Total Synthesis of Indole Alkaloid Alsmaphorazine D**

Chenlong Zhu, Zhaobo Liu, Guanyu Chen, Kai Zhang, and Hanfeng Ding*

Abstract: A concise total synthesis of rac-alsmaphorazine D has been described for the first time. The efficient synthetic strategy features four key transformations: 1) a catalytic intramolecular oxidative cyclization for the δ-lactamindole backbone; 2) an oxidative cyclic aminal formation for the hexahydropropyrolo[2,3-b]pyrrole framework; 3) a transannular radical cyclization for the construction of the diazabicyclo-[3.3.1]nonane structure; and 4) a one-pot desilylation/double epimerization reaction that affirms the relative stereochemistry.

Alstonia plants, abundant species in the tropical regions of Africa and Asia, are well-known as a rich source of unique heterocyclic alkaloids containing a monoterpenoid indole skeleton. These alkaloids have attracted great attention in the biogenetic and biological fields[1] for their anticancer, antibacterial, anti-inflammatory, antitussive, and antimalarial properties.[2] Recently, further investigation on extracts of the leaves of Alstonia pneumatophore (Apocynaceae) by Morita and co-workers led to the isolation of three novel biogenetically related alkaloids, which were subsequently named alsmaphorazines C–E (1–3, Figure 1).[3] The stereochemistry of alsmaphorazines was originally assigned based on a combination of one- and two-dimensional NMR experiments and CD studies. Among them, alsmaphorazines D (2) and E (3) consist of an unprecedented hexahydropropyrolo[2,3-b]pyrrole fused diazabicyclo[3.3.1]nonane core structure featuring six contiguous stereogenic centers and a benzylic tertiary alcohol. Their intriguing structures as well as potential biological activities render alsmaphorazines D and E notable as targets for synthetic studies. Herein, we describe our recent efforts culminating in a concise total synthesis of (±)-alsmaphorazine D (2), which is also the first total synthesis of a member of this family.

Our retrosynthetic analysis depicts a systematic approach in the deconstruction of the complex fused tetracyclic system (Scheme 1). We rationalized that 2 might be synthesized from 4 through a substrate-controlled hydroboration[5] of the Δ19,20-olefin from the convex face of the skeleton. For the construction of 4, we envisaged a metal-mediated cyclization[5] of 5 to forge the rest ring of the diazabicyclo-[3.3.1]nonane structure with concomitant stereoselective control of the desired (E)-olefin moiety. The essential tricyclic pyrroloindole 5 could be achieved through an oxidative cyclic aminal formation[6] from 6. Finally, the construction of the δ-lactam of 6 would be realized by an intramolecular oxidative coupling[7] of 7, which could in turn be prepared from readily available indoline 8 and acetyl chloride 9.

The synthesis commenced with the construction of δ-lactamindole 6. Acylation of indoline 8 with acetyl chloride 9 afforded 7 in 83% yield.[8] It is worth to note that the much lower reactivity was observed for N-Boc tryptamine due to its weak nucleophilicity, which produced the corresponding indole product in only 25% yield (see the Supporting Information). Based on the elegant work reported by the groups of Oisaki and Kanai,[9] and Rawal[10] on stoichiometric Mn(OAc)₃-mediated intramolecular oxidative cyclization, and inspired by recent advances on manganese-catalyzed dehydrogenative coupling from the groups of Oisaki and Kanai,[9] and Yamaguchi,[11] we planned to develop a catalytic method for the tandem indoline oxidation/malonate radical cyclization to form the δ-lactamindole scaffold of the molecule (Table 1). The use of 10 mol % of Mn(OAc)₃·2H₂O or Mn(OAc)₃·4H₂O, the tandem indoline oxidation/malonate radical cyclization to form the δ-lactamindole scaffold of the molecule (Table 1). The use of 10 mol % of Mn(OAc)₃·2H₂O or Mn(OAc)₃·4H₂O,
and 2.2 equivalents of NaIO₄ as co-oxidant in acetic acid, afforded 6 in moderate yields of 54 % and 50 %, respectively (entries 1 and 2). To our delight, upon switching the catalyst to CAN (cerium ammonium nitrate), [12] the reaction also proceeded and provided a higher yield (entry 3). Screening of the oxidants led to the formation of 6 in 75 % yield by exposure to dry air at elevated temperature (entry 7). In a 10 mmol scale reaction, the yield could be further improved to 80 %. As a comparison, other catalysts such as Mn(acac)₃ (entries 8 and 9), whereas CeCl₃ [18] did not promote the reaction at all (entry 10).

Encouraged by the facile construction of 6, we turned our attention to building up the hexahydropyrrolo[2,3-b]pyrrole fused diazabicyclo[3.3.1]nonane skeleton (Scheme 2). To this end, Krapcho decarboxylation of 10 gave the monoester 11 in 86 % yield, setting the stage for one-pot Boc removal and TES protection of benzylic alcohol moiety. Treatment of 11 with tetracycle 15, affording 16 in 78 % yield as a ca. 1.2:1 mixture of inseparable olefin isomers. After being converted to AIBN,[18] the desired cyclization occurred to provide 16 in 70 % yield as a ca. 1.2:1 mixture of inseparable olefin isomers.

With tetracyle 4 in hand, the subsequent hydroboration of the exocyclic olefin was investigated. However, the alkene moiety turned out to be inert under conventional conditions employing boranes such as BH₃-MeS, BH₃-THF, 9-borabicyclo[3.3.1]nonane (9-BBN), bis(1,2-dimethylpropyl)borane (Si₃B₃H), and thexylborane. Treatment of 4 with BH₃-THF in refluxing THF gave a ca. 20 % yield of the Markovnikov adduct, which unfortunately could not undergo further rearrangement to provide the required less substituted borane after prolonged reaction time. We found that only catalytic hydroboration [Rh(PPh₃)₃Cl] (10 mol %), catecholborane, THF (5.0 equiv) successfully afforded the expected alcohol 18 as a 1.2:1 mixture of epimers at C(19), albeit with AIBN,[13] the desired cyclization occurred to provide 16 in 70 % yield as a ca. 1.2:1 mixture of inseparable olefin isomers.
the opposite relative configuration at C(20) and in low yield (25%). Lactone 18 was formed in 10% yield from 17 under the same conditions, whose relative configuration at C(16) and C(20) could be unambiguously determined.\[9\] The observed complete concave-face selectivity of the hydroboration indicated the prior formation of an N-b-borane complex,\[9\] which blocked the convex face of the diazabicyclo[3.3.1]nonane skeleton during the process. Swern oxidation of 18 delivered ketone 19 in 64% yield with concomitant epimerization at C(20) by the addition of a large excess of Et3N.\[4d\] To our disappointment, sodium borohydride reduction gave the undesired 19-epi-2 in 96% yield as a single diastereomer.

Having failed in accessing (±)-alsmaphorazine D (2) by C(19) ketone reduction, and in view of the unsatisfactory overall efficiency of the previous route due to the rather low-yielding hydroboration reaction, a revised strategy was put forward (Scheme 3). Thus, attachment of the side chain 20 to 12 gave 21 in 83% yield. Surprisingly, 22 was formed in only 5% yield under dehydrogenation conditions, accompanied by the ring-opening product 23 as the major product (75% yield).\[21\] We envisioned that 23 would undergo a tran-annual radical cyclization\[22\] to afford 25 as well through a presumable nine-membered intermediate 24 and followed by intramolecular Michael-type cyclization of amine at the C(2) position.\[23\] However, treatment of 23 with nBu3SnH/ AIBN in benzene at 80°C only afforded trace amounts of 25. To our pleasure, under milder conditions (nBu3SnH, Et3B, toluene, –78°–0°C) with oxygen as a radical initiator,\[24\] 25 could indeed be obtained in 72% yield. Due to less steric hindrance around the olefin moiety in comparison to 4, the catalytic hydroboration of 25 occurred smoothly to provide 26 in 70% yield (85% based on recovered starting material).

With the rapid accumulation of alcohol 26, Dess–Martin periodinane oxidation delivered 27 in 90% yield. We then planned to wrap up the total synthesis with a challenging one-pot desilylation/double epimerization reaction to obtain the desired aldehyde 28c in a straightforward manner. After extensive experimentation, HF·py was found to be the most suitable reagent for this transformation. By increasing the reaction temperature, we were able to realize the gradual conversion of 28a to 28c via 28b by taking advantage of the steric repulsion between the ester and aldehyde moieties.\[25\] As a result, subjection of 27 to the solution of HF·py (50 equiv) in refluxing acetonitrile afforded 28c in 73% yield. Other fluoride sources (KF/18-crown-6, CsF, TBAF, TBAF/AcOH, aq. HF) and acids such as aq. HCl, AcOH, trifluoroacetic acid (TFA), p-TsOH (Ts = tosyl), and pyridinium p-toluenesulphonate (PPTS) either caused the decomposition of 27 or gave a lower yield of 28c. Finally, careful treatment of 28c with MeMgBr at –78°C delivered (±)-alsmaphorazine D (2) in 80% yield. Synthetic 2 exhibited 1H and 13C NMR spectra identical in all respects to those reported for the natural product,\[3a\] thus confirming its relative stereochemistry.

In summary, we have developed a concise and efficient approach for the first total synthesis of (±)-alsmaphorazine D. The key steps of the strategy include a CAN-catalyzed intramolecular oxidative cyclization, an oxidative cyclic amidal formation, a transannular radical cyclization, and a one-pot desilylation/double epimerization reaction. The described strategy and methods could be readily applied to the synthesis of (±)-alsmaphorazine E and rationally designed analogues for further chemical and biological investigations. Meanwhile, we are also pursuing an asymmetric total synthesis of (+)-alsmaphorazines D and E by the enantioselective oxidation of indole.\[29\] These studies are currently underway in our laboratory and will be reported in due course.

Received: October 7, 2014
Published online: 2014-11-08

Keywords: cyclization · epimerization · oxidative coupling · pyrroloindoles · total synthesis


These are not the final page numbers!
These are not the final page numbers!
The total synthesis of (±)-alsmaphorazine D was achieved in a concise and efficient fashion. The key features of the strategy are based on a catalytic intramolecular oxidative cyclization, an oxidative cyclic aminal formation, a transannular radical cyclization, and a one-pot desilylation/double epimerization reaction. CAN = cerium(IV) ammonium nitrate.