Natural Product Synthesis

DOI: 10.1002/anie.201409827

Total Synthesis of Indole Alkaloid Alsmaphorazine D**

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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 hexahydropyrrolo[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 monoterpene 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

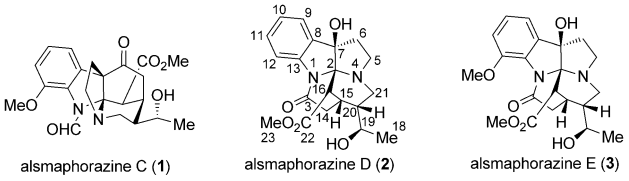
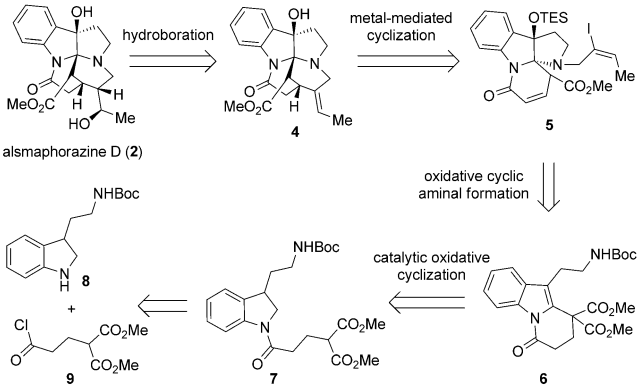


Figure 1. Structures of alsmaphorazines C–E (**1**–**3**).

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 hexahydropyrrolo[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 the potentially important 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



Scheme 1. Retrosynthetic analysis of alsmaphorazine D (**2**).

4 through a substrate-controlled hydroboration[4] of the $\Delta^{19,20}$ 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 acyl chloride **9**.

The synthesis commenced with the construction of δ-lactamindole **6**. Acylation of indoline **8** with acyl chloride **9** afforded **7** in 83% yield.[8a] 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 Kerr[8] and Rawal[9] 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,[10] and Yamaguchi,[11] we planned to develop a catalytic method for the tandem indoline oxidation/malonic radical cyclization to form the δ-lactamindole scaffold of the molecule (Table 1). The use of 10 mol% of $Mn(OAc)_3{\cdot}2H_2O$ or $Mn(OAc)_2{\cdot}4H_2O$,

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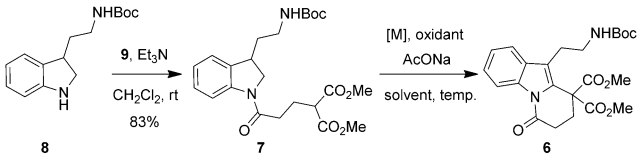
[**] This work was supported by NSFC (21202144, 21472167), the New Teacher's Fund for Doctor Stations, the Ministry of Education (20120101120087), the Fundamental Research Funds for the Central Universities (2014QNA3009), and Zhejiang University. We thank Dr. Kok Ping Chan (Institute of Chemical & Engineering Sciences, A*STAR, Singapore) for helpful discussions during the preparation of this manuscript.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201409827.

Table 1: Optimization of the catalytic oxidative cyclization.[a]

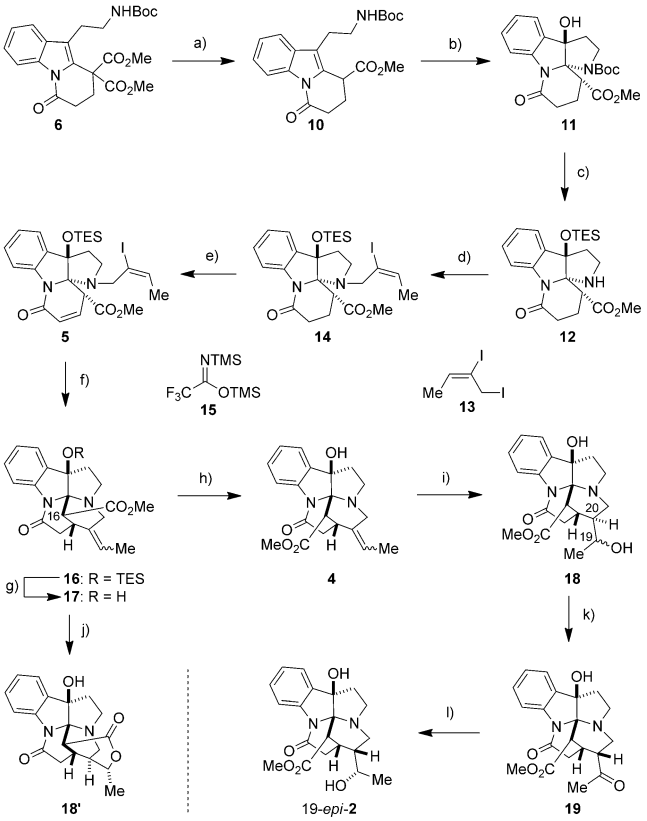


Entry	Cat. [M]	Oxidant	Solvent	Temp. [°C]	Yield [%][b]
1[c]	$Mn(OAc)_3{\cdot}2H_2O$	$NaIO_4$	AcOH	70	54
2[c]	$Mn(OAc)_2{\cdot}4H_2O$	$NaIO_4$	AcOH	70	50
3	$(NH_4)_2Ce(NO_3)_6$	$NaIO_4$	AcOH	70	67
4	$(NH_4)_2Ce(NO_3)_6$	$KMnO_4$	AcOH	70	43
5	$(NH_4)_2Ce(NO_3)_6$	DDQ	AcOH	70	54
6	$(NH_4)_2Ce(NO_3)_6$	TBHP	PhMe	100	16
7	$(NH_4)_2Ce(NO_3)_6$	dry air	AcOH	110	75, 80[d]
8	$Mn(acac)_3$	dry air	PhMe	110	40
9[e]	$Cu(OAc)_2$	dry air	THF	65	31
10	$CeCl_3$	dry air	AcOH	110	n.d.[f]

[a] Unless stated otherwise, the reaction was carried out with **7** (0.1 mmol), [M] (10 mol%), oxidant (2.2 equiv), and NaOAc (2.0 equiv) in solvent (2 mL) at the indicated temperature. [b] Yields of isolated products. [c] PPh_3 (10 mol%) was employed as an additive. [d] 10 mmol scale reaction. [e] $Cu(OAc)_2$ (30 mol%), DBU (2.0 equiv). [f] Not detected. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DBU = 1,8-diazabicycloundec-7-ene, acac = acetylacetonate, TBHP = *t*-butyl hydroperoxide, THF = tetrahydrofuran.

and 2.2 equivalents of $NaIO_4$ 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 $Mn(acac)_3$ and $Cu(OAc)_2$[13] gave a lower yield (entries 8 and 9), whereas $CeCl_3$[14] 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 **6** was firstly executed and gave monoester **10** in 86% yield. Treatment of **10** with dimethyldioxirane generated in situ[5d,15] provided the desired epoxy intermediate, which was then readily transformed to pyrroloindole **11** as a single diastereomer through cyclic aminal formation upon exposure to silica gel in 72% yield. A one-pot Boc removal and TES protection of benzylic alcohol enabled the installation of the vinyl iodide side chain to proceed smoothly to deliver **14**. Direct dehydrogenation of **14** by using DDQ and BSTFA [*N*,*O*-bis(trimethylsilyl)trifluoroacetamide, **15**][16] afforded **5** in 78% yield, setting the stage for the metal-mediated cyclization. Disappointingly, an attempted $[Ni(cod)_2]$-mediated cyclization[5a–f] of **5** led only to the decomposition of the starting material. Palladium-catalyzed reductive Heck coupling[5g–i] with different combinations of catalysts, ligands, bases, and additives, also failed to give any desired product.[17] Fortunately, the radical cyclization was found more productive. In the presence of nBu_3SnH/AIBN,[18] the desired cyclization occurred to provide **16** in 70% yield as a ca. 1.2:1 mixture of inseparable olefin isomers. After being converted to **17** by desilylation, DBU-induced epimerization at C(16) afforded **4** in 94% yield.



Scheme 2. Initial synthetic route leading to 19-*epi*-**2**. Reagents and conditions: a) LiCl, DMSO/H_2O (40:1), 130°C, 86%; b) oxone, acetone, 0°C, 72%; c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0→25°C, 82%; d) **13**, K_2CO_3, MeCN, 70°C, 85%; e) **15**, DDQ, 1,4-dioxane, 100°C, 78%; f) nBu_3SnH, AIBN, benzene, 80°C, ca. 1.2:1 ratio of olefin isomers, 70%; g) TBAF (1.0 M in THF), THF, 0°C, ca. 1.2:1 ratio of olefin isomers, 85%; h) DBU, toluene, 100°C, ca. 1.2:1 ratio of olefin isomers, 94%; i) $Rh(PPh_3)_3Cl$, catecholborane, THF, 0→25°C; then H_2O_2 (30% wt/wt in H_2O), NaOH, d.r. = 1.2:1, 25%; j) $Rh(PPh_3)_3Cl$, catecholborane, THF, 0→25°C; then H_2O_2 (30% wt/wt in H_2O), NaOH, 10%; k) $(COCl)_2$, DMSO, CH_2Cl_2, −78→0°C; then excess Et_3N, 0→25°C, 64%; l) $NaBH_4$, MeOH, 0°C, 96%. DMSO = dimethyl sulfoxide, TESOTf = triethylsilyl trifluoromethanesulfonate, AIBN = 2,2′-azobis(2-methylpropionitrile), TBAF = tetrabutylammonium fluoride.

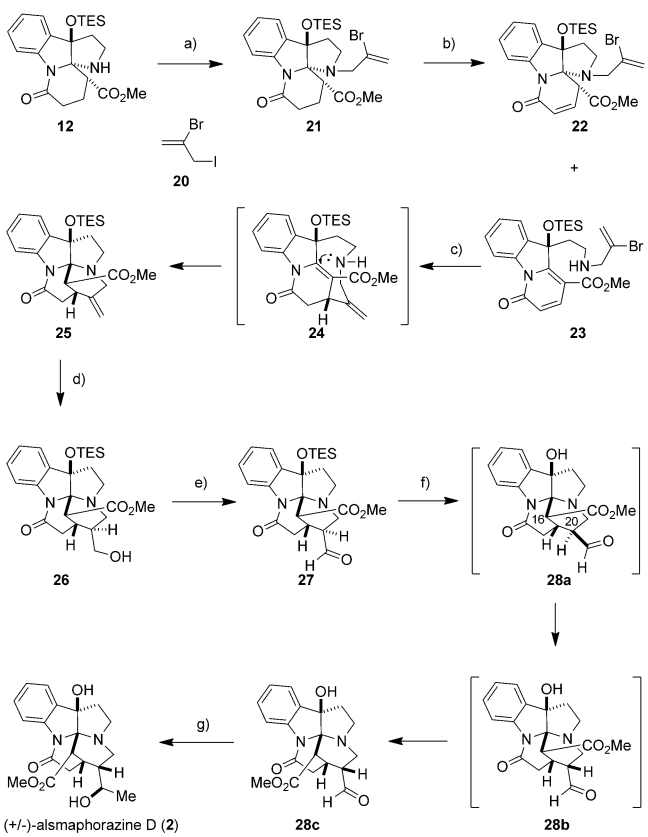
With tetracycle **4** in hand, the subsequent hydroboration of the exocyclic olefin was investigated. However, the alkene moiety turned out to be inert under conventional conditions employing boranes such as $BH_3{\cdot}Me_2S$, $BH_3{\cdot}THF$, 9-borabicyclo(3.3.1)nonane (9-BBN), bis(1,2-dimethylpropyl)-borane (Sia_2BH), and thexylborane. Treatment of **4** with $BH_3{\cdot}THF$ 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 [$Rh(PPh_3)_3Cl$ (10 mol%), catecholborane (5.0 equiv)][19] successfully afforded the expected alcohol **18** as a 1.2:1 mixture of epimers at C(19), albeit with

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.[20] The observed complete concave-face selectivity of the hydroboration indicated the prior formation of an N_b-borane complex,[4a] 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 Et_3N.[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** onto **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 transannular 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 nBu$_3$SnH/AIBN in benzene at 80°C only afforded trace amounts of **25**. To our pleasure, under milder conditions (nBu$_3$SnH, Et_3B, 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*-toluenesulfonate (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 ^{1}H and ^{13}C 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 aminal 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.[26] These studies are currently underway in our laboratory and will be reported in due course.



Scheme 3. Total synthesis of (±)-alsmaphorazine D (**2**). Reagents and conditions: a) **20**, K_2CO_3, MeCN, 70°C, 83%; b) **15**, DDQ, 1,4-dioxane, 100°C, **22** (5%), **23** (75%); c) nBu$_3$SnH, Et_3B, O_2, toluene, −78→0°C, 72%; d) Rh(PPh$_3$)$_3$Cl, catecholborane, THF, 0→25°C; then H_2O_2 (30% wt/wt in H_2O), NaOH, 70% (85% brsm); e) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 25°C, 90%; f) HF·py, MeCN, 82°C, 73%; g) MeMgBr (1.0 M in THF), −78°C, THF, 80%. py = pyridine, brsm = based on recovered starting material.

Received: October 7, 2014
Published online: ■■ ■■, ■■■■

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

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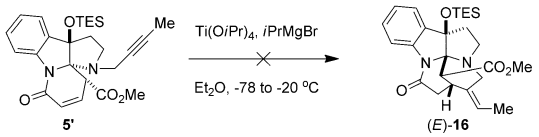

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[20] Compound **18′** could also be obtained by treatment of **28a** with MeMgBr in 83% yield, see the Supporting Information for details.

[21] In contrast, only trace amount of the corresponding ring-opening products were observed along with the formation of **5** and **5′**; the reasons are under exploration.

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[25] In comparison, the isomerization of 16-*epi*-**28a** proceeded much slower and afforded **28c** in ca. 15% yield over 48 h by treatment with HF·py.

[26] a) F. Kolundzic, M. N. Noshi, M. Tjandra, M. Movassaghi, S. J. Miller, *J. Am. Chem. Soc.* **2011**, *133*, 9104; for modified Katsuki-Sharpless asymmetric epoxidation conditions, see: b) T. Sunazuka, T. Hirose, T. Shirahata, Y. Harigaya, M. Hayashi, K. Komiyama, S. Ōmura, A. B. Smith III, *J. Am. Chem. Soc.* **2000**, *122*, 2122; c) T. Ideguchi, T. Yamada, T. Shirahata, T. Hirose, A. Sugawara, Y. Kobayashi, S. Ōmura, T. Sunazuka, *J. Am. Chem. Soc.* **2013**, *135*, 12568.

Communications

Natural Product Synthesis

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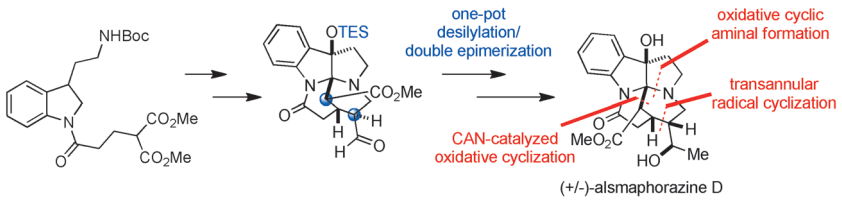
Total Synthesis of Indole Alkaloid Alsmaphorazine D



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.