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Bioinspired Total Synthesis of Gymnothelignan N

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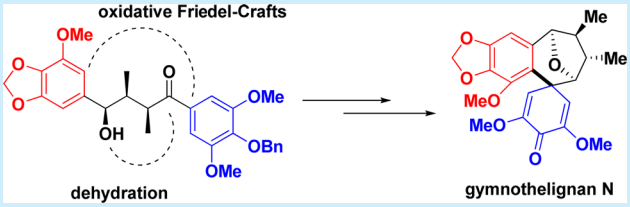
Supporting Information

ABSTRACT: Bioinspired total synthesis of gymnothelignan N was accomplished in 13 steps and 6.7% overall yield. The synthesis features a *syn* Evans aldol reaction, an intramolecular hydrogenative dehydration reaction, and a phenol oxidative dearomatization/Friedel–Crafts reaction, which provides a new plausible biosynthetic pathway for the gymnothelignans and other symbiotic members. Meanwhile, another tetrahydrofuran-type lignan beilschmin A was also synthesized.



Lignans feature a range of complex and important natural products with diverse structure types.[1] Among them, tetrahydrofuran (THF) type lignans form a huge subgroup of lignans with various important biological activities.[2] These compounds have attracted the attention of synthetic chemists for a tong time.[3,9] The biosynthetic pathway of the newly isolated lignans is inconclusive, although some classical proposals are widely accepted.[4] The proposed biosynthetic pathways have become a rich source of synthetic strategies for biomimetic total synthesis of lignans.[5] More recently, Kan and Hamashima have accomplished a biomimetic synthesis of the furofuran lignan skeleton of Hydeltol A via a quinomethide intermediate.[3p]

In 2012, Xu and Zhou reported the isolation of 15 new THF-type lignans, gymnothelignans A–O (Figure 1), from *Gymnotheca chinensis* Decne, a widely used perennial Chinese herb of Saururacese.[6] Besides structure elucidation, the authors have also proposed the possible biosynthetic pathways of these compounds and accomplished some chemical transformations between them. Among the 15 gymnothelignans, gymnothelignan N and O attracted our attention because their unique 10,11-benzospiro[5.6]dodec-13,15-dien-14-one motif across a THF ring is unprecedented in lignans, which makes the structures of gymnothelignans N and O more complex than other members as well. In connection with our long-time interest in biomimetic total synthesis of natural products,[7] we started a synthetic research program toward these compounds. Herein we describe the bioinspired total synthesis of gymnothelignan N.

Through investigating the structures of gymnothelignans and other related lignans, a plausible biosynthetic pathway is proposed and outlined in Scheme 1. Sinapyl alcohol undergoes a self-dimerization to form the dibenzylbutane type lignan **A** based on the known proposal.[4] The bibenzylbutanes **A** could be further oxidized at benzyl position to deliver **B** with a higher

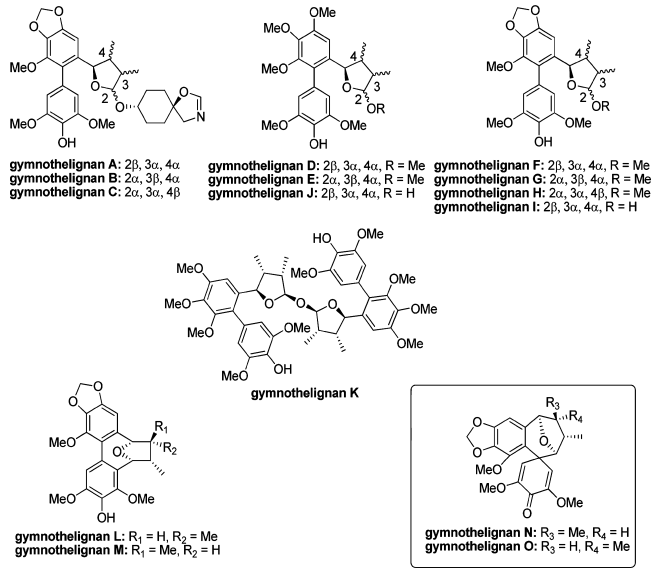


Figure 1. Structures of gymnothelignan A–O.

level oxidation state. Dehydration of **B** could provide the corresponding 2,5-diaryltetrahydronfuran type lignan structure **C**.

We speculated that the eupodienone skeleton **D** (gymnothelignan N and O) could come from 2, 5-diaryltetrahydronfuran type lignan **C** via an oxidative Friedel–Crafts process, since the electron-rich diaryl lignans are important antioxidants for scanvenging free radicals.[8] The eupodienone **D** could rearrange to the eupomatilone-type lignan skeleton **E**

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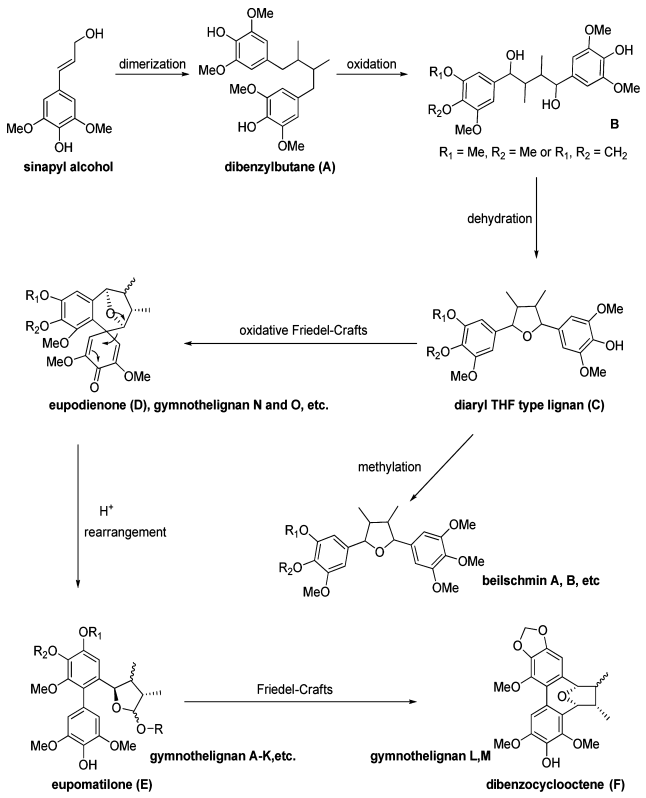
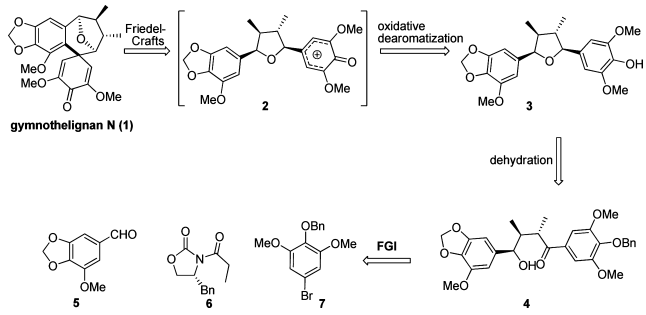
Scheme 1. Plausible Biosynthetic Pathway of Gymnthelignans



(gymnothelignans A–K) with diverse substitution on the exocyclic oxygen atom.[9] Moreover, the dibenzocyclooctene skeleton **F** (gymnothelignan M and L) could be accessed from eupomatilone **E** by an intramolecular Friedel–Crafts reaction through an oxonium cation intermediate. On the other hand, intermediate **C** could be transformed to beilschmins A and B and other analogues through simple methylation.[10] Since there are already some cases of dearomatization/Friedel–Crafts in lignan biogenesis proposals, it is noteworthy that our proposal is different from Xu and Zhou's point[6] on gymnothelignans and other proposed biogenetic pathway[11] for eupomatilones in the following respects. First, in our biosynthetic pathway, the oxidative Friedel–Crafts step occurs after the THF ring formation. Then, structures of eupomatilone **E** and dibenzocyclooctene **F** are generated from eupodienone **D** rearrangement, which is not in accordance with the previous view. Since rearrangement from eupodienone **D** to eupomatilone **E** has already been illustrated,[6] the eupodienone structure **D** is of utmost importance in our proposed biosynthetic pathway. To confirm this proposal, we focused our attention on the synthesis of eupodienone-type member gymnothelignan N (**1**).

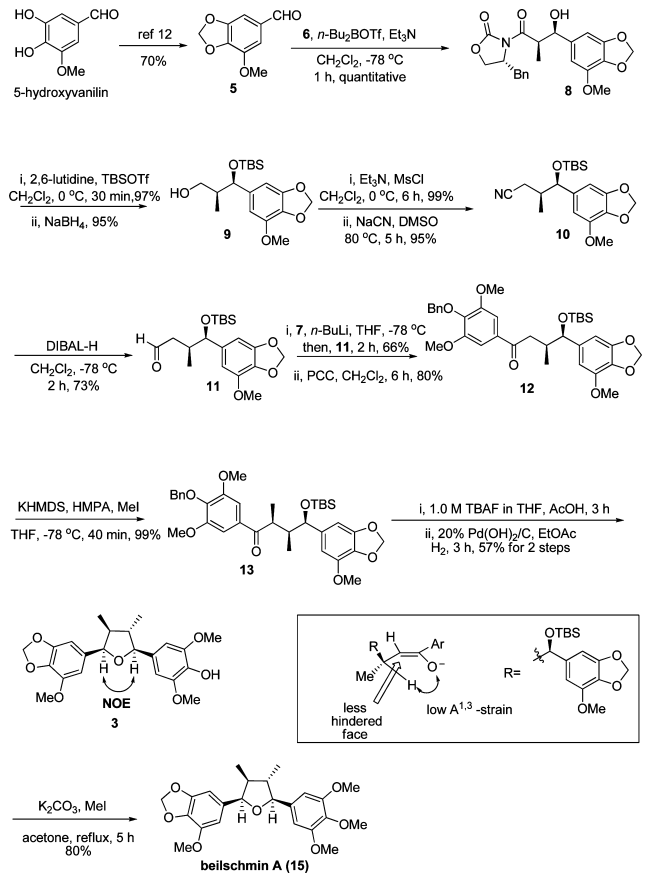
Retrosynthetic analysis of gymnothelignan N (**1**) is shown in Scheme 2. The spirodienone motif could be derived from an intramolecular Friedel–Crafts reaction of cation intermediate **2** which could be accessed from diaryl THF compound **3** through an oxidative dearomatization process. The *cis*-substituted THF ring could be further traced back to the open-chain structure **4** by intramolecular dehydration of the hydroxyl group with carbonyl group. Compound **4** could be further simplified into known fragments aldehyde **5**,[12] chiral precursor (*R*)-4-benzyl-3-propionyloxazolidin-2-one **6**[13] and aryl bromide **7**[7c] by functional group interconversions.

Scheme 2. Retrosynthetic Plan of Gymnothelignan N



Our synthesis commenced with synthesis of the key precursor **3**. As shown in Scheme 3, conversion of

Scheme 3. Synthesis of the Key Intermediate 3 and Beilschmin A



commercially available 5-hydroxyvanilin to aldehyde **5** was achieved on the basis of literature operation.[12] Dibutylboron triflate catalyzed Evans *syn* aldol reaction of aldehyde **5** with (*R*)-4-benzyl-3-propionyloxazolidin-2-one **6** smoothly provided compound **8** (dr >20:1).[14] Subsequent TBS protection of the secondary alcohol and reductive removal of the chiral oxazolidinone delivered alcohol **9**. Mesylation and cyanidation provided cyanide compound **10**. However, attempts to introduce the *syn* methyl group at α position of the cyanide group[15] resulted in low diastereoselectivity, which prompted us to put off the methylation step. Thus, DIBAL-H reduction of cyanide **10** afforded aldehyde **11**, which was further converted into ketone **12** by installation of the second aryl group via

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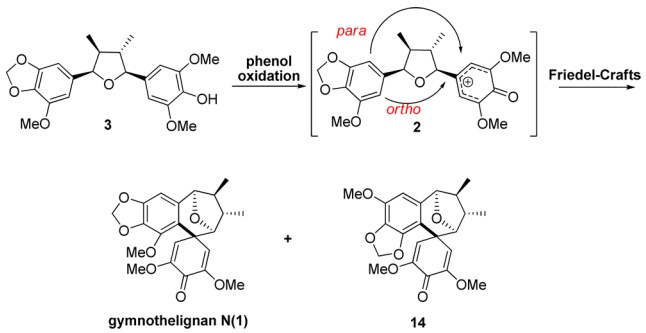
nucleophilic addition and subsequent PCC oxidation. Up to this stage, introduction of the second methyl group under the KHMDS/HMPA/MeI conditions gave *syn* product **13** with good yield and diastereoselectivity (dr >12:1).[16] According to Maezaki's speculation, the high selectivity of this reaction is due to methylation from the less hindered face of the preferred enolate conformation minimizing $A^{(1,3)}$-strain (as shown in the box in Scheme 3). Then, TBAF-promoted desilylation followed by AcOH catalyzed hemiketalization furnished the corresponding hemiketal, which was immediately subjected to the next dehydration step under 20% $Pd(OH)_2/H_2$ condition producing the desired tetrasubstituted THF ring compound **3** (dr >5:1) with removal of the benzyl group simultaneously. The major product was determined as *cis* substitution of the two aryl group on the THF ring according to NOE experiment. In this process, AcOH was essential for this reaction probably due to the hemiketal formation step was hard to occur under the basic condition of TBAF.[17] It is worthy to note that all of the above-mentioned reactions were operated on gram scale.[18] Methylation of **3** could furnish a simple 2,5-diaryltetrahydronfuran type lignan beilschmin A (**15**) with cytotoxic activity isolated from *Beilschmiedia Tsangii* Merr. (Lauraceae).[10]

With enough key intermediate **3** in hand, the stage was set to the critical bioinspired oxidative Friedel–Crafts reaction. Although there are many cases of phenol oxidative dearomatization/Friedel–Crafts reaction applied in natural product synthesis,[19,20] in our substrate, it is considered to be challenging for two aspects. The first one is the expected intramolecular Friedel–Crafts should occur across the THF ring to form the seven-membered ring with an all-carbon quaternary center as linkage, while the presumed cation intermediate **2** is in situ generated. The second one is the site selectivity of the Friedel–Crafts reaction. The *para* and *ortho* positions of the methoxyl group are in competition in this reaction.[20] To find the appropriate conditions, we systematically screened the phenol oxidative dearomatization conditions (Table 1). First, inorganic oxidants Ag_2O and $FeCl_3$ used by Tang[19j] were proven to be ineffective on our substrate (entries 1 and 2). Disappointly, $NaNO_2$ also led our substrate to decompose as well[21] (entry 3). Faced with the failure of inorganic oxidants, we turned our attention to common phenol oxidation hypervalent iodine(III) reagents, such as iodobenzene diacetate (PIDA) and phenyliodine bis-trifluoracetate (PIFA). Under Canesi's conditions,[20] PIFA in hexafluoroisopropyl alcohol (HFIP) also led to substrate decomposition, which was probably caused by the strong trifluoroacetic acid released in this process. Pleasingly, when PIFA was changed to PIDA, the Friedel–Crafts product was obtained in 70% yield (entry 5). The selectivity of *ortho*/*para* ratio was 2.6/1 determined by the ^{1}H NMR integral. Changing the solvent to trifluoroethanol (TFE) gave not only lower selectivity but also lower yield instead (entry 6). Reducing the reaction temperature also failed to increase the *ortho* site selectivity as well (entry 7). Although the site selectivity ratio of this Friedel–Crafts reaction was not very high, to our delight, the *ortho* Friedel–Crafts product, namely gymnothelignan N, could be separated by careful flash chromatography using CH_2Cl_2/MeOH as the eluent system. At this stage, the total synthesis of gymnothelignan N was accomplished in 13 steps from 5-hydroxyvanilin in 6.7% overall yield. Physical data of our synthetic sample are in agreement with that of the isolated natural sample reported by Xu and Zhou.[22] Gymnothelignan H could be further accessed through an acid-catalyzed rearrangement of gymnothelignan N,[6] providing strong support for our biosynthetic proposal.

Table 1. Screening the Oxidative/Friedel–Crafts Condition for Synthesis of Gymnothelignan N



entry	conditions[a]	yield[b] (%)	ratio (**1**:**14**)[c]
1	Ag_2O, CH_2Cl_2, rt	no reaction	
2	$FeCl_3$, CH_2Cl_2, rt	decomposed	
3	$NaNO_2$, CH_2Cl_2/TFA = 5/1, rt	decomposed	
4	PIFA, HFIP, 0 °C	decomposed	
5	PIDA, HFIP, 0 °C, 10 min	70	2.6:1
6	PIDA, TFE, 0 °C, 10 min	45	2.5:1
7	PIDA, TFE, −50 °C, 10 min	19	2.3:1

[a]PIDA = iodobenzene diacetate, PIFA = phenyliodine bis-trifluoracetate, HFIP = hexafluoroisopropyl alcohol, TFE = trifluoroethanol. [b]Yield is the total yield of **1** and **14**. [c]Determined by ^{1}H NMR integral.

In conclusion, a new plausible biosynthetic pathway of the 15 gymnothelignans as well as other related congeners is proposed by investigation of their structure relationship. Efficient asymmetric total synthesis of the structurally novel gymnothelignan N, together with another THF-type lignan beilschmin A, was achieved on the basis of the biosynthetic pathway. Key steps of the synthetic sequence involve a *syn* Evans aldol reaction, an intramolecular hydrogenative dehydration reaction, and a phenol oxidative dearomatization/Friedel–Crafts reaction. According to Xu and Zhou's preliminary chemical transformation work, the eupomatilone-type member gymnothelignan H could be further accessed. Bioinspired synthesis of other important members of gymnothelignans based on this proposal is in progress in our laboratory and will be reported in the near future.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and full spectroscopic data for all new compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(22) See the Supporting Information for data comparison of the synthetic sample with naturally occurring gymnothelignan N.