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Total Syntheses of Clausamines A–C and Clausevatine D

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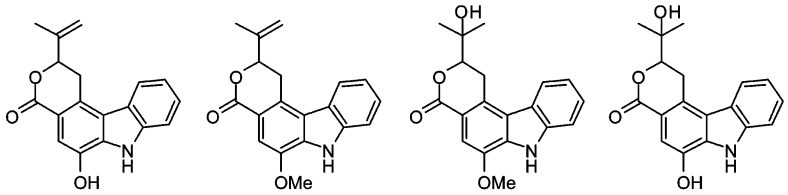
ABSTRACT



The first total syntheses of clausamines A–C and clausevatine D are reported. The key step involves a Diels–Alder reaction between an imine quinone and cyclic diene, allowing for the subsequent construction of the carbazole core in a regiospecific manner. Stereochemistry of the natural products is also discussed.

In 1998, Ito and co-workers reported the isolation of clausamines A−C (Figure 1) from the dried branches of

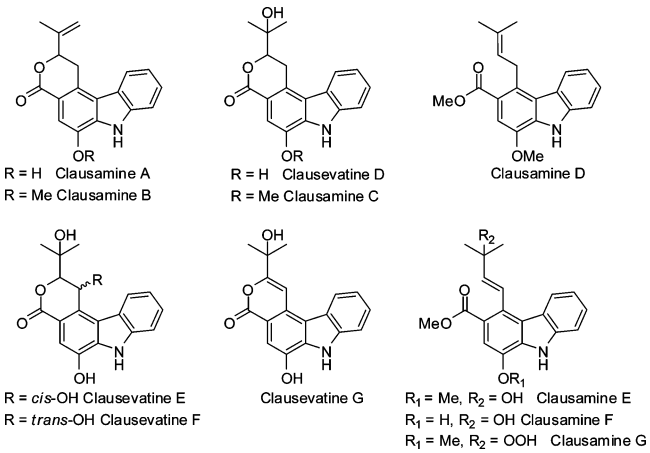


Figure 1. Clausamines A−G and clausevatines E−G.

Clausena anisata in Thailand. Prominent structural features of these carbazole alkaloids[1] include a 1-oxygenated carbazole framework to which is appended a six-membered lactone at the 3,4-position; as such, the clausamines are given the distinction of being the first alkaloids containing this lactonic carbazole motif to be isolated from nature.[2] Shortly after, Wu and co-workers identified four other carbazole alkaloids which they named clausevatines D−G, along with known clausamine A, from the root bark of *Clausena excavata*,[3] a wild shrub used in folk medicine for the treatment of snakebites, abdominal pain, and also as a detoxificant.[4] Further study of the extracts of *C. excavata* by Itoigawa in 2000 yielded four new carbazoles, clausamines D−G, in addition to previously known alkaloids. In the same account, it was reported that clausamines A−D and F possessed antitumor-promoting properties during short-term in vitro assays of TPA-induced EBV-EA activation in Raji cells.[5]

Recently, we have reported that the Diels−Alder adducts obtained from an imine quinone and cyclic diene allow

(1) For a comprehensive review of carbazole alkaloids see: Knölker, H. J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303.
(2) Ito, C.; Katsuno, S.; Ruangrungsi, N.; Furukawa, H. *Chem. Pharm. Bull.* **1998**, *46*, 344.
(3) Wu, T.-S.; Huang, S.-C.; Wu, P.-L. *Chem. Pharm. Bull.* **1998**, *46*, 1459.
(4) Sasaki, S. *KhoyoTaiwan Minkan Yakuyo Shokubutso Shi* (khobunkan), Taipei, 1924; p 36.
(5) Ito, C.; Katsuno, S.; Itoigawa, M.; Ruangrungsi, N.; Mukainaka, T.; Okuda, M.; Kitagawa, Y.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **2000**, *63*, 125.

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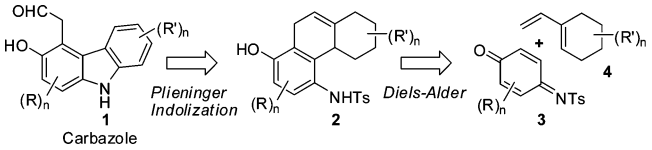
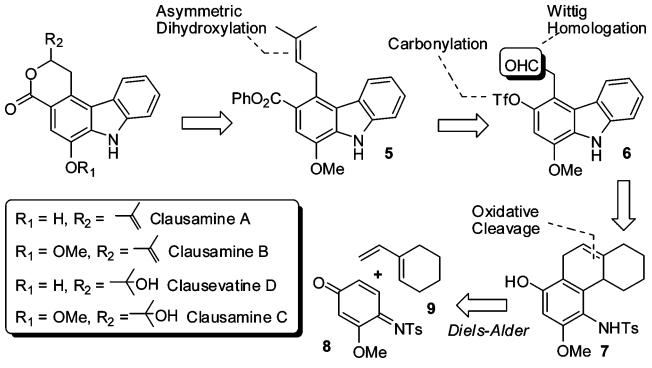
Scheme 1. Synthesis of Carbazoles



access to functionalized carbazoles in a highly regiocontrolled fashion (Scheme 1).[6] The utility of this transformation was demonstrated in the first total syntheses of eustifolines A−C and alternative syntheses of eustifoline D and glycomaurrol. Herein we report a further application of this methodology which has enabled the first total syntheses of clausamines A−C and clausevatine D.

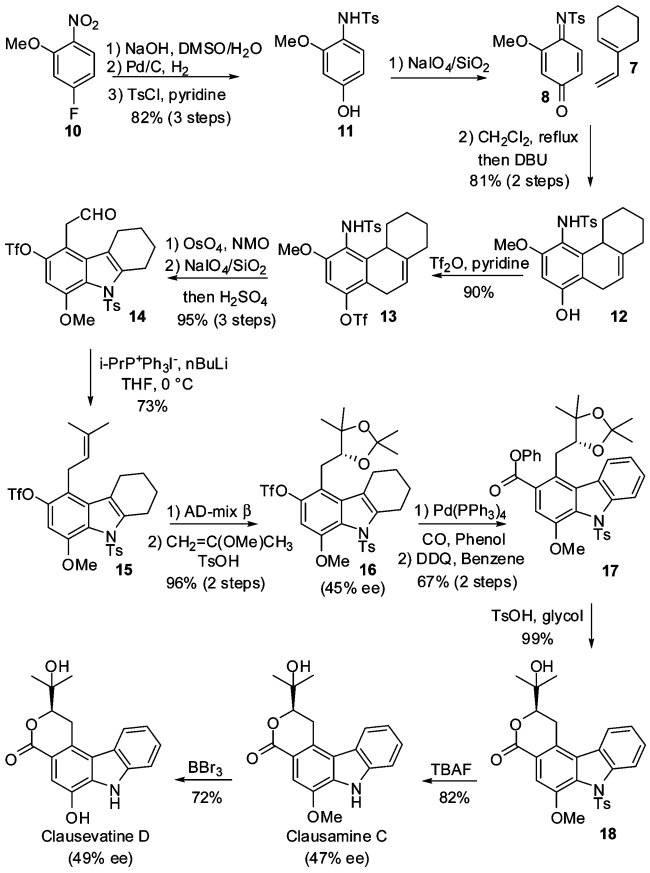
To date the only reported syntheses of any of the above compounds are the semi-syntheses of clausamines E and G (from clausamine D) by Itoigawa and co-workers in their attempts to confirm their assigned structures.[4] Furthermore, the absolute stereochemistry of clausamines A−C and clausevatines D−F is not yet known. Interestingly, while clausevatines D−F were reported to have optical rotations of −5.7°, −92.4°, and −199.0° respectively, clausamines A−C were reported to have no optical rotation at all. Considering that nature does not often carry out chemistry in a racemic fashion and the fact that clausevatines D−F possess optical rotations, we postulated that perhaps the lack of optical activity of clausamines A−C was due to a combination of an inherent small optical rotation and the low concentration used in the measurement (approximately an order of magnitude less than that for clausevatine D) and not because the molecules were racemic. Therefore, with the hopes of testing this hypothesis and shedding some light on the stereochemistry of these natural products, we set out to synthesize clausamines A−C and clausevatine D in an asymmetric fashion.

Scheme 2. Synthetic Strategy



A brief synthetic strategy is shown in Scheme 2. We envisioned all four natural products coming from the elaboration of an intermediate such as **5** in which an asymmetric dihydroxylation would set the stereochemistry of the chiral center. Intermediate **5** would in turn come from carbazole **6** via Wittig homologation of the aldehyde and carbonylation of the triflate. Intermediate **6** would be accessible from the aromatized Diels−Alder adduct **7** via oxidative cleavage of the double bond and acid-catalyzed cyclization. Adduct **7** would come from a Diels−Alder cycloaddition between imine quinone **8** and diene **9**, themselves easily prepared from commercially available starting materials.

Scheme 3. Synthesis of Clausamine C and Clausevatine D



Our synthetic endeavors (see Scheme 3) began with the commercially available nitro-aryl derivative **10** which was readily converted to the tosylated amino phenol **11** in a three-step sequence involving nucleophilic aromatic substitution, reduction of the nitro group, and tosylation of the resulting amine in 82% overall yield. Treatment of the tosylated amino phenol **11** with $NaIO_4/SiO_2$ then gave access to the desired imine quinone **8**. Treatment of **8** with diene **9**[7] in refluxing CH_2Cl_2 allowed for a facile Diels−Alder cycloaddition. The resulting adduct was treated with catalytic DBU affording the aromatized species **12** in 81% yield over the two steps. Derivatization of the phenolic moiety as the triflate was then carried out using triflic anhydride and pyridine in 90% yield. Conversion of dihydronaphthalene **12** to the tetrahydrocar-

(6) Lebold, T. P.; Kerr, M. A. *Org. Lett.* **2007**, *9*, 1883.

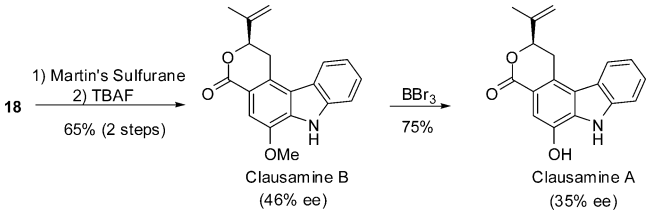
(7) Rodriguez, J.; Brun, P.; Waegell, B. *J. Organomet. Chem.* **1989**, *359*, 343.

bazole was accomplished via oxidative cleavage of the double bond (via the diol) followed by treatment of the resulting dicarbonyl with acid to afford **14** in 95% yield over the three steps. Treatment of tetrahydrocarbazole **14** with triphenylphosphonium isopropyl ylide produced the desired prenyl moiety and alkene **15** in 73% yield. Subjecting alkene **15** to Sharpless asymmetric dihydroxylation conditions[8] using $(DHQD)_2PHAL$ resulted in diol formation in 98% yield and 45% ee.[9] While the enantioselectivity for the dihydroxylation was less then optimal, it was deemed sufficient to obtain optical rotations and provide insight into the stereochemistry of the natural products and was therefore carried through the synthesis as the scalemic mixture. With the diol in hand treatment with 2-methoxypropene under acidic conditions provided acetonide **16** in 98% yield. Subjection of **16** to carbonylative conditions yielded the corresponding ester in 59% yield along with unreacted starting material which could be resubjected to the reaction conditions to give the desired ester in 71% (96% BRSM) after two cycles.[10]

With the phenoxy ester in hand treatment with DDQ afforded the fully aromatized carbazole **17** in 94% yield. Simple deprotection of the acetonide with TsOH in ethylene glycol allowed for the formation of desired lactone **18** in nearly quantitative yield. Finally, removal of the tosyl group with TBAF[11] produced clausamine C in 82% yield and 47% ee. Treatment of clausamine C with BBr_3 then revealed the hydroxyl group, thus affording clausevatine D in 72% yield and 49% ee.

With the completion of clausamine C and clausevatine D, we turned our attention to the syntheses of clausamines A and B (see Scheme 4). Our initial attempts to form the

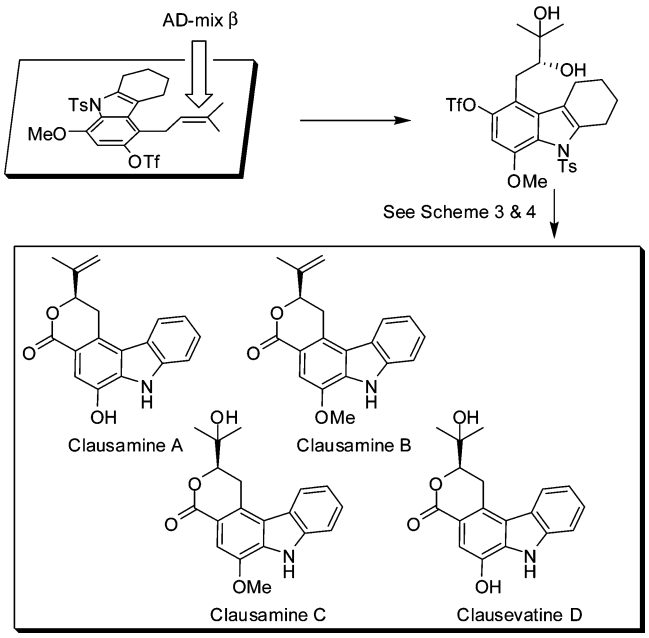
Scheme 4. Synthesis of Clausamines A and B



required isopropenyl moiety from alcohol **18** using typical dehydration conditions ($POCl_3$, pyridine; $SOCl_2$, pyridine; MsCl, NEt_3 or $NEt(iPr)_2$) resulted in significant formation of the undesired *endo* tetrasubstituted double bond being formed. Fortunately, this could be circumvented by treatment of the alcohol with Martin's sulfurane[12] which formed the desired *exo* methylene almost exclusively in 77% yield. Detosylation was then carried out with TBAF to yield clausamine B in 84% and 46% ee. Again the hydroxyl group was relinquished via treatment of clausamine B with BBr_3 allowing access to clausamine A in 75% yield and 35% ee.[13]

The stereochemistry of the diol and natural products were assigned by using the Sharpless mnemonic[8] (Scheme 5) in

Scheme 5. Assignment of Stereochemistry



which dihydroxylation occurs from the top face of the alkene leading to the formation of the (*R*)-alcohol. With the successful completion of clausamines A−C and clausevatine D the optical rotations were measured. Interestingly, contrary to what was expected, all compounds gave strong positive rotations of 62.8°, 33.2°, 50.0°, and 50.7° for clausamines A−C and clausevatine D, respectively, despite their modest enantiomeric excess. Even at the low concentrations reported in the literature for clausamines A−C a rotation was observed. Furthermore, the optical rotation observed for clausevatine D was an order of magnitude larger than that which was reported (note also, opposite in sign). Although a more detailed comparison of the rotations of the synthetic samples to the natural products is warranted, we were unable to obtain natural samples toward this end.

While these results may raise more questions than they answer, several possible explanations exist. It is clear that these molecules do not have inherently small rotations since our samples with modest enantiomeric purities gave significant rotations. It is possible that the natural products then, are racemic (or nearly so). Assuming that an enzymatic process produced enantiomerically distinct products, racemization may have occurred post-biosynthesis, either in nature or during laboratory handling in the isolation process. What is known, however, is that, based on the generally

(8) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768.

(9) A modest increase to 55% ee could be obtained by cooling reaction to 0 °C but required significantly longer reaction times.

(10) Initial attempts to carry out a carbonylative lactonization on the unprotected diol leading directly to the lactone ring were unsucessful, forming instead a benzodihydrofuran.

(11) Yasuhara, A.; Sakamoto, T. *Tetrahedron Lett.* **1998**, *39*, 595.

(12) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.

(13) The slight erosion in ee which was observed is likely due to Lewis acid-mediated epimerization via an allylic carbocation.

accepted mnemonic for the Sharpless dihydroxylation, the (*R*)-enantiomers of these natural products possess positive optical rotations.

In conclusion, we have reported the first total syntheses of clausamines A−C and clausevatine D in an enantioenriched fashion, allowing for the assignment of a positive rotation for the (*R*)-enantiomers. The overall yields for the natural products are excellent, allowing for access to clausamine A−C and clausevatine D in 13% (35% ee), 17% (46% ee), 22% (47% ee), and 16% (49% ee), respectively.

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Supporting Information Available: Full experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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