Organic LETTERS

Letter

Cite This: Org. Lett. 2018, 20, 4358–4361

pubs.acs.org/OrgLett

Total Synthesis of (±)−Exotine B

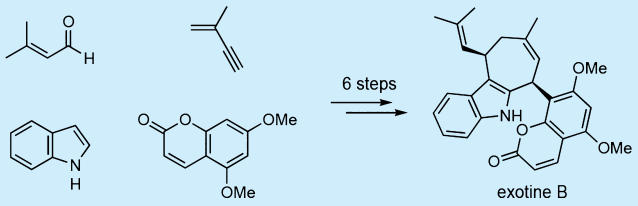
Bichu Cheng,*[†,‡] Giulio Volpin,[‡] Johannes Morstein,[‡] and Dirk Trauner[‡]

[†]School of Science, Harbin Institute of Technology (Shenzhen), Shenzhen 518055, China

[‡]Department of Chemistry, New York University, 100 Washington Square East, New York, New York 10003, United States

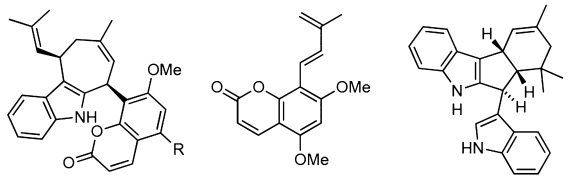
Supporting Information

ABSTRACT: The heterodimeric indole/coumarin natural product exotine B was synthesized for the first time. The carbon skeleton of the natural product was formed rapidly by a palladium-catalyzed Suzuki cross-coupling reaction and a gallium-catalyzed three-component [4 + 3] cycloaddition reaction. An alternative biosynthesis of exotine B is proposed based on the total synthesis. Improved syntheses of coumarin natural products gleinadiene and coumurrayin are also reported.



The leaves and roots of the *Murraya* plants have been used in traditional Chinese medicine to treat inflammatory diseases, such as abdominal pain, eczema, and rheumatism. The bioactive ingredients underlying these activities, mostly coumarins, flavonoids, and alkaloids, have been under investigation for a long time.[1]

Recently, two cyclohepta[*b*]indole natural products, exotines A (**1**) and B (**2**), were isolated from the roots of *Murraya exotica* (Figure 1).[2] They are heterodimers of isopentenyl-



R = H, exotine A (**1**)
R = OMe, exotine B (**2**)

gleinadiene (**3**)

yuehchukene (**4**)

Figure 1. Structures of exotines A and B and related natural products.

substituted indole and coumarin derivatives and were found to inhibit the nitric oxide production in lipopolysaccharide-induced BV-2 microglial cells. Indoles and coumarins are two of the most common heterocyclic structures found in natural products, but their hybridized structures are very rare.[3] To the best of our knowledge, exotines A and B are the only two natural products of such type. In addition, the two *cis*-substituents on the seven-membered carbocyclic ring and two nonconjugated olefins make the exotines rather unusual from a structural perspective.

Biosynthetically, it was originally proposed that exotine B is derived from gleinadiene (**3**)[4] and a tautomer of indole diene **5**. A formal Diels−Alder reaction would give spiroindolenine **6** that could undergo ring expansion (Scheme 1a).[2] A related natural product yuehchukene (**4**), most likely a dimer of **5**, was also previously isolated in the same plant.[5]

Herein, we report our studies and final success in the concise total synthesis of exotine B (**2**). Regioselective iodination of readily available 5,7-dimethoxycoumarin (**7**) at position 8 with trifluoroacetic acid (TFA) activated *N*-iodosuccinimide (NIS) afforded the corresponding iodide **8** in high yield on multigram scale (Scheme 2).[6] Previous syntheses of this compound required a stoichiometric amount of toxic mercury salts or a multistep approach.[7]

Iodide **8** is a versatile precursor to several coumarin natural products, many of which are substituted at position 8.[8] A magnesium−iodide exchange reaction under Knochel's conditions[9] afforded the corresponding Grignard reagent, which underwent a transmetalation reaction with CuI followed by a substitution reaction with prenyl bromide to give the naturally occurring coumurrayin (**9**) in good yield. Additionally, a Suzuki cross-coupling reaction of iodide **8** with boronate ester **10** under Buchwald's conditions[10] furnished gleinadiene (**3**) in excellent yield on multigram scale. Previous syntheses of these two natural products required additional steps, were carried out in smaller scale, and gave lower overall yields.[7b,11]

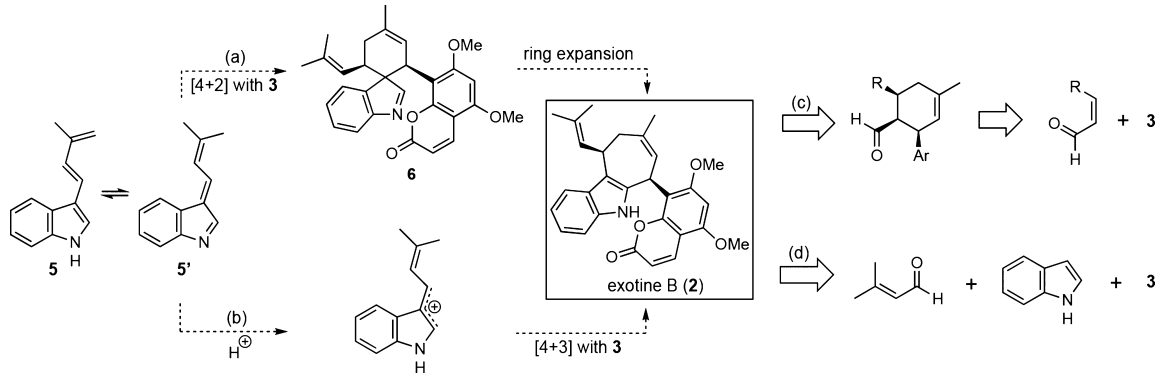
With an ample supply of gleinadiene (**3**) in hand, we began to investigate the fragment union with diene **5** according to the originally proposed biosynthesis (Scheme 1a). However, the reaction of gleinadiene (**3**) and diene **5** under a variety of conditions did not afford the heterodimer exotine B or its spirocyclic precursor **6**. Interestingly, we observed trace amounts of yuehchukene (**4**) in several reaction trials. The latter had been previously synthesized starting from **5** or its precursors.[5b−d]

Spiroindolenines such as **6** could also be generated from interrupted Fischer indolization of the corresponding cyclohexenylcarbaldehydes,[12] which in turn are available from Diels−Alder reactions of diene **3** with the appropriate dienophiles (Scheme 1c).

Received: June 11, 2018
Published: July 6, 2018

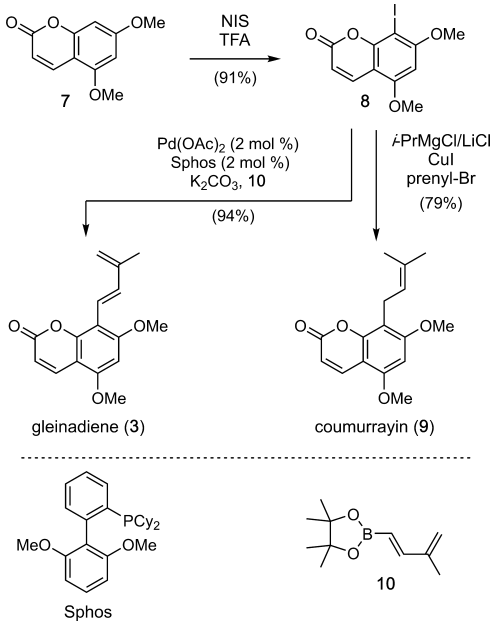
DOI: 10.1021/acs.orglett.8b01817
Org. Lett. 2018, 20, 4358−4361

Scheme 1. Biosynthetic Proposals and Retrosynthetic Disconnections of Exotine B[a]

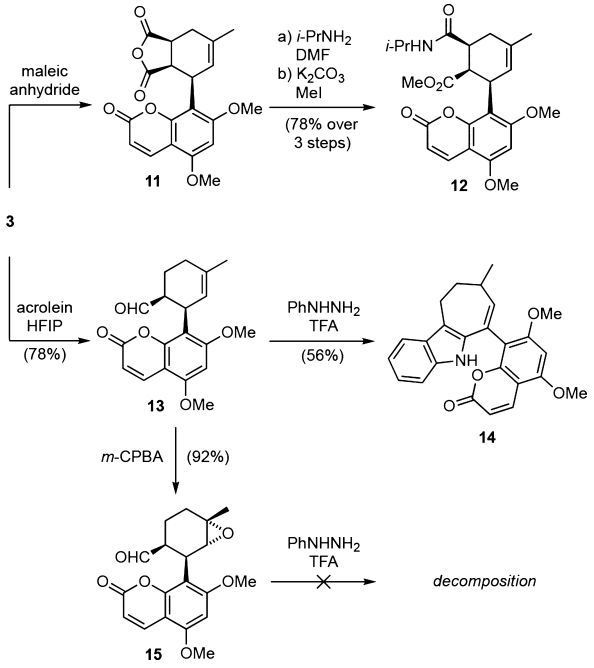


[a](a) The proposed biosynthesis of exotine B; (b) an alternative biosynthetic proposal with a [4 + 3] cycloaddition reaction; (c) retrosynthetic analysis of exotine B with a Diels–Alder reaction and Fischer indolization-induced rearrangement reaction; (d) retrosynthetic analysis of exotine B based on a three-component [4 + 3] reaction.

Scheme 2. Rapid Syntheses of Coumarin Natural Products Gleinadiene (3) and Coumurrayin (9)



Scheme 3. Diels–Alder/Fischer Indolization Approach toward Exotine B



Gleinadiene (**3**) underwent a facile Diels–Alder reaction with maleic anhydride at ambient temperature to give adduct **11** in high yield and as a single isomer. Ring opening of the resulting anhydride with nucleophiles was known to be nonselective.[13] We discovered that the reaction of anhydride **11** with isopropylamine (*i*-PrNH$_2$) in dimethylformamide (DMF) afforded the ring-opening product in high yield and >10:1 regioselectivity.[14] The resulting carboxylic acid could be further derivatized. While Fischer esterification resulted in a complex reaction mixture, methylation under basic conditions afforded methyl ester **12** in good yield after recrystallization. Unfortunately, further selective reduction of the amide or the carboxylic acid (or ester) was not observed, and the coumarin was not inert either (Scheme 3).

In an attempt to access a simpler indolization precursor to use as a model substrate, we submitted gleinadiene to a Diels–Alder reaction with acrolein. Using hexafluoroisopropanol (HFIP) as a solvent, the desired product **13** was obtained at room temperature on gram scale in high yield and selectivity.[15]

Upon treatment with phenylhydrazine (PhNHNH$_2$) and acid, aldehyde **13** underwent the expected Fischer indolization and the ensuing 1,2-rearrangement to give a cyclohepta[*b*]indole structure.[16] However, the olefin isomerized during the reaction to give product **14**, in which the alkene resides in conjugation with both the indole and the coumarin. Epoxidation of **13** with *m*-CPBA afforded **15** as a single product in high yield. Unfortunately, the epoxide was not stable to the Fischer indolization conditions and a complex mixture of products was obtained (Scheme 3).

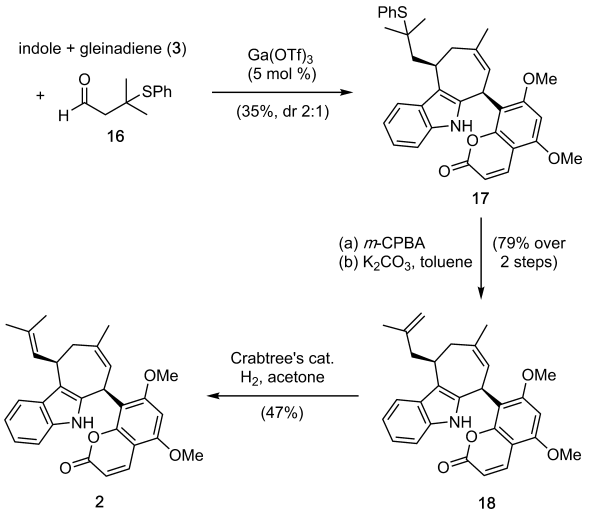
The high propensity of olefin isomerization under the acidic conditions required for the rearrangement of spiroindolenine led us to consider an alternative synthetic route to exotine B.[16] To this end, we attempted a gallium(III)-catalyzed three-component [4 + 3] cycloaddition reaction developed by Wu and co-workers (Scheme 1d).[17] Unfortunately, the first trial with prenal failed to provide any desired cyclohepta[*b*]indole product, presumably due to its attenuated reactivity compared

DOI: 10.1021/acs.orglett.8b01817
Org. Lett. 2018, 20, 4358–4361

to saturated aldehydes. Instead, the readily available saturated aldehyde **16** was then selected as a surrogate for prenal.[18] The $Ga(OTf)_3$ catalyzed three-component reaction of indole, aldehyde **16**, and diene **3** afforded the desired cyclohepta[*b*]-indole product **17** under Wu's conditions. The reaction was further optimized with the more precious diene component **3** as the limiting reagent. Slow addition of a solution of **3** over 2 h via syringe pump to the reaction mixture led to the formation of the desired product **17** and its diastereomer. The reaction was modest in yield and selectivity, but it is scalable and more than 1 g of cyclohepta[*b*]indole products have been obtained in a single reaction. The pure major isomer **17** could be obtained via crystallization.

The thioether group of compound **17** was selectively oxidized in the presence of the indole and alkene functionalities using *m*-CPBA at low temperature. Thermal elimination of the resulting sulfoxide in refluxing toluene afforded a complex mixture, while a clean reaction was obtained in the presence of basic additives such as K_2CO_3 or Et_3N. Iso-exotine B (**18**) bearing an external alkene was formed in good yield as a 7/1 mixture with exotine B (**2**). Conversion of iso-exotine B (**18**) to exotine B (**2**) was found to be challenging; only Crabtree's catalyst in acetone or THF resulted in productive isomerization to **2**.[19] The reaction had to be carefully controlled, since a second isomerization product derived from the positional shift of the endocyclic olefin was also observed (see Supporting Information for details). The so-obtained racemic exotine B fully matched the reported data for the natural isolate (Scheme 4).

Scheme 4. Total Synthesis of Exotine B



Based on our studies on the chemical synthesis of exotine B, an alternative biosynthesis of exotines could be proposed (Scheme 1b). Protonation of diene **5** or its tautomer **5′** would generate a conjugate cationic intermediate, which could undergo a [4 + 3] cycloaddition reaction with gleinadiene (**3**) to form the cyclohepta[*b*]indole structure and give natural product exotine B (**2**). Since exotine B was found to be optically active, an enzymatic pathway is probably operative during this process.

In summary, the unusual heterodimeric indole/coumarin natural product exotine B (**2**) was synthesized for the first time. The carbon skeleton of the natural product was formed in a single synthetic step. An alternative biosynthesis of exotines from a [4 + 3] cycloaddition reaction is proposed based on our findings. Additionally, we developed an efficient route to 8-substituted coumarin natural products such as gleinadiene (**3**) and coumurrayin (**9**).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01817.

Experiment procedures and analytical data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cbcatca@hotmail.com.

ORCID

Bichu Cheng: 0000-0003-2162-2960

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank New York University for financial support and Dr. Chin Lin (NYU) for assistance with NMR spectrometry and mass spectrometry. NMR spectra were acquired using the TCI cryoprobe supported by The National Institutes of Health (OD016343). J.M. thanks the German Academic Scholarship Foundation for a PhD fellowship and New York University for a MacCracken PhD fellowship.

■ REFERENCES

(1) Chinese Pharmacopoeia Commission. *Pharmacopoeia of the Peoples's Republic of China. Part 1*; Medical Science and Technology Press: Beijing, China, 2010; p 10.

(2) Liu, B. Y.; Zhang, C.; Zeng, K. W.; Li, J.; Guo, X. Y.; Zhao, M. B.; Tu, P. F.; Jiang, Y. *Org. Lett.* **2015**, *17*, 4380−4383.

(3) (a) Stempel, E.; Gaich, T. *Acc. Chem. Res.* **2016**, *49*, 2390−2402. (b) Stefanachi, A.; Leonetti, F.; Pisani, L.; Catto, M.; Carotti, A. *Molecules* **2018**, *23*, 250.

(4) Kumar, V.; Reisch, J.; Wickremaratne, D. B. M.; Hussain, R. A.; Adesina, K. S.; Balasubramaniam, S. *Phytochemistry* **1987**, *26*, 511−514.

(5) Isolation: (a) Kong, Y. C.; Cheng, K. F.; Cambie, R. C.; Waterman, P. G. *J. Chem. Soc., Chem. Commun.* **1985**, 47−48. Total synthesis: (b) Cheng, K. F.; Kong, Y. C.; Chan, T. Y. *J. Chem. Soc., Chem. Commun.* **1985**, 48−49. (c) Wenkert, E.; Moeller, P. D. R.; Piettre, S. R.; Mcphail, A. T. *J. Org. Chem.* **1988**, *53*, 3170−3178. (d) Sheu, J. H.; Chen, Y. K.; Hong, Y. L. *J. Org. Chem.* **1993**, *58*, 5784−5787.

(6) Castanet, A. S.; Colobert, F.; Broutin, P. E. *Tetrahedron Lett.* **2002**, *43*, 5047−5048.

(7) (a) Concannon, S.; Ramachandran, V. N.; Smyth, W. F. *Rapid Commun. Mass Spectrom.* **2000**, *14*, 1157−1166. (b) Reisch, J.; Wickramasinghe, A.; Wickremaratne, D. B. M. *Liebigs Ann. Chem.* **1990**, *1990*, 209−210. (c) The corresponding bromide can be obtained by reaction of **7** with NBS, but it was much less reactive for further functionalization.

(8) Estévez-Braun, A.; González, A. G. *Nat. Prod. Rep.* **1997**, *14*, 465−475.

(9) Boymond, L.; Rottlander, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701−1703.

(10) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461−1473.

DOI: 10.1021/acs.orglett.8b01817
Org. Lett. 2018, 20, 4358−4361

(11) Murray, R. D. H.; Jorge, Z. D. *Tetrahedron* **1984**, *40*, 3129−3132.
(12) James, M. J.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Chem. - Eur. J.* **2016**, *22*, 2856−2881.
(13) Birman, V. B.; Danishefsky, S. *J. Am. Chem. Soc.* **2002**, *124*, 2080−2081.
(14) The regioselectivity of anhydride ring opening depends on the nucleophile and solvent. MeOH (2:1); *i*-PrOH (2.9:1), Ph_2CHOH (3.5:1 in CH_2Cl_2, 5:1 in DMF); *i*-$PrNH_2$ (7:1 in CH_2Cl_2, >10:1 in DMF), pyrrolidine (10:1 in DMF).
(15) Cativiela, C.; García, J. I.; Mayoral, J. A.; Salvatella, L. *Can. J. Chem.* **1994**, *72*, 308−311.
(16) (a) Maligres, P. E.; Houpis, I.; Rossen, K.; Molina, A.; Sager, J.; Upadhyay, V.; Wells, K. M.; Reamer, R. A.; Lynch, J. E.; Askin, D.; Volante, R. P.; Reider, P. J.; Houghton, P. *Tetrahedron* **1997**, *53*, 10983−10992. (b) Liu, K. G.; Robichaud, A. J.; Lo, J. R.; Mattes, J. F.; Cai, Y. *Org. Lett.* **2006**, *8*, 5769−5771.
(17) Han, X.; Li, H.; Hughes, R. P.; Wu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 10390−10393.
(18) Kodato, S.; Nakagawa, M.; Hongu, M.; Kawate, T.; Hino, T. *Tetrahedron* **1988**, *44*, 359−377.
(19) Krel, M.; Lallemand, J. Y.; Guillou, C. *Synlett* **2005**, 2043−2046.

NOTE ADDED AFTER ASAP PUBLICATION

This paper was published July 6, 2018. Schemes 2 and 4 have been updated. The revised version was re-posted July 10, 2018.

DOI: 10.1021/acs.orglett.8b01817
Org. Lett. 2018, 20, 4358−4361