ORGANIC LETTERS

2008
Vol. 10, No. 21
5007−5010

Total Syntheses of Racemic, Natural (−) and Unnatural (+) Glyceollin I

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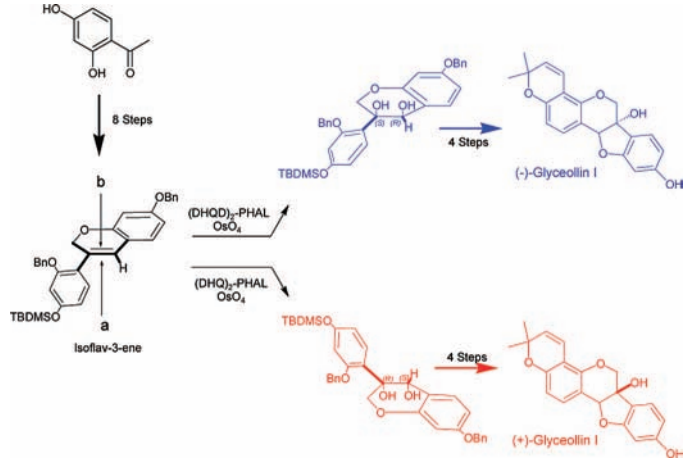
Received September 9, 2008

ABSTRACT



The first total syntheses of racemic glyceollin I and its enantiomers are described. A Wittig approach was utilized as an entry to the appropriately substituted isoflav-3-ene so that an osmium tetroxide mediated asymmetric dihydroxylation could be deployed for stereospecific introduction of the 6a-hydroxy group. While using triphenylphosphine hydrobromide, a novel method was found for gently removing MOM from protected phenolic hydroxyl groups present within sensitive systems.

Already known for its beneficial cardiovascular effects, there is growing interest in the common *Glycine max* as a possible dietary supplement for the prevention of cancer.[1] Of particular note are soy's phytoalexins that are produced as a defense mechanism in response to various insults.[2] The glyceollins (GLYs) are pterocarpan phytoalexins[3] that can be elicited in trace amounts as a mixture having three family members when soybean cotyledons are stressed by infection with *Aspergillus*.[4] In contrast to the more prevalent soy isoflavonoids like genistein and daidzein, the GLYs exhibit marked antiestrogenic activity in some tissues,[5] as well as demonstrating anticancer properties[6] and promise for use as selective estrogen receptor modulators or SERMs.[7]

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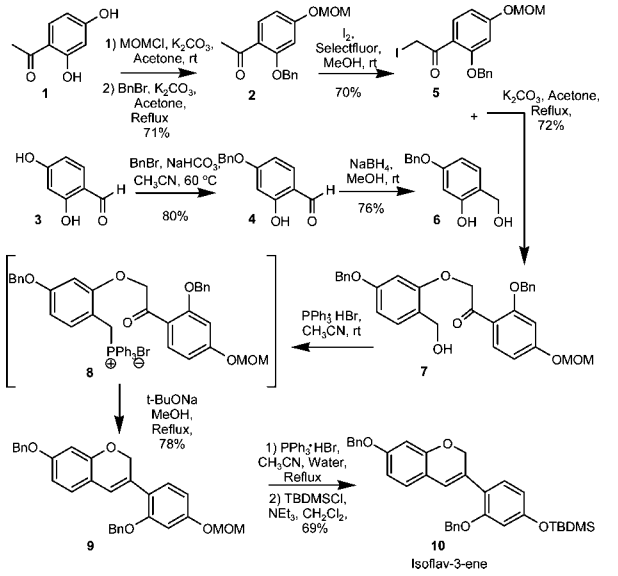
10.1021/ol802112r CCC: $40.75
Published on Web 09/26/2008

Efforts in our laboratory have been directed toward synthesizing the individual GLYs.[8] To date, there have been four GLYs isolated from natural sources but none have undergone total synthesis. GLY I is the most prevalent family member and its synthesis is described herein.

The isoflav-3-ene is a key intermediate in our overall synthesis, and devising a robust method for establishment of its double bond was important. We imagined that if a Wittig olefination reaction was set up to occur in an intramolecular fashion, the desired isoflav-3-ene could be obtained as a consequence of the ring-closure.[9] Our synthetic route to this key intermediate is depicted in Scheme 1.

Scheme 1



Because the *o*-hydroxy group in **1** forms a tight hydrogen bond with the adjacent carbonyl, regioselective protection of the *p*-hydroxy group as the MOM ether occurs cleanly. This is followed by benzyl-protection of the *o*-hydroxy group, using more rigorous conditions. α-Bromination of the orthogonally protected ketone by using conventional methods resulted in a complex mixture of products, namely due to loss of MOM and ring bromination.[10] Alternatively, iodination with 0.5 equiv of iodine and 0.6 equiv of Selectfluor gave the desired halide **5** in 70% yield.[11] Unlike **1**, initial attempts to regioselectively protect **3** resulted in significant amounts of dibenzylated material (30%). The latter can be circumvented by specifically deploying sodium bicarbonate in acetonitrile, whereupon we observed less than 5% dibenzylation.[12] Reduction to the salicylalcohol derivative **6** by using sodium borohydride in MeOH followed by conventional workups also proved to be problematic, perhaps owing to ready formation of the quinone-methide under either basic or even acidic conditions. Review of the literature indicates that alternate methods are typically used for making salicylalcohol from salicylaldehyde.[13] In the end, we were able to conduct a standard sodium borohydride reduction in MeOH by adopting a workup where after evaporation of solvent, 0.1 N sulfuric acid was carefully added so as to achieve an acidic pH of not less than 6.0. Addition of water then conveniently precipitated high-purity product in nearly 80% yield. Coupling of **5** and **6** was accomplished by using potassium carbonate in acetone[14] to obtain product **7** in high yield (72%).

When formation of phosphonium salt **8** was attempted by treatment of **7** with triphenylphosphine hydrobromide (TPP•HBr) in refluxing acetonitrile, a mixture of products was produced wherein inadvertent loss of the MOM group was also observed. Alternatively, when this reaction was done in freshly distilled acetonitrile at room temperature, a quantitative yield of **8** was obtained.[15] Intramolecular condensation of **8** was then accomplished by using sodium *tert*-butoxide as base in refluxing methanol, after which product precipitated from the reaction medium.[16] Crystallization of this material from methanol afforded pure **9** in 78% yield for the two-step process. To avoid the possibility for acid-catalyzed 1,2-elimination of the 6a-hydroxy group during removal of MOM as the last step of the overall synthesis, at this point we replaced MOM with a TBDMS group. Since we repeatedly found **9** to be sensitive to the various acidic conditions typically deployed to remove MOM, we exploited our earlier observation wherein the MOM group was inadvertently lost during treatment of **7** with TPP•HBr. Thus, refluxing **9** in acetonitrile:water (20:1) in the presence of TPP•HBr produced the sensitive phenolic intermediate, which after a quick column chromatographic purification was used immediately in the next step. Treatment with TBDMS-chloride and triethylamine in DCM gave the stable TBDMS-protected isoflav-3-ene **10** as a white solid that was crystallized from DCM and methanol to afford a

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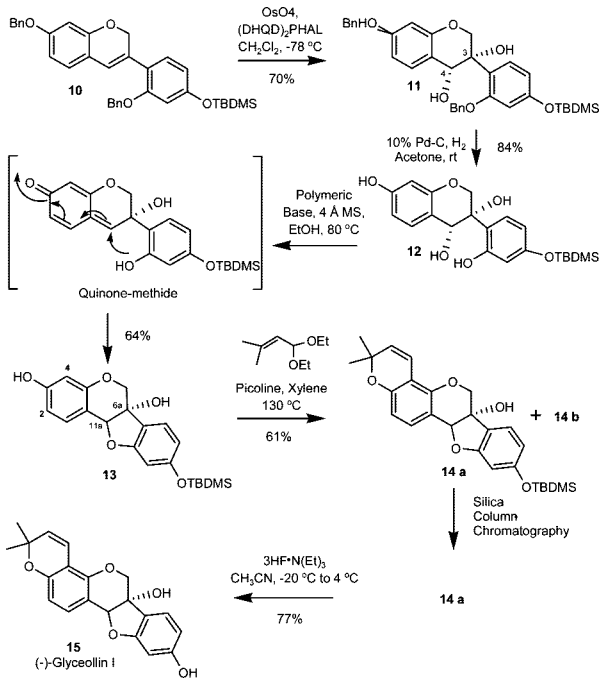
69% yield for the two-step process. The overall yield of **10** from **1** by this route consistently occurs in ca. 20%.

The remaining portions of the syntheses followed the path shown in Scheme 2. Distinct stereochemistry was established

Scheme 2



during the osmium tetroxide (OT) dihydroxylation step. This approach has been utilized for other 6a-hydroxypterocarpans wherein the dihydrobenzopyran system then dictates that subsequent formation of the dihydrobenzofuran ring results in the desired 6a,11a-cis-arrangement.[17,18]

Stoichiometric amounts of OT are typically required because the OT generally forms a stable osmate ester during the reaction that precludes recycling of osmium. Exploring the possibility for reducing the OT load by adding a secondary oxidant, as well as by surveying different conditions, we observed that when 1 equiv of methanesulfonamide (MSA) is added, breaking of the osmate ester appears to be facilitated such that this can allow for recycling of osmium.[19a] From our survey, *N*-methylmorpholine oxide (NMO) proved to be the most efficient secondary oxidant, while acetone:water proved to be the best solvent media. Remarkably, this combination of MSA and NMO enables the desired transformation to take place in high yield (90%) for racemic **11** while using only 10 mg of OT for 10 mmol of reactant compared to the typical stoichiometric amount that would have required 2.5 g of OT.

By using the Sharpless model, the cinchona alkaloids can be deployed as chiral ligands to dictate the stereospecificity of this step.[19] Our analysis indicated that use of $(DHQD)_2$-PHAL as a chiral catalyst should cause the two oxygen atoms to be delivered from the β-face so as to ultimately provide the (6a*S*,11a*S*) stereochemistry desired for the natural (−)-GLY I. Alternatively, use of $(DHQ)_2$PHAL should provide the (6a*R*,11a*R*) stereochemistry desired for the unnatural (+)-enantiomer.

However, when we now added the DHQD reagent to our procedure, the anticipated enantioselectivity was not observed. We speculate that the chiral ligand needs to become tightly bound with the osmate ester complex to display its enantioselectivity, such that disruption of this arrangement under the conditions of our modified OT reaction also leads to a loss of asymmetric induction. Thus, while our method having reduced OT levels remains very useful for the production of large quantities of racemic material, to pursue the pure enantiomers of GLY I we returned to the more traditional method of using stoichiometric amounts of OT and each chiral ligand. These higher loading conditions gave each enantiomer in greater than 95% ee. Enantiomeric purity and absolute configuration were assessed by NMR chiral shift reagent studies and by CD studies.

The rest of the syntheses (Scheme 2) were conducted in parallel for each enatiomer of **11** after refining the chemistry for the individual steps by deploying the racemic mixture as a model system. Absolute stereochemistry and ee were assesed at each step by using CD and NMR studies. The next step involved debenzylation of diol **11** to the tetrol **12** with the likelihood for spontaneous cyclization to the protected glycinol **13** via the quinone-methide depicted in Scheme 2. A "one-pot" method for reductive cyclization has been described[20] and used successfully during a synthesis of pisatin.[18a] Using this procedure, we observed only small amounts of cyclized product. Alternatively, we found tetrol **12** to be stable and conveniently isolable, and therefore performed the cyclization as a separate step. To avoid polymerization of the reactive quinone-methide and thus promote intramolecular ring closure, we used a dilute solution. In addition, use of molecular sieves to remove water formed as byproduct helped to drive this cyclization forward. In the end, polymer-bound 1,3,4,6,7,8-hexahydro-2*H*-pyrimido(1,2-*a*)pyrimidine[21] was deployed as a base in anhydrous ethanol over molecular sieves, and a 64% overall yield across these two steps was achieved. The NMR shift of the C-11a proton is particularly diagnostic for defining a cis versus a trans ring closure within these types of systems. Our C-11a signal at 5.2 ppm was in accord with those of the cis isomers for variabilin and for pisatin as reported by others.[18]

Two approaches were contemplated for assembly of the final isoprenyl-ring systems, namely a modified aldol con-

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densation[22] and a Harfenist−Thom rearrangement of the propargyl ether.[23] In either strategy, ring closure to position 4 of **13** was expected to give the desired **14a** as the major product, while closure to the alternative position 2 would provide regioisomer **14b** that can be additionally elaborated to produce glyceollin II. Introduction of a dimethylpropargyl group proved to be tedious and appeared to cause collapse of the GLY skeleton. Alternatively, the aldol approach proved to be quite useful upon condensing the tautomeric keto-form of the phenol with the unsaturated aldehyde masked as its acetal. This was done in refluxing *p*-xylene by using 0.25 equiv of picoline as base with continuous removal of the liberated alcohol. As anticipated, the TBDMS-protected forms of both GLY I and GLY II were obtained, with the significantly more abundant being the GLY I regioisomer when assessed at the crude product stage by NMR. Separation of these regioisomers was accomplished by using silica column chromatography to afford ca. 50% yields of the racemic and enantiomeric forms of TBDMS-GLY I (**14a**). A 10% yield of the (±) form of TBDMS-GLY II (**14b**) was also obtained during the model chemistry when larger quantities of the racemic mixture were deployed.

In the final step, attempted deprotection with basic reagents like silica-supported TBAF or TAS-F[24] largely resulted in degradation of the formed products. After isolating small quantities of racemic GLY I and conducting a stability study by using HPLC, we deduced that this ring system is not stable in basic pH above 8, or in acidic pH below 4. Thus, we explored mildly acidic reagents that might be used for deprotection. In the end, $NEt_3 \cdot 3HF$,[25] which provides a pH in the range of 4−5 when run on the 0.1 mmol scale in anhydrous acetonitrile, was utilized for this transformation and allowed for 70% to 80% yields. Starting from building block **1**, the overall yield for the total stereoselective synthesis of natural (−)-GLY I (**15**) was 3.4%.

The proton NMR spectra of our synthesized GLYs resemble the data reported for the materials obtained from nature, all of which bear cis (6a*S*,11a*S*) stereochemistry.[26] Most conspicuous are the protons at C-6 which appear as two separate doublets with the C-6 equatorial proton appearing downfield compared to the C-6 axial proton, and wherein W coupling occurs with the C-11a and C-6 equatorial proton, an event not possible for the trans system. Both COSY and NOSEY spectra also confirm this relationship between the C-6 equatorial and C-11a protons. Absolute stereochemistry was confirmed by CD and chiral HPLC studies which deployed an authetic sample of (−)-GLY I from nature as a standard. High-resolution mass spectral data were in agreement with theoretical values for each enantiomer, as well as for racemic GLY I, and correctly support a common molecular formula of $C_{20}H_{18}O_5$.

In addition to conveying the first total syntheses of racemic GLY I and its enantiomers, this report describes a useful entry to substituted isoflav-3-ene systems via a Wittig approach, as well as the use of sulfonamides for reducing OT load during dihydroxylation reactions when control of stereochemistry is not essential. Of particular note is a novel method for gently removing MOM from protected phenolic hydroxyl groups present within sensitive structures by using triphenylphosphine hydrobromide. The scope and selectivity for this type of deprotection procedure is presently being surveyed within the CD3 laboratories.

Acknowledgment. This work was supported by a grant from the United Sates Department of Agriculture (USDA) Southern Regional Research Center (SRRC) in New Orleans. We thank Dr. Steve Boue of the SRRC for a natural GLY I sample isolated from elicited soy, Dr. Michael Ogawa and Mr. Fei Xie of the Bowling Green State University Department of Chemistry for assistance during the CD studies, and Dr. Jared Anderson of The Univeristy of Toledo Department of Chemistry for discussions during the chiral HPLC studies.

Supporting Information Available: Experimental procedures, NMR and CD studies including selected spectra, chiral HPLC, and NMR spectra for new intermediates and final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802112R

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