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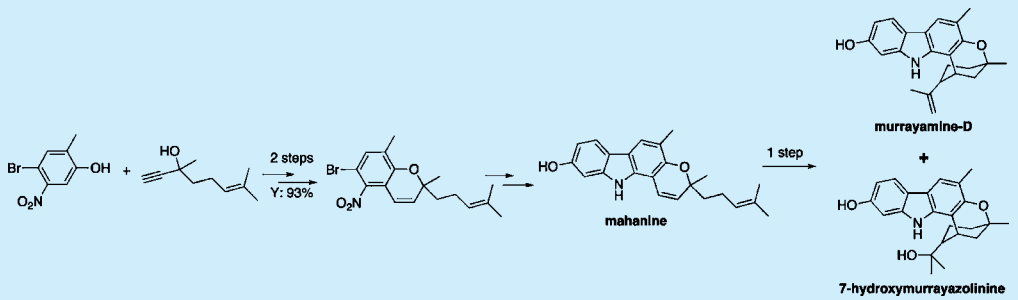
Total Synthesis of 7-Hydroxymurrayazolinine, Murrayamine D, and Mahanine via *m*-Nitro Group Activated Pyran Annulation

Shujie Hou,[†] Yong Liu,[†] Yali Kong, and Milton L. Brown*

Center for Drug Discovery, Georgetown University Medical Center, Research Building, EP07, 3970 Reservoir Road, NW, Washington, D.C. 20057, United States

Supporting Information



ABSTRACT: The facile total synthesis of the natural product (±)-mahanine was obtained in eight steps with an overall 52% yield from readily accessible known nitrophenol derivative **6**. After a one-step, acid-catalyzed annulation, two additional natural products were formed including 7-hydroxymurrayazolinine, representing its first reported total synthesis. In the whole process, the introduction of the *m*-nitro group significantly enhanced the key pyran annulation reaction through inductive effects.

Natural products hold high potential for discovery of new drug treatments. Among the 175 anticancer drugs discovered from the 1940s to 2006, 100 drugs were either natural products or derived from natural products.[1]

In our search to identify new anticancer drugs,[2−6] we noticed that the natural product mahanine (Figure 1), a carbazole alkaloid, has received increasing interest.[7−17] (−)-Mahanine was originally isolated by Narasimhan et al. from the leaves of *Murraya koenigii* in 1970.[18] In the past decade, more and more studies showed the anticancer activities of mahanine.[9−17] With increased interest to evaluate the in vivo activity of mahanine and derivatives[16,17] (especially those with free 7-OH and 9-NH[15]), efficient, practical, and high-yielding synthetic procedures are required. Even to date, other structurally related carbazoles such as murrayamine D[19] and 7-hydroxymurrayazolinine[20] (Figure 1), isolated in 1995 and 2011, respectively, have not been fully evaluated biologically, due to limited availability. With this in mind, new high-yielding and scalable synthetic strategies are needed for these important natural compounds.

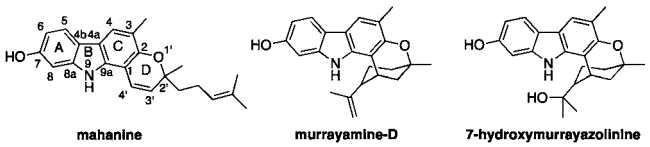


Figure 1. Mahanine and natural derivatives.

Mahanine and its derivatives belong to dioxygenated and pyranocarbazole alkaloids, which have one free phenol group. Although carbazole alkaloids have been extensively synthesized,[21,22] total syntheses of this type of carbazole alkaloid were only recently reported.[23−25] Even though various methods for annulation of a *gem*-dimethylpyran ring have been developed,[27−33] syntheses of these natural pyranocarbazole molecules were prepared dominantly via Claisen rearrangement mediated pyran annulation as key step which usually suffered from mild yield and lack of regioselectivity.[23,26] Advances by Knölker's group toward optimizing phenylboronic acid mediated reactions[24] (non-Claisen rearrangement) improved the annulation yield to 75% and eventually led to the first total synthesis of mahanine and murrayamine D but also resulted in prolonged reaction times (3 days). Other challenges in mahanine total synthesis include installing the carbazole ring[22] without harming the existing pyran ring,[34] manipulation of two phenol groups (protecting group strategy),[23,24] and construction of the 2*H*-pyran ring onto the sterically unfavorable phenolic side of the carbazole framework.[35] Herein, we report a highly efficient total synthesis of mahanine, *O*-methylmahanine, murrayamine D, and 7-hydroxymurrayazolinine through a nitro group activated pyran annulation (via Claisen rearrangement), which overcomes the synthetic challenges mentioned above.

In view of the good stability of the long side chain substituted 2*H*-chromene under high temperature,[36] we sought to improve synthetic efficiency by building the carbazole ring in the late stage via a nitrene insertion reaction. We envisioned that the early formation of the pyran ring would reduce the number of phenol protecting groups. We proposed to use a Suzuki coupling

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reaction to bring together the protected phenol **4** and the substituted chromene **3**. The chromene **3** could be obtained by Claisen rearrangement mediated pyran annulation from polyfunctionalized phenol **5** (Figure 2). The nitro group

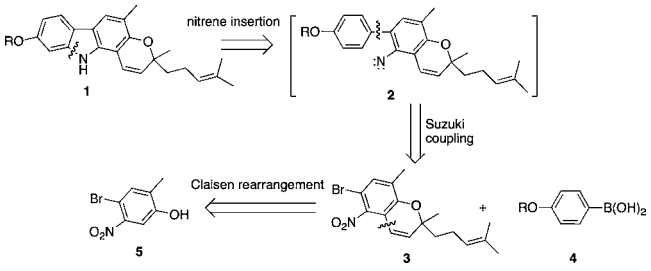
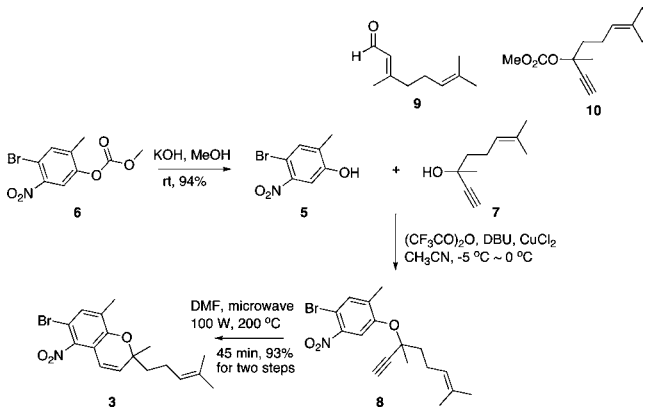


Figure 2. Retrosynthetic analysis for mahanine.

introduction is the key of this strategy. It would not only facilitate the final nitrene insertion reaction but also mask the free amine from the very beginning, so as to mitigate complications of the basicity of the nitrogen atom and its susceptibility to oxidation.[36] We also assumed that the nitro group would activate the pyran annulation process (vide infra).[34,38,39]

The key intermediate for the total synthesis was the substituted 2*H*-chromene **3**. The chromene **3** was obtained from readily accessible known compound 4-bromo-2-methyl-5-nitrophenyl methyl carbonate **6**[40] (Scheme 1), which was deprotected with KOH in methanol at room temperate affording the free phenol **5**.

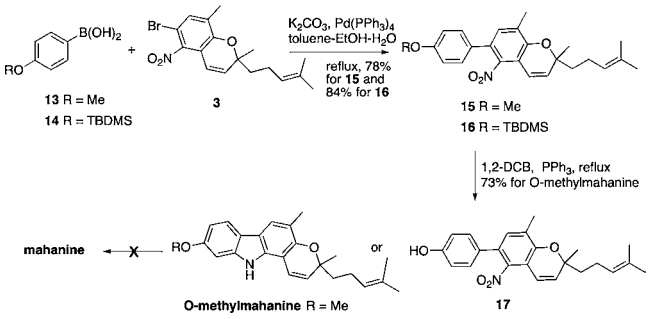
Scheme 1. Synthesis of the Chromene Fragment 3



Synthesis of the Claisen rearrangement precursor **8** proved not to be trivial. The nitro group appeared to significantly change the electron density of the benzene ring, which resulted in unsuccessful addition of citral **9**.[33] Utilization of the methyl carbonate **10** also resulted in low yield.[36] A successful yield was not achieved until the reaction was optimized by coupling **5** with the propargyl alcohol **7** using a copper(II) catalyst and trifluoroacetate in the presence of DBU.[41] Without further purification, the subsequent thermal cyclization was carried out with the crude product **8** affording the target 2*H*-chromene **3** in a yield of 93% over two steps.

With the key chromene **3** in hand, the phenyl boronic acid **13** was used to carry out the Suzuki coupling reaction (Scheme 2). The biaryl adducts **15** were obtained in high yield and cyclized by a reductive Cadogan reaction[42] to afford *O*-methylmahanine.[23,24,35,43] Since the demethylation of *O*-methylmahanine remained unsolved for more than four decades,[35] we were not

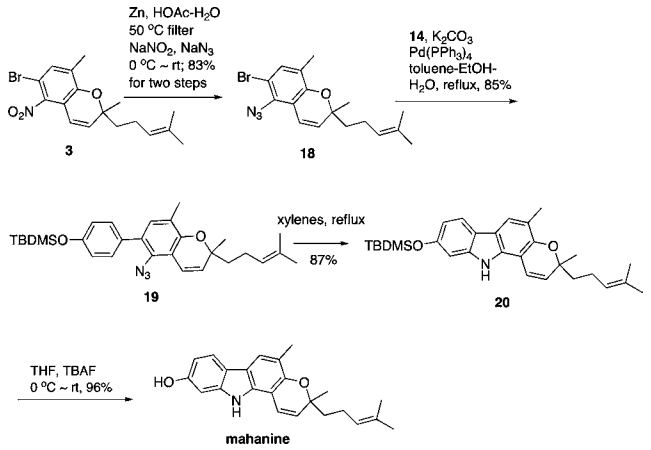
Scheme 2. Synthesis of *O*-Methylmahanine



surprised that our initial attempts at demethylation were unsuccessful and failed to provide mahanine (see the Supporting Information). To overcome the troublesome demethylation step, we envisioned deployment of a TBDMS-protected *O*-phenyl boronic acid (commercially available) as an alternative solution.

To our surprise, we continued to encounter some synthetic challenges. First, the TBDMS group was very sensitive to standard Suzuki coupling conditions, and only a trace of desired product was detected. However, after optimization, an 84% yield was achieved using toluene−ethanol−water system as a solvent. When the diaryl adduct **16** was used to construct the corresponding carbazole under Cadogan cyclization conditions, we were disappointed to find that the TBDMS group was removed again, producing the corresponding free phenol (which is intact even after prolonging the reaction to 72 h). We assumed that the process of nitro reduction might be associated with the TBDMS deprotection. Since the nitrene can also be generated from the azide precursor,[44,45] we prepared the azide diaryl **19** from the chromene **18**, which was transformed from **3** by reduction, diazotization, and azide displacement in a continuous fashion without the need for stepwise product isolation (Scheme 3). After refluxing the azide **19** with xylene for 5 h, the cyclization

Scheme 3. Synthesis of Mahanine



successfully formed the TBDMS-protected mahanine **20** in a yield of 87%. With compound **20** in hand, the final deprotection using TBAF cleanly furnished the target molecule with a yield of 96%.

The acid-catalyzed cyclization of mahanine and analogues has been reported.[24,26] We hypothesize that under acid conditions mahanine could be transformed directly not only to murrayamine D but also to 7-hydroxymurrayazolinine (Scheme 4) in the

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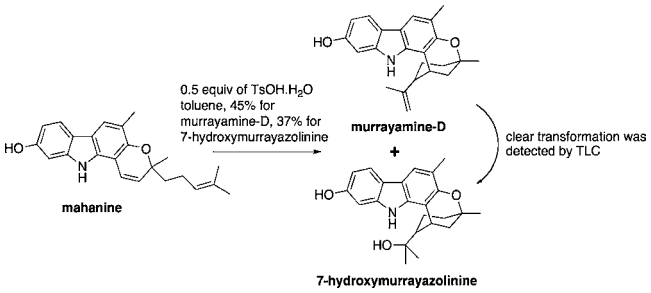
Scheme 4. Synthesis of Murrayamine D and 7-Hydroxymurrayazolinine



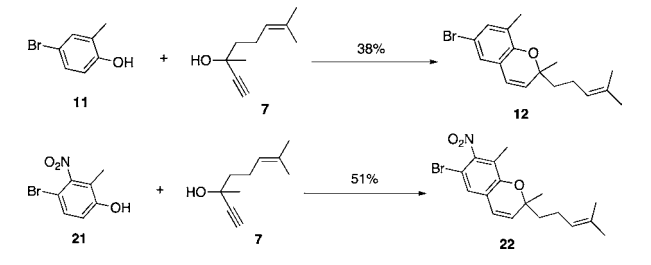
presence of a stoichiometric amount of water. This would significantly shorten the procedure reported by Knölker in the synthesis of murrayazolinine.[26] In addition, our strategy would overcome potential problems in the reported synthesis that might occur in the presence of a free phenol group.

After several attempts, we found both cyclization and subsequent hydrolysis could be successfully obtained for the target compounds in good yield. The cyclization takes place through a carbocation rearrangement reaction;[26] we found under certain conditions (protic solvents) that this reaction did not occur. However, the cyclization and hydrolysis reactions were successful under the conditions of *p*-toluenesulfonic acid monohydrate in toluene. Under these conditions, murrayamine D could also be partially converted to 7-hydroxymurrayazolinine (transformation was carefully detected by TLC), suggesting that the hydrolysis occurred after cyclization.

It is worth noting that with the *m*-nitro group the Claisen rearrangement works in almost quantitative yield, which is in stark contrast to the results without nitro group involvement.[23]

For comparison, two model reactions were performed on substrates either without the nitro group or with the nitro group in different position under the same reaction conditions. We obtained only 38% and 51% yields, respectively (Scheme 5).

Scheme 5. Model Reactions Utilizing Pyran Annulation



These results support Yamaguchi's conclusion that the electron-withdrawing inductive effects on the aromatic ring activate this aryl 1,1-disubstituted propargyl ether Claisen rearrangement mediated pyran annulation.[38]

In summary, we have described the total synthesis of the natural product mahanine in eight steps with a 52% overall yield and its natural derivatives *O*-methylmahanine, murrayamine D, and 7-hydroxymurrayazolinine from readily accessible known nitrophenol derivative **6**. Among them, the synthesis of 7-hydroxymurrayazolinine represents the first total synthesis of this natural product. The short synthetic route (nine steps) and relatively high overall yield (19%) now provide an opportunity to evaluate the in vitro and in vivo biological activities of these natural products. Finally, two model reactions were also utilized to understand the contribution of the inductive effects in the *m*-nitro group assisted pyran annulation reaction.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, analytical data, and copies of NMR spectra of the products. This material is available free from charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mb544@georgetown.edu.

Author Contributions

†S.H. and Y.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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