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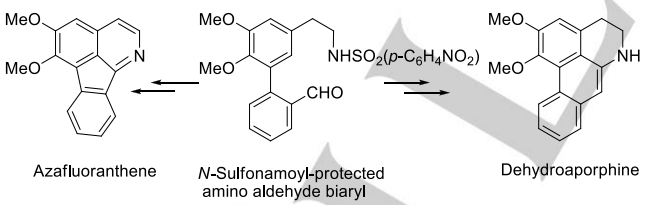
Efficient one-pot synthesis of tetrahydronaphtho[2,1-*f*]isoquinoline under domino Pictet–Spengler/Friedel–Crafts type reactions

Nisachon Khunnawutmanotham,[a] Poolsak Sahakitpichan,[b] Nitirat Chimnoi,[b] and Supanna Techasakul*[a]

Abstract: This study described a facile and efficient one-pot method for the synthesis of tetrahydronaphtho[2,1-*f*]isoquinoline alkaloid. *N*-protected amino aldehyde biaryl underwent domino cyclization under Pictet–Spengler/Friedel–Crafts type reactions to produce a tetrahydronaphtho[2,1-*f*]isoquinoline skeleton. Litebamine, a naturally occurring compound, was prepared using the proposed method to exemplify its utility.

Introduction

Our previous report presented the utilization of *N*-sulfonamoyl-protected amino aldehyde biaryl to construct two scaffolds of the natural product of alkaloids, namely, azafluoranthene and dehydroaporphine (Scheme 1).[1] In the course of our continuing study, we further investigated the use of this *N*-protected amino aldehyde biaryl as a precursor for the synthesis of tetrahydronaphtho[2,1-*f*]isoquinoline alkaloid. Only two natural products that contain tetrahydronaphtho[2,1-*f*]isoquinoline skeleton, namely, litebamine and annoretine, have been reported (Figure 1). Litebamine was isolated from the wood of *Litsea cubeba*[2] and was reported to be an antiplatelet aggregation agent.[3] Recently, the anti-acetylcholinesterase activity of litebamine and its *N*-homologues has been described.[4] Annoretine was isolated from the leaves of *Annona montana*, and its cytotoxicity against KB, P-388, A-548, and HT-29 cells was reported.[5]



Scheme 1. Synthesis of azafluoranthene and dehydroaporphine alkaloids from *N*-sulfonamoyl-protected amino aldehyde biaryl.

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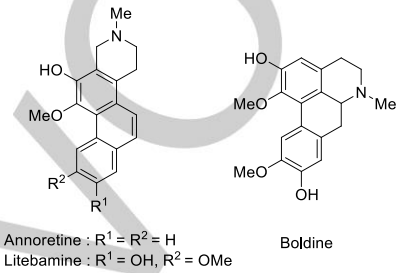
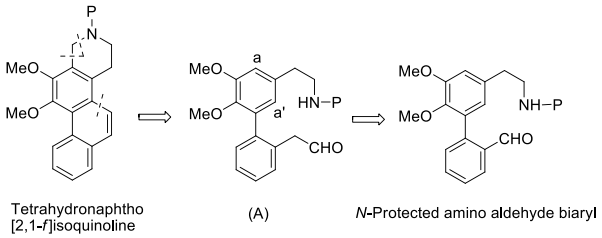


Figure 1. Structures of annoretine, litebamine and boldine.

Many published reports on the syntheses of tetrahydronaphtho[2,1-*f*]isoquinoline scaffold have been released from the Estévez's group. The key steps involved the use of Bischler–Napieralski reaction to form an isoquinoline unit and photocyclization to install the tetrahydronaphthoisoquinoline skeleton[6], these procedures were later adopted to complete the total syntheses of annoretine and litebamine.[7,8] Alternatively, 1-methyl tetrahydronaphtho[2,1-*f*]isoquinolines has been successfully prepared by the same group in reverse order of either photochemical[9] or free radical cyclization[10] to construct the corresponding phenanthrene ring system followed by the Bischler–Napieralski reaction. A few biomimetic syntheses of litebamine from its plausible biogenetic precursor, boldine, have also been reported.[4,11,12]

We aimed to develop a facile strategy for reaching the tetrahydronaphtho[2,1-*f*]isoquinoline scaffold from an *N*-protected amino aldehyde biaryl. A retrosynthetic analysis was proposed in Scheme 2. A phenanthrene ring system was constructed by an acid-mediated cyclization of the aldehyde whereas the isoquinoline unit could be constructed by the Pictet–Spengler reaction. In addition, two key steps could occur successively in one step under appropriate reaction condition. As such, this strategy could be considered as a novel domino Pictet–Spengler/Friedel–Crafts type reaction sequence. This anticipated facile synthesis will give us access to structurally diverse derivatives for further biological studies.

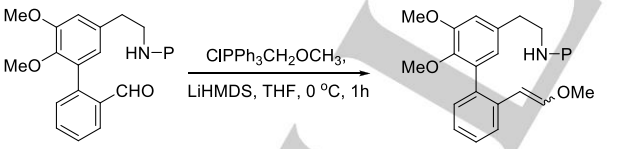


Scheme 2. Retrosynthetic analysis of tetrahydronaphtho[2,1-*f*]isoquinoline.

When considering the precursor for the cyclization (A), the Pictet–Spengler reaction could provide two different regioisomers depending on the position on the aromatic ring that undergoes cyclization (*a* or *a′*, as shown in Scheme 2). By contrast, the formation of phenanthrene unit could take place only at the position *a′* of the aromatic ring. Thus, the phenanthrene formation at the position *a′* must precede the Pictet–Spengler cyclization at the position *a* to achieve the synthesis of the desired tetrahydronaphtho[2,1-*f*]isoquinoline framework. If the Pictet–Spengler reaction occurred first, cyclization on position *a′* is possible, and this phenomenon would not result in the formation of the desired product.

Results and Discussion

On the basis of our hypothesis, we prepared the corresponding one–carbon homologated analog of the *N*-protected amino aldehyde biaryl as the precursor. Wittig reaction of the *N*-sulfonamoyl-protected amino aldehyde biaryl with (methoxymethyl)triphenylphosphonium chloride provided the corresponding inseparable mixture of (*E*)- and (*Z*)-enol ether **1a** (Scheme 3).[1] Then, **1a** was treated successively with a solution of trifluoroacetic acid (TFA) in dichloromethane (1:9 v/v) and formaldehyde. With stirring at room temperature for 1 h, **1a** smoothly underwent the anticipated double cyclizations, and high yield of tetrahydronaphtho[2,1-*f*]isoquinoline **2a** was obtained (Table 1, entry 1). The result suggested that the rate of the phenanthrene formation for enol ther **1a** (a masked form of two–carbon aldehyde) is faster than that of the Pictet–Spengler cyclization, thereby leading to tetrahydronaphtho[2,1-*f*]isoquinoline. To achieve the purpose of this method, enol ethers with different amino protecting groups (**1b** and **1c**) were prepared and subjected to acids using different aldehydes. Table 1 summarizes the results.

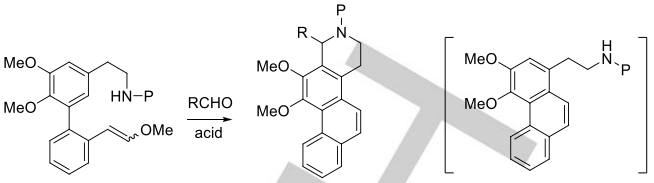


N-Protected amino aldehyde biaryl

1a: P = $SO_2C_6H_4NO_2$ (65%)
1b; P = COOMe (90%)
1c; P = COO*t*Bu (73%)

Scheme 3. Preparation of the substrates for one-pot cyclization study.

For the *N*-nitrosulfonamoyl-protected amino enol ether biaryl substrate **1a**, a high yield of product **2a** was obtained within 1 h after treatment with a 1:9 solution of TFA in dichloromethane and formaldehyde (entry 1). The completion of treatment of **1a** with acetaldehyde in a 1:9 TFA-CH_2Cl_2 solution required a longer reaction time (24 h) and a high yield of product **2b** was obtained (entry 2). Shorter reaction time (2h) of **2a** with acetaldehyde to furnish **2b**, which gave a comparable yield, was



1a-c

2a; R = H, P = $SO_2C_6H_4NO_2$
2b; R = CH_3, P = $SO_2C_6H_4NO_2$
2c; R = Ph, P = $SO_2C_6H_4NO_2$
2d; R = H, P = COOMe
2e; R = CH_3, P = COOMe
2f; R = H, P = COO*t*Bu
2g; R = H, P = H

3; P = $SO_2C_6H_4NO_2$

Table 1. Percentage yields of products obtained under various conditions.

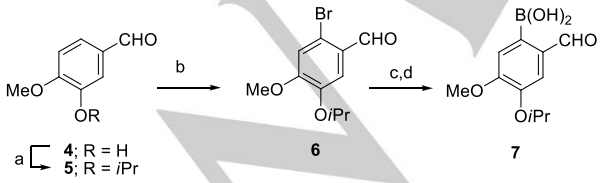
Entry	Compound	RCHO	Condition	Time (h)	Product (isolated yield)
1	**1a**	HCHO	A[a]	1	**2a** (88%)
2	**1a**	CH_3CHO	A	24	**2b** (89%)
3	**1a**	CH_3CHO	B[b]	2	**2b** (89%)
4	**1a**	C_6H_5CHO	A	24	**2c** (10%) + **3** (82%)
5	**1a**	C_6H_5CHO	B	48	**2c** (50%) + **3** (33%)
6	**1b**	HCHO	A	1	**2d** (76%)
7	**1b**	CH_3CHO	A	24	**2e** (65%)
8	**1b**	CH_3CHO	B	4	**2e** (72%)
9	**1c**	HCHO	A	1	**2f** (30%) + **2g** (8.5%)
10	**1c**	HCHO	B	0.5	Provided a complex mixture of polar compounds

[a] Condition A: TFA/CH_2Cl_2(1:9 v/v), rt. [b] Condition B: $BF_3.OEt_2$, CH_2Cl_2, rt.

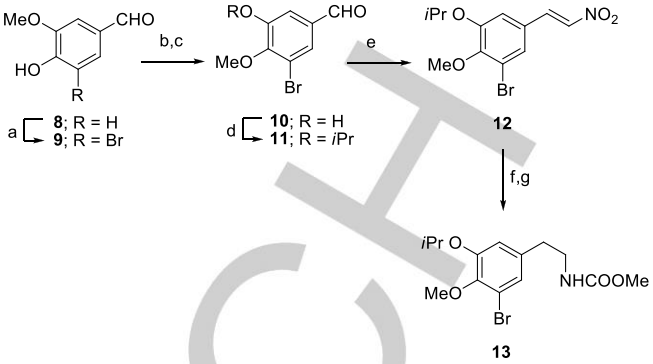
achieved when boron trifluoride diethyl etherate ($BF_3.OEt_2$) was used (entry 3). With benzaldehyde, the conversion of **1a** to the corresponding product **2c** was very slow. After 24 h of using TFA in CH_2Cl_2, product **2c** was isolated in only 10% yield along with phenanthrene **3** in 82% yield (entry 4). When $BF_3.OEt_2$ condition was used, product **2c** yield increased to 50% together with **3** at 33% yield after 48 h (entry 5). The results suggested that phenanthrene was an intermediate during this reaction. Following the phenanthrene formation, Pictet–Spengler cyclization took place, thereby furnishing the desired tetrahydronaphtho[2,1-*f*]isoquinoline. For the methylcarbamoyl-protected amino enol ether biaryl substrate **1b** (entries 6–8), the results were similar to those of the sulfonamide substrate **1a**, except that slightly lower yields were obtained. Treatment of the carbamate **1b** with formaldehyde in a 1:9 TFA-CH_2Cl_2 solution for 1 h yielded product **2d** at 76% yield (entry 6). When acetaldehyde was used instead of formaldehyde, a 24 h-reaction

time was need for complete the conversion of **1b** to the corresponding product **2e**, which was produced as a pair of amide rotamers in a 1:1 ratio (entry 7). $BF_3.OEt_2$ was used as an acid, and the reaction of **1b** with acetaldehyde was completed in 4 h to provide **2e** at a comparable yield (entry 8). Then, substrate **1c** was designed to process the Boc group. Both cyclization and deprotection were expectedly affected in the same step under acidic conditions. However, treatment of the *tert*-butylcarbamoyl-protected amino enol ether biaryl substrate **1c** with formaldehyde in a 1:9 TFA-CH_2Cl_2 solution provided the isolated product **2f** at only 30% yield, together with a small amount of the hydrolyzed product **2g** at 8.5% yield (entry 9). A complex mixture of polar compounds was obtained (entry 10) using $BF_3.OEt_2$ as the acid. The results demonstrated a successful one-pot reaction to construct the tetrahydronaphtho[2,1-*f*]isoquinoline scaffold from the corresponding amino aldehyde biaryl. The method was facile and resulted in a high product yield.

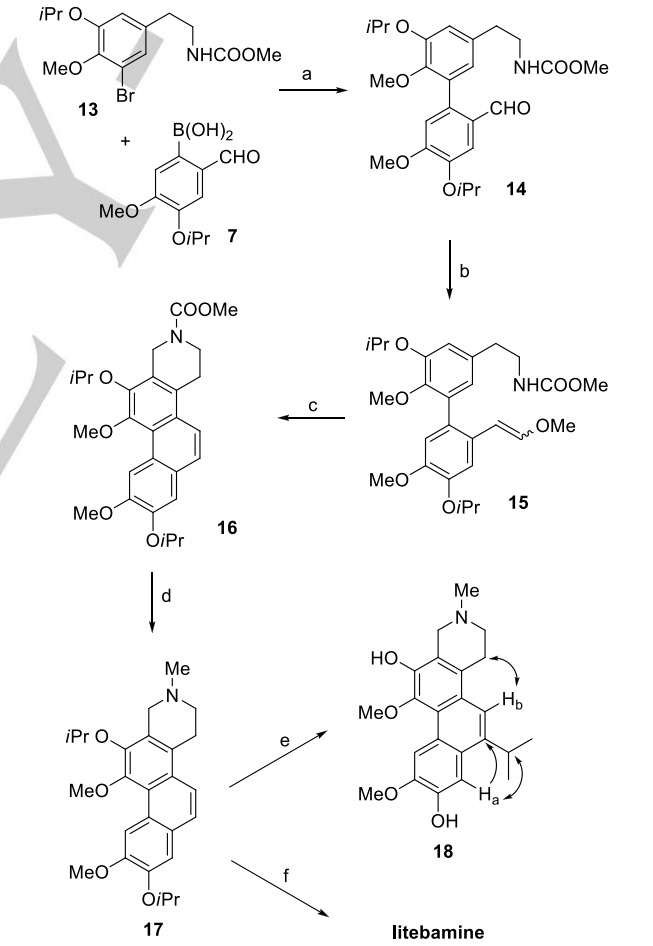
Moreover, the total synthesis of the natural product litebamine was contemplated and pursued to illustrate the utilization of this approach. The corresponding boronic acid **7** and aryl bromide **13** were the requisite precursors for the preparation of the amino aldehyde biaryl. Boronic acid **7** could be prepared in a straightforward manner in four steps from isovanillin (**4**) at 27% overall yield (Scheme 4). Aryl bromide **13** could be prepared from vanillin (**8**) in seven steps at 17% overall yield (Scheme 5). The key steps involved $AlCl_3$-mediated demethylation of bromovanillin (**9**) in pyridine followed by selective methylation with Li_2CO_3 and MeI in *N*,*N*-dimethylformamide.[13] Subsequent isopropylation of the remaining phenolic group furnished the corresponding aldehyde **11**. Bromonitrostyrene **12**, which was obtained from the Henry nitroaldol reaction of **11**, was then reduced by $NaBH_4$ in the presence of $BF_3{\cdot}OEt_2$ in tetrahydrofuran at reflux to afford the corresponding phenethylamine, which was converted to carbamate **13**. Methylcarbamate was chosen as the amino protecting group for functionalization purpose at a later stage. Suzuki cross-coupling reaction of boronic acid **7** with aryl bromide **13** was carried out smoothly to yield the *N*-carbamoyl-protected amino aldehyde biaryl **14** (Scheme 6). *C*-Homologation reaction of **14** by treatment with (methoxymethyl)triphenylphosphonium chloride gave a mixture



Scheme 4. *Reagents and conditions:* (a) 2-bromopropane, K_2CO_3, DMF, rt, 24 h (91%); (b) NBS, DMF, 80 °C, 24 h (64%, 74%BRSM); (c) $HOCH_2CH_2OH$, *p*-TsOH, toluene, reflux, 7 h; (d) (i) *n*BuLi, THF, −78 °C, 1 h (ii) then $B(iPrO)_3$, 0 °C to rt, 2.5 h (iii) then 2M HCl, rt, 2 h (40% from **6**).



Scheme 5. *Reagents and conditions:* (a) Br_2, KOAc, AcOH, rt (90%); (b) $AlCl_3$, pyridine, CH_2Cl_2, reflux, 6 h (92%); (c) Li_2CO_3, DMF, 45 °C, 1 h then MeI, 45 °C, 5 h (55%); (d) 2-bromopropane, K_2CO_3, DMF, rt, 24 h (99%); (e) CH_3NO_2, NH_4OAc, AcOH, 90 °C, 7 h (91%); (f) $NaBH_4$, $BF_3{\cdot}OEt_2$, THF, reflux, 4 h; (g) ClCOOMe, CH_2Cl_2, Na_2CO_3, H_2O, rt, 24 h (41%, 2 steps).



Scheme 6. *Reagents and conditions:* (a) $Pd(PPh_3)_4$, K_2CO_3, toluene:EtOH:H_2O (3:3:2), reflux, 24h (88%); (b) $ClPPh_3CH_2OCH_3$, LiHMDS, THF, 0 °C, 1 h (88%); (c) CF_3COOH:CH_2Cl_2 (1:9 V/V), HCHO, rt, 1 h (76%); (d) $LiAlH_4$, THF, reflux, 4 h (83%); (e) $AlCl_3$, CH_2Cl_2, rt, 3 h (71%); f) BCl_3, CH_2Cl_2, −78 °C for 1 h then 0 °C for 2 h (83%).

of (*E*)- and (*Z*)-enol ether **15**, which smoothly underwent cyclization under acidic conditions in the presence of formaldehyde to yield tetrahydronaphtho[2,1-*f*]isoquinoline **16** in 76% isolated yield. Then, the methyl carbamate group of **16** was reduced by $LiAlH_4$ in refluxing tetrahydrofuran to provide the methylamino group of compound **17**. Attempted removal of both isopropoxy groups using $AlCl_3$ in dichloromethane at room temperature led to the formation of the undesired *C*-isopropylated litebamine **18** at 71% yield. ^1H and ^{13}C NMR supported the existence of one isopropyl group in the molecule, but its methine proton was shifted to high field at 3.5 ppm, thereby indicating the attachment of the isopropyl group to a carbon atom rather than to an oxygen atom. In addition, HMBC correlation between H_a signal (δ_H 7.49) and an aromatic carbon connected to the isopropyl group (δ_C 138.0), NOESY correlations between H_a signal and the methine proton of the isopropyl group (δ_H 3.5), and between H_b signal (δ_H 7.52) and CH_2 protons (δ_H 3.2) confirmed the position of the isopropyl moiety of compound **18**. Thus, we turned to use BCl_3 for the deprotection and found that both isopropoxy groups could be smoothly removed to furnish the desired litebamine in 83% yield.

Conclusions

The one-pot domino Pictet–Spengler/Friedel–Crafts type reaction sequence reported in this work provided a facile and effective method for the construction of a tetrahydronaphtho[2,1-*f*]isoquinoline skeleton. The key feature involved a sequence of successive cyclizations of the *N*-protected amino enol ether biaryls under acid-catalyzed Pictet–Spengler conditions. The developed strategy could be utilized for the synthesis of natural tetrahydronaphtho[2,1-*f*]isoquinoline alkaloid litebamine which was obtained in 46% overall yield from **14** in four steps.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded with the Bruker Avance 300 and Bruker Avance IIIHD400 spectrometers. Chemical shifts were reported relative to tetramethylsilane. Mass spectra were obtained with a Finnigan Polaris ion-trap mass spectrometer, and HRMS data were recorded with a Bruker MicroTOF mass spectrometer. Infrared spectra were determined with a PerkinElmer Spectrum One FTIR spectrometer. Column chromatography was performed on Merck silica gel 60 (70–230 mesh).

Compound 1a: Lithium bis(trimethylsilyl)amide (LiHMDS, 1.0 M in tetrahydrofuran; 3.83 mL, 3.83 mmol) was added dropwise to a 0 °C cooled suspension of (methoxymethyl)triphenylphosphonium chloride (1.09 g, 3.18 mmol) in anhydrous tetrahydrofuran (15 mL). The deep red mixture was stirred at 0 °C under argon for 20 min. Then solution of *N*-nitrosulfonamoyl-protected amino aldehyde biaryl (500 mg, 1.06 mmol) in anhydrous tetrahydrofuran (15 mL) was added dropwise to the solution, and the mixture was stirred at 0 °C for another 1 h. Then, water was added to the reaction mixture, and tetrahydrofuran was removed under reduced pressure. The residue was extracted with dichloromethane. The combined organic layers were washed with water, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography to provide enol ether **1a**,[1] at a 4:5 mixture of *E*/*Z* isomers, as a yellow gum (345 mg, 65%).

Compound 1b: This compound was prepared from methylcarbamoyl-protected amino aldehyde biaryl (646 mg, 1.88 mmol) by the same method as described for **1a**. Compound **1b** has a 1:1.3 mixture of *E*/*Z* epimers, in the form of a colorless gum (630 mg, 90%). ^1H-NMR ($CDCl_3$, 300 MHz), δ: 8.13 (d, J = 7.8 Hz, 1H, *Z*), 7.41 (d, J = 7.5 Hz, 1H, *E*), 7.33–7.23 (m, 2H, *E* and *Z*), 7.19–7.16 (m, 4H, *E* and *Z*), 6.88 (d, J = 12.9 Hz, 1H, *E*), 6.74 (s, 2H, *E* and *Z*), 6.59 (s, 2H, *E* and *Z*), 6.02 (d, J = 7.2 Hz, 1H, *Z*), 5.65 (d, J = 12.9 Hz, 1H, *E*), 5.02 (d, J = 7.2 Hz, 1H, *Z*), 4.78 (br s, 2H, *E* and *Z*), 3.89 (s, 3H, *E*), 3.88 (s, 3H, *Z*), 3.72 (s, 3H, *Z*), 3.66 (s, 3H, *E*), 3.51 (s, 3H, *E*), 3.50 (s, 3H, *E*), 3.49 (s, 6H, *Z*), 3.44 (q, J = 6.6 Hz, 4H, *E* and *Z*), 2.77 (t, J = 6.6 Hz, 4H, *E* and *Z*); ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 156.9 (*E* and *Z*), 152.7 (*E*), 152.6 (*Z*), 148.9 (*E*), 147.8 (*Z*), 145.3 (*E* and *Z*), 136.4 (*Z*), 136.2 (*E*), 135.8 (*Z*), 135.5 (*E*), 134.6 (*E* and *Z*), 134.0 (*E*), 133.9 (*Z*), 130.3 (*E*), 129.8 (*Z*), 128.7 (*Z*), 127.5 (*E*), 127.2 (*Z*), 125.3 (*E*), 125.2 (*Z*), 124.1 (*E*), 123.5 (*Z*), 123.4 (*E*), 112.0 (*E*), 111.8 (*Z*), 104.2 (*E*), 103.5 (*Z*), 60.5 (*E*), 60.4 (*Z*), 56.5 (*E* and *Z*), 55.9 (*E*), 55.8 (*Z*), 52.0 (*E* and *Z*), 42.2 (*E* and *Z*), 35.9 (*E* and *Z*); FT-IR, ν_{max} (cm^{-1}): 3355, 1701, 1638, 1520, 1463, 1251, 1230, 1137, 1006; MS (EI), *m/z* (relative intensity): 339 ([M-MeOH]$^+$, 8), 251 (7), 225 (3), 178 (3), 149 (4), 75 (100); HRMS (ESI-POS), *m/z* calculated for $C_{21}H_{25}NO_5Na$[M + Na]$^+$: 394.1625, measured: 394.1622.

Compound 1c: This compound was prepared from *tert*-butylcarbamoyl-protected amino aldehyde biaryl (1.39 g, 3.61 mmol) by the same method as described for **1a**. Compound **1c** has a 1:1 mixture of *E*/*Z* epimers as a colorless gum (1.09 g, 73%). ^1H-NMR ($CDCl_3$, 300 MHz), δ: 8.13 (d, J = 7.8 Hz, 1H, *Z*), 7.41 (d, J = 7.5 Hz, 1H, *E*), 7.35–7.23 (m, 2H, *E* and *Z*), 7.20–7.15 (m, 4H, *E* and *Z*), 6.89 (d, J = 12.9 Hz, 1H, *E*), 6.75 (d, J = 1.8 Hz, 2H, *E* and *Z*), 6.59 (d, J = 1.8 Hz, 2H, *E* and *Z*), 6.02 (d, J = 7.2 Hz, 1H, *Z*), 5.65 (d, J = 12.9 Hz, 1H, *E*), 5.03 (d, J = 7.2 Hz, 1H, *Z*), 4.62 (br s, 2H, *E* and *Z*), 3.89 (s, 3H, *E*), 3.88 (s, 3H, *Z*), 3.72 (s, 3H, *Z*), 3.51 (s, 3H, *Z*), 3.50 (s, 3H, *E*), 3.49 (s, 3H, *E*), 3.37 (q, J = 6.9 Hz, 4H, *E* and *Z*), 2.75 (t, J = 6.9 Hz, 4H, *E* and *Z*), 1.43 (s, 18H); ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 155.9 (*E* and *Z*), 152.7 (*E*), 152.6 (*Z*), 148.9 (*E*), 147.8 (*Z*), 145.2 (*E* and *Z*), 136.5 (*Z*), 136.3 (*E*), 135.8 (*Z*), 135.4 (*E*), 134.6 (*E*), 134.3 (*Z*), 134.2 (*E*), 133.9 (*Z*), 130.4 (*E*), 129.9 (*Z*), 128.7 (*Z*), 127.5 (*E*), 127.3 (*Z*), 125.3 (*E*), 125.2 (*Z*), 124.1 (*E*), 123.7 (*Z*), 123.5 (*E*), 112.0 (*E*), 111.8 (*Z*), 104.2 (*E*), 103.6 (*Z*), 79.3 (*E* and *Z*), 60.6 (*E*), 60.5 (*Z*), 56.6 (*E* and *Z*), 55.9 (*E*), 55.8 (*Z*), 41.8 (*E* and *Z*), 36.0 (*E* and *Z*), 28.4 (3C, *E* and *Z*); FT-IR, ν_{max} (cm^{-1}): 3374, 1698, 1480, 1250, 1231, 1164, 1138, 735; MS (EI), *m/z* (relative intensity): 381 ([M-MeOH]$^+$, 5), 325 (3), 251 (9), 239 (4), 225 (5), 75 (100); HRMS (ESI-POS), *m/z* calculated for $C_{24}H_{31}NO_5Na$[M + Na]$^+$: 436.2094, measured: 436.2092.

General procedure for one-pot cyclization to tetrahydronaphtho[2,1-f]isoquinoline

***Condition A*:** The compound (0.3 mmol) was dissolved in a solution of trifluoroacetic acid in dichloromethane (1:9 v/v, 5 mL), and aldehyde (1.5 mmol) was added. After stirring at room temperature at the indicated time, the reaction mixture was added to water, washed with saturated aqueous

sodium hydrogen carbonate, and extracted with dichloromethane. The combined organic layers were washed with water, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to yield the product.

***Condition B*:** The compound (0.3 mmol) was dissolved in dichloromethane (5 mL). Borontrifluoride etherate (1.5 mmol) and aldehyde (1.5 mmol) were successively added. After stirring at room temperature for the indicated time, the reaction mixture was added to water, washed with saturated aqueous sodium hydrogen carbonate, and extracted with dichloromethane. The combined organic layers were washed with water, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to yield the product.

Compound 2a: This compound was obtained as a pale yellow solid. ^{1}H-NMR ($CDCl_3$, 300 MHz), δ: 9.60 (dd, J = 8.1, 1.5 Hz, 1H), 8.38 (d, J = 9.0 Hz, 2H), 8.09 (d, J = 9.0 Hz, 2H), 7.87 (dd, J = 7.2, 2.1 Hz, 1H), 7.73 (d, J = 2.4 Hz, 2H), 7.68–7.57 (m, 2H), 4.47 (s, 3H), 4.06 (s, 3H), 3.90 (s, 3H), 3.57 (t, J = 6.0 Hz, 2H), 3.31 (t, J = 6.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 150.2, 149.5, 148.4, 142.7, 132.4, 129.8, 128.8(2C), 128.4, 128.1, 127.7, 127.3, 126.9, 126.6, 125.4, 125.2, 124.4(2C), 124.1, 120.9, 60.8, 59.7, 44.0, 43.5, 26.3; FT-IR, ν_{max} (cm^{-1}): 1529, 1342, 1164, 1091, 1024, 969, 753, 740; MS (EI), *m/z* (relative intensity): 478 (M^+, 69), 291 (36), 265 (22), 249 (23), 221 (34), 149 (29), 104 (63); HRMS (ESI-POS), *m/z* calculated for $C_{25}H_{23}N_2O_6S[M + H]^+$: 479.1271, measured: 479.1266.

Compound 2b: This compound was obtained as a yellow solid. ^{1}H-NMR ($CDCl_3$, 300 MHz), δ: 9.57 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.7 Hz, 2H), 7.98 (d, J = 8.7 Hz, 2H), 7.84 (dd, J = 7.5, 1.8 Hz, 1H), 7.69–7.56 (m, 4H), 5.48 (q, J = 6.6 Hz, 1H), 4.19 (dd, J = 14.0, 6.0 Hz, 1H), 4.11 (s, 3H), 3.89 (s, 3H), 3.72–3.61 (m, 1H), 3.18–2.99 (m, 2H), 1.55 (d, J = 6.6 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 149.6, 148.1, 146.7, 132.3, 131.0, 129.6, 128.3, 128.0(2C), 127.7, 127.2, 126.9, 126.6, 124.3, 124.2, 124.0(2C), 120.7, 61.0, 59.6, 48.7, 38.3, 24.7, 21.3; FT-IR, ν_{max} (cm^{-1}): 1528, 1347, 1159, 1032, 972, 738; MS (EI), *m/z* (relative intensity): 492 (M^+, 40), 477 (100), 447 (10), 291 (43), 276 (27), 249 (12); HRMS (ESI-POS), *m/z* calculated for $C_{26}H_{24}N_2O_6SNa[M + Na]^+$: 515.1247, measured: 515.1254.

Compound 2c: This compound was obtained as a yellow solid. ^{1}H-NMR ($CDCl_3$, 400 MHz), δ: 9.59 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.92–7.86 (m, 3H), 7.71–7.59 (m, 4H), 7.28–7.20 (m, 5H), 6.65 (s, 1H), 4.10 (dd, J = 12.0, 8.0 Hz, 1H), 3.86 (s, 3H), 3.57 (s, 3H), 3.54–3.43 (m, 1H), 3.15–3.00 (m, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz), δ: 149.8, 149.5, 148.5, 146.6, 140.1, 132.4, 129.7, 128.6(2C), 128.4(2C), 128.1, 128.0(3C), 127.8, 127.7, 127.4, 127.0, 126.8, 125.5, 124.8, 123.7(2C), 120.6, 60.4, 59.6, 55.5, 38.7, 24.1; FT-IR, ν_{max} (cm^{-1}): 1528, 1347, 1163, 1106, 1033, 966, 737; MS (EI), *m/z* (relative intensity): 554 (M^+, 100), 477 (75), 366 (18), 291 (35), 276 (20), 264 (40); HRMS (ESI-POS), *m/z* calculated for $C_{31}H_{27}N_2O_6S[M + H]^+$: 555.1584, measured: 555.1571.

Compound 2d: This compound was obtained as a colorless gum. ^{1}H-NMR ($CDCl_3$, 300 MHz), δ: 9.63 (d, J = 8.1 Hz, 1H), 7.87 (dd, J = 7.8, 1.2 Hz, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.72–7.56 (m, 2H), 4.79 (s, 2H), 4.07 (s, 3H), 3.94 (s, 3H), 3.85 (t, J = 5.7 Hz, 2H), 3.21 (t, J = 5.7 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 156.1, 149.5, 148.8, 132.3, 129.9, 128.4, 128.3, 128.0, 127.7, 127.2, 126.9, 126.7, 126.3, 123.7, 121.3, 60.6, 59.7, 52.7, 42.4, 41.1, 25.9; FT-IR, ν_{max} (cm^{-1}): 1699, 1445, 1393, 1237, 1117, 1035, 973, 734; MS (EI), *m/z* (relative intensity): 351 (M^+, 100), 336 (98), 320 (15), 304 (10), 276 (12), 264 (13), 249 (22), 221 (39); HRMS (ESI-POS), *m/z* calculated for $C_{21}H_{21}NO_4Na[M + Na]^+$: 374.1363, measured: 374.1374.

Compound 2e: This compound was obtained as a white solid at a 1:1 mixture of two rotamers (^{1}H-NMR temperature course study of compound **2e** at 25 °C–60 °C in benzene-d_6 was shown in the supporting information). ^{1}H-NMR ($CDCl_3$, 300 MHz), δ: 9.62 (d, J = 8.4 Hz, 1H), 7.87–7.79 (m, 2H), 7.70–7.55 (m, 3H), 5.63 (q, J = 6.3 Hz, 0.5H), 5.50 (q, J = 6.3 Hz, 0.5H), 4.50–4.43 (m, 0.5H), 4.30–4.24 (m, 0.5H), 4.11 (s, 1.5H), 4.09 (s, 1.5H), 3.92 (s, 3H), 3.78 (s, 1.5H), 3.76 (s, 1.5H), 3.52–3.35 (m, 1H), 3.23–3.18 (m, 2H), 1.60–1.53 (m, 3H),; ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 155.7, 155.4, 149.7, 149.5, 148.9, 148.7, 132.8, 132.3, 132.2, 129.8, 128.2, 127.7, 126.8, 126.7, 126.6, 126.3, 125.9, 123.9, 121.3, 60.8, 59.5, 52.7, 52.5, 46.9, 36.8, 36.4, 25.7, 25.5, 20.4, 20.1; FT-IR, ν_{max} (cm^{-1}): 1696, 1443, 1389, 1207, 1117, 1035, 974, 766; MS (EI), *m/z* (relative intensity): 365 (M^+, 25), 350 (100), 334 (20), 320 (3), 292 (5), 248 (4); HRMS (ESI-POS), *m/z* calculated for $C_{22}H_{23}NO_4Na[M + Na]^+$: 388.1519, measured: 388.1517.

Compound 2f: This compound was obtained as a yellow solid. ^{1}H-NMR ($CDCl_3$, 300 MHz), δ: 9.63 (d, J = 8.4 Hz, 1H), 7.86 (dd, J = 7.7, 1.8 Hz, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.70 (d, J = 9.0 Hz, 1H), 7.66–7.57 (m, 2H), 4.75 (s, 2H), 4.06 (s, 3H), 3.95 (s, 3H), 3.80 (t, J = 6.0 Hz, 2H), 3.19 (t, J = 6.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 154.9, 149.4, 148.9, 132.3, 130.0, 128.4, 128.3, 127.9, 127.7, 127.0, 126.8, 126.7, 126.3, 123.6, 121.3, 79.9, 60.6, 59.7, 42.3, 40.9, 28.5(3C), 26.1; FT-IR, ν_{max} (cm^{-1}): 1693, 1421, 1393, 1240, 1163, 1117, 1035, 974, 754; MS (EI), *m/z* (relative intensity): 393 (M^+, 16), 336 (100), 249 (19), 221 (21), 178 (29), 149 (37); HRMS (ESI-POS), *m/z* calculated for $C_{24}H_{27}NO_4Na[M + Na]^+$: 416.1832, measured: 416.1832.

Compound 2g: This compound was obtained as a yellow solid. ^{1}H-NMR ($CDCl_3$, 300 MHz), δ: 9.63 (dd, J = 8.3, 0.9 Hz, 1H), 7.87 (dd, J = 7.8, 1.8 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 7.70 (d, J = 9.0 Hz, 1H), 7.66–7.58 (m, 2H), 4.24 (s, 2H), 4.03 (s, 3H), 3.94 (s, 3H), 3.33 (t, J = 5.7 Hz, 2H), 3.18 (t, J = 5.7 Hz, 2H), 2.65 (bs, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 149.3, 148.9, 132.3, 130.0, 129.0, 128.7, 128.3, 127.7, 126.9, 126.8, 126.6, 126.2, 123.6, 121.2, 60.6, 59.7, 43.9, 43.3, 26.0; FT-IR, ν_{max} (cm^{-1}): 1445, 1386, 1338, 1201, 1102, 1037, 976, 753, 733; MS (EI), *m/z* (relative intensity): 293 (M^+, 90), 276 (26), 264 (86), 249 (100), 221 (73), 206 (23), 178 (25); HRMS (ESI-POS), *m/z* calculated for $C_{19}H_{20}NO_2[M + H]^+$: 294.1489, measured: 294.1481.

Compound 11: 2-Bromopropane (0.9 ml, 9.6 mmol) was added to a mixture of **10** (1.53 g, 6.6 mmol) and potassium carbonate (2.76 g, 20.0 mol) in *N*,*N*-dimethylformamide (30 ml). The mixture was stirred at room temperature under argon for 24 h. Next, the reaction mixture was added to water and extracted with ethyl acetate. The combined organic layers were washed with water, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a quantitative yield of compound **11** as pale yellow oil, which was used in the next step without purification. ^{1}H-NMR ($CDCl_3$, 300MHz), δ: 9.83 (s, 1H), 7.63 (d, J = 1.5 Hz, 1H), 7.38 (d, J = 1.5 Hz, 1H), 4.70–4.62 (m, 1H), 3.95 (s, 3H), 1.40 (d, J = 6.0 Hz, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz), δ: 189.8, 152.7, 152.2, 132.9, 128.2, 118.1, 113.0, 71.7, 60.6, 21.9 (2C); FT-IR, ν_{max} (cm^{-1}): 1695, 1586, 1564, 1481, 1423, 1385, 1274, 1127, 1107, 996; MS (EI), *m/z* (relative

intensity): 272 (M^+, 20), 230 (100), 215 (22), 187 (14), 178 (6); HRMS (ESI-POS), *m/z* calculated for $C_{11}H_{14}O_3Br[M + H]^+$: 273.0121, measured: 273.0120.

Compound 12: A solution of **11** (4.0 g, 16.5 mmol), nitromethane (4.0 ml, 73.5 mmol), and ammonium acetate (3.4 g, 44.1 mmol) in acetic acid (40 ml) was heated at 90 °C for 7 h. After cooling down to room temperature, the reaction mixture was poured to ice-water and stirred for an additional 0.5 h. The precipitates were collected, washed with water, and dried to yield **12** as a yellow solid (4.1 g, 90%). The product was used in the next step without purification. ^{1}H-NMR ($CDCl_3$, 300 MHz), *δ*: 7.86 (d, *J* = 13.5 Hz, 1H), 7.49 (d, *J* = 13.5 Hz, 1H), 7.36 (d, *J* = 1.8 Hz, 1H), 7.00 (d, *J* = 1.8 Hz, 1H), 4.64–4.56 (m, 1H), 3.92 (s, 3H), 1.40 (d, *J* = 6.0 Hz, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz), *δ*: 152.1, 150.9, 137.6, 137.0, 126.7, 126.1, 118.7, 115.1, 72.1, 60.7, 21.9 (2C); FT-IR, ν_{max} (cm^{-1}): 1544, 1484, 1429, 1281, 1136, 1107, 994; MS (EI), *m/z* (relative intensity): 315 (M^+, 85), 273 (72), 226 (43), 211 (50), 194 (100), 178 (48), 149 (66); HRMS (ESI-POS), *m/z* calculated for $C_{12}H_{15}NO_4Br[M + H]^+$: 316.0179, measured: 316.0167.

Compound 13: Boron trifluoride diethyl etherate (5.67 ml) was added dropwise to a suspension of sodium borohydride (1.25 g, 33.0 mmol) in tetrahydrofuran (40 ml), and the reaction was stirred at room temperature under argon atmosphere for 15 min. Then a solution of **12** (2.2 g, 7.0 mmol) in tetrahydrofuran (50 ml) was added dropwise, and the reaction was refluxed for 4 h. Then, the reaction mixture was cooled down in ice bath, and water was added dropwise until *gas* evolution had *ceased*. The reaction was then acidified with 10% aqueous hydrochloric acid, the ice bath was removed, and the solution was heated at 80–85 °C for 2 h. After cooling down to room temperature, the reaction mixture was washed twice with diethyl ether. The aqueous layer was basified with 10% aqueous sodium hydroxide and extracted with dichloromethane. The organic layer was combined and washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 2-(3-bromo-4-methoxy-5-isopropoxyphenyl)ethanamine as a colorless oil. The compound was redissolved in dichloromethane (40 ml), and the solution was then added with methyl chloroformate (1.1 ml, 14.3 mmol) followed by a solution of sodium carbonate (1.85 g, 17.45 mol) in water (3 ml). After stirring at room temperature for 24 h, the reaction mixture was added to water and extracted with dichloromethane. The combined organic layers were washed with water, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to yield compound **13** as colorless oil (980 mg, 41% from **12**). ^{1}H-NMR ($CDCl_3$, 300 MHz), *δ*: 6.95 (d, *J* = 1.8 Hz, 1H), 6.68 (d, *J* = 1.8 Hz, 1H), 4.79 (br s, 1H), 4.58–4.50 (m, 1H), 3.83 (s, 3H), 3.67 (s, 3H), 3.39 (q, *J* = 6.6 Hz, 2H), 2.71 (t, *J* = 6.6 Hz, 2H), 1.35 (d, *J* = 6.3 Hz, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz), *δ*: 156.9, 151.8, 146.3, 135.7, 124.9, 117.7, 116.0, 71.6, 60.3, 52.0, 42.0, 35.6, 22.0 (2C); FT-IR, ν_{max} (cm^{-1}): 3338, 1701, 1524, 1485, 1270, 1234, 1136, 1109, 1003; MS (EI), *m/z* (relative intensity): 345 (M^+, 25), 228 (97), 215 (37), 149 (7), 88 (81); HRMS (ESI-POS), *m/z* calculated for $C_{14}H_{20}BrNO_4Na$ [M + Na]$^+$: 368.0468, measured: 368.0475.

Compound 14. A mixture of **7** (504 mg, 2.12 mmol), **13** (608 mg, 1.76 mmol), tetrakis(triphenylphosphine)palladium(0) (81.7 mg, 0.07 mmol), and potassium carbonate (487 mg, 3.52 mmol) in toluene–ethanol–water (3:3:2) (80 ml) was heated at 120 °C under argon atmosphere for 24 h. After cooling down to room temperature, the reaction mixture was mixed with water and extracted with ethyl acetate. The combined organic layers were washed with water, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to yield compound **14** as a yellow gum (708 mg, 88%). ^{1}H-NMR ($CDCl_3$, 300 MHz), *δ*: 9.70 (s, 1H), 7.53 (s, 1H), 6.83 (s, 1H), 6.82 (d, *J* = 1.8 Hz, 1H), 6.67 (d, *J* = 1.8 Hz, 1H), 4.78 (br s, 1H), 4.75–4.67 (m, 1H), 4.64–4.56 (m, 1H), 3.93 (s, 3H), 3.67 (s, 3H), 3.52 (s, 3H), 3.45 (q, *J* = 6.9 Hz, 2H), 2.79 (t, *J* = 6.9 Hz, 2H), 1.44–1.40 (m, 12H); ^{13}C-NMR ($CDCl_3$, 75 MHz), *δ*: 191.1, 157.0, 154.3, 150.9, 147.0, 146.5, 136.5, 134.3, 132.1, 127.0, 123.7, 116.4, 113.5, 111.3, 71.3, 71.2, 60.3, 56.2, 52.1, 42.2, 35.9, 22.2, 22.1, 22.0, 21.9; FT-IR, ν_{max} (cm^{-1}): 1702, 1681, 1594, 1509, 1265, 1111, 1093, 1012; MS (EI), *m/z* (relative intensity): 459 (M^+, 35), 428 (100), 396 (29), 386 (31), 354 (25), 312 (53), 269 (45); HRMS (ESI-POS), *m/z* calculated for $C_{27}H_{33}NO_6Na[M + Na]^+$: 482.2149, measured: 482.2165.

Compound 15: This compound was obtained from compound **14** (708 mg, 1.54 mmol) by using the same method described for **1a**. This compound has a 1:1 mixture of *E*/*Z* epimers in a form of pale yellow gum (662 mg, 88%). ^{1}H-NMR ($CDCl_3$, 300 MHz), *δ*: 7.78 (s, 1H), 6.93 (s, 1H), 6.78–6.70 (m, 5H), 6.62–6.58 (m, 2H), 5.94 (d, *J* = 7.2 Hz, 1H), 5.60 (d, *J* = 12.9 Hz, 1H), 4.98 (d, *J* = 7.2 Hz, 1H), 4.78–4.70 (m, 1H), 4.63–4.58 (m, 5H), 3.81 (s, 6H), 3.72 (s, 3H), 3.66 (s, 6H), 3.54 (s, 3H), 3.52 (s, 3H), 3.50 (s, 3H), 3.38 (q, *J* = 6.3 Hz, 4H), 2.75 (t, *J* = 6.3 Hz, 4H), 1.45–1.37 (m, 24H); ^{13}C-NMR ($CDCl_3$, 75 MHz), *δ*: 156.9, 151.0, 148.4, 147.7, 147.6, 146.8, 146.7, 146.5, 146.2, 146.0, 135.8, 135.5, 133.7, 133.6, 129.5, 129.2, 126.9, 126.5, 124.2, 124.1, 115.8, 115.6, 115.2, 114.3, 113.6, 112.0, 104.3, 103.7, 71.5, 71.2, 71.1, 71.0, 60.4, 60.3, 56.5, 56.0, 55.9, 52.0, 42.2, 35.8, 22.2; FT-IR, ν_{max} (cm^{-1}): 3362, 1716, 1593, 1509, 1464, 1264, 1237, 1108; MS (EI), *m/z* (relative intensity): 455 [(M-MeOH)$^+$, 100], 423 (27), 413 (24), 367 (22), 325 (34), 283 (50), 269 (26); HRMS (ESI-POS), *m/z* calculated for $C_{27}H_{37}NO_7Na[M + Na]^+$: 510.2462, measured: 510.2480.

Compound 16: Compound **15** (662 mg, 1.36 mmol) was dissolved in a solution of trifluoroacetic acid in dichloromethane (1:9, 15 mL), and 38% formaldehyde (0.5 ml, 6.9 mmol) was added. After stirring at room temperature for 1 h, the reaction mixture was added to water, washed with saturated aqueous sodium hydrogen carbonate, and extracted with dichloromethane. The combined organic layers were washed with water, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to yield compound **16** as a white solid (480 mg, 76%). ^{1}H-NMR ($CDCl_3$, 300 MHz), *δ*: 9.20 (s, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.24 (s, 1H), 5.00–4.92 (m, 1H), 4.82–4.74 (m, 3H), 4.07 (s, 3H), 3.91 (s, 3H), 3.90–3.80 (q, *J* = 5.7 Hz, 2H), 3.77 (s, 3H), 3.19 (t, *J* = 5.7 Hz, 2H), 1.48 (d, *J* = 6.0 Hz, 6H), 1.39 (d, *J* = 6.0 Hz, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz), *δ*: 156.1, 149.8, 148.7, 147.0, 146.0, 127.9 (2C), 127.5, 126.6, 125.6, 124.4, 123.2, 119.5, 111.1, 109.1, 74.9, 70.8, 59.4, 55.9, 52.6, 42.9, 41.2, 25.8, 22.9 (2C), 22.0 (2C); FT-IR, ν_{max} (cm^{-1}): 1701, 1512, 1465, 1442, 1402, 1236, 1104 ; MS (EI), *m/z* (relative intensity): 467 (M^+, 100), 425 (94), 383 (48), 368 (88), 350 (22), 309 (30) ; HRMS (ESI-POS), *m/z* calculated for $C_{27}H_{33}NO_6Na[M + Na]^+$: 490.2200, measured: 490.2212.

Compound 17: A suspension of **16** (280 mg, 0.6 mmol) and lithium aluminiumhydride (341 mg, 9.0 mmol) in tetrahydrofuran (30 ml) was heated at reflux for 4 h. After cooling down in ice-water, saturated aqueous sodium sulfate was added dropwise to the reaction mixture to destroy lithium aluminiumhydride. The mixture was filtered, and the filtrate was extracted with ethyl acetate. The combined organic layers were washed with water, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to yield compound **17** as a yellow solid (206 mg, 83%). ^{1}H-NMR ($CDCl_3$, 300 MHz), *δ*: 9.21 (s, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.56 (d, *J* = 9.0 Hz, 1H), 7.23 (s, 1H), 4.95–4.87 (m, 1H), 4.80–4.72 (m, 1H), 4.06 (s, 3H), 3.90 (s, 3H), 3.72 (s, 2H), 3.25 (t, *J* = 6.0 Hz, 2H), 2.81(t, *J* = 6.0 Hz, 2H), 2.55 (s, 3H), 1.48 (d, *J* = 6.0 Hz, 6H), 1.36 (d, *J* = 6.0 Hz, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz), *δ*: 149.7, 148.5, 146.8, 146.1, 128.9, 127.8, 127.6, 126.4, 125.3, 124.5, 122.9, 119.9, 111.2, 109.1, 74.7, 70.8, 59.4, 55.9, 54.2, 52.8, 46.2, 27.0, 22.9 (2C), 22.0 (2C); FT-IR, v_{max} (cm^{-1}): 1613, 1591, 1513, 1464, 1372, 1263, 1243, 1106; MS (EI), *m/z* (relative intensity): 423 (M^+, 77), 380 (77), 337 (100), 323 (26), 309 (23), 178 (18), 149(27); HRMS (ESI-POS), *m/z* calculated for $C_{26}H_{34}NO_4$ $[M + H]^+$: 424.2482, measured: 424.2480.

Reaction of 17 with aluminum (III) chloride. $AlCl_3$ (126 mg, 0.94 mmol) was added to a solution of **17** (100 mg, 0.23 mmol) in dichloromethane (10 ml) and the reaction was stirred at room temperature for 3 h. Then, the reaction was mixed with water and stirred for an additional 0.5 h. The mixture was extracted with dichloromethane several times, and the combined organic layers were washed with water, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to yield compound **18** as a gray solid (46 mg, 71%). ^{1}H-NMR (DMSO-d_6, 300 MHz), *δ*: 9.07 (s, 1H), 7.53 (s, 1H), 7.49 (s, 1H), 3.96 (s, 3H), 3.71 (s, 3H), 3.57 (s, 2H), 3.54–3.45 (m, 1H), 3.13 (t, *J* = 5.7 Hz, 2H), 2.73 (t, *J* = 5.7 Hz, 2H), 2.44 (s, 3H), 1.37 (d, *J* = 6.9 Hz, 6H); ^{13}C-NMR (DMSO-d_6, 75 MHz), *δ*: 147.2, 146.2, 144.5, 140.7, 138.0, 126.3, 126.1, 123.3, 123.2, 123.0, 120.5, 115.1, 108.5, 107.5, 59.6, 55.2, 53.2, 52.1, 45.7, 28.5, 26.3, 23.1 (2C); FT-IR, v_{max} (cm^{-1}): 3149, 1602, 1530, 1462, 1414, 1246, 1132, 1102; MS (EI), *m/z* (relative intensity): 381 (M^+, 92), 338 (100), 323 (58), 295 (39), 178 (85), 97 (68); HRMS (ESI-POS), *m/z* calculated for $C_{23}H_{28}NO_4$ $[M + H]^+$: 382.2013, measured: 382.2009.

Reaction of 17 with boron trichloride. BCl_3 (1.0 M in dichloromethane; 0.9 ml, 0.9 mmol) was added dropwise to a cooled (–78 °C) solution of **17** (30 mg, 0.07 mmol) in dichloromethane (8 ml), and the reaction was stirred at –78 °C for 1 h; then, the temperature was raised to 0 °C. After stirring at 0 °C for an additional 0.5 h, the reaction was mixed with water, and dichloromethane was removed under reduced pressure. The residue was mixed with saturated aqueous sodium chloride and extracted with 10% ethanol/ethyl acetate. The combined organic layers were concentrated under reduced pressure. The residue was purified by column chromatography to yield litebamine as a white solid (20 mg, 83%). ^{1}H-NMR (DMSO-d_6, 300 MHz), *δ*: 8.95 (s, 1H), 7.62 (d, *J* = 9.3 Hz, 1H), 7.46 (d, *J* = 9.3 Hz, 1H), 7.23 (s, 1H), 3.96 (s, 3H), 3.74 (s, 3H), 3.69 (s, 2H), 3.14 (br t, 2H), 2.84 (br t, 2H), 2.52 (s, 3H); ^{13}C-NMR (DMSO-d_6, 75 MHz), *δ*: 147.9, 146.4, 144.9, 141.1, 127.9, 126.2, 123.4, 123.3, 122.4, 122.2, 121.8, 119.8, 111.6, 107.9, 59.6, 55.2, 52.7, 51.7, 45.2, 25.9; FT-IR, v_{max} (cm^{-1}): 3146, 1603, 1466, 1442, 1411, 1248, 1114; MS (EI), *m/z* (relative intensity): 339 (M^+, 39), 296 (43), 281 (31), 178 (89), 167 (41), 149 (70), 71 (83), 52 (100); HRMS (ESI-POS), *m/z* calculated for $C_{20}H_{22}NO_4$ $[M + H]^+$: 340.1543, measured: 340.1541.

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Keywords: One-pot synthesis • Pictet–Spengler/Friedel–Crafts type reactions • Cyclization • Isoquinoline • Alkaloid

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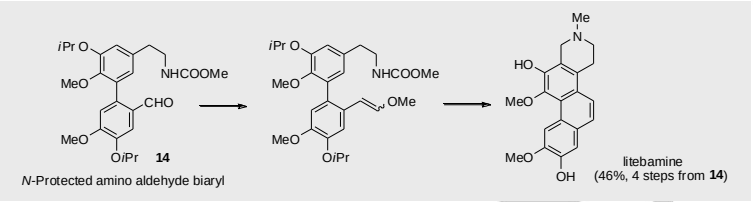

A facile and efficient one-pot method for the synthesis of tetrahydronaphtho [2,1-*f*]isoquinoline alkaloid using domino Pictet–Spengler/Friedel–Crafts type cyclizations has been reported. The natural litebamine was prepared by using the proposed method to exemplify its utility.

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One-pot strategy

*Nisachon Khunnawutmanotham, Poolsak Sahakitpichan, Nitirat Chimnoi, Supanna Techasakul**

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Efficient one-pot synthesis of tetrahydronaphtho[2,1-*f*]isoquinoline under domino Pictet–Spengler/Friedel–Crafts type reactions