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Graphical Abstract

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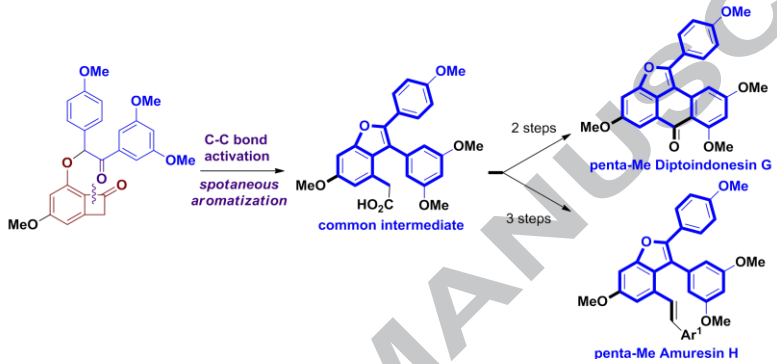

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Total Synthesis of penta-Me Amurensin H and Diptoindonesin G Featuring a Rh-catalyzed Carboacylation/Aromatization Cascade Enabled by C-C Activation.

Yuting Qin[a,†], Jun-Ling Zhan[a,†], Tian-tian Shan[a] and Tao Xu[a,b]*

[a] *Key Laboratory of Marine Drugs, Ministry of Education; School of Medicine and Pharmacy, Ocean University of China, Qingdao 266003, China.*
[b] *Laboratory for Marine Drugs and Bioproducts and Open Studio for Druggability Research of Marine Natural Products, Pilot National Laboratory for Marine Science and Technology(Qingdao), 1 Wenhai Road, Qingdao 266237, China*

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ABSTRACT

Oligostilbenoids represented a family of natural products, which contained one or several multifused benzofuran substructures and displayed promising biological activities towards cancer as well as immunological therapeutic targets. A convergent-divergent strategy featuring Rh-catalyzed carboacylation/aromatization cascade reaction based on C-C activation of benzocyclbutenones had been conceived. penta-Methyl amurensin H and diptoindolnesin G were successfully synthesized without any protecting groups, constituting a new entry towards oligostilbenoids' natural product synthesis. The synthesis completed within 10 steps for both natural products, suggesting conciseness and efficacy of the C-C activation in complex natural product synthesis.

* Corresponding author. Tel.: +86-532-8590-6822; e-mail: xutao@ouc.edu.cn

† These authors contributed equally to this work.

Oligostilbenoids represented a family of natural products, which contained one or several multifused benzofuran substructures and displayed promising biological activities towards cancer as well as immunological therapeutic targets.[1] As a representative member, diptoindonesin G (DipG) was isolated from *Hopea mengarawan* in Indonesia by Syah group in 2009 and at roughly the same time by Tan group from a Chinese stem bark as well.[2] DipG featured a rather rigid tetracyclic polyfused benzofuran skeleton and four phenolic OH groups, which might be the structural basis for its unique biological activities. It showed potent growth-inhibitory effect towards P-388 cell line. Recently, it was reported that diptoindonesin G displayed regulatory effects towards nuclear receptor family namely, estrogen receptor α/β, which are validated target proteins for breast cancer therapy.[3] Diptoindonesin G also showed anti-proliferation ability by inducing G2/M phase arrest and cell differentiation in acute myeloid leukemia(AML) cell lines and primary AML cells, making it a potential new candidate for AML differentiation therapy.[4] On the other hand, amurensin H also known as viniferifuran, malibatol A and shoreaphenol all belonged to oligostilbenoids family containing multisubstituted benzofuran skeleton. These natural products also exhibited a wide variety of pharmacological activities including anti-inflammatory, antioxidant, antifungal, antibacterial, anti-HIV, and anticarcinogenic activities[5].(Figure 1) Outstanding total synthesis of these molecules had been achieved by Krause[6], Kim[7], Tang[8] and Chen[9] using different Lewis acid promoted cyclization and/or gold-catalysis. A recent report from Kim's group, displayed skeletal rearrangement strategy towards Dip G[7d]. We are particularly intrigued by utilization of the C-C bond activation strategy into the total synthesis of oligostilbenoids.[10]

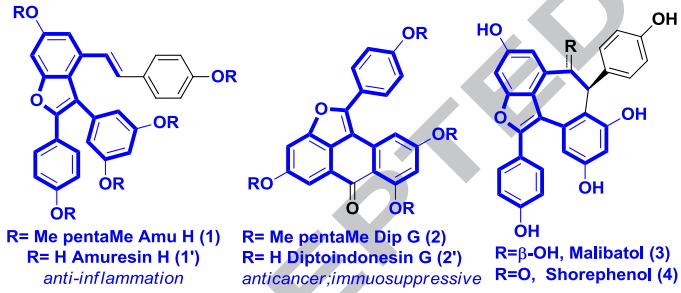
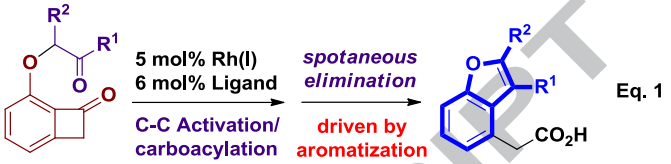


Figure 1. Representative oligostibenoids containing multi-substituted benzofuran skeleton.

Transition metal-catalyzed formal [4+2] cycloadditions between four-membered cyclic ketones and a 2π component through C−C σ-bond activation has established as an attractive approach for preparing complex ring systems.[11] These methods generally operated at near pH and redox neutral conditions in an atom-economical fashion. Carbon-Carbon bond activation has emerged as a unique booming area in modern transition metal catalysis although tandem design and application in natural product synthesis are still rare. To the best of our knowledge, only two examples of application in natural product synthesis utilizing metal-catalyzed carboacylation of olefins through C–C bond cleavage of four-membered ketones have been reported,[10,12] in which simple non-polar olefins were employed as coupling partners. This approach allows converting one relatively inert C–C bond into two reactive M–C bonds, providing unusual strategies to access 2,3-disubstituted benzofuran skeletons in a single step.

Recently, our group had developed a cascade transformation initiated by regioselective activation of benzocyclobutenone, which was followed by insertion into C=O and spontaneous aromatization, furnishing a variety of 2,3 substituted benzofuran analogues(Eq. 1).[10a] While the field of C−C activation methodologies based on benzocyclobutenones has seen limited use in complex natural product synthesis, there remains great potential in its application into total synthesis oligostilbenoids natural products.



The core structural features as well as their important biological activities of amuresin H and diptoindonesin G prompted us to embark on the total synthesis of these multi-substituted benzofuran-containing oligostilbenoids.(Figure 2) Our retrosynthetic analysis is based on a convergent-divergent design. We hypothesized that penta-Me amuresin H (**1**) and diptoindonesin G (**2**) could be accessed through Wittig olefination and Friedel-Crafts cyclization, respectively from a common intermediate **5**. The benzofuran compound **5** could be reached by the key transformation: Rh-catalyzed carboacylation/aromatization cascade via intermediate I, from the coupling product **7**. The starting material **7** can be readily synthesized from benzocyclobutenone **8** and the known ketone **9**.[10a] This design join the two fragments together and diversified at later stage of the synthesis, which allowed introduction of different aromatic rings in each part that could ultimately serve as a key plat-form for further SAR studies in medicinal research.

Our forward synthesis commenced with synthesizing benzocyclobutenone **9**. (Figure 3) We started from commercially available 1-bromo-3,5-dimethoxybenzene (**10**) by performing a [2+2] cycloaddition between an *in situ* generated benzyn (from LiTMP and purchased arylbromide **10**) and the freshly made

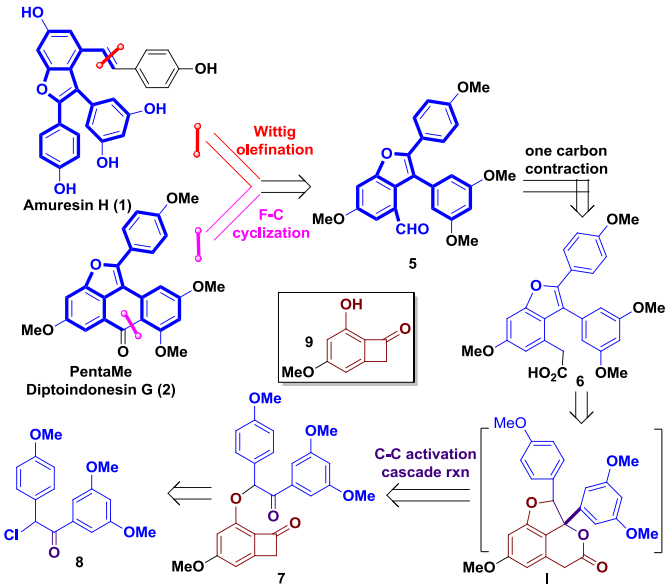


Figure 2. A convergent-divergent strategy featuring Rh-catalyzed carboacylation/aromatization cascade towards amuresin H and pentaMe diptoindonesin G.

liuthium-enolate (**11**), following a modified procedure of Dong and coworkers.[13] The resulting benzocyclobutenol (**12**) was -oxidized with DMP under basic condition to afford methylated benzocyclobutenone **13** in an 85% yield. The selective demethylation was carried out with extensive optimization, only obtaining regioisomers **9** and **9'** as mixtures in a ratio of 1:1 with 50% combined yield. The isomer mixture was alkylated with literature known α–chloro ketone **8**[10] and yielded compound **7** as inseperable mixtures, too. They were nevertheless subjected to the previously reported[10b] reaction condition employing 10 mol% $[Rh(cod)(MeCN)_2]BF_4$ and 12 mol% DPPF in THF for the carboacylation/aromatization cascade transformation. Gratifyingly, the only isolated product was the desired 2,3-substituted benzofuran **6** in a 76% yield based on the benzocyclobutenone C_3 regioisomer **9**. The robustness and efficacy of this key step paved way for following synthesis of the target molecules. One carbon abstraction was realized using a three-step sequence. Benzofuran **6** was reduced by $LiAlH_4$ and converted to meslate **15** in an 80% yield over two steps.

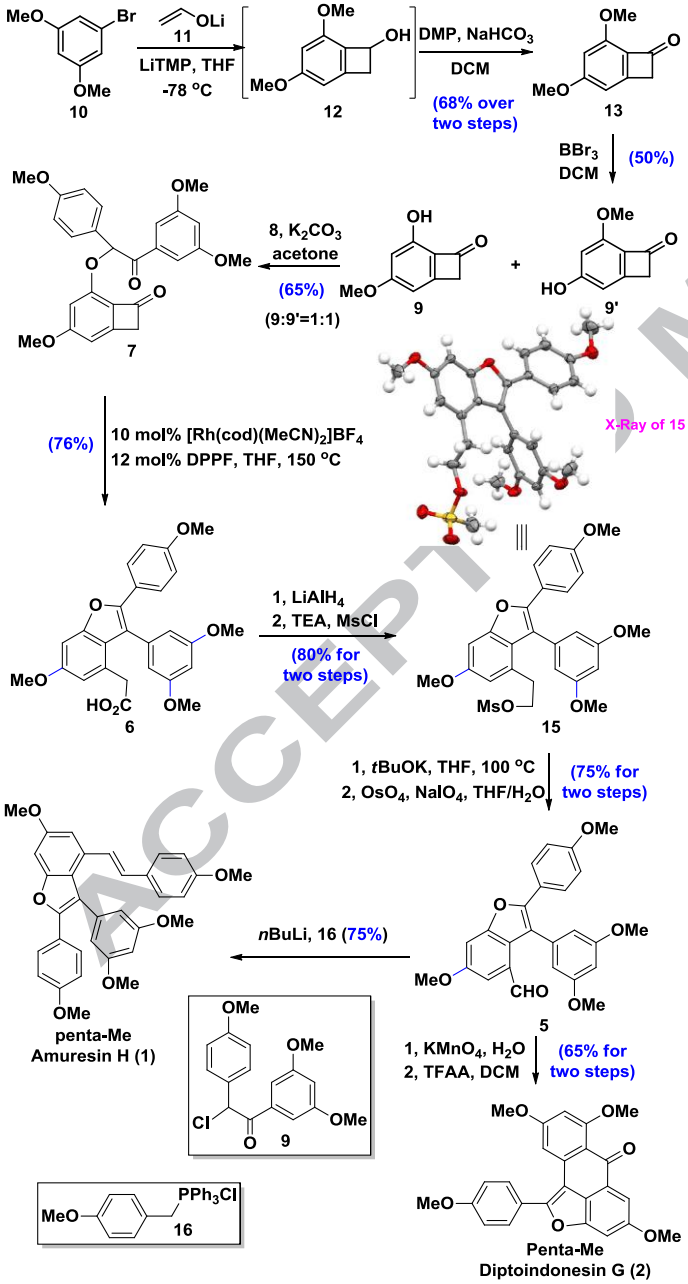


Figure 3. Synthetic sequence towards amuresin H (**1**) and pentaMe diptoindonesin G (**2**).

Elimination with tBuOK followed by dihydroxylation and diol cleavage afforded the common intermediate **5** in a total of 75% yield over two steps. The aldehyde **5** was advanced to penta-Me amuresin H (**1**) through Wittig olefination in a satisfactory 75% yield. The spectra of synthesized penta-Me amuresin H (**1**) matched very well with the previously reported data.[5a] As for penta-Me diptoindonesin G, the aldehyde **5** was first oxidized with unusual $KMnO_4$ in acetone and water to carboxylic acid, which was activated by trifluoroacetic anhydride (TFAA) to induce a Fredel-Crafts cyclization to afford the desired tetracyclic core of diptoindonesin G in a combined 75% yield over two steps. The spectra of penta-Me diptoindonesin G (**2**) was in well accordance with the reported data[7].

In summary, a new entry towards two oligostilbenoids' natural product namely, penta-Me amuresin H and penta-Me diptoindonesin G had been conceived and total synthesis realized. Rh-catalyzed carboacylation/aromatization cascade initiated by C-C activation of benzocyclobutenone was employed as the key step. Total synthesis of penta-Me amurensin H and penta-Me diptoindonesin G were completed without using any protecting groups. We believe that this convergent-divergent strategy featuring C-C activation will find further application in complex natural product synthesis.

Acknowledgments

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