Enantioselective Synthesis of Cryptopleurine and Boehmeriasin A via Organocatalytic Intramolecular Aza-Michael Addition

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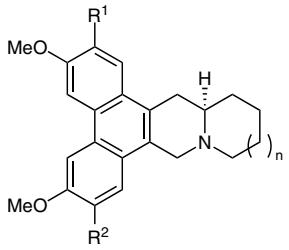
Abstract: The enantioselective synthesis of phenanthroquinolizidine alkaloids cryptopleurine and boehmeriasin A was achieved in eight steps from commercial available Cbz-protected 2-piperidinone in 22% and 20% overall yield, respectively. The key steps of this route are intramolecular enantioselective aza-Michael addition, intramolecular aldol addition, and oxidative coupling.

Key words: alkaloids, enantioselectivity, ketones, Michael addition, total synthesis

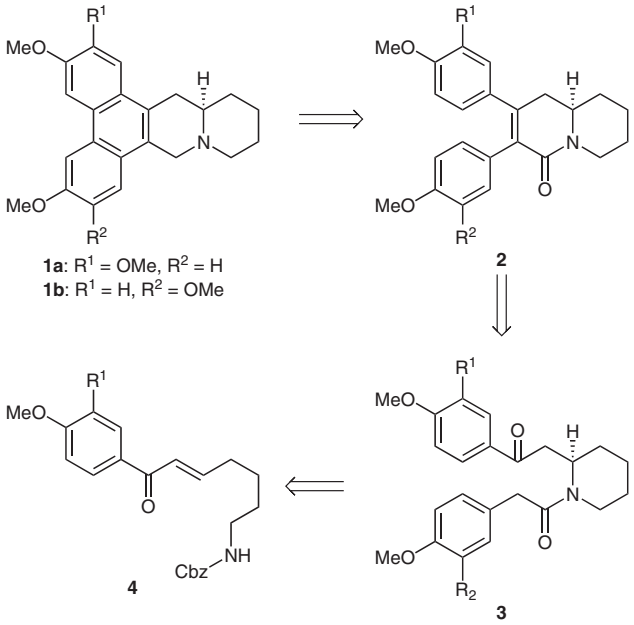
The phenanthroindolizidine and phenanthroquinolizidine alkaloids, typified by cryptopleurine, boehmeriasin A, and tylophorine, are a family of plant-derived natural alkaloids with significant therapeutic potential.[1] Although clinical trials of tylocrebrine failed due to CNS toxicity in the 1960s, the studies on this class of natural products revived in the 1990s because of their growth inhibition to drug-sensitive and multidrug-resistant cancer cells with novel action mechanism.[1c] So far few compounds in these classes have fully passed clinical trial due to low *in vivo* cytotoxicity, central nervous system toxicity, as well as low natural availability.[1c] Further structural modifications leading to lower cytotoxicity are highly desirable.



(*R*)-cryptopleurine (**1a**): n = 1, R^1 = OMe, R^2 = H
(*R*)-boehmeriasin A (**1b**): n = 1, R^1 = H, R^2 = OMe
(*R*)-tylophorine (**1c**): n = 0, R^1 = R^2 = OMe

Figure 1 Typical phenanthroizidine alkaloids

To date, more than 60 phenanthroindolizidines have been isolated and only five natural phenanthroquinolizidines are known. So it is not surprising that intense synthetic efforts on phenanthroindolizidines were reported but their six-membered counterparts have received less attention.[2] Although as minority of phenanthroindolizidines, phenanthroquinolizidines also carry interesting properties.[3] For example, boehmeriasin A, isolated by Zhang and co-workers in 2003, have proved more potent than taxol on a panel of twelve cancer cell lines.[4] Whereas four synthetic routes to boehmeriasin A (Figure 1),[5] three of which are asymmetric based on chiral pool or auxiliary strategies, have been reported, no catalytic enantioselective total synthesis of this natural product has been developed. Herein, we would like to describe a catalytic asymmetric route to boehmeriasin A, as well as cryptopleurine.[6]



Scheme 1 Retrosynthetic analysis of boehmeriasin A and cryptopleurine

Our synthetic plan is shown in Scheme 1. Boehmeriasin A and cryptopleurine could be constructed through oxidative coupling from arylquinolidine **2**, which could be delivered by intramolecular aldol and dehydration from 2-substituted piperidine **3**. We envisaged that the key intermediate **3** could be prepared from enone carbamate **4** via organocatalytic intramolecular aza-Michael addition.[7,8] Quite recently, the Fan and Fustero groups reported an elegant highly enantioselective intramolecular aza-Michael addition of enone carbamates independently.[9] Great success has been achieved on unsaturated aliphatic ketones, and reactions with unsaturated aromatic ketones

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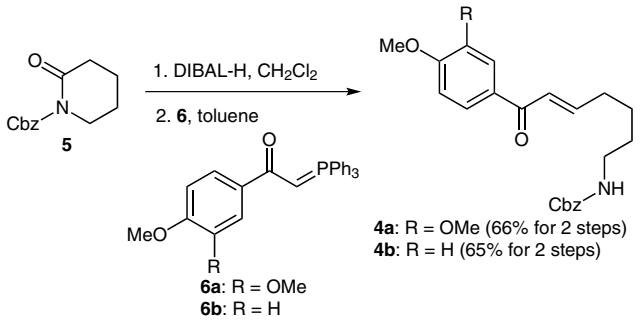
were less efficient in lower yield and ee value. The reaction with electron-rich aromatic enone carbamates were even worse and only one of this kind of substrates in both papers failed to give any desired Michael adduct. The route we designed here was challenging, but very promising, which prompted us to carry it out.

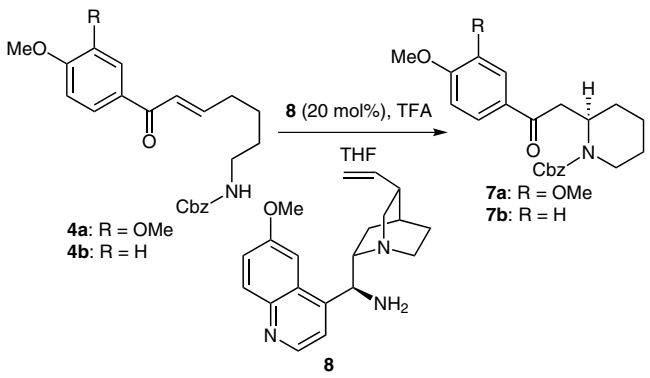
Firstly, we synthesized the Michael addition precursors as shown in Scheme 2. Reduction of Cbz-protected 2-piperidinone **5** with DIBAL-H, followed by Wittig reaction[10] with ylides **6a** and **6b**, gave enone carbamates **4a** and **4b**, respectively, in good yields over two steps.



Scheme 2 Synthesis of the Michael addition precursors

With the precursors in hand, we next tested the aza-Michael addition (Table 1). We followed Fan and Fustero's protocols using quinine-derived primary amine **8** as the catalyst.[9] Not surprisingly, the aza-Michael addition of **4a** catalyzed by 20 mol% amine **8** with 60 mol% TFA as additive gave the desired adduct **7a** in very low conversion although good enantioselective ratio (Table 1, entry 1). When less TFA was used, the enantioselectivity of this reaction could be increased up to 97:3 enantioselective ratio, but still with low conversion (Table 1, entries 2 and 3). We were pleased to find that full conversion of this reaction could be reached with slightly loss of enantioselectivity (93:7 er) when the reaction mixture was heated up to 60 °C (Table 1, entry 4). When the precursor **4b** was employed under the same conditions, comparable results (86% yield and 95:5 er) was obtained (Table 1, entry 5).

Table 1 Optimization of the Aza-Michael Addition[a]



Entry	4/7	TFA (mol%)	Temp (°C)	Time (d)	Yield (%)[b]	er (%)[c]
1	**4a**/**7a**	60	r.t.	7	<10	89:11
2	**4a**/**7a**	40	r.t.	7	<10	91: 9
3	**4a**/**7a**	20	r.t.	7	<10	97: 3
4	**4a**/**7a**	20	60	3	84	93: 7
5	**4b**/**7b**	20	60	3	86	95: 5

[a] A mixture of **4** (0.5 mmol), **8** (0.1 mmol), and TFA (0.1–0.3 mmol) in THF (1 mL) was stirred at indicated temperature for indicated time.
[b] Isolated yield.
[c] The er was determined by HPLC on a chiral stationary phase.

After we succeeded in the enantioselective intramolecular aza-Michael addition, we next turned our attention to the synthesis of boehmeriasin A and cryptopleurine. As shown in Scheme 3, the Cbz group in **7a** could be removed under hydrogenation, followed by amide-bond formation with acyl chloride **11a**, to give amide **3a**.[6h] Intramolecular aldol addition was then conducted under basic conditions to provide arylquinolidine **2a**[6h] in 53% overall yield for three steps.[5c] Given that the five-membered analogue of **3a** could be racemized under acidic or basic conditions,[11] we checked the optical purity of **2a** with HPLC on a chiral stationary phase. To our delight, the er value of **2a** was 95:5, which indicated that no racemization occurred. Amide-bond reduction of **2a** with Red-Al produced alkaloid julandine (**10a**)[6h] in 95% yield. Oxidative coupling of julandine (**10a**) with VOF_3 and TFAA gave cryptopleurine (**1a**) in 80% yield.[5d] The physical data of the synthetic cryptopleurine was identical to those reported.[6,12] In addition, the specific rotation of **1a** gave a matching sign and magnitude with those reported for the *R* enantiomer (observed: –79, $CHCl_3$; lit.[6h] –97, $CHCl_3$), which confirmed that the absolute configuration of our synthetic natural product was *R*. With a similar reaction sequence, the enantioenriched boehmeriasin A (**1b**) could be accessed. The aldol adduct **2b** could be accessed from **7b** in 53% overall yield in three steps. The optical purity slightly decreased from 95:5 to 92:8. After reduction and oxidative coupling, (*R*)-boehmeriasin A (**1b**) could be completed. The physical data of the synthetic (*R*)-boehmeriasin A was in agreement with those found in the literature.[5c,d,13]

In summary, phenanthroquinolizidine alkaloids boehmeriasin A and cryptopleurine could be finished in eight steps from commercial available Cbz-protected 2-piperidinone **5** in 22% and 20% overall yield, respectively. The key steps of this route are intramolecular enantioselective aza-Michael addition, intramolecular aldol addition and oxidative coupling. Synthesis of the other phenanthroindolizidine and phenanthroquinolizidine alkaloids with similar manner is under way and will be reported in due course.

Acknowledgment

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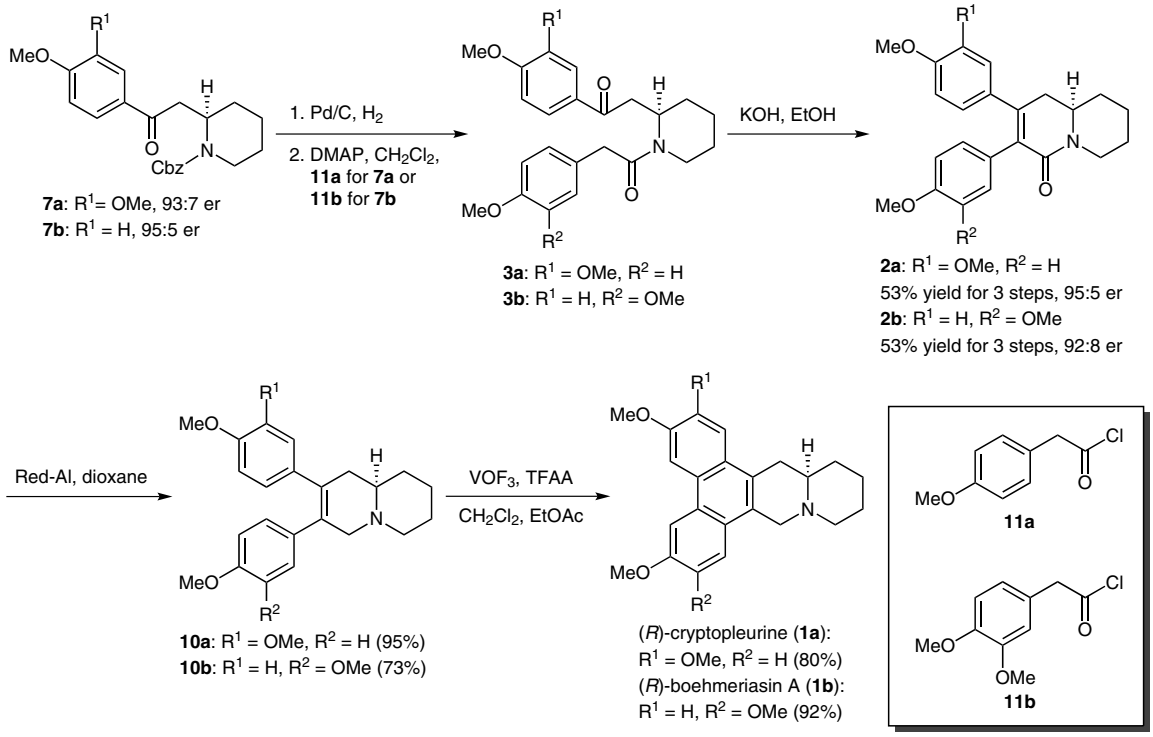

Scheme 3 Synthesis of (*R*)-cryptopleurine and (*R*)-boehmeriasin A

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **The Physical Data of the Synthetic (*R*)-Cryptopleurine (1a)**

$[\alpha]_D^{20}$ –78.8 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.88 (s, 2 H), 7.77 (d, *J* = 9.0 Hz, 1 H), 7.22–7.14 (m, 2 H), 4.42 (d, *J* = 15.6 Hz, 1 H), 4.09 (s, 3 H), 4.05 (s, 3 H), 4.00 (s, 3 H), 3.61 (d, *J* = 15.6 Hz, 1 H), 3.27 (d, *J* = 10.8 Hz, 1 H), 3.05 (d, *J* = 16.3 Hz, 1 H), 2.97–2.78 (m, 1 H), 2.53–2.16 (m, 2 H), 2.10–2.02 (m, 1 H), 1.94–1.69 (m, 2 H), 1.67–1.32 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 149.4, 148.3, 130.1, 126.4, 125.2, 124.3, 124.0, 123.5, 123.4, 114.8, 104.7, 103.8, 57.5, 56.13, 56.0, 55.9, 55.7, 55.5, 34.4, 33.5, 25.7, 24.2. IR: ν_{max} = 2930, 2915, 2910, 1700, 1683, 1610, 1511, 1470, 1466, 1455, 1450, 1440, 1435, 1417, 1405, 1270, 1255, 1231, 1188, 1177, 1152, 1130, 1124, 1101, 1072, 1041, 1022, 1012, 845, 833, 809, 783, 761, 634 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{24}H_{28}NO_3$ $[M + H]^+$: 378.2069; found: 378.2087.

(13) **The Physical Data of the Synthetic (*R*)-Boehmeriasin A (1b)**

$[\alpha]_D^{27}$ –66.1 (*c* 0.15, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.84 (m, 3 H), 7.20 (dd, *J* = 9.0, 2.5 Hz, 1 H), 7.10 (s, 1 H), 4.34 (d, *J* = 15.3 Hz, 1 H), 4.09 (s, 3 H), 4.04 (s, 3 H), 4.00 (s, 3 H), 3.61 (d, *J* = 14.8 Hz, 1 H), 3.29 (d, *J* = 11.1 Hz, 1 H), 3.16 (dd, *J* = 16.7, 3.1 Hz, 1 H), 2.98–2.91 (m, 1 H), 2.44–2.24 (m, 2 H), 2.06–1.96 (m, 1 H), 1.92–1.71 (m, 3 H), 1.60–1.36 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 149.4, 148.2, 130.3, 125.8, 125.1, 125.01, 124.9, 123.3, 114.8, 104.6, 104.0, 103.0, 57.5, 56.3, 56.98, 55.96, 55.5, 34.4, 33.5, 25.8, 24.2. IR: ν_{max} = 2916, 1670, 1604, 1514, 1501, 1470, 1448, 1415, 1410, 1372, 1274, 1256, 1232, 1169, 1138, 1133, 1124, 1098, 1093, 1070, 1035, 1013, 999, 966, 941, 904, 844, 805, 796, 785, 760, 735 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{24}H_{28}NO_3$ $[M + H]^+$: 378.2069; found: 378.2131.

