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An unexpected aziridination/rearrangement/oxidation tandem reaction leading to the total synthesis of (−)-mersicarpine

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ABSTRACT

With the aim to synthesize anti-mitotic natural product (−)-rhazinal, we proposed a strategy based on a dearomative intramolecular [3+2] cycloaddition between alkyl azide and indole, followed by rearrangement to furnish the featured tetracyclic framework. During the reaction condition screening, we accidentally encountered a tandem [3+2] cycloaddition/rearrangement/oxidation reaction, which enabled the synthesis of another alkaloid, (−)-mersicarpine, in four steps with 35% overall yield from a reported intermediate. The tandem [3+2] cycloaddition/rearrangement reaction disclosed herein could provide a method for the synthesis of other structurally intriguing alkaloids.

1. Introduction

Monoterpene indole alkaloids constitute an important family of natural products with significant biological activities, which have demonstrated utility as anti-cancer, anti-malarial and anti-arrhythmic agents.[1] Biosynthetically, these diverse small molecules derived from the combination of tryptamine and a C9 or C10 fragment originating from secologanin.[1] Based on the different structures of C9 or C10 fragments, subfamilies of monoterpenoid indole alkaloids have been discerned, such as *corynanthe*, *iboga* and *aspidosperma* classes.[2] We have recently reported a novel synthesis of *iboga* alkaloids, which also led to the efficient preparation of vinblastine, an anti-microtubule agent widely used in both clinical and basic research.[3] As a matter of fact, (−)-rhazinal (**1**, Fig. 1) and its congener (−)-rhazinilam (**2**) have also been reported to interfere with microtubule dynamics in vitro and exhibit cytotoxicity towards various cancer cell lines at low micromolar range.[4] First isolated from the stem-bark extract of *Kopsia* species,[5] (−)-rhazinal (**1**) contains a strained nine-membered lactam ring fused to a tetrahydroindolizine skeleton and bears a quaternary carbon linked to the C2-position of pyrrole. Besides **1** and **2**, a series of *aspidosperma* alkaloids such as mersicarpine (**3**), secoleuconoxine, and leuconoxine were isolated from the *Kopsia* species of flowering plants,[6] which is presumed to have biogenetic relations.[7]

Due to the unusual structure as well as intriguing biological activity, rhazinal (**1**) and rhazinilam (**2**) have attracted wide attention from the synthetic chemistry community, providing a platform to demonstrate novel methodologies. Furthermore, recent divergent syntheses of representative *aspidosperma* alkaloids not only accomplished rhazinilam (**2**) as one of the targets but illustrated their structural relation as well.[8] Strategically, most syntheses of rhazinal (**1**) or rhazinilam (**2**) depended on a sequence of constructing the tetrahydroindolizine ring system followed by the final installment of the nine-membered lactam.[8,9] One exception was to establish the tetrahydroindolizine and nine-membered lactam in one step via an elegant transannular cyclization, which was reported by Zakarian group in 2010.[10]

Keen on using rearrangement reactions to facilitate the synthesis of biologically important natural products,[3,11] we proposed a new approach (Fig. 2) to (−)-rhazinal (**1**) in order to further the associated chemical biology studies. However, during the investigation of this synthetic plan, we serendipitously obtained (−)-mersicarpine (**3**), another interesting alkaloid that has also

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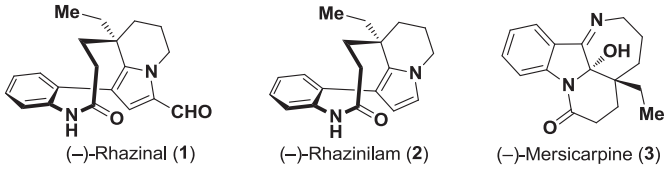


Fig. 1. *Aspidosperma* alkaloids discussed in this report.

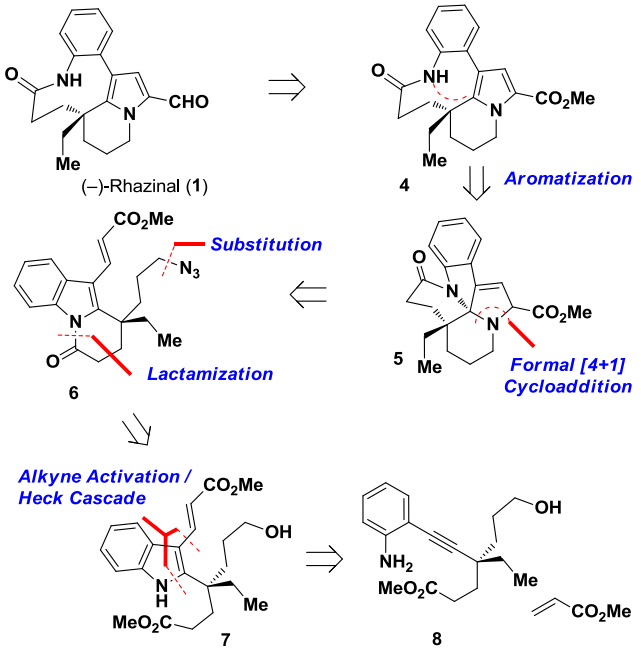
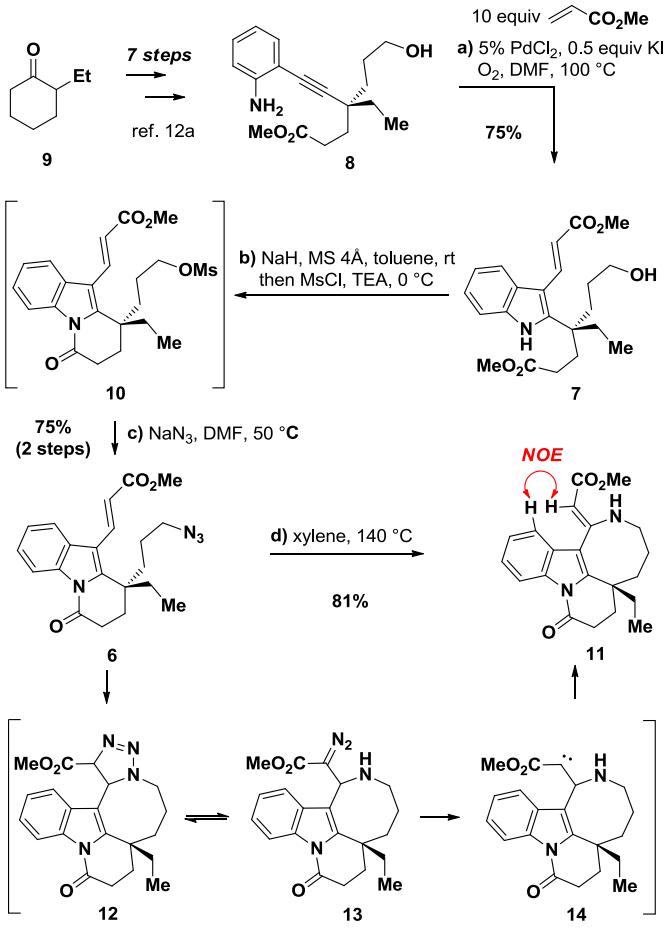


Fig. 2. Retrosynthetic analysis of (−)-rhazinal (**1**) based on the formal [4+1] cycloaddition followed by C−N bond scission.



Scheme 1. Attempted approach towards (−)-rhazinal (**1**).

been widely appreciated as the target for total synthesis.[7b,8c,12] Herein, we detail our discovery of the unexpected tandem process leading to this indole alkaloid.

2. Results and discussion

We envisioned the pyrrole ring and nine-membered lactam of (−)-rhazinal (**1**) could be constructed in the final stage by a tandem process involving cycloaddition and fragmentation (Fig. 2). Specifically, intermediate **4** could be afforded by the scission of one C−N bond in pentacyclic compound **5** driven by the aromatization into a pyrrole. The fused dihydropyrrole ring system in **5** could be formed by the intramolecular formal [4+1] cycloaddition of azidodienes developed by the groups of Hudlicky and Pearson,[13] which involved the sequence of intramolecular azide-alkene 1,3-diplor cycloaddition, nitrogen extrusion,[14] and vinylaziridine ring-expansion.[15] Admittedly, this desired transformation in our scenario would be a challenging one and azide has not been employed in the dearomative annulation of substituted indoles.[16] Azide **6** could be derived from alcohol **7** via lactamization and substitution manipulations. We planned to construct the substituted indole in **7** from alkynylaniline **8**, a known compound,[12a] using a Pd-catalyzed heterocyclization/oxidative Heck coupling.[17]

Starting from commercially available cyclohexanone **9** (Scheme 1), we first prepared enantiopure **8** bearing the desired quaternary stereogenic center following the seven-step sequence reported by the Fukuyama group.[12a] After some optimization (see Table S1 in Supporting Information for details), the $PdCl_2$-KI catalytic system using oxygen as the oxidant successfully converted alkynylaniline **8** to indole **7** in 75% yield. Sequential lactam formation followed by mesylation of the primary alcohol provided the corresponding **10**, and the crude mesylate **10** was converted to **6** directly upon treatment with sodium azide. With the precursor of the key cycloaddition/rearrangement tandem process in hand, we first investigated the thermal conditions. When **6** was heated at reflux in xylene, product **11** was isolated as the only product in 81% yield, where the geometry of olefin was assigned by NOESY experiment. This result suggested the [3+2] reaction took place between the azide and the double bond conjugated to indole to give triazoline **12** at first, which could isomerize to diazoester **13** and generate carbene **14** at high temperature, while the 1,2-hydrogen shift of **14** eventually generated **11** (see Fig. S1 in Supporting Information for another possible mechanism).[18] The aromaticity of indole and steric factors could rationalize the preference of the azide to react with the exocyclic double bond, leading to a strained 8-membered ring. In contrast, most of the reported examples of intramolecular 1,3-dipolar cycloaddition of azide to olefin were dominated by the formation of 5-membered or 6-membered tethered rings.[13,18,19] To our knowledge, only one example has been reported that constructed an 8-membered ring.[20]

Other reaction conditions were also evaluated in order to enable our desired transformation on substrate **6**. Lewis acids have been reported to mediate not only the cycloaddition of alkyl azides and enones but also the rearrangement of resulting triazoline

intermediates by Aubé and co-workers,[21] which took place at ambient temperature. Inspired by this work, we found a new product indicated by TLC was generated when **6** was heated in refluxing dichloromethane in the presence of 3 equivalents TMSOTf under a nitrogen atmosphere. Even though a significant amount of the starting material **6** still remained after 3 h, we were able to isolate the new product that was subsequently identified to be (−)-mersicarpine (**3**) by comparing its analytic data to those in the literature (entry 1, Table 1). Although surprising, an oxidation process was obviously involved. Therefore, we repeated the reaction under an oxygen atmosphere, which afforded **3** in 62% yield (entry 2). Replacing TMSOTf with $Sc(OTf)_3$ also furnished **3**, but only 15% isolated yield was obtained (entry 3). In comparison, other Lewis acids such as AgOTf, $Zn(OTf)_2$, or $Cu(OTf)_2$, failed to promote this transformation (entries 4–6). Subjecting **11** to the same reaction condition (TMSOTf, O_2, reflux in DCM) did not produce **3** at all, implying that the Lewis acid significantly altered the reaction pathway.

A possible mechanism for this unexpected transformation is formulated in Fig. 3 (see Fig. S2 in Supporting Information for another possible mechanism).[22] The first step could also be the intramolecular 1,3-dipolar cycloaddition to give triazoline **12**, which decomposes to aziridine **16** via **15** under current reaction conditions. The Lewis acid could further catalyze the 1,2-migration of electronic-rich indole to the nitrogen atom with concomitant cleavage of C–N bond, which is essentially a ring contraction process. The acid-promoted removal of the enolate side chain in **17** could produce cyclic enamine **18** as an unstable species, which can be readily oxidized by oxygen to afford (−)-mersicarpine (**3**) as the final product.[12a]

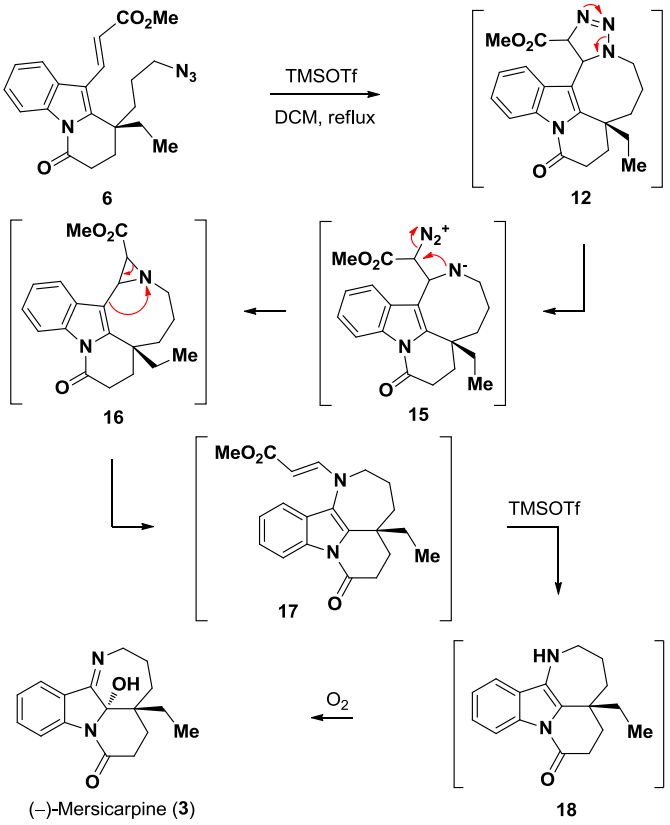
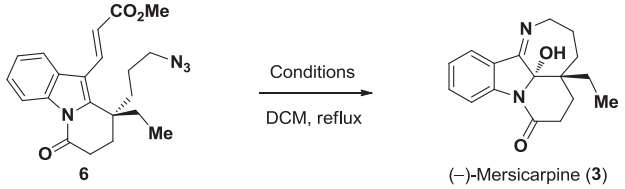


Fig. 3. A possible mechanism of the tandem reaction leading to the synthesis of (−)-mersicarpine (**3**).

3. Conclusion

In summary, we originally proposed to explore a dearomative [3+2] cycloaddition of azide and indole followed by rearrangement for the total synthesis (−)-rhazinal (**1**), but an unexpected reaction emerged during our investigation of the key transformation. In the presence of a Lewis acid, azide **6** underwent a facile intramolecular [3+2] cycloaddition followed by rearrangement and oxidation to provide natural product (−)-mersicarpine (**3**). Even though the Fukuyama group has successfully converted **8** to (−)-mersicarpine (**3**) in four steps,[12a] we are glad to find a serendipitously discovered tandem process could do the job in an alternative way. The mechanism and utility of this novel tandem process are under further studies and will be reported in due course.

Table 1
Optimization of the Lewis acid-mediated tandem reaction.



Entry	Conditions[a]	Yield[b]
1	3 equiv. TMSOTf, N_2 balloon, 3 h	19%[c]
2	3 equiv. TMSOTf, O_2 balloon, 12 h	62%
3	3 equiv. $Sc(OTf)_3$, O_2 balloon, 12 h	15%
4	3 equiv. AgOTf, O_2 balloon, 12 h	N.R.
5	3 equiv. $Zn(OTf)_2$, O_2 balloon, 12 h	N.R.
6	3 equiv. $Cu(OTf)_2$, O_2 balloon, 12 h	N.R.

[a] [**6**] = 0.1 M (0.05 mmol).
[b] Isolated yield after flash chromatography.
[c] Starting material **6** was recovered in 40% yield.

4. Experimental section

4.1. General remarks

Unless otherwise mentioned, all reactions were carried out under a nitrogen atmosphere under anhydrous conditions and all reagents were purchased from commercial suppliers without further purification. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials.

Reactions were monitored by Thin Layer Chromatography on plates (GF254) supplied by Yantai Chemicals (China) visualized by UV or stained with ethanolic solution of phosphomolybdic acid. If not specially mentioned, flash column chromatography was performed using silica gel (200–300 mesh) supplied by Tsingtao Haiyang Chemicals (China). NMR spectra were recorded on Bruker AV400, Bruker AV500 instruments and calibrated by using residual undeuterated chloroform (δ_H = 7.26 ppm) and $CDCl_3$ (δ_C = 77.0 ppm), or undeuterated dimethyl sulfoxide (δ_H = 2.50 ppm) and dimethyl sulfoxide-d6 (δ_C = 39.5 ppm) as internal references. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, b = broad, td = triple doublet, dt = double triplet, dq = double quartet, m = multiplet. Infrared (IR) spectra were recorded on a Thermo Nicolet Avatar 330 FT-IR spectrometer or a Thermo Nicolet iS5 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker Apex IVFTMS mass spectrometer using ESI (electrospray ionization) as the ionization method. Mass spectrometric data were obtained using Waters 2545 Binary Gradient Module using ESI (electrospray ionization) as the ionization method.

4.2. Synthetic studies towards (−)-rhazinal leading to total synthesis of (−)-mersicarpine (**3**)

4.2.1. Synthesis of **7**

$PdCl_2$ (3 mg, 0.016 mmol) and KI (27 mg, 0.16 mmol) were added to the Schlenk tube and degassed with oxygen. A solution of **8** (100 mg, 0.33 mmol) in dimethylformamide (1.5 mL) was added to the Schlenk tube under oxygen, then methyl acrylate (0.3 mL, 3.3 mmol) was added sequentially. The mixture was heated directly at 100 °C for 10 h under oxygen. The mixture was allowed to cool to room temperature and water was added, the organic phase was washed with water (10 mL × 3) and the water phase was extracted with ethyl acetate (10 mL), the combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed. The residue was purified by silica flash column chromatography under ethyl acetate/petroleum ether = 2:1 (R_f = 0.35, petroleum ether/ethyl acetate = 1:1, 95.4 mg, 75% yield). [α]20 D = +14 (c = 0.25 in $CHCl_3$); IR (neat): ν_{max} = 3727, 3702, 3626, 3598, 3358, 2948, 2176, 2016, 1714, 1608, 1457, 1430, 1278, 1175, 1053, 747, 678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.02 (s, 1H), 8.23 (d, J = 15.7 Hz, 1H), 7.88 (dd, J = 6.6, 2.7 Hz, 1H), 7.40–7.30 (m, 1H), 7.23–7.12 (m, 2H), 6.42 (d, J = 15.7 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.66 (q, J = 5.9, 4.9 Hz, 3H), 3.60 (s, 3H), 2.23–2.19 (m, 4H), 1.95 (d, J = 7.4 Hz, 3H), 1.72 (t, J = 4.7 Hz, 1H), 1.65 (s, 1H), 1.49 (dq, J = 11.9, 6.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H), 0.82 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 168.4, 145.6, 138.5, 135.0, 127.1, 122.3, 121.3, 120.4, 114.4, 111.1, 109.3, 77.3, 77.2, 77.0, 76.7, 62.8, 60.1, 51.8, 43.4, 31.9, 30.0, 29.1, 26.8, 14.5, 8.2 ppm; HRMS (ESI): m/z calcd for $C_{22}H_{30}NO_5^+$ $[M + H]^+$: 388.2079, found 388.2078.

4.2.2. Synthesis of **6**

To a stirred solution of **7** (150 mg, 0.39 mmol) in toluene (8 mL) was added 4 Å molecular sieves. After stirring for 1 h at room temperature, 50% sodium hydride (45 mg, 1.88 mmol) was added to the reaction mixture. After stirring for 10 min at room temperature, the mixture was cooled to 0 °C, to which triethyl amine (156 μL, 1.12 mmol) and methanesulfonyl chloride (88 μL, 1.12 mmol) were added. After stirring for 5 min at 0 °C, acetic acid (62 μL), aqueous saturated sodium bicarbonate and dichloromethane were added to the reaction mixture, which was allowed to warm to room temperature. Then the mixture was extracted with dichloromethane. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used directly in the next step.

The crude product of **10** was dissolved in dimethylformamide (2 mL) and sodium azide (76 mg, 1.17 mmol) was added to the mixture. The solution was heated at 50 °C for 3 h and cooled to room temperature. The mixture was diluted with ethyl acetate and the organic phase was washed with water (5 mL × 3). The organic phase was dried over anhydrous sodium sulfate and the solvent was removed. The residue was purified by silica flash chromatography under petroleum ether/ethyl acetate = 8:1 (R_f = 0.45, petroleum ether/ethyl acetate = 6:1, 110.8 mg, 75% yield over two steps), [α]20 D = −27 (c = 0.5 in $CHCl_3$); IR (neat): ν_{max} = 2948, 2877, 2094, 1710, 1629, 1455, 1434, 1361, 1308, 1278, 1247, 1175, 1138, 1093, 1042, 980, 922, 862, 753, 727, 568 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.02 (s, 1H), 8.23 (d, J = 15.7 Hz, 1H), 7.88 (dd, J = 6.6, 2.7 Hz, 1H), 7.40–7.30 (m, 1H), 7.23–7.12 (m, 2H), 6.42 (d, J = 15.7 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.66 (q, J = 5.9, 4.9 Hz, 3H), 3.60 (s, 3H), 2.23–2.19 (m, 4H), 1.95 (d, J = 7.4 Hz, 3H), 1.72 (t, J = 4.7 Hz, 1H), 1.65 (s, 1H), 1.49 (dq, J = 11.9, 6.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H), 0.82 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 168.4, 145.6, 138.5, 135.0, 127.1, 122.3, 121.3, 120.4, 114.4, 111.1, 109.3, 77.3, 77.2, 77.0, 76.7, 62.8, 60.1, 51.8, 43.4, 31.9, 30.0, 29.1, 26.8, 14.5, 8.2 ppm; HRMS (ESI): m/z calcd for $C_{22}H_{30}NO_5^+$ $[M + H]^+$: 388.2079, found 388.2078.

4.2.3. Synthesis of **11**

Compound **6** (20 mg, 0.05 mmol) was dissolved in xylene (1 mL) and heated to reflux for 4 h. Then the mixture was cooled to room temperature and concentrated under reduced pressure and purified by silica flash chromatography under petroleum ether/ethyl acetate = 12:1 (R_f = 0.48, petroleum ether/ethyl acetate = 8:1, 15.1 mg, 81% yield), [α]20 D = −52 (c = 0.1 in $CHCl_3$); IR (neat): ν_{max} = 2923, 1720, 1657, 1564, 1364, 1285, 1225, 1170, 1028, 764, 638, 576, 517 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.87 (s, 1H), 8.50 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.37–7.31 (m, 1H), 7.29 (dd, J = 7.6, 1.2 Hz, 1H), 4.82 (s, 1H), 3.73 (s, 3H), 3.22 (tdq, J = 12.6, 8.9, 4.9, 3.8 Hz, 2H), 3.05–2.75 (m, 2H), 2.25 (dddd, J = 44.8, 13.5, 10.3, 5.1 Hz, 2H), 1.82 (ddt, J = 31.0, 15.4, 6.3 Hz, 4H), 1.72–1.59 (m, 2H), 0.84 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.05, 157.71, 135.03, 125.32, 124.35, 119.48, 116.40, 83.41, 50.23, 40.66, 32.42, 30.54, 30.16, 29.71, 25.63, 8.44 ppm; HRMS (ESI): m/z calcd for $C_{21}H_{25}N_2O_3^+$ $[M + H]^+$: 353.1863, found 353.1860.

4.2.4. Synthesis of (−)-mersicarpine (**3**)

Compound **6** (20 mg, 0.05 mmol) was dissolved in dichloromethane (0.5 mL) and TMSOTf (14 μL, 0.15 mmol) was added dropwise to the solution. The mixture was heated reflux for 8 h under an oxygen atmosphere (balloon), and then cooled to room temperature. The mixture was neutralized with saturated $NaHCO_3$ and extracted with dichloromethane (3 mL × 3). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica flash chromatography under petroleum ether/ethyl acetate = 8:1 (R_f = 0.38, petroleum ether/ethyl acetate = 1:1, 9.3 mg, 62% yield); [α]20 D = −17.4 (c = 0.45 in $CHCl_3$); IR(neat): ν_{max} = 3316, 2918, 1658, 1647, 1467, 1382, 1303, 1163, 1129, 1068, 1042, 913 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, J = 8.1 Hz, 1H), 7.63 (dd, J = 7.8, 1.3 Hz, 1H), 7.38 (ddd, J = 8.4, 7.3, 1.4 Hz, 1H), 7.09 (td, J = 7.5, 1.0 Hz, 1H), 4.04–3.80 (m, 2H), 2.62–2.49 (m, 1H), 2.39 (ddd, J = 18.1, 9.0, 7.9 Hz, 1H), 2.14–2.01 (m, 1H), 1.99–1.85 (m, 1H), 1.83–1.55 (m, 5H), 1.37 (ddd, J = 14.5, 7.5, 1.6 Hz, 2H), 1.19–1.07 (m, 1H), 0.75 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.39, 168.49, 146.53, 133.24, 124.43, 124.32, 122.13, 116.84, 93.78, 77.26, 77.21, 77.00, 76.75, 67.06, 50.71, 39.31, 34.35, 29.69, 29.17, 25.46, 22.99, 21.15, 6.83 ppm; HRMS (ESI): m/z calcd for $C_{17}H_{21}N_2O_2^+$ $[M + H]^+$: 285.1603, found 285.1602.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2016.11.049.

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