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Synthesis of 6a-hydroxypterocarpans via intramolecular benzoin condensation

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ABSTRACT

A novel approach for the syntheses of 6a-hydroxypterocarpans is reported. Its practicality is demonstrated by the synthesis of (±)-glycinol. The main feature is an intramolecular benzoin condensation catalyzed by nucleophilic carbenes to initiate assembly of the benzopyran and establish the 6a-hydroxy center. In addition, a one-pot method was developed to form an epoxide that facilitates subsequent cyclization leading to the benzofuran and direct production of (±)-glycinol.

Pterocarpans are the second largest group of isoflavonoids. Derived mostly from legumes, they are potent phytoalexins that act as plant defensive agents in response to attacking pathogens.[1] A distinguishing structural feature of pterocarpans is the presence of *cis*-fused benzofuran–benzopyran rings which gives rise to two asymmetric centers at positions 6a and 11a.[2] Several of the 6a-hydroxypterocarpans are associated with promising medicinal properties.[3] Of particular interest are glycinol (GLO) and the glyceollins (GLYs) (Fig. 1). These intriguing molecules are produced only in trace amounts when soy plants or seeds are stressed.[4]

Despite their promising therapeutic potential, complete pharmacological characterization of the 6a-hydroxypterocarpans remains hampered by limited access to these systems either from natural or synthetic sources. Only a few routes have been reported to establish the 6a-hydroxy group.[5] The most common method deploys a Sharpless dihydroxylation using OsO_4 to produce a benzopyran-diol that can subsequently be closed to the benzofuran *cis*-fused system (Scheme 1).

Herein, we describe a carbene-catalyzed intramolecular benzoin cyclization approach for the synthesis of *cis* 6a-hydroxypterocarpans. This versatile route is delineated using racemic GLO as an example. Our strategy toward the synthesis of GLO centered on the 3-hydroxy chromanone **12** which can be obtained from commercially available materials through the series of reactions as depicted in Scheme 2.

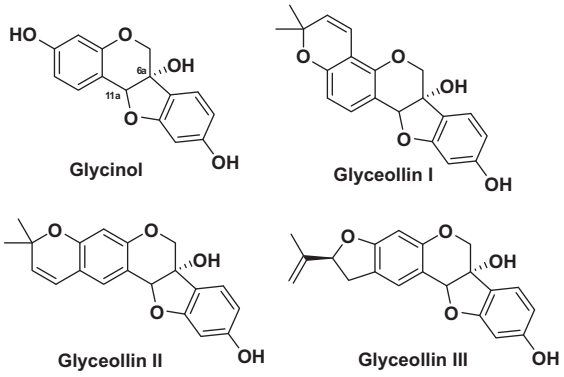

Figure 1. Soy phytoalexins: glycinol (GLO) and glyceollin isomers (GLYs) I, II, III.

Synthesis of **2** followed our published procedure.[6] Masking of the aldehyde group was then essential to prevent an intramolecular Aldol condensation which we observed when attempting to couple **2** and α-iodoketone **6**, the latter likely being due to generation of a reactive enolate in the presence of base. A one-step approach toward acetalization of **2** that utlilized catalytic *p*-toluenesulfonic acid and trimethylorthoformate as a dehydrating agent,[7] resulted in a mixture of starting aldehyde and low yields of **3**. Alternatively, the three-step protocol developed by Takikawa and Suzuki[8] proved successful. After acetylation of **2**, the aldehyde group was masked as a 1,3-dioxane acetal using tetrabutylammonium tribromide (TBATB) as a promoter.[9] Deprotection of the acetate group provided acetal **3** in 68% overall yield. Ketone **4** was

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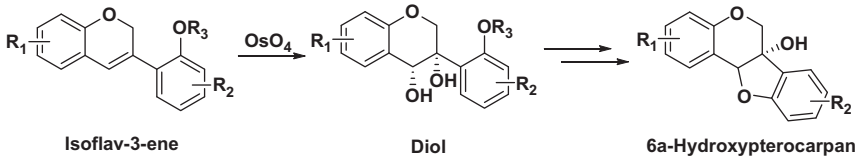
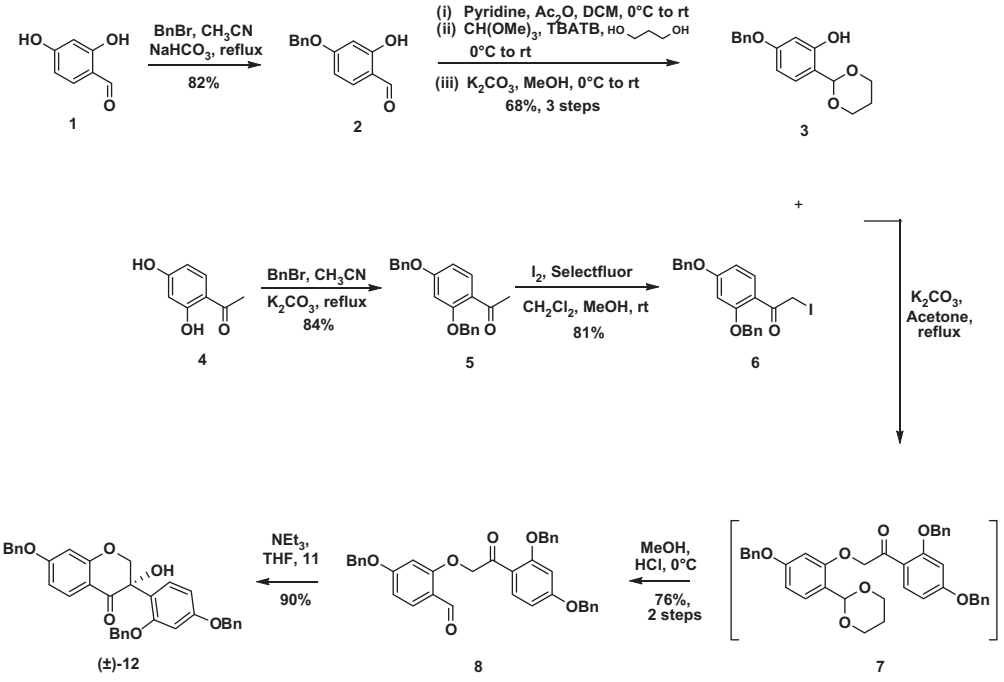
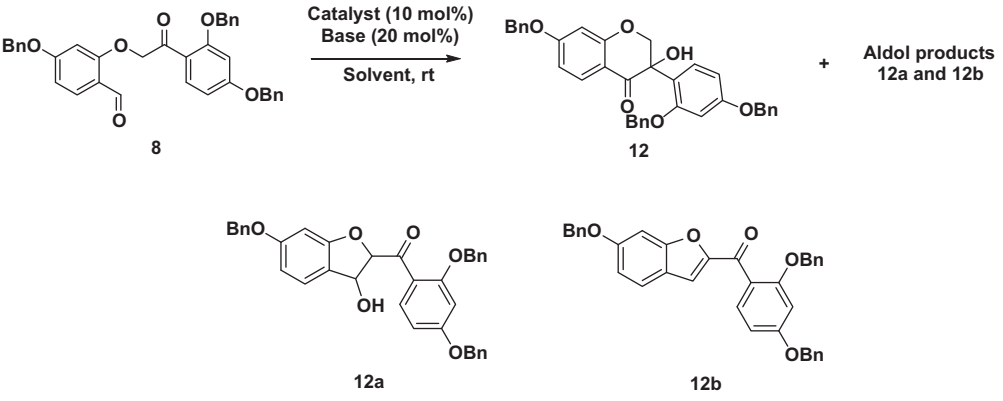


Scheme 1. OsO_4 mediated asymmetric dihydroxylation as an entry to 6a-hydroxypterocarpans.



Scheme 2. Preparation of the 3-hydroxy chromanone.



Scheme 3. Intramolecular benzoin condensation of keto-aldehyde **8**.

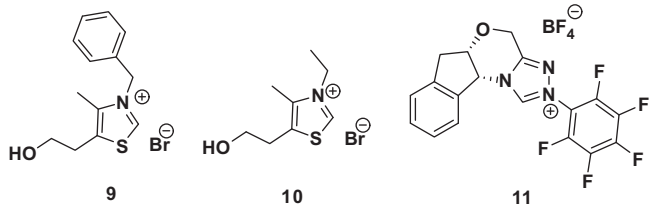


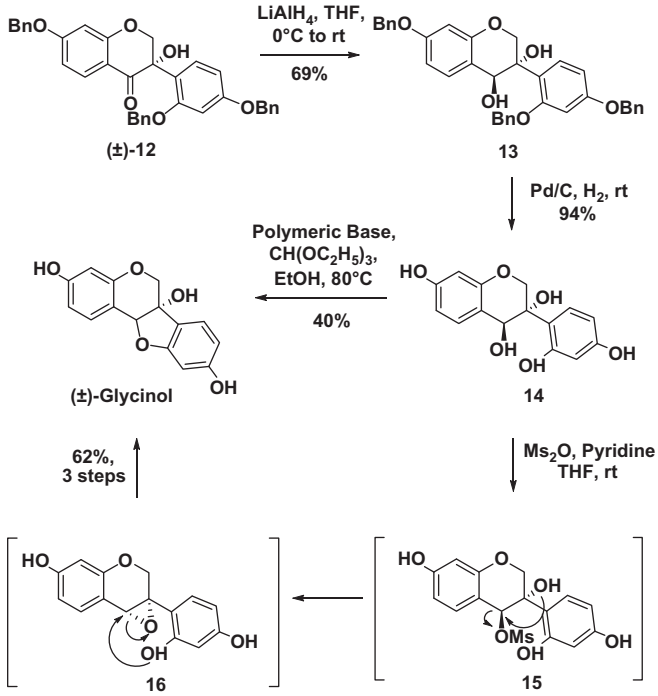
Figure 2. Commercially available catalysts tried during the intramolecular benzoin condensation.

protected at both hydroxyl-groups to give dibenzylated product **5**. α-Iodination of **5** occurred in an uneventful manner to yield crystalline α-iodoketone **6** in high yields.[6] Coupling of **3** and **6** was conducted in refluxing acetone with potassium carbonate as base. Intermediate **7** was isolated in crude form and used in the next step without further purification. Hydrolysis of the acetal protecting group in **7** resulted in keto-aldehyde **8** which conveniently precipitated from the reaction mixture and could be purified by recrystallization. Keto-aldehyde **8** was then subjected to the key step in our synthesis, namely, the intramolecular benzoin cyclization (Scheme 3).[8,10]

Table 1
Catalysts and bases deployed during the benzoin cyclization step shown in Scheme 3

Entry	Catalyst	Base	Solvent	Time (h)	Products (yield %)	
					12	**12b**
1	**9**	DBU	THF	5	—	91
2	**9**	KOtBu	THF	3	—	85
3	**9**	NEt_3	THF	12	<5	78
4	**10**	NEt_3	Toluene	12	<5	83
5	**11**	NEt_3	THF	12	90	—

All reactions were conducted using 0.2 mmol of **8** with catalysts **9**–**11** (10 mol %) and base (20 mol %) at room temperature and were monitored by TLC and ^{1}H NMR.



Scheme 4. Synthesis of (±)-glycinol.

A range of commercially available heterocyclic catalysts **9**–**11** (Fig. 2) and common bases were tried to enhance this cyclization. Table 1 summarizes these attempts. Little to no desired product was formed using catalysts **9** or **10** in the presence of bases like DBU, KOtBu, and NEt_3 (Table 1, entries 1–4).

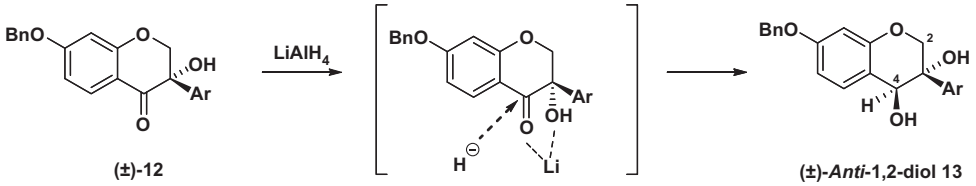
A major competing reaction in this case is the intramolecular Aldol condensation due to the presence of a highly enolizable keto-moiety. This leads to the formation of **12a, b** (Scheme 3) during reaction (TLC) and eventual isolation of **12b** as a side-product. However, Rovis triazolium catalyst **11**[11] proved to be very effective for inducing the benzoin cyclization and provided the desired 3-hydroxy chromanone **12** in high yields (Table 1, entry 5). We attribute this to the electron withdrawing aryl-substituent present in catalyst **11** that requires only a mild base to generate the nucleophilic carbene species. The weaker base helps minimize the occurrence of the Aldol reaction.[8] A possibility of conducting this step stereoselectively was also envisioned due to the chiral nature of the triazolium catalyst **11**. However, the catalyst did not provide any enantioselectivity and **12** was obtained as a racemic mixture. Having the 3-hydroxy chromanone intermediate **12**, we were poised to explore the remaining portion of the synthesis as depicted in Scheme 4.

Reduction of 3-hydroxy chromanone **12** was first attempted using $NaBH_4$ in THF but this resulted in poor yields of diol **13.** Alternatively, $LiAlH_4$ provided the desired diol in 69% yield. Diol **13** was subjected to hydrogenolysis to provide **14** in high yields. The final intramolecular cyclization step to furnish (±)-glycinol was accomplished via a quinone methide intermediate using polymer bound 1,3,4,6,7,8-hexahydro-2*H*-pyrimido(1,2-*a*)pyrimidine as base in anhydrous EtOH over molecular sieves.[5a,12] Triethylorthoformate was added to remove water as a byproduct and drive the reaction toward product formation. The reaction was performed in dilute conditions to avoid polymerization of the reactive quinone-methide. The diagnostic shift of the C-11a proton to 5.25 ppm was observed by ^{1}H NMR and is indicative of a *cis* ring closure versus *trans* within these types of fused systems.[5a,13] The ^{1}H NMR and ^{13}C NMR spectra were in accordance with our previously published values for (±)-glycinol.[5b] Although the yield of the final step was not as high as expected, we were able to isolate unreacted starting material **14** which could be then recycled into subsequent reactions.

The low yields of the final step encouraged us to devise a different route for this step. Close examination of the ^{1}H NMR spectra of diol **13** revealed that the $LiAlH_4$ mediated reduction had taken place via chelation control resulting in a racemic mixture of *anti*-1,2-diols (Scheme 5). There was no sign of the diastereomeric *syn*-1,2-diol in the ^{1}H NMR spectra. As a result of chelation, the hydride attacks from the side of the smallest substituent according to the Cram-chelation model,[14] that is, from below and opposite the phenyl ring. Previous studies[5a] on a similar system where OsO_4 was used to prepare the *syn*-diol showed that the 2-position hydrogens appear at δ 4.02 and δ 4.72 and the 4-position hydrogen appears at δ 5.51 in the ^{1}H NMR spectra. For the *anti*-diol these protons appear at δ 4.30, δ 4.73, and at δ 4.88, respectively.

The *anti*-arrangement of diol **13** suggested the possibility of synthesizing (±)-glycinol via epoxide formation from **14** to **16** which can then cyclize intramolecularly to obtain the required 6a-hydroxypterocarpan as shown in Scheme 4. This reaction was conducted with mesylate as a leaving group to obtain the epoxide intermediate **16**.[15] Several attempts to isolate epoxide **16** were unsuccessful due to the inherent instability of this intermediate. This transformation was therefore performed in one step from **14** using Ms_2O in Pyridine/THF and provided (±)-glycinol in 62% overall yield, considerably higher when compared to the quinone-methide closure.

In summary, we have devised a novel route to synthesize 6a-hydroxypterocarpans. Its feasibility has been demonstrated on (±)-glycinol which can be produced in ca. 20% overall yield after



Scheme 5. $LiAlH_4$ mediated reduction of **(±)-12**; only one enantiomer is depicted.

10-steps with only two column purifications. Moreover, the later stage of the synthesis involving an epoxide intermediate, opens up possibilities for obtaining 6a-hydroxypterocarpans that cannot be synthesized via the quinone-methide pathway. Thus, this chemical route has general applicability and is especially useful for future process chemistry initiatives that may be undertaken within the context of this interesting class of natural products.

Acknowledgments

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Supplementary data

Supplementary data (experimental details and spectroscopic data (^{1}H NMR, ^{13}C NMR, COSY) for new intermediates and final compound are provided) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.121.

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