon (10% Pd/C) (0.1 g, 20% w/w) was added to a dry ice/Me_2CO-bath chilled solution of **11** (0.5 g, 0.85 mmol) in anhydrous EtOH (ca. 10 mL). The mixture was set for hydrogenolysis at 35 psi at rt. The reaction was followed by TLC and was complete in ca. 4 h. Prolonged reaction times can cause reductions in overall yield. The reaction mixture was passed through a pad of Celite and washed with EtOH (3 × 10 mL). The solvents were evaporated under vacuum to obtain **13** (0.28 g, 0.72 mmol) as an off-white powder in 85% yield: mp >170 °C; $[\alpha]^{25}_D$ −209.5 (*c* 0.3, MeOH); TLC R_f 0.41 [hexanes/CH_2Cl_2/MeOH (10:10:1)]; *anal*. (%) calcd for $C_{21}H_{26}O_5Si$, C 65.26, H 6.78, found C 65.75, H 6.76.

(±)-Glycinol (racemic 1). Racemic 9-(*tert*-butyldimethylsilyloxy)-glycinol (0.038 g, 0.1 mmol) was dissolved in 1 mL of CH_3CN, and the solution cooled to −20 °C. $Et_3N·3HF$ in CH_3CN (1.2 mL solution, 0.12 mmol) was added, and the mixture stirred for 8 h at 4 °C. After disappearance of reactant (TLC), the pH was adjusted to 7−8 by addition of Et_3N, and the mixture filtered through a silica column (ca. 20 g) using CH_2Cl_2/MeOH (10:1) as eluent. Evaporation of the solvent at 20 °C provided a brownish oily residue, which was further purified using preparative TLC [Me_2CO/MeOH (20:1)]. The yellow band (R_f ca. 0.7) was scraped from the plate, and the product was extracted using Me_2CO/MeOH (20:1) to obtain racemic **1** (18 mg, 66 μmol) as an orange solid in 66% yield: TLC R_f 0.50 [hexanes/EtOAc (3:7)]; ^{1}H NMR ($(CD_3)_2CO$, 600 MHz) δ 8.51 (1H, s, Ar-OH), 8.43 (1H, s, Ar-OH), 7.29 (1H, d, J = 9.0 Hz, H1), 7.19 (1H, d, J = 8.4 Hz, H7), 6.54 (1H, dd, J = 8.4, 2.4 Hz, H2); (1H, dd, J = 8.4, 2.4 Hz, H8), 6.30 (1H, d, J = 2.4 Hz, H4), 6.23 (1H, d, J = 1.8 Hz, H10), 5.25 (1H, s, H11a), 4.91 (1H, s, 6a-OH), 4.10 (1H, d, J = 11.4 Hz, H6′), 4.01 (1H, d, J = 11.4 Hz, H6); ^{13}C NMR ($(CD_3)_2CO$, 100 MHz) δ 161.3, 160.0, 158.9, 156.4, 132.6, 124.5, 120.8, 112.7, 110.0, 106.4, 103.1, 97.9, 85.2, 76.0, 69.9; HREIMS *m/z* calcd for $C_{15}H_{12}O_5·Na$, 295.0582, found 295.0571; *anal*. (%) calcd for $C_{15}H_{12}O_5·1.0C_2H_6O·0.05\ H_2O$, C 65.28, H 5.51, O 29.23, found C 64.88, H 5.33, O 29.23.

(−)-Glycinol (1). To a solution of **13** (25 mg, 65 μmol) in ca. 1 mL of CH_2Cl_2 and MeOH (5:1) was added $Et_3N·3HF$ (33 μL, 195 μmol) buffered to pH 5−6 with excess pyridine. The reaction mixture was allowed to stir for ca. 10 h at rt. The reaction was followed by TLC. After completion, the mixture was directly applied to CC [ca. 10 g silica gel; CH_2Cl_2/MeOH (10:1)]. The eluting solvents were evaporated under vacuum, and the resulting yellowish solid was lyophilized to obtain **1** (14 mg, 51 μmol) as a yellow solid in ca. 78% yield: mp 108−112 °C; $[\alpha]^{25}_D$ −221.0 (*c* 0.3, MeOH); TLC R_f 0.49 [hexanes/EtOAc (3:7)]; chiral HPLC retention time 17.92 min (see Supporting Information, Table 1, for specific details); ^{1}H NMR[9] ($(CD_3)_2CO$, 600 MHz) δ 8.55 (1H, s, Ar-OH), 8.47 (1H, s, Ar-OH), 7.30 (1H, d, J = 9 Hz, H1), 7.20 (1H, d, J = 7.8 Hz, H7), 6.55 (1H, dd, J = 8.4, 2.4 Hz, H2), 6.42 (1H, dd, J = 8.4, 2.4 Hz, H8), 6.31 (1H, d, J = 2.4 Hz, H4), 6.24 (1H, d, J = 2.4 Hz, H10), 5.26 (1H, s, H11a), 4.95 (1H, s, 6a-OH), 4.11 (1H, d, J = 11.4 Hz, H6′), 4.02 (1H, d, J = 11.4 Hz, H6); ^{13}C NMR (CD_3OD, 150 MHz) δ 162.1, 161.1, 160.0, 157.3, 133.2, 125.1, 121.2, 113.0, 111.0, 109.2, 104.0, 98.9, 85.9, 77.2, 70.2; HREIMS *m/z* calcd for $C_{15}H_{12}O_5$ 272.0685, found 272.0678; *anal*. (%) calcd for $C_{15}H_{12}O_5·0.50H_2O·0.40CH_3OH$, C 62.90, H 5.00, found C 63.16, H 5.38.

Acknowledgment. We are grateful to the U.S. Department of Agriculture and the Southern Regional Research Center (New Orleans) for their financial support.

Supporting Information Available: Chemical route and experimental details for the synthesis of chiral catalyst; Table 1, having chiral HPLC data and methods; Table 2, having physical properties and structural data; and proton and carbon NMR spectra for racemic and natural (−)-glycinol (**1**) syntheses. This material is available free of charge via the Internet at http://pubs.acs.org.

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NP900509F