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$Mg(ClO_4)_2$-catalyzed intramolecular allylic amination: application to the total synthesis of demethoxyfumitremorgin C

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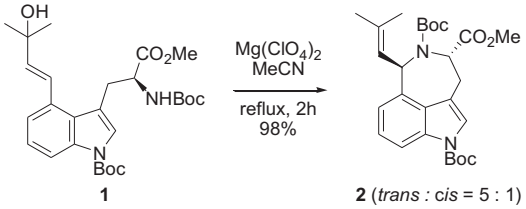
ABSTRACT

A $Mg(ClO_4)_2$-catalyzed intramolecular amination of allylic alcohols with carbamate or sulfonamide nucleophiles to form substituted piperidine and pyrrolidine derivatives has been developed. This method has been successfully applied to the total synthesis of demethoxyfumitremorgin C.

1. Introduction

Naturally occurring nitrogen heterocycles are compounds of great interest due to their interesting and diverse biological properties.[1] The development of efficient methods for the formation of C–N bond has been the subject of intensive research, and a variety of well-documented traditional and modern methods are now available.[2] However, the development of general and efficient methods for C–N bond formation from simple and easily accessible starting materials remains an active research field.[3] In this context, direct amination of allylic alcohols with amine nucleophiles to form the C–N bond has recently emerged as an attractive area of research because this process is atom-economy and eco-friendly as water is the only byproduct.[4,5] In fact, a variety of metal-based catalyst systems such as palladium,[6] gold,[7] iron,[8] bismuth,[9] Molybdenum,[10] and mercury,[11] I_2,[12] as well as Brønsted acids[13] in combination with carbamate or sulfonamide nucleophiles have been documented. Of these, the Pd(II)-catalyzed methods are most extensively developed and have been widely used in natural product synthesis.[6]

During the course of our synthesis of (−)-*trans*-clavicipitic acid, we unexpectedly discovered that $Mg(ClO_4)_2$ could catalyze an intramolecular amination of allylic alcohol **1**, which gave the desired product **2** in higher yield and similar diastereoselectivity comparing with those using $PdCl_2(CH_3CN)_2$ (Scheme 1).[14] Thus, $Mg(ClO_4)_2$ might be a powerful alternative candidate for traditional Pd catalyst systems in the intramolecular allylic amination. The mechanism of $Mg(ClO_4)_2$-mediated cyclization is postulated that the magnesium cation, acting as a mild Lewis acid, coordinates to the alcohol oxygen and activates the allylic alcohol, thus facilitating the intramolecular S_N2' substitution reaction. Since $Mg(ClO_4)_2$ is also low-toxic, inexpensive, and has not been demonstrated in allylic amination, these intriguing results inspired us to explore the scope of this reaction. Herein, we demonstrate that $Mg(ClO_4)_2$ is able to catalyze the intramolecular amination of a variety of allylic alcohols to produce the desired *N*-containing hetercycles and this method can be applied to the total synthesis of demethoxyfumitremorgin C.



1 **2** (*trans* : *cis* = 5 : 1)

Scheme 1. $Mg(ClO_4)_2$-mediated intramolecular amination.

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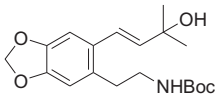
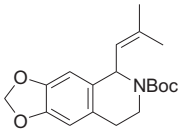
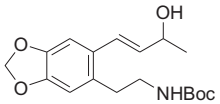
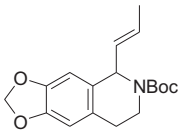
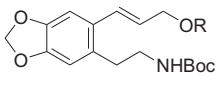
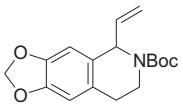
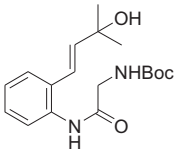
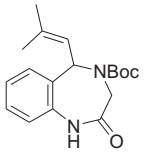
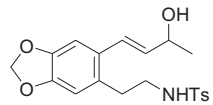
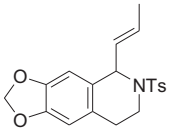
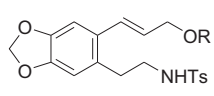
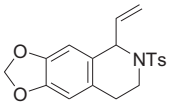
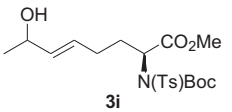
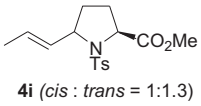
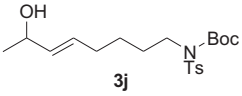
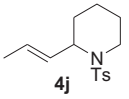
2. Results and discussions

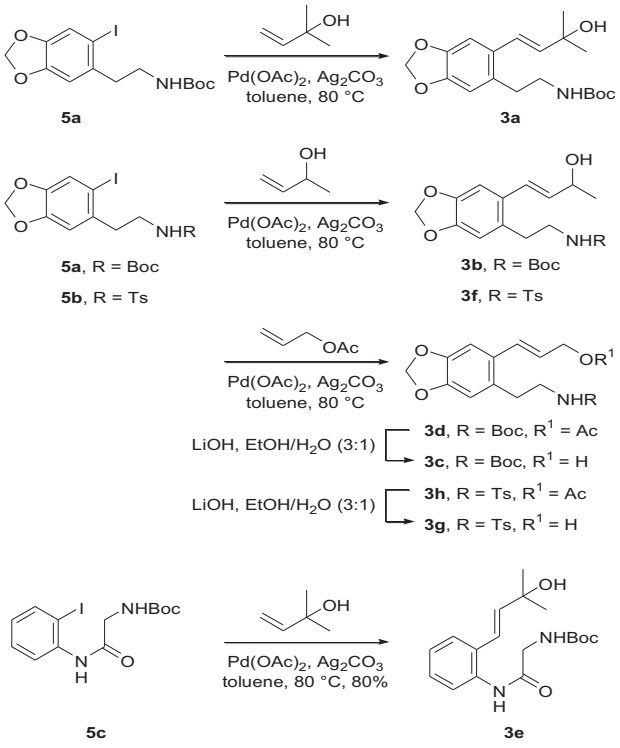
2.1. Preparation of allylic alcohol substrates

To explore the scope of this reaction, a variety of allylic alcohols **3a**–**j** (see Table 1) were prepared. The synthesis of **3a**–**h** is illustrated in Scheme 2. Heck reaction of **5a**–**c** with different allylic alcohols in air under ligand-free conditions provided the desired product **3a**, **3b**, **3f**, and **3e**.[14] Heck reaction of **5a** and **5b** with allyl acetate under above-mentioned conditions provided the corresponding product **3d** and **3h**, respectively. Basic hydrolysis of acetate **3d** and **3h** gave allylic alcohols **3c** and **3g**, respectively.

Table 1
Substrate scope of $Mg(ClO_4)_2$-catalyzed intramolecular amination of allylic alcohols

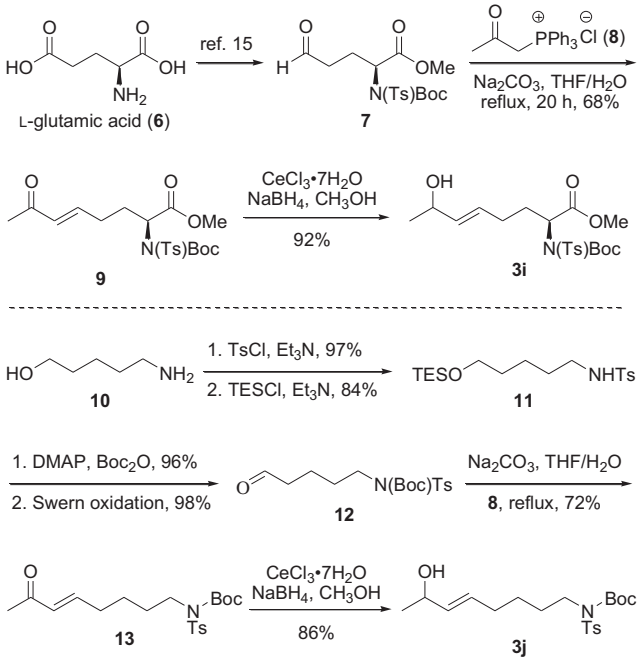
Entry	Substrate	Product	Yield (%)[a]
1	 **3a**	 **4a**	98%
2	 **3b**	 **4b**	94%
3[b]	 **3c**: R = H	 **4c**	26%
4	**3d**: R = Ac	**4c**	50%
5[c]	 **3e**	 **4e**	41%
6	 **3f**	 **4f**	90%
7	 **3g**: R = H	 **4g**	73%
8	**3h**: R = Ac	**4g**	76%
9	 **3i**	 **4i** (*cis* : *trans* = 1:1.3)	82%
10[b]	 **3j**	 **4j**	95%

[a] Concentration 0.1 M in CH3CN, 0.10 equiv of Mg(ClO4)2, 1.0 equiv of 3, 80 oC. All the yields are isolated yields.[b] Mg(ClO4)2 (1 equiv).[c] The reaction time was 7 d.



Scheme 2. Preparation of allylic alcohols **3a**–**h**.

The synthesis of allylic alcohols **3i** and **3j** was shown in Scheme 3. The known aldehyde **7** was prepared from L-glutamic acid according to Martín's procedure.[15] Wittig olefination of **7** with 2-oxopropyltriphenylphosphonium chloride (**8**) in THF/H_2O at reflux furnished the (*E*)-α,β-unsaturated ketone **9**. Luche reduction of ketone **9** afforded the desired allylic alcohol **3i** as a pair of diastereomers

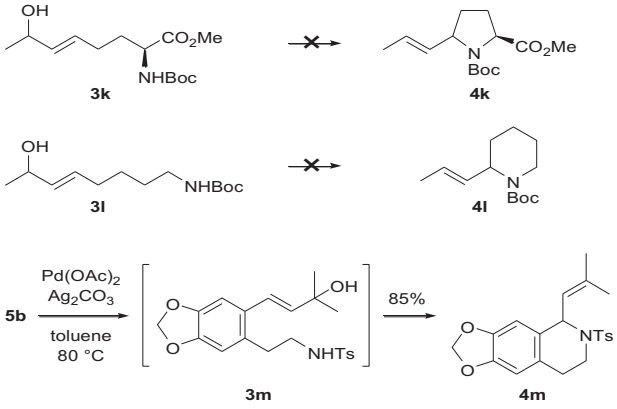


Scheme 3. Preparation of allylic alcohols **3i** and **3j**.

in a ratio of 1:1.3, which could not be separated by either careful chromatography or HPLC. The allylic alcohol **3j** was prepared from 5-aminopentan-1-ol **10** following a similar scheme as described for **3i**.

2.2. Amination of allylic alcohols

The reactivity of NHBoc with different substituents and ring systems of allylic alcohols was examined first (Table 1). When *tert*-alcohol **3a** was treated with $Mg(ClO_4)_2$ (0.1 equiv) in CH_3CN at 80 °C, a smooth and fast reaction took place and the desired tetrahydroisoquinoline **4a** was obtained in 98% yield (Table 1, entry 1). Similarly, the secondary alcohol **3b** also worked well and gave **4b** in 94% yield, albeit a longer reaction time was needed (Table 1, entry 2). However, the reaction of primary alcohol **3c** was sluggish even with higher catalyst loadings (1 equiv), which gave the corresponding product **4c** in only 26% yield (Table 1, entry 3). The allylic acetate **3d** could enhance the reactivity and produce **4c** in 50% yield (Table 1, entry 4). The reaction also could be used to form the seven-membered ring, which was difficult to obtain. Under the optimized reaction conditions, compound **3e** was converted to **4e** in 41% yield. Besides the aromatic allylic alcohol, γ- and δ-amino allylic alcohol derivatives **3k** and **3l** were trailed (Scheme 4). However, no desired cyclized products **4k** and **4l** were detected.



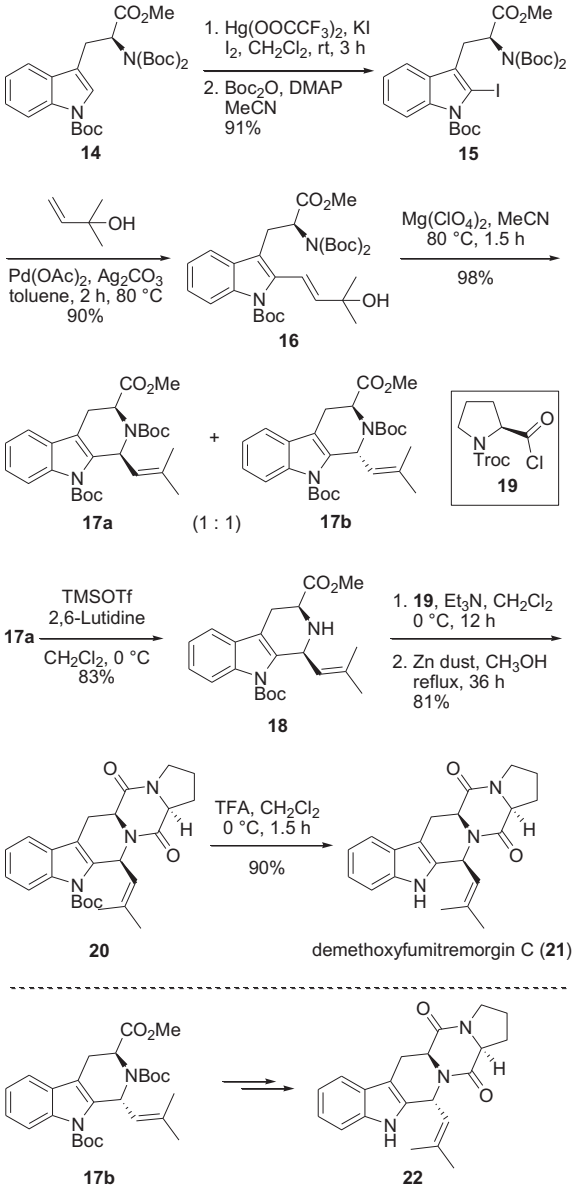
Scheme 4.

The effects of the protecting group on the nitrogen were next investigated. The *N*-tosyl derivatives, exhibiting stronger reactivity, were chosed as substrates. When we attempted to prepare allylic alcohol **3m** by Heck reaction of **5b** with 2-methyl-3-buten-2-ol, to our great surprise, the cyclized product **4m** was isolated in 85% yield (Scheme 4). These results indicated that *N*-tosyl derivatives exhibited stronger reactivity than carbamates.

Thus, more *N*-tosyl allylic alcohols were investigated as shown in Table 1 (Table 1, entries 6–10). Although **3f** gave **4f** in almost the same yield as those of **3b**, **3g** and its acetate **3h** gave the corresponding product in much higher yields compared with **3c** and **3d** (Table 1, entries 7 and 8). Since selective cleavage of Boc group in compounds **3i** and **3j** to produce the corresponding *N*-tosyl allylic alcohols by using $Mg(ClO_4)_2$ is well-known. We planed to perform $Mg(ClO_4)_2$-promoted deprotection/cyclization cascade reaction for **3i** and **3j** in one-pot manner, thus streamlining the synthesis.[14] Gratefully, *N*-tosyl allylic alcohols **3i** as a pair of diastereomers in a ratio of 1:1.3 and **3j** worked smoothly and gave the pyrrolidine **4i** (*cis*/*trans*=1:1.3) in 82% yield and piperidine **4j** in 95% yield, respectively (Table 1, entries 9 and 10).

2.3. Total synthesis of demethoxyfumitremorgin C

The utility of this new method is demonstrated by a rapid total synthesis of demethoxyfumitremorgin C, a fungal inhibitor of mammalian cell cycle progression at the G(2)/M transion.[16] So far, the groups of Ottenheijm,[17] Nakagawa,[18] Bailey,[19] and Ganesan[20] have finished the total synthesis of demethoxyfumitremorgin C, all of which took advantage of the Pictet–Spengler reaction as the key step to construct the tetrahydro-β-carboline. Now we managed to apply the $Mg(ClO_4)_2$-catalyzed intramolecular allylic amination reaction to construct the tetrahydro-β-carboline, and then finished the total synthesis of demethoxyfumitremorgin C (Scheme 5).



Scheme 5. Total synthesis of demethoxyfumitremorgin C.

Tryptophan derivative **14** was treated with $Hg(CF_3CO_2)_2$ and I_2 to provide the desired iodide **15** (33%), together with 58% NHBoc product.[21] Treating the crude products with Boc_2O and DMAP in acetonitrile yielded **15** in 91% overall yield. Heck reaction of **15** with 2-methyl-3-buten-2-ol gave allylic alcohol **16** in 90% yield. Treatment of **16** with $Mg(ClO_4)_2$ under our optimized conditions provided the diastereoisomers **17a** and **17b** in 98% yield with a *trans* to *cis* ratio of 1:1, which could be separated by careful chromatography. Conversion of **15** to **17a** and **17b** also could be done in a one-pot manner.[14] Since the relative configuration of **17a** and **17b** was impossible to be determinated by NOESY studies at this stage, it had to await completion of the synthesis of **21**. Selective deprotection of Boc in **17a** with TMSOTf in the presence of 2,6-lutidine gave amine **18** in 83% yield. Coupling **18** with L-Troc-Pro-Cl **19**, followed by treatment of the corresponding product with Zn dust gave diketopiperazine **20** in 81% yield. Finally, deprotection of Boc with

CF_3CO_2H provided the target molecule demethoxyfumitremorgin C (**21**) in 90% yield. The physical properties (^1H, and ^{13}C NMR, MS data) of **21** are in accord with those described in the literature.[17–20] Synthetic demethoxyfumitremorgin C had an optical rotation of $[\alpha]_D^{28}$ +4.0 (*c* 0.2, $CHCl_3$), lit.: natural[16] $[\alpha]_D^{30}$ +8.0 (*c* 0.2, $CHCl_3$), synthetic[20a] $[\alpha]_D^{24}$ +16.4 (*c* 0.14, $CHCl_3$).

The epimer **17b** was readily converted to *epi*-demethoxyfumitremorgin C **22** following the same synthetic scheme as described for demethoxyfumitremorgin C. The physical properties (^1H and ^{13}C NMR, MS data) of **22** are in accord with those described in the literature.[17a] Synthetic *epi*-demethoxyfumitremorgin C had an optical rotation of $[\alpha]_D^{28}$ −312 (*c* 0.1, CH_3OH), lit.: synthetic[17a] $[\alpha]_D^{22}$ −436 (*c* 0.1, CH_3OH). These results also confirmed the absolute configurations of **17a** and **17b**.

3. Conclusion

In summary, we have demonstrated that $Mg(ClO_4)_2$ could catalyze direct intramolecular amination of allylic alcohols with a variety of substrates. This method is the operational simplicity. Inexpensive and non-toxic $Mg(ClO_4)_2$ was used as catalyst, which render this methodology to be eco-friendly. Its utility can be seen in the total synthesis of demethoxyfumitremorgin C.

4. Experimental section

4.1. General

Infrared spectra were recorded on Thermo Nicolet Nexus-470 FT-IR spectrometers. Mass spectra were recorded on a Bruker APEX IV FT-MS (ESI) spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance III 400 MHz spectrometer. Chemical shifts (in parts per million) were referenced to tetramethylsilane (δ=0 ppm) in the deuterated solvent as an internal standard. Flash column chromatography was performed using silica gel (200–300 mesh) with solvents distilled prior to use. Visualization was achieved under a UV lamp (254 nm and 365 nm), and by developing the plates with phosphomolybdic acid in ethanol.

4.2. Preparation of allylic alcohols 3a–j

A suspension of **5a** (270 mg, 0.69 mmol), 2-methyl-3-buten-2-ol (0.72 mL, 6.9 mmol), $Pd(OAc)_2$ (22.5 mg, 0.069 mmol), and Ag_2CO_3 (114 mg, 0.42 mmol) in toluene (1.75 mL) was heated at 80 °C for 13 h. The reaction mixture was filtered and evaporated. The residue was purified by FCC to afford **3a** (221 mg, 92%).

*4.2.1. tert-Butyl 2-(5-((E)-3-hydroxy-3-methylbut-1-enyl)benzo[d][1,3]dioxol-6-yl) ethylcarbamate (**3a**).* Isolated yield 92% as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.91 (d, *J*=16.0 Hz, 1H), 6.60 (s, 1H), 6.09 (d, *J*=16.0 Hz, 1H), 5.91 (s, 2H), 4.81 (br s, 1H), 3.20 (q, *J*=7.2 Hz, 2H), 3.04 (br s, 1H), 2.78 (t, *J*=7.6 Hz, 2H), 1.44 (s, 9H), 1.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 146.7, 146.6, 138.7, 130.2, 130.0, 123.4, 109.8, 106.2, 100.8, 79.5, 70.9, 41.5, 34.6, 29.9, 28.4; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{27}NO_5Na$ $(M+Na)^+$ 372.1781, found 372.1778; IR (KBr) 3420, 2973, 2930, 1691, 1482, 1366, 1245, 1164, 1038 cm^{-1}.

*4.2.2. tert-Butyl 2-(5-((E)-3-hydroxybut-1-enyl)-benzo[d][1,3]dioxol-6-yl) ethylcarbamate (**3b**).* Isolated yield 54% as while solid, mp 86–89 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.83 (d, *J*=15.4 Hz, 1H), 6.59 (s, 1H), 6.01 (dd, *J*=5.2, 15.4 Hz, 1H), 5.90 (s, 2H), 4.77 (br s, 1H), 4.48 (br s, 1H), 3.19 (dt, *J*=6.2, 7.2 Hz, 2H), 2.96 (br s, 1H), 2.76 (t, *J*=7.2 Hz, 2H), 1.43 (s, 9H), 1.34 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 146.9, 146.6, 134.8, 130.1, 129.8, 126.0, 109.8, 106.1, 100.9, 79.5, 68.4, 41.5, 34.2, 28.4, 23.3; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{25}NNaO_5$ $(M+Na)^+$ 358.1625, found 358.1628; IR (KBr) 3427, 3304, 3054, 2983, 2931, 2896, 1677, 1541, 1502, 1486, 1280, 1253, 1165, 1040, 954, 936, 872, 852, 663, 628, 603 cm^{-1}.

*4.2.3. tert-Butyl 2-(5-((E)-3-hydroxyprop-1-enyl)-benzo[d][1,3]dioxol-6-yl) ethylcarbamate (**3c**).* Lithium hydroxide mono-hydrate (50.0 mg, 1.19 mmol) was added to a solution of **3d** (290 mg, 0.798 mmol) in 75% aqueous ethanol (8 mL). The solution was stirred for 4 h at rt. Upon completion of reaction, the mixture was partitioned between water and ethyl acetate, and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed successively with saturated sodium hydrogen carbonate, water, and brine, then dried over anhydrous magnesium sulfate and evaporated to dryness. The residue was purified by FCC (pet ether/EtOAc=2:1) to provide **3c** (184 mg, 72%) as a white solid, mp 147–149 °C. ^1H NMR (400 MHz, DMSO) δ 7.04 (s, 1H), 6.70 (d, *J*=16.0 Hz, 1H), 6.68 (s, 1H), 6.14 (dt, *J*=5.0, 16.0 Hz, 1H), 5.94 (s, 2H), 4.08 (d, *J*=5.0 Hz, 2H), 3.00 (t, *J*=7.4 Hz, 2H), 2.66 (t, *J*=7.4 Hz, 2H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, DMSO) δ 155.5, 146.4, 146.2, 130.5, 130.4, 129.1, 125.6, 109.7, 105.2, 100.8, 77.6, 61.8, 41.1, 32.6, 28.3; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{23}NNaO_5$ $(M+Na)^+$ 344.1468, found 344.1469; IR (KBr) 3733, 3398, 3261, 3073, 2978, 2928, 2872, 1680, 1561, 1503, 1487, 1299, 1257, 1164, 1040, 1003, 978, 956 cm^{-1}.

*4.2.4. tert-Butyl 2-(5-((E)-3-acetoxyprop-1-enyl)-benzo[d][1,3]dioxol-6-yl) ethylcarbamate (**3d**).* Isolated yield 78% as white solid, mp 93–94 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.84 (d, *J*=15.6 Hz, 1H), 6.63 (s, 1H), 6.05 (dt, *J*=6.4, 15.6 Hz, 1H), 5.94 (s, 2H), 4.72 (d, *J*=6.4 Hz, 2H), 4.58 (br s, 1H), 3.26 (br d, *J*=6.8 Hz, 2H), 2.80 (t, *J*=6.8 Hz, 2H), 2.10 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 155.7, 147.5, 146.6, 131.2, 130.8, 128.7, 123.3, 109.8, 105.8, 101.0, 79.1, 65.2, 41.5, 33.3, 28.3, 20.9; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{25}NNaO_6$ $(M+Na)^+$ 386.1574, found 386.1579; 3340, 3033, 2978, 2928, 2880, 1734, 1701, 1682, 1527, 1504, 1486, 1455, 1392, 1366, 1288, 1243, 1167, 1135, 1040, 971, 956, 931, 872 cm^{-1}.

*4.2.5. tert-Butyl (2-((E)-3-hydroxy-3-methylbut-1-enyl)phenylcarbamoyl) methylcarbamate (**3e**).* Isolated yield 80% as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.73 (br s, 1H), 7.34 (d, *J*=7.2 Hz, 1H), 7.20 (t, *J*=7.2 Hz, 1H), 7.10 (t, *J*=7.2 Hz, 1H), 6.67 (d, *J*=15.6 Hz, 1H), 6.21 (d, *J*=15.6 Hz, 1H), 5.72 (br s, 1H), 3.91 (br s, 2H), 2.46 (br s, 1H), 1.44 (s, 9H), 1.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 156.5, 141.7, 134.0, 130.3, 127.8, 126.8, 125.5, 123.8, 121.2, 80.5, 71.0, 45.1, 29.7, 28.3; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{30}N_3O_4$ $(M+NH_4)^+$ 352.2231, found 352.2226; IR (KBr) 3396, 2974, 2930, 1685, 1528, 1453, 1368, 1257, 1164, 1101, 1052, 968, 909, 864, 755 cm^{-1}.

*4.2.6. (E)-4-(5-(2-(Tosylamino)ethyl)benzo[d][1,3]-dioxol-6-yl)but-3-en-2-ol (**3f**).* Isolated yield 21% as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J*=8.0 Hz, 2H), 7.25 (d, *J*=8.0 Hz, 2H), 6.87 (s, 1H), 6.69 (d, *J*=15.6 Hz, 1H), 6.49 (s, 1H), 5.96 (dd, *J*=6.0, 15.6 Hz, 1H), 5.89 (s, 2H), 5.09 (br s, 1H), 4.45 (br s, 1H), 3.05 (br s, 2H), 2.82 (dd, *J*=7.2, 13.8 Hz, 1H), 2.74 (dd, *J*=7.2, 13.8 Hz, 1H), 2.61 (br s, 1H), 2.39 (s, 3H), 1.33 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 146.8, 143.3, 137.0, 134.8, 129.7, 129.6, 129.3, 126.9, 126.0, 109.7, 106,1, 101.0, 68.6, 44.0, 33.6, 23.3, 21.4; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{23}NNaO_5S$ $(M+Na)^+$ 412.1189, found 412.1195; IR (KBr) 3517, 3281, 2968, 2923, 2884, 1717, 1503, 1484, 1325, 1158, 1040, 662, 551 cm^{-1}.

*4.2.7. (E)-3-(5-(2-(Tosylamino)ethyl)benzo[d][1,3]-dioxol-6-yl)prop-2-en-1-ol (**3g**).* As yellow solid, mp 76–78 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J*=8.2 Hz, 2H), 7.28 (d, *J*=8.2 Hz, 2H), 6.92 (s, 1H), 6.76 (d, *J*=15.6 Hz, 1H), 6.51 (s, 1H), 6.11 (dt, *J*=5.6, 15.6 Hz, 1H), 5.93

(s, 2H), 4.46 (t, *J*=6.0 Hz, 1H), 4.30 (d, *J*=5.6 Hz, 2H), 3.10 (dt, *J*=6.0, 6.8 Hz, 2H), 2.82 (t, *J*=6.8 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 147.0, 143.4, 137.1, 129.9, 129.8, 129.7, 129.3, 127.9, 127.0, 109.8, 106.3, 101.1, 63.6, 44.1, 33.6, 21.5; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{21}NNaO_5S$ $(M+Na)^+$ 398.1033, found 398.1037; IR (KBr) 3443, 2963, 2926, 1730, 1599, 1503, 1484, 1261, 1095, 1023, 865, 802, 708, 665 cm^{-1}.

*4.2.8. (E)-3-(5-(2-(Tosylamino)ethyl)benzo[d][1,3]-dioxol-6-yl)allyl acetate (**3h**).* Isolated yield 34% as yellow solid, mp 134–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J*=8.0 Hz, 2H), 7.28 (d, *J*=8.0 Hz, 2H), 6.89 (s, 1H), 6.72 (d, *J*=15.6 Hz, 1H), 6.51 (s, 1H), 5.98 (dt, *J*=6.4, 15.6 Hz, 1H), 5.93 (s, 2H), 4.68 (dd, *J*=0.8, 6.4 Hz, 2H), 4.45 (t, *J*=6.0 Hz, 1H), 3.10 (dt, *J*=6.0, 7.2 Hz, 2H), 2.78 (t, *J*=7.2 Hz, 2H), 2.42 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 147.6, 146.9, 143.3, 137.0, 131.1, 129.6, 129.5, 128.9, 127.0, 123.9, 109.8, 106.1, 101.1, 65.1, 43.8, 33.3, 21.4, 21.0; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{27}N_2O_6S$ $(M+NH_4)^+$ 435.1584, found 435.1587; IR (KBr) 3278, 2920, 2862, 1738, 1504, 1487, 1327, 1250, 1159, 1041, 936, 697, 548 cm^{-1}.

*4.2.9. Compound (**3i**).* The aldehyde **7** (1.29 g, 3.23 mmol), 2-oxopropyltriphenylphosphonium chloride **8** (1.72 g, 4.84 mmol), and sodium carbonate (390 mg, 3.68 mmol) were stirred with 40 mL tetrahydrofuran and 10 mL water at reflux for 15 h. Ether was added, the layers were separated, and the organic material was washed with brine and dried over magnesium sulfate. Evaporation of the solvent was followed by the addition of hexane and gravity filtration to remove the crystalline tri-phenylphosphine oxide. The hexane was evaporated and the residue was purified by silica gel column chromatography (PE/EtOAc=4:1) to afford **9** (3.23 g, 68%) as yellow oil. $[\alpha]_D^{17}$ −64 (*c* 0.2, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J*=8.0 Hz, 2H), 7.33 (d, *J*=8.0 Hz, 2H), 6.88 (dt, *J*=6.4, 16.0 Hz, 1H), 6.17 (d, *J*=16.0 Hz, 1H), 5.07 (dd, *J*=4.4, 9.4 Hz, 1H), 3.72 (s, 3H), 2.45 (s, 3H), 2.36–2.49 (m, 3H), 2.26 (s, 3H), 2.23 (m, 1H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 170.0, 149.8, 146.3, 144.4, 136.4, 132.0, 129.0, 128.6, 85.1, 58.7, 52.4, 29.1, 28.9, 27.7, 26.8, 21.5; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{29}NNaO_7S$ $(M+Na)^+$ 462.1557, found 462.1565; IR (KBr) 3471, 2981, 2951, 1744, 1675, 1631, 1449, 1361, 1293, 1255, 1150, 1088, 1041, 978, 719, 663, 585, 548 cm^{-1}.

To a stirred solution of ketone **9** (889 mg, 2 mmol) in methanol (18 mL) was added cerium chloride heptahydrate (1.12 g, 3 mmol). After 5 min, the mixture was cooled to 0 °C, and $NaBH_4$ (84 mg, 2.2 mmol) was added. The reaction mixture was stirred at 0 °C until total consumption of starting material (30 min). The reaction was quenched by adding a few drops of 50% acetic acid to neutral pH. Water and CH_2Cl_2 were added, and the heterogeneous mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine. The combined organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to afford **3i** (810 mg, 92%) as a pair of diastereomers in a ratio of 1:1.3 (yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$). Mixture of diastereomers δ 7.92–7.94 (m, 2H), 7.32 (d, *J*=8.4 Hz, 2H), 5.61–5.73 (m, 2H), 5.08 (m, 1H), 4.31 (m, 1H), 3.72 (s, 1.7H), 3.71 (s, 1.3H), 2.45 (s, 3H), 2.01–2.42 (m, 4H), 1.70 (br s, 2H), 1.30 (s, 4.0H), 1.29 (s, 5.0H), 1.26–1.28 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$). Mixture of diastereomers δ 170.5, 150.0, 144.3, 136.6, 135.9, 129.2, 129.0, 128.9, 128.7, 85.0, 68.9, 68.8, 58.6, 58.5, 52.4, 29.9, 29.8, 28.9, 28.8, 27.8, 23.2, 23.1, 21.6.

*4.2.10. Compound (**3j**).* Compound **11**: TESCl (6 mL, 35 mmol) were sequentially added to a stirred solution of alcohol (6 g, 23.3 mmol) in CH_2Cl_2 (80 mL) at 0 °C. The resulting mixture was stirred at 0 °C overnight. Then EtOAc was added to dilute the reaction mixture, which was further washed with water and brine. The organic solution was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (PE/EtOAc=6:1) to provide **11** (7.3 g, 84%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J*=8.0 Hz, 2H), 7.30 (d, *J*=8.0 Hz, 2H), 4.93 (t, *J*=6.0 Hz, 1H), 3.53 (t, *J*=6.4 Hz, 2H), 2.92 (dt, *J*=6.7, 6.8 Hz, 2H), 2.42 (s, 3H), 1.42–1.51 (m, 4H), 1.28–1.34 (m, 2H), 0.94 (t, *J*=8.0 Hz, 9H), 0.57 (q, *J*=8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 137.0, 129.6, 127.0, 62.4, 43.1, 32.1, 29.2, 22.8, 21.4, 6.7, 4.3; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{34}NO_3SSi$ $(M+H)^+$ 372.2023, found 372.2025; IR (KBr) 3560, 3283, 3031, 2951, 2875, 2734, 1916, 1807, 1726, 1599, 1459, 1417, 1327, 1238, 1160, 1094, 1013, 813, 729, 664, 573, 552 cm^{-1}.

Compound **12**: to a stirred solution of **11** (7.26 g, 11.6 mmol) and DMAP (477 mg, 3.9 mmol) in dry CH_3CN (40 mL) was added $(Boc)_2O$ (4.69 g, 21.5 mmol) at rt. After the mixture was stirred for 2 h, more $(Boc)_2O$ (4.69 g, 21.5 mmol) was added and the mixture was additionally stirred overnight. The solvent was evaporated, and the residue was purified by silica gel column chromatography (PE/EtOAc=14:1) to afford the desired product (8.8 g, 96%).

To a solution of oxalyl chloride (0.5 mL, 5.9 mmol) in CH_2Cl_2 (10 mL) cooled at −78 °C was added dropwise a solution of DMSO (0.84 mL, 11.8 mmol) in CH_2Cl_2 (10 mL). After 30 min, a solution of the above product (2.54 g, 5.38 mmol) in CH_2Cl_2 (30 mL) was added. The reaction mixture was then stirred for 1.5 h at −78 °C and triethylamine (3.74 mL, 26.9 mmol) was added in one portion. The mixture was allowed to warm to rt to react 3 h and quenched with saturated aqueous solution of NH_4Cl and extract with CH_2Cl_2 and washed with brine. The organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to afford aldehyde **12** (1.21 g, 98%) as colorless oil and the starting material (800 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, *J*=1.4 Hz, 1H), 7.77 (d, *J*=8.4 Hz, 2H), 7.31 (d, *J*=8.0 Hz, 2H), 3.84 (t, *J*=7.2 Hz, 2H), 2.52 (dt, *J*=1.4, 7.3 Hz, 2H), 2.44 (s, 3H), 1.77–1.84 (m, 2H), 1.67–1.74 (m, 2H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 150.9, 144.1, 137.3, 129.2, 127.7, 84.2, 46.6, 43.3, 29.5, 27.8, 21.5, 19.0; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{25}NO_5NaS$ $(M+Na)^+$ 378.1346, found 378.1352; IR (KBr) 3035, 2967, 2873, 1723, 1597, 1427, 1395, 1357, 1289, 1249, 1157, 1106, 1087, 1003, 675, 584, 547 cm^{-1}.

Compound **13**: isolated yield 72% as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J*=8.0 Hz, 2H), 7.31 (d, *J*=8.0 Hz, 2H), 6.81 (dt, *J*=6.8, 16.0 Hz, 1H), 6.10 (d, *J*=16.0 Hz, 1H), 3.84 (t, *J*=7.2 Hz, 2H), 2.44 (s, 3H), 2.30 (dt, *J*=6.8, 6.9 Hz, 2H), 2.25 (s, 3H), 1.78–1.84 (m, 2H), 1.52–1.59 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 150.9, 147.5, 144.1, 137.5, 131.6, 129.2, 127.7, 84.2, 46.7, 31.9, 29.6, 27.8, 26.9, 25.1, 21.5; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{29}NO_5NaS$ $(M+Na)^+$ 418.1659, found 418.1663; IR (KBr) 3634, 2979, 2935, 2866, 1725, 1674, 1628, 1598, 1456, 1356, 1288, 1256, 1154, 1088, 999.8, 848, 813, 772, 721, 674, 576, 545 cm^{-1}.

Compound **3j**: isolated yield 86% as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J*=8.4 Hz, 2H), 7.30 (d, *J*=8.4 Hz, 2H), 5.63 (dt, *J*=6.4, 15.4 Hz, 1H), 5.55 (dd, *J*=6.0, 15.4 Hz, 1H), 4.27 (m, 1H), 3.81 (t, *J*=8.0 Hz, 2H), 2.44 (s, 3H), 2.06–2.11 (m, 2H), 1.73–1.81 (m, 2H), 1.68 (d, *J*=3.6 Hz, 1H), 1.42–1.49 (m, 2H), 1.32 (s, 9H), 1.26 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 144.0, 137.5, 134.8, 130.1, 129.2, 127.7, 84.1, 68.8, 46.9, 31.5, 29.4, 27.8, 25.9, 23.3, 21.5; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{31}NNaO_5S$ $(M+Na)^+$ 420.1815, found 420.1822; IR (KBr) 3548, 3421, 2971, 2931, 2865, 1726, 1598, 1455, 1356, 1287, 1259, 1157, 1088, 1043, 1018, 812, 721, 674, 579, 546 cm^{-1}.

4.3. General procedure for the direct amination of allylic alcohols

A stirred solution of **3a** (61 mg, 0.175 mmol) and $Mg(ClO_4)_2$ (4 mg, 0.0175 mmol) in CH_3CN (1.75 mL) was heated to reflux for

8 h. The reaction was allowed to cool and evaporated. The residue was purified by FCC to afford **4a** (56.8 mg, 98%).

*4.3.1. tert-Butyl 7,8-dihydro-5-(2-methylprop-1-enyl)-[1,3]dioxolo [4,5-g]isoquinoline-6(5H)-carboxylate (**4a**).* Isolated yield 98% as white solid, mp 54–56 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (s, 1H), 6.47 (s, 1H), 5.88 (m, 2H), 5.66 (br s, 1H), 5.31 (dt, *J*=1.6, 9.6 Hz, 1H), 4.16 (br s, 1H), 3.12 (t, *J*=12.0, 1H), 2.82 (m, *J*=4.4, 12.0, 16.0 Hz, 1H), 2.58 (d, *J*=4.4, 16.0 Hz, 1H), 1.93 (s, 3H), 1.72 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 146.0, 132.7, 130.5, 127.3, 124.8, 108.3, 107.1, 100.7, 79.6, 52.4, 37.7, 28.9, 28.5, 25.7, 18.6; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{26}NO_4$ $(M+H)^+$ 332.1856, found 332.1860; IR (KBr) 2974, 2925, 1690, 1481, 1415, 1237, 1162, 1106, 1038, 931, 859, 834, 767 cm^{-1}.

*4.3.2. tert-Butyl 7,8-dihydro-5-((E)-prop-1-enyl)-[1,3]dioxolo[4,5-g] isoquinoline-6(5H)-carboxylate (**4b**).* Isolated yield 94% as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (s, 2H), 5.90 (s, 2H), 5.47–5.59 (m, 2H), 5.38 (br s, 1H), 4.05 (br s, 1H), 3.13 (br s, 1H), 2.80 (m, 1H), 2.60 (m, 1H), 1.68 (d, *J*=5.2 Hz, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 146.2, 145.9, 130.8, 128.9, 127.9, 127.2, 108.4, 107.8, 100.8, 79.7, 55.9, 37.6, 28.8, 28.5, 17.6; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{24}NO_4$ $(M+H)^+$ 318.1700, found 318.1702; IR (KBr) 3504, 3367, 2974, 2929, 1692, 1503, 1484, 1417, 1242, 1164, 1039, 945, 929, 861, 822, 766, 674, 632, 540, 463 cm^{-1}.

*4.3.3. tert-Butyl 7,8-dihydro-5-vinyl-[1,3]dioxolo-[4,5-g]isoquinoline-6(5H)-carboxylate (**4c**).* Isolated yield 26% and 50% as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 1H), 6.58 (s, 1H), 5.91 (s, 2H), 5.90 (m, *J*=5.9, 10.4, 16.8 Hz, 1H), 5.39 (br s, 1H), 5.15 (d, *J*=10.4 Hz, 1H), 5.06 (d, *J*=16.8 Hz, 1H), 4.08 (br s, 1H), 3.16 (br s, 1H), 2.81(m, 1H), 2.61 (m, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 146.4, 146.0, 137.6, 128.1, 115.7, 108.4, 107.7, 100.8, 79.8, 56.9, 38.2, 28.7, 28.5; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{22}NO_4$ $(M+H)^+$ 304.1543, found 304.1538; IR (KBr) 3086, 2976, 2928, 2768, 1693, 1503, 1483, 1415, 1366, 1241, 1223, 1165, 1140, 929 cm^{-1}.

*4.3.4. tert-Butyl 2,3-dihydro-5-(2-methylprop-1-enyl)-2-oxo-1H-benzo[e][1,4]diazepine-4(5H)-carboxylate (**4e**).* Isolated yield 41% as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 0.5H) 8.03 (s, 0.5H), 7.21 (m, 2H), 7.04 (t, *J*=7.6 Hz, 1H), 6.89 (d, *J*=7.6 Hz, 1H), 5.93 (s, 0.5H), 5.62 (s, 0.5H), 5.35 (s, 0.5H), 5.33 (s, 0.5H), 4.73 (s, 0.5H), 4.50 (s, 0.5H), 4.15 (s, 0.5H), 4.11 (s, 0.5H), 1.76 (s, 6H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 154.1, 139.5, 134.6, 132.2, 130.1, 128.3, 123.9, 121.7, 120.5, 80.9, 57.2, 47.3, 28.3, 25.7, 18.3; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{25}N_2O_3$ $(M+H)^+$ 317.1860, found 317.1860; IR (KBr) 3216, 2976, 2920, 1698, 1160, 757 cm^{-1}.

*4.3.5. 5,6,7,8-Tetrahydro-5-((E)-prop-1-enyl)-6-tosyl-[1,3]dioxolo [4,5-g]isoquinoline (**4f**).* Isolated yield 90% as white solid, mp 93–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J*=8.0 Hz, 2H), 7.20 (d, *J*=8.0 Hz, 2H), 6.49 (s, 1H), 6.44 (s, 1H), 5.89 (s, 1H), 5.88 (s, 1H), 5.41–5.49 (m, 2H), 5.35 (d, *J*=5.6 Hz, 1H), 3.83 (dd, *J*=5.7, 13.3 Hz, 1H), 3.25 (m, *J*=4.3, 12.0, 13.3 Hz, 1H), 2.68 (m, *J*=5.7, 12.0, 15.8 Hz, 1H), 2.50 (br d, *J*=15.8 Hz, 1H), 2.37 (s, 3H), 1.60 (d, *J*=5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 146.0, 142.9, 138.0, 130.3, 129.3, 129.0, 127.7, 127.2, 126.6, 108.3, 107.6, 100.8, 57.8, 39.1, 27.9, 21.4, 17.5; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{22}NO_4S$ $(M+H)^+$ 372.1264, found 372.1266; IR (KBr) 3493, 3438, 3357, 2915, 1486, 1332, 1229, 1159, 1091, 1031, 968, 930, 807, 558 cm^{-1}.

*4.3.6. 5,6,7,8-Tetrahydro-6-tosyl-5-vinyl-[1,3]dioxolo[4,5-g]isoquinoline (**4g**).* Isolated yield 73% and 76% as white solid, mp 128–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J*=8.0 Hz, 2H), 7.19 (d, *J*=8.0 Hz, 2H), 6.51 (s, 1H), 6.44 (s, 1H), 5.90 (s, 1H), 5.89 (s, 1H), 5.85 (m, 1H), 5.41 (d, *J*=6.4 Hz, 1H), 5.16 (d, *J*=10.0 Hz, 1H), 5.05 (d, *J*=16.8 Hz, 1H), 3.80 (m, *J*=2.3, 6.0, 13.6 Hz, 1H), 3.29 (m, *J*=4.2, 11.4, 13.6 Hz, 1H), 2.49 (m, *J*=6.0, 11.4, 16.2 Hz, 1H), 2.45 (m, *J*=2.3, 4.2, 16.2 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 146.0, 143.1, 137.8, 137.3, 129.4, 127.1, 126.9, 126.6, 117.6, 108.4, 107.6, 100.9, 58.1, 39.2, 27.6, 21.4; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{20}NO_4S$ $(M+H)^+$ 358.1108, found 358.1111; IR (KBr) 3400, 3077, 3032, 2962, 2926, 2896, 2845, 1730, 1632, 1597, 1484, 1333, 1229, 837, 806, 669, 543 cm^{-1}.

*4.3.7. (2S,5R)-Methyl 5-((E)-prop-1-enyl)-1-tosylpyrrolidine-2-carboxylate (**4i**-cis).* As yellow solid, mp 89–90 °C. $[\alpha]_D^{17}$ −11 (*c* 0.21, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J*=8.0 Hz, 2H), 7.28 (d, *J*=8.0 Hz, 2H), 5.68 (dq, *J*=6.4, 15.0 Hz, 1H), 5.32 (ddq, *J*=1.4, 7.0, 15.0 Hz, 1H), 4.44 (t, *J*=6.8 Hz, 1H), 4.19 (dd, *J*=7.0, 13.6 Hz, 1H), 3.74 (s, 3H), 2.42 (s, 3H), 1.97–2.02 (m, 2H), 1.82 (m, 1H), 1.67 (m, 1H), 1.58 (dd, *J*=1.4, 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 143.3, 136.4, 131.0, 129.3, 127.9, 127.8, 63.0, 61.4, 52.3, 32.4, 29.3, 21.5, 17.5; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{22}NO_4S$ $(M+H)^+$ 324.1264, found 324.1265; IR (KBr) 2961, 2923, 1752, 1345, 1215, 1163, 1088, 667, 594, 551 cm^{-1}.

*4.3.8. (2S,5S)-Methyl 5-((E)-prop-1-enyl)-1-tosylpyrrolidine-2-carboxylate (**4i**-trans).* As colorless oil. $[\alpha]_D^{17}$ −26 (*c* 0.19, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J*=8.4 Hz, 2H), 7.25 (d, *J*=8.4 Hz, 2H), 5.57 (dq, *J*=6.4, 15.0 Hz, 1H), 5.05 (ddq, *J*=1.2, 8.8, 15.0 Hz, 1H), 4.47 (t, *J*=8.0 Hz, 1H), 4.38 (dd, *J*=1.2, 8.8 Hz, 1H), 3.74 (s, 3H), 2.41 (s, 3H), 2.35 (m, 1H), 2.20 (m, 1H), 1.95 (m, 1H), 1.66 (m, 1H), 1.54 (d, *J*=1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 143.0, 138.2, 130.1, 129.0, 128.1, 127.8, 62.3, 60.9, 52.3, 31.6, 29.1, 21.5, 17.4; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{22}NO_4S$ $(M+H)^+$ 324.1264, found 324.1266; IR (KBr) 2953, 2920, 1747, 1449, 1343, 1204, 1155, 1097, 671, 594 cm^{-1}.

*4.3.9. 2-((E)-Prop-1-enyl)-1-tosylpiperidine (**4j**).* Isolated yield 95% as yellow solid, mp 148–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J*=8.0 Hz, 2H), 7.25 (d, *J*=8.0 Hz, 2H), 5.55 (m, 1H), 5.33 (dd, *J*=6.4, 15.3 Hz, 1H), 4.54 (br s, 1H), 3.67 (d, *J*=13.2 Hz, 1H), 2.93 (t, *J*=12.2 Hz, 1H), 2.41 (s, 3H), 1.57 (d, *J*=6.4 Hz, 3H), 1.39–1.52 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 137.8, 129.2, 128.2, 127.4, 127.4, 54.8, 41.6, 30.4, 25.1, 21.4, 19.0, 17.7; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{22}NO_2S$ $(M+H)^+$ 280.1366, found 280.1367; IR (KBr) 3543, 2939, 2859, 2732, 1920, 1730, 1668, 1599, 1495, 1451, 1337, 1305, 1290, 1187, 1159, 1093, 1057, 1017, 935, 815, 719, 661, 603, 547 cm^{-1}.

*4.3.10. 5,6,7,8-Tetrahydro-5-(2-methylprop-1-enyl)-6-tosyl-[1,3]dioxolo[4,5-g]isoquinoline (**4m**).* Isolated yield 85% as white solid, mp 141–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J*=8.0 Hz, 2H), 7.20 (d, *J*=8.0 Hz, 2H), 6.47 (s, 1H), 6.41(s, 1H), 5.88 (d, *J*=1.2 Hz, 1H), 5.86 (d, *J*=1.2 Hz, 1H), 5.63 (d, *J*=10.0 Hz, 1H), 5.03 (dt, *J*=1.2, 10.0 Hz, 1H), 3.92 (m, *J*=1.5, 6.0, 13.0 Hz, 1H), 3.19 (m, *J*=3.6, 12.0, 13.0 Hz, 1H), 2.83 (m, *J*=6.0, 12.0, 16.0 Hz, 1H), 2.56 (m, *J*=1.5, 3.6, 16.0 Hz, 1H), 2.38 (s, 3H), 1.91 (d, *J*=1.2 Hz, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 146.2, 142.8, 137.8, 134.0, 129.4, 129.1, 127.1, 126.0, 123.2, 108.3, 106.9, 100.8, 53.8, 39.4, 28.6, 25.6, 21.4, 18.4; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{24}NO_4S$ $(M+H)^+$ 386.1421, found 386.1425; IR (KBr) 3435, 3043, 2978, 2913, 2878, 2772, 1670, 1599, 1506, 1488, 1337, 1234, 1157, 1093, 1038, 755, 678, 569, 552 cm^{-1}.

4.4. Total synthesis of demethoxyfumitremorgin C

*4.4.1. Compound **16**.* It was prepared from **15** (220 mg, 0.342 mmol) and 2-methylbut-3-en-2-ol (0.720 mL, 6.84 mmol) according to the standard conditions. The crude product was purified by FCC (PE/EtOAc=3:1) to provide **16** (186 mg, 90%) as colorless oil. $[\alpha]_D^{33}$ −107 (*c* 1.04, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J*=7.6 Hz, 1H), 7.47 (d, *J*=7.6 Hz, 1H), 7.25 (t, *J*=7.6 Hz, 1H), 7.19 (t, *J*=7.6, Hz, 1H), 6.72 (d, *J*=16.0 Hz, 1H), 6.02 (d, *J*=16.0 Hz, 1H), 5.13 (dd, *J*=4.0, 10.4 Hz, 1H), 3.75 (s, 3H), 3.62 (dd, *J*=4.0, 14.8 Hz,

1H), 3.52 (dd, *J*=10.4, 14.8 Hz, 1H), 2.19 (br s, 1H), 1.64 (s, 9H), 1.46 (s, 3H), 1.44 (s, 3H), 1.29 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 152.1, 150.3, 141.6, 135.7, 135.1, 130.3, 124.2, 122.6, 118.7, 118.4, 116.0, 115.3, 83.7, 82.8, 70.7, 59.0, 52.3, 29.5, 29.3, 28.3, 27.7, 25.1; HRMS (ESI) *m*/*z* calcd for $C_{32}H_{50}N_3O_9$ $(M+NH_4)^+$ 620.3542, found 620.3557; IR (KBr) 3480, 2076, 1638, 473 cm^{-1}.

To a solution of compound **14** (3.07 g, 5.94 mmol) in dry CH_2Cl_2 (60 mL) was added mercury (II) trifluoroacetate (3.29 g, 7.71 mmol). The solution was stirred at rt for 30 min, washed with a saturated aqueous solution of potassium iodide, dried over Na_2SO_4, filtered and then treated with iodine (2.26 g, 8.91 mmol). The resulting purple solution was stirred for 3 h and filtered. The filtrate was next successively washed with a 10% wt aqueous sodium thiosulfate solution and brine, dried over Na_2SO_4, filtered and concentrated. The residue was then purified by flash chromatography over silica gel to afford compound **15** (1.25 g, 33%) and NHBoc product (1.86 g, 58%). Then to the solution of NHBoc compound (1.86 g, 3.4 mmol) and DMAP (84 mg, 0.68 mmol) in dry CH_3CN (25 mL) was added $(Boc)_2O$ (0.89 g, 4.1 mmol) at rt. The mixture was stirred overnight. The solvent was evaporated, and the residue was purified by silica gel column chromatography to afford compound **15** quantitatively as yellow oil. Compound **15**: $[\alpha]_D^{32}$ −85.3 (*c* 0.4, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J*=1.0, 7.2 Hz, 1H), 7.47 (dd, *J*=1.0, 7.2 Hz, 1H), 7.20 (dt, *J*=1.0, 7.2 Hz, 1H), 7.16 (dt, *J*=1.0, 7.2 Hz, 1H), 5.23 (dd, *J*=5.2, 9.3 Hz, 1H), 3.79 (s, 3H), 3.57 (dd, *J*=9.3, 14.8 Hz, 1H), 3.52 (dd, *J*=5.2, 14.8 Hz, 1H), 1.70 (s, 9H), 1.28 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 151.6, 149.2, 138.0, 130.1, 125.8, 124.3, 122.7, 118.2, 115.4, 85.0, 82.8, 79.9, 58.0, 52.3, 28.4, 28.2, 27.6; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{37}NaN_2O_8I$ $(M+Na)^+$ 667.1487, found 667.1484; IR (KBr) 3433, 2980, 2933, 1797, 1741, 1700, 1600, 1477, 1448, 1369, 1315, 1254, 1143, 1096, 1059, 1013, 759 cm^{-1}.

*4.4.2. Compound **17a** and **17b**.* They were prepared from **16** (134 mg, 0.220 mmol) according to general procedure. The residue was purified by FCC to provide **17a** (53 mg, 49%) and **17b** (53 mg, 49%). Compound **17a**: as colorless oil. $[\alpha]_D^{26}$ +71.9 (*c* 0.2, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J*=7.2 Hz, 1H), 7.46 (d, *J*=7.2 Hz, 1H), 7.21–7.29 (m, 2H), 6.50 (br s, 1H), 5.48 (s, 1H), 4.99 (d, *J*=6.8 Hz, 1H), 3.61 (s, 3H), 3.36 (br d, *J*=13.6 Hz, 1H), 2.97 (dd, *J*=7.6, 16.0 Hz, 1H), 1.76 (s, 3H), 1.68 (s, 3H), 1.63 (s, 9H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 154.8, 149.7, 136.9, 136.1, 128.6, 124.2, 123.1, 122.6, 118.1, 115.4, 112.8, 83.5, 81.1, 51.9, 49.4, 28.4, 28.0, 26.3, 20.6, 18.8; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{37}N_2O_6$ $(M+H)^+$ 485.2646, found 485.2662; IR (KBr) 3454, 2978, 2932, 1739, 1694, 1458, 1142, 869, 749 cm^{-1}. Compound **17b**: as colorless oil. $[\alpha]_D^{26}$ −91.8 (*c* 0.2, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J*=7.2 Hz, 1H), 7.45 (d, *J*=7.2 Hz, 1H), 7.23–7.31 (m, 2H), 6.41 (s, 0.5H), 6.31 (s, 0.5H), 5.21 (s, 1H), 4.14 (d, *J*=8.8 Hz, 1H), 3.78 (s, 3H), 3.31 (s, 0.5H), 3.19 (s, 0.5H), 2.95 (d, *J*=16.4 Hz, 1H), 1.84 (s, 3H), 1.76 (s, 3H), 1.63 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 154.8, 149.7, 138.7, 136.4, 128.7, 124.3, 123.0, 122.8, 117.9, 115.7, 114.6, 83.9, 81.3, 53.2, 51.9, 29.3, 25.9, 22.8, 22.0, 18.6; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{37}N_2O_6$ $(M+H)^+$ 485.2646, found 485.2662; IR (KBr) 3435, 2979, 2933, 1736, 1700, 1457, 1367, 1160, 1137, 750 cm^{-1}.

*4.4.3. Compound **18**.* To a vigorously stirred solution of **17a** (164 mg, 0.337 mmol) and 2,6-lutidine (0.20 mL, 1.69 mmol) in CH_2Cl_2 (3.00 mL) at 0 °C was added TMSOTf (0.250 mL, 1.35 mmol). After 1 h, the reaction mixture was quenched with saturated $NaHCO_3$ and then extracted with CH_2Cl_2, The combined organic extracts were washed with saturated brine, dried (Na_2SO_4), filtered. The residue was purified by FCC (PE/EtOAc=10:1 then 5:1) to provide **18** (108 mg, 83%) as yellow solid, mp 87–88 °C. $[\alpha]_D^{30}$ −87.3 (*c* 0.2, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J*=7.6 Hz, 1H), 7.42 (d, *J*=7.6 Hz, 1H), 7.27 (t, *J*=7.6 Hz, 1H), 7.22 (t, *J*=7.6 Hz, 1H), 5.19 (br s, 2H), 3.83 (dd, *J*=3.5, 10.8 Hz, 1H), 3.81 (s, 3H), 3.06 (dd, *J*=3.5, 15.6 Hz, 1H), 2.77 (dd, *J*=10.8, 15.6 Hz, 1H), 1.86 (br s, 1H), 1.80 (s, 3H), 1.70 (s, 3H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 149.9, 137.3, 136.6, 136.4, 128.7, 125.4, 124.0, 122.4, 117.9, 115.4, 114.7, 83.4, 55.2, 52.0, 51.8, 28.0, 26.5, 25.7, 18.6; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{29}N_2O_4$ $(M+H)^+$ 385.2122, found 385.2129; IR (KBr) 3433, 2916, 1736, 1365, 1321, 1261, 1139, 1030, 736 cm^{-1}.

*4.4.4. Compound **20**.* To a solution of compound **18** (154 mg, 0.40 mmol) in CH_2Cl_2 (3 mL) was added Et_3N (0.12 mL, 0.86 mmol) at 0 °C under nitrogen. A solution of acid chloride **19** (186 mg, 0.60 mmol) in 2 mL CH_2Cl_2 was added slowly dropwise. The mixture was allowed to react at 0 °C overnight and extracted with CH_2Cl_2. The combined organic extracts were washed with saturated brine, dried (Na_2SO_4), filtered, and evaporated. The residue was purified by FCC (PE/EtOAc=4:1). The acid amide was dissolved in methanol (5 mL), and zinc dust (85 mg) was added. The mixture was stirred at reflux under nitrogen for 36 h. The reaction mixture was filtered, washed with methanol. The residue was purified by FCC (PE/EtOAc=1:1) to provide **20** (144 mg, 81%) as white solid. $[\alpha]_D^{26}$ −34.7 (*c* 0.167, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J*=1.6, 7.2 Hz, 1H), 7.53 (dd, *J*=1.8, 7.2 Hz, 1H), 7.29 (dt, *J*=1.6, 7.2 Hz, 1H), 7.26 (dt, *J*=1.8, 7.2 Hz, 1H), 6.98 (d, *J*=9.6 Hz, 1H), 4.79 (br d, *J*=9.6 Hz, 1H), 4.09–4.17 (m, 2H), 3.61–3.65 (m, 2H), 3.53 (dd, *J*=5.0, 16.2 Hz, 1H), 3.07 (dd, *J*=11.8, 16.2 Hz, 1H), 2.42 (m, 1H), 2.31 (m, 1H), 2.08 (m, 1H), 1.96 (m, 1H), 2.00 (br s, 3H), 1.69 (s, 9H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 165.7, 149.7, 136.3, 136.0, 136.0, 127.8, 124.3, 122.8, 118.2, 115.8, 114.2, 84.3, 59.5, 56.2, 50.7, 45.4, 28.4, 28.2, 26.1, 23.2, 21.5, 18.8; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{32}N_3O_4$ $(M+H)^+$ 450.2387, found 450.2385; IR (KBr) 3420, 2966, 2924, 2854, 1736, 1668, 1455, 1369, 1159, 1144, 1119, 1028 cm^{-1}.

*4.4.5. Demethoxyfumitremorgin C (**21**).* A solution of **20** (23.0 mg, 0.05 mmol) and TFA (0.4 mL) in CH_2Cl_2 (1.6 mL) was stirred at 0 °C for 1.5 h. The reaction mixture was evaporated to dryness and the residue was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated to dryness. The residue was purified by FCC (PE/EtOAc=1:1) to provide **21** (16.1 mg, 90%) as pale yellow solid. $[\alpha]_D^{28}$ +4.0 (*c* 0.2, $CHCl_3$), lit.: natural[16] $[\alpha]_D^{30}$ +8.0 (*c* 0.2, $CHCl_3$), synthetic[20a] $[\alpha]_D^{24}$ +16.4 (*c* 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.58 (d, *J*=7.6 Hz, 1H), 7.35 (d, *J*=7.6 Hz, 1H), 7.20 (dt, *J*=1.1, 7.6 Hz, 1H), 7.15 (dt, *J*=1.1, 7.6 Hz, 1H), 6.03 (br d, *J*=9.6 Hz, 1H), 4.92 (br d, *J*=9.6 Hz, 1H), 4.20 (br dd, *J*=5.0, 11.8 Hz, 1H), 4.12 (br dd, *J*=7.5, 8.0 Hz, 1H), 3.63–3.67 (m, 2H), 3.57 (dd, *J*=5.0, 15.7 Hz, 1H), 3.13 (br d, *J*=11.7, 15.7 Hz, 1H), 2.42 (m, 1H), 2.24 (m, 1H), 2.08 (m, 1H), 2.01 (s, 3H), 1.95 (m, 1H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 165.7, 136.2, 134.3, 133.5, 126.3, 124.0, 122.2, 120.1, 118.4, 111.2, 106.5, 59.3, 56.9, 51.0, 45.4, 28.6, 25.7, 23.1, 21.9, 18.1; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{24}N_3O_2$ $(M+H)^+$ 350.1863, found 350.1863; IR (KBr) 3424, 2963, 2924, 2863, 1723, 1650, 1452, 1375, 1161 cm^{-1}.

*4.4.6. epi-Demethoxyfumitremorgin C **22**.* Intermediate **1**: isolated yield 83% as yellow solid, mp 65–68 °C. $[\alpha]_D^{31}$ −79 (*c* 0.2, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (br d, *J*=7.6 Hz, 1H), 7.42 (br d, *J*=7.6 Hz, 1H), 7.27 (t, *J*=7.6 Hz, 1H), 7.22 (t, *J*=7.6 Hz, 1H), 5.39 (d, *J*=7.6 Hz, 1H), 5.35 (d, *J*=7.6 Hz, 1H), 3.95 (dd, *J*=4.8, 10.0 Hz, 1H), 3.80 (s, 3H), 3.07 (dd, *J*=4.8, 15.6 Hz, 1H), 2.83 (dd, *J*=10.0, 15.6 Hz, 1H), 2.31 (br s, 1H), 1.81 (s, 3H), 1.71 (s, 3H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 149.9, 137.2, 136.2, 136.0, 129.1, 125.5, 124.0, 122.5, 117.8, 115.4, 113.7, 83.5, 52.0, 51.3, 50.4, 28.1, 25.9, 25.4, 18.6; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{29}N_2O_4$ $(M+H)^+$ 385.2122, found 385.2128; IR (KBr) 3435, 2975, 2930, 1732, 1455, 1363, 1292, 1263, 1214, 1142, 1116, 1018, 746 cm^{-1}.

Intermediate **2**: isolated yield 73% as white solid, mp 186–188 °C. $[\alpha]_D^{30}$ −220 (*c* 0.167, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$)

δ 8.06 (d, J=7.4 Hz, 1H), 7.42 (d, J=7.4 Hz, 1H), 7.29 (t, J=7.4 Hz, 1H), 7.24 (t, J=7.4 Hz, 1H), 7.10 (d, J=8.0 Hz, 1H), 5.23 (d, J=8.0 Hz, 1H), 4.50 (dd, J=5.0, 11.0 Hz, 1H), 4.15 (m, 1H), 3.95 (m, 1H), 3.52 (dd, J=5.0, 16.0 Hz, 1H), 3.45 (m, 1H), 2.84 (dd, J=11.0, 16.0 Hz, 1H), 2.51 (m, 1H), 1.81–2.09 (m, 3H), 1.84 (s, 3H), 1.70 (s, 3H), 1.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 163.9, 149.5, 139.4, 136.0, 133.9, 128.3, 124.4, 122.8, 121.9, 118.1, 115.5, 112.8, 84.0, 59.3, 52.8, 48.3, 45.0, 30.1, 28.1, 26.0, 21.6, 19.4; HRMS (ESI) m/z calcd for $C_{26}H_{32}N_3O_4$ $(M+H)^+$ 450.2387, found 450.2382; IR (KBr) 3435, 2971, 2932, 1741, 1665, 1456, 1421, 1366, 1307, 1256, 1224, 1165, 1145, 1122 cm^{-1}.

epi-Demethoxyfumitremorgin C **22**: isolated yield 96% as yellow solid, mp 144–146 °C. $[\alpha]_D^{28}$ −312 (c 0.1, CH_3OH), lit.: synthetic[17a] $[\alpha]_D^{22}$ −436 (c 0.1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.51 (d, J=7.6, 1H), 7.31 (d, J=7.6 Hz, 1H), 7.18 (t, J=7.6 Hz, 1H), 7.12 (t, J=7.6 Hz, 1H), 6.43 (d, J=9.6 Hz, 1H), 5.24 (d, J=9.6 Hz, 1H), 4.45 (dd, J=3.3, 11.3 Hz, 1H), 4.14 (m, 1H), 3.93 (m, 1H), 3.66 (dd, J=3.3, 15.7 Hz, 1H), 3.49 (m, 1H), 2.85 (dd, J=11.3, 15.7 Hz, 1H), 2.50 (m, 1H), 2.05 (m, 1H), 2.05 (3H), 1.84–1.96 (m, 2H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 164.3, 138.0, 136.4, 131.7, 126.6, 122.3, 121.1, 119.9, 118.4, 110.9, 106.7, 59.3, 54.7, 48.7, 45.1, 30.1, 27.9, 25.9, 21.5, 18.7; HRMS (ESI) m/z calcd for $C_{21}H_{24}N_3O_2$ $(M+H)^+$ 350.1863, found 350.1863; IR (KBr) 3526, 3452, 3272, 2974, 2921, 1728, 1650, 1622, 1440, 1323, 1300, 749 cm^{-1}.

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Supplementary data

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