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Total synthesis of acronycine and noracronycine: An aryne amination approach

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ABSTRACT

Acronycine and noracronycine are chromene-containing alkaloids with significant biological activity. We have accomplished a concise total synthesis of acronycine and noracronycine. The key step, regioselective nucleophilic addition of anthranilate to chromene-type arynes under mild and transition-metal-free conditions was achieved. In addition, further modifications of nucleophilic addition products, such as hydrogenation, *O*-functionalization and palladium-catalyzed coupling reactions have also been developed, providing a concise procedure for these alkaloids and their derivatives.

1. Introduction

Chromene-containing acridones are representative members of acridone alkaloids [1], such as acronycine [2] and noracronycine [3], have long been attractive targets due to their strong antitumor and antiproliferative activities [4]. Many synthetic methods toward these alkaloids have been developed [5], such as Ullmann reactions (Scheme 1a and d) [5a,b,f], Friedel-Crafts reactions (Scheme 1a, b and d) [5a,b,f] and S_NAr reactions (Scheme 1b) [5d]. However, most of the existing methods either require transition-metal catalysis (Scheme 1a and d) [5a,b,f,g], or rely on strong acids (Scheme 1a) [5a,b]/strong bases (Scheme 1b-d) [5c-f], and regioselectivity control is of great challenge in some reported examples (Scheme 1a, b) [5a,d]. Among these synthetic methods, Watanabe group completed the synthesis of acronycine in one step by using aryne nucleophilic cyclization strategy (Scheme 1c) [5e]. However, the harsh reaction conditions and low yield somehow limited further application of this strategy. Our experience with chromene-type Kobayashi aryne precursors [6] suggested an opportunity to construct C–N bond under mild and transition-metal-free conditions [7] as well as introducing chromene fragment (Scheme 2). Herein, we report a concise total synthesis of acronycine and noracronycine by the amination of chromene-type arynes.

2. Results and discussion

In order to construct tetracyclic acridone **6** in one step according to Larock's work [8], methyl 2-(methylamino)-benzoate (**3**) and chromene-type aryne precursor **4a** were first employed as model substrates. Larock conditions [8] were also applied to the reaction, however, only nucleophilic addition product **5** was obtained in 88% yield (Table 1, entry 1), and neither ring-closure products nor regioisomers were observed. Then the reaction conditions such as fluoride sources, solvents and temperature were screened in order to obtain the ring-closure product **6**. When tetrabutylammonium fluoride (TBAF) was used, compound **5** was obtained in 36% yield (entry 2). Similar yields could be achieved by using KF/18-crown-6 or CsF (entry 3 and 4), but the latter gave less by-products and was more conducive to product purification. Solvent effect was also examined. Moderate-to-good yields were achieved in dioxane, THF and MeCN (entries 5–7). DCE and toluene were proven to be inapplicable (entries 8 and 9). By using DME, product **5** was obtained in 88% yield (entry 10), and enhancement of the reaction temperature to 80 °C led to a higher yield (93%, entry 11). On the contrast, only trace amount of **5** was observed when lowering the reaction temperature to 0 °C, with a large amount of substrates **3**

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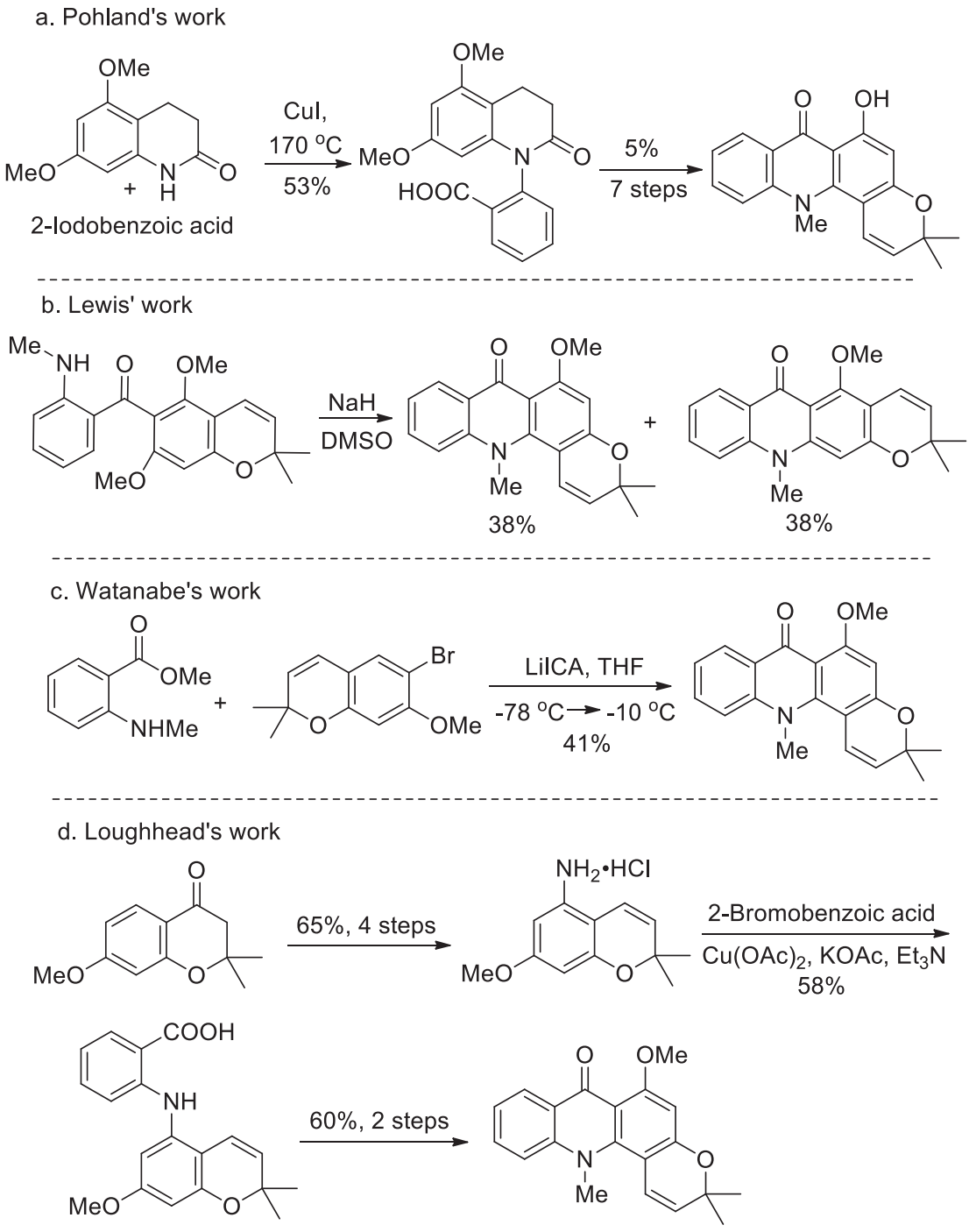
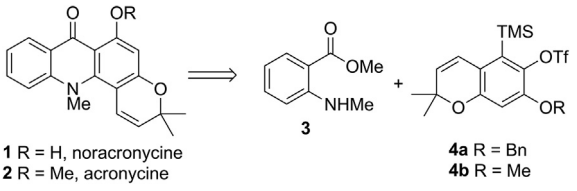


Scheme 1. Selected synthetic methods towards acronycine.

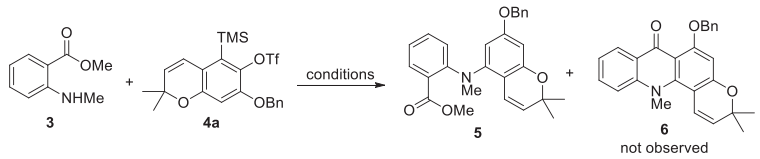


Scheme 2. Retrosynthetic analysis of acronycine and noracronycine.

and **4a** remained (entry 12). Changes in the reaction conditions including fluorine sources, solvents and temperatures failed to obtain ring-closure product **6**. Furthermore, we assumed that the phenyl anion intermediate could be quenched by intramolecular proton transfer, and addition of base may prevent such process. Therefore, different kinds of bases were used as additives. However, Cs_2CO_3, NaH or DIPEA was used as additive gave product **5** in good yield, and product **6** was not observed (entries 13–15). DBU caused the decomposition of the precursor **4a**, with only a trace amount of product **5** observed (entry 16).

We then turned our attention to obtaining ring-closure product

Table 1
Study towards synthesis of acronycine and noracronycine[a].



Entry	F^- source (equiv.)	Solvent	Temp (°C)	Time (h)	Additive	Yield (%)[b]
1[c]	CsF (4.0)	THF	65	24	–	88
2	TBAF (3.0)	THF	60	4	–	36
3	KF/18-C-6 (3.0)	THF	60	2	–	75
4	CsF (3.0)	MeCN	60	1	–	76
5	CsF (3.0)	MeCN	60	24	–	85
6	CsF (3.0)	Dioxane	60	24	–	58
7	CsF (3.0)	THF	60	24	–	89
8	CsF (3.0)	DCE	60	48	–	trace
9	CsF (3.0)	Toluene	60	48	–	0
10	CsF (3.0)	DME	60	24	–	88
11	**CsF (3.0)**	**DME**	**80**	**24**	–	**93**
12	CsF (3.0)	DME	0	48	–	trace
13	CsF (3.0)	DME	80	24	Cs_2CO_3	86
14	CsF (3.0)	DME	80	4	NaH	88
15	CsF (3.0)	DME	80	24	DIPEA	82
16	CsF (3.0)	DME	80	4	DBU	trace

[a] Unless stated otherwise, The reactions were carried out with **3** (1.05 mmol), **4a** (1.00 mmol), F^- source (based on **4a**) and additive (1.50 mmol) in 10.0 mL solvent under a nitrogen atmosphere.
[b] Isolated yield.
[c] The reaction was carried out with Larock conditions.

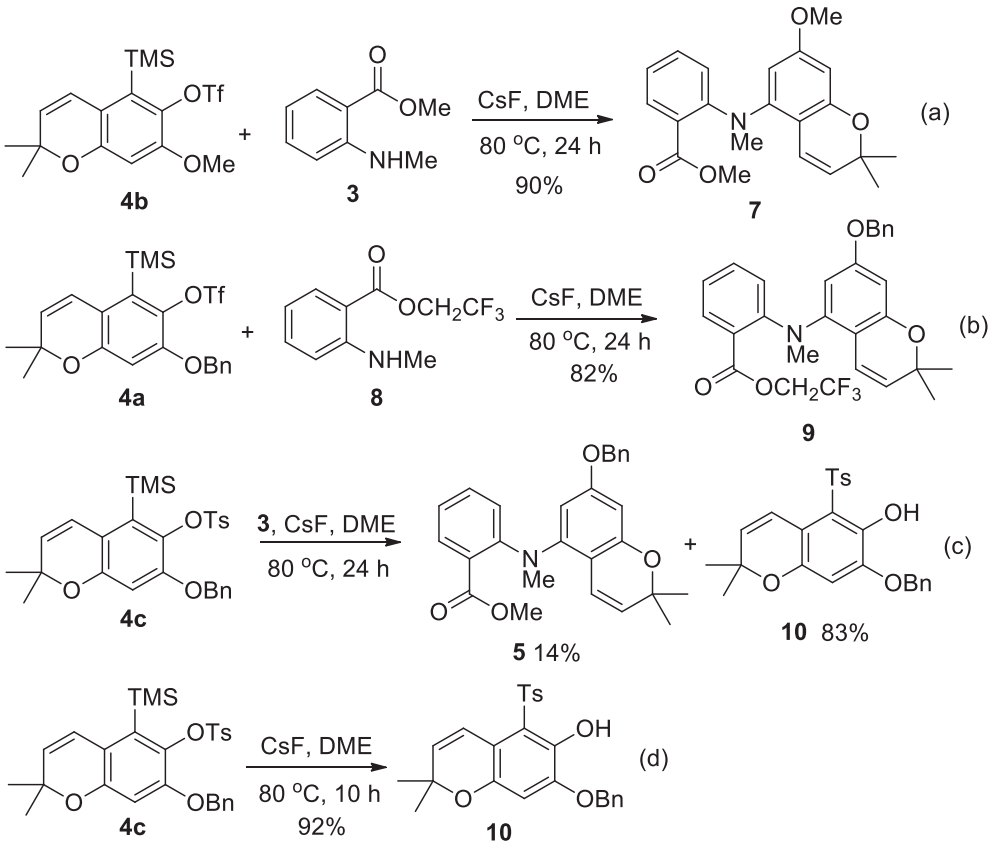
6 by other approaches (Scheme 3). We first considered the influence of the steric hindrance at C-7 position, and precursor **4b** was selected as the reaction substrate. However, the reaction between **3** and **4a** gave similar results. Diarylamine **7** was obtained in 90% yield and no ring-closure product was observed. Then we tried to enhance the electrophilicity of the carbonyl group of the substrate in order to obtain the ring-closure product. According to Zhu's work [9], we assumed that using trifluoroethyl ester **8** instead of methyl ester **3** as a substrate might be more conducive. No ring-closure product was observed while compound **9** was still obtained in 82% yield. Based on the report of Watanabe and coworkers, who claiming that the bromobenzene-type precursor can undergo a nucleophilic cyclization reaction with anthranilate in 41% yield [5e], we further speculated whether it is possible to control the release rate of aryne by changing the leaving group of the Kobayashi precursor [10] to obtain ring-closure product. However, when toluenesulfonate **4c** was used as aryne precursor, the thia-Fries rearrangement [11] product **10** was obtained in 83% yield, which indicated that precursor **4c** is not suitable for this reaction. For further verification, treatment of **4c** directly with CsF afforded **10** in 92% yield.

The above results showed that the ring-closure product cannot be obtained by changing the reaction conditions and substrates. We further suspected that the phenyl anion may be quenched by protons during the reaction, and the source of protons was studied. Adding D_2O during the reaction (Table 2, entries 1 and 2) or using deuterated solvents (entries 3 and 4) cannot give compound **5-d$_1$**, indicating that the protons are likely to originate from anthranilate **3**. Then we tried to add D_2O at the initial stage of the reaction (entry 5) to produce deuterated anthranilate **3**, which might be converted to compound **5-d$_1$**. Unfortunately, water inhibited the occurrence of the reaction, with a large amount of substrates **3** and **4a** remained. The above results suggested that the reaction intermediate was likely to be **I** instead of **II** (Scheme 4), and the zwitterionic intermediate **I** wasn't stable with an alkoxyl group adjacent to the aryne. It's possible that the tendency of intramolecular proton transfer was much greater than the nucleophilic addition of anions to the ester group, resulting that ring-closure product **6** was not observed.

Considering that the benzoate structure on diarylamine **5** can be regarded as a potential electrophile, synthesis of noracronycine **1** was designed by Friedel-Crafts acylation without additional catalysts or reagents [12]. As shown in Scheme 5, hydrolysis of methyl ester **5** afforded acid **11** in 97% yield, which then underwent cyclization by using oxalyl chloride. Treatment of the crude ring-closure compound with Pd/C under a balloon pressure of H_2 gave noracronycine **1** in 80% yield without losing double bond. This transformation can be carried out in gram scale. With the successful example, we tried to apply the same strategy to synthesize acronycine. Inspiringly, acronycine **1** was obtained in 70% yield over 3 steps.

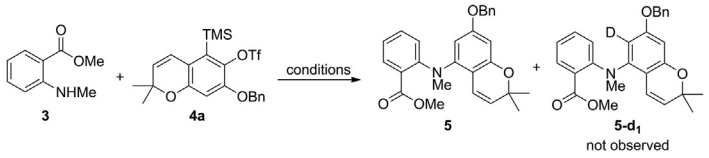
Except for the benzoate, the presence of olefin and the benzyloxy group furnishes opportunities to further construct biologically active molecules with various structures. As shown in Scheme 6, treatment of chromene **5** with $Pd(OH)_2/C$ under a balloon pressure of H_2 afforded chromane **13** in 78% yield, as some reported examples have shown that modification of the pyran ring can improve the biological activity [13]. Furthermore, the acylation and alkylation reactions of chromane **13** were also carried out, ester **14** and ether **15** were obtained in 87% and 90% yields, respectively. It is worth mentioning that the introduction of prenyl groups is also helpful to improve the biological activity of the molecule according to the previous report [14].

Moreover, different from the reported C–N bond construction methods by using transition metal catalysis, halogen atoms on the substrates could be tolerated in our approach. As shown in Scheme 7, the reaction of bromoarylamine **16** with aryne gave diarylamine **17** in 86% yield, and alkenyl, aryl, heteroaryl groups can be



Scheme 3. Trials of different substrates of the key step.

Table 2
Trapping experiment of reaction intermediate.



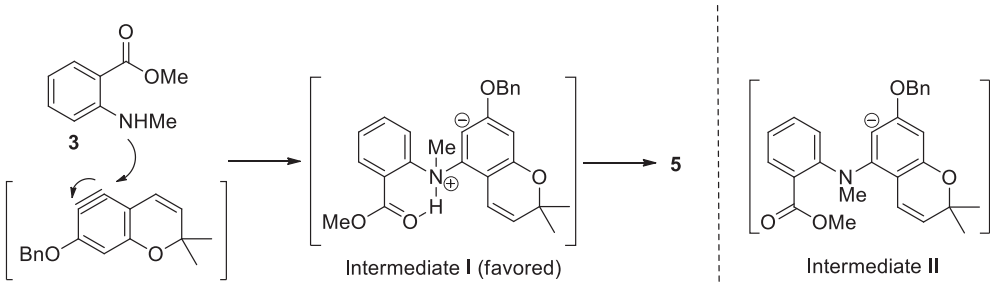
Entry	Conditions	Yield (%)[d]
1[a]	CsF, THF, 60 °C, 0.5 h, then cooled to 0 °C, D_2O, 0.5 h	7
2[a]	CsF, THF, 60 °C, 4 h, then cooled to 0 °C, D_2O, 0.5 h	58
3[b]	CsF, THF-d_8, 60 °C, 24 h	88
4[c]	CsF, MeCN-d_3, 60 °C, 12 h	81
5[a]	CsF, THF, D_2O, 60 °C, 24 h	-[e]

[a] The reactions were carried out with **3** (1.05 mmol), **4a** (1.00 mmol), CsF (3.00 mmol) and D_2O (0.5 mL) in 10.0 mL THF under a nitrogen atmosphere.
[b] The reaction was carried out with **3** (0.105 mmol), **4a** (0.10 mmol), CsF (0.30 mmol) in 1.0 mL THF-d_8 under a nitrogen atmosphere.
[c] The reaction was carried out with **3** (0.525 mmol), **4a** (0.50 mmol), CsF (1.50 mmol) in 2.5 mL MeCN-d_3 under a nitrogen atmosphere.
[d] Isolated yield.
[e] Not determined.

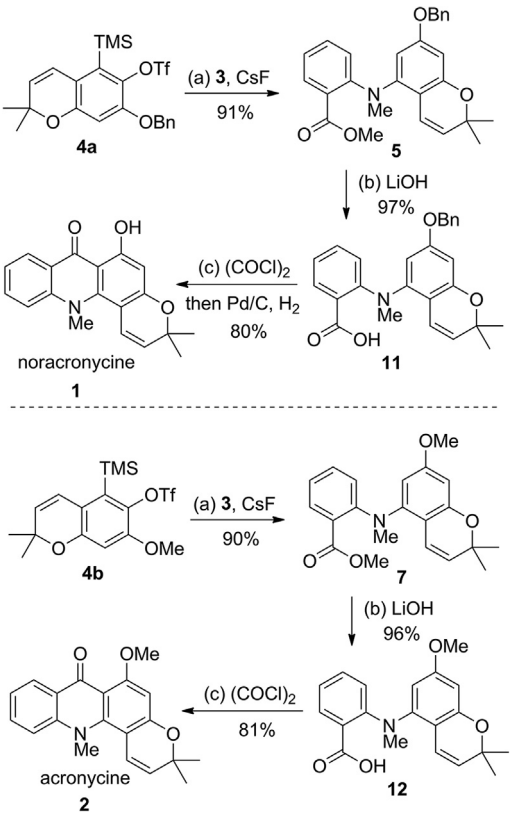
introduced in good yield by Suzuki coupling. Furthermore, cyclization of diarylamine **19** was carried out according to the protocol described in Scheme 5, and the following hydrolysis and Friedel-Crafts acylation gave acridone **22** in 74% yield over 2 steps. The above results disclosed the concise synthetic approach to the complex chromene-containing acridones.

3. Conclusion

In summary, total synthesis of acronycine and noracronycine has been accomplished. More than 600 mg of these alkaloids can be prepared through this approach. The key step, efficient formation of C–N bond was achieved under transition-metal-free and mild conditions. Further modifications of nucleophilic addition products were also developed, providing assistance for the biological and



Scheme 4. Proposed mechanism and intermediates.



Scheme 5. Total synthesis of noracronycine and acronycine.

pharmacological studies of such alkaloids.

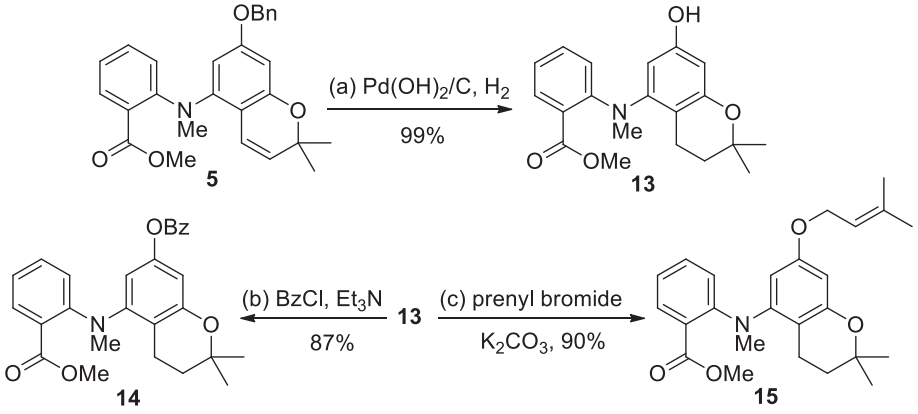
4. Experimental section

4.1. General information

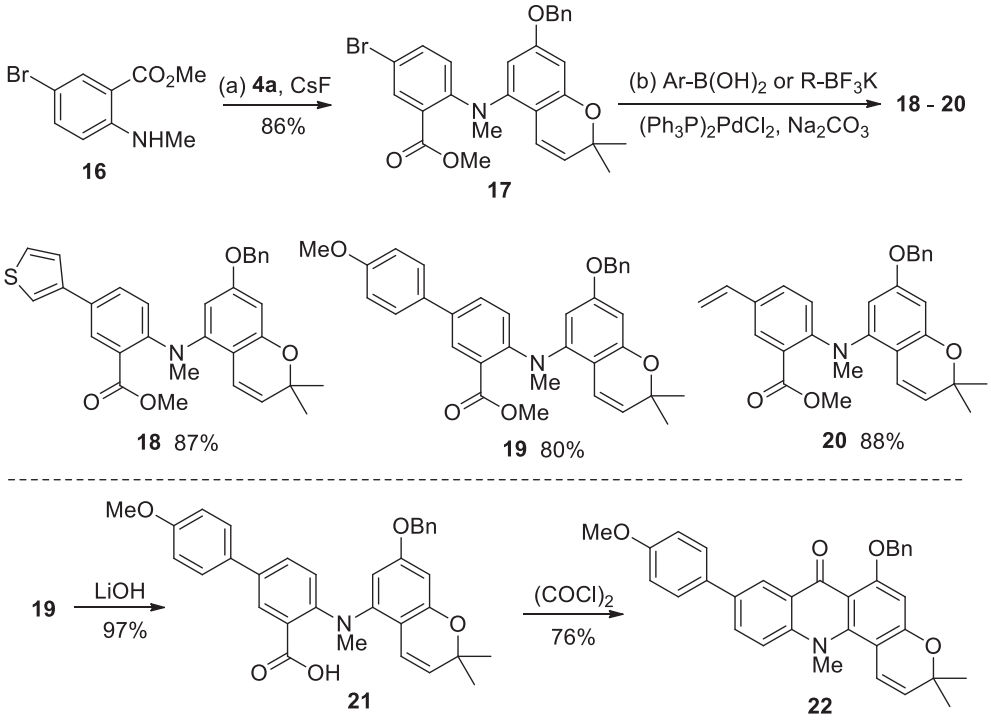
Unless otherwise mentioned, all reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions. Anhydrous solvents were distilled prior to use: THF, dioxane and toluene were distilled from sodium-benzophenone; MeCN was distilled from P_2O_5; CH_2Cl_2, DCE and Et_3N were distilled from CaH_2; acetone was distilled from Drierite and stored under a nitrogen atmosphere. Petroleum ether refers to the fraction with boiling point in the range of 60–90 °C. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated.

Reactions were monitored by thin-layer chromatography (TLC) on silica gel using UV light as the visualizing agent or $KMnO_4$ and heat as developing agents. Flash column chromatography uses silica gel (300–400 mesh) supplied by Tsingtao Haiyang Chemicals (China).

NMR spectra were recorded on Bruker III 400 (^{1}H 400 MHz, ^{13}C 101 MHz) or Ascend 600 (^{1}H 600 MHz, ^{13}C 151 MHz). TMS was used as internal standard for ^{1}H NMR (0.00 ppm), and solvent signal was used as reference for ^{1}H NMR (Acetone-d_6 2.05 ppm), ^{13}C NMR ($CDCl_3$, 77.00 ppm) or ^{13}C NMR (Acetone-d_6 206.26 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution mass spectrometry data were obtained using a XEVO G2 TOF using ESI (electrospray ionization), or a Wa-



Scheme 6. Further elaboration of chromene **5**.



Scheme 7. Diversification of bromine-substituted chromene.

ters GCT Premier using EI (electron impact). IR spectra were measured on an FT-IR spectrometer. Melting points were recorded without correction.

4.2. Experimental procedures and data for synthetic compounds

4.2.1 *Synthesis of compound **5*** To a stirred solution of silyltriflate **4a** (486.6 mg, 1.00 mmol) and methyl 2-(methylamino)benzoate (**3**) (173.4 mg, 1.05 mmol) in DME (10 mL) was added CsF (455.7 mg, 3.00 mmol). The solution was stirred at 80 °C for 24 h, then cooled to room temperature, filtered over silica gel (CH_2Cl_2 eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (100/1 PE/EtOAc) afforded compound **5** (398.7 mg, 93%) as a white solid.

m.p. 121.0–121.6 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 7.39–1.34 (m, 5H), 7.32–7.30 (m, 1H), 7.01 (dd, J = 8.0 Hz, 0.4 Hz, 1H), 6.95 (td, J = 7.2 Hz, 0.8 Hz, 1H), 6.39 (d, J = 10.0 Hz, 1H), 6.25 (d, J = 2.4 Hz, 1H), 6.15 (d, J = 2.4 Hz, 1H), 5.41 (d, J = 10.0 Hz, 1H), 4.94 (s, 2H), 3.56 (s, 3H), 3.20 (s, 3H), 1.38 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 159.8, 155.3, 149.3, 147.7, 136.7, 132.0, 131.0, 128.4, 127.9, 127.5, 126.8, 124.2, 120.8, 120.4, 119.4, 110.0, 102.9, 98.5, 75.5, 69.9, 51.7, 42.4, 27.4.

IR (KBr): ν_{max} 3418, 2971, 2947, 1718, 1564, 1487, 1473, 1301, 1261, 1143, 1113, 863, 761 cm^{-1}

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{28}NO_4^+$ 430.2013, found 430.2018.

4.2.2 *Synthesis of compound **7*** To a stirred solution of silyltriflate **4b** (410.5 mg, 1.00 mmol) and methyl 2-(methylamino)benzoate (**3**) (173.4 mg, 1.05 mmol) in DME (10 mL) was added CsF (455.8 mg, 3.00 mmol). The solution was stirred at 80 °C for 24 h, and then cooled to room temperature, filtered over silica gel (CH_2Cl_2 eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (80/1 PE/EtOAc) afforded compound **7** (319.5 mg, 90%) as a white solid.

m.p. 73.9–74.5 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.36 (ddd, J = 8.0 Hz, 7.6 Hz, 1.6 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.95 (td, J = 7.6 Hz, 0.8 Hz, 1H), 6.39 (d, J = 10.0 Hz, 1H), 6.17 (d, J = 2.0 Hz, 1H), 6.06 (d, J = 2.0 Hz, 1H), 5.41 (d, J = 10.0 Hz, 1H), 3.69 (s, 3H), 3.56 (s, 3H), 3.21 (s, 3H), 1.38 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 160.7, 155.4, 149.3, 147.8, 132.0, 131.0, 126.8, 124.1, 120.7, 120.2, 119.5, 109.9, 102.2, 97.7, 75.5, 55.3, 51.7, 42.4, 27.4.

IR (KBr): ν_{max} 2947, 1717, 1610, 1569, 1377, 1301, 1145, 1112, 1045, 1019, 959, 794 cm^{-1}

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{24}NO_4^+$ 354.1700, found 354.1704.

4.2.3 *Synthesis of compound **8*** Cesium carbonate (6.52 g, 20.0 mmol) was added to a solution of 2-(methylamino)benzoic acid (3.02 g, 20.0 mmol) in dry MeCN (200 mL). The resulting mixture was stirred at room temperature for 15 min, and then 2,2,2-trifluoroethyl trifluoromethanesulfonate (4.32 mL, 30,0 mmol) was added in one portion. The reaction mixture was stirred until complete consumption of the starting material (40 min) and filtered through Celite. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (150/1 PE/EtOAc) to give compound **8** (4.16 g, 89%) as white solid.

m.p. 69.7–70.5 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 7.49 (brs, 1H), 7.45–7.40 (m, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.64–6.60 (m, 1H), 4.63 (q, J = 8.4 Hz, 2H), 2.93 (d, J = 4.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 152.4, 135.6, 131.7, 123.3 (q, J_{C-F} = 278.4 Hz), 114.6, 110.9, 107.9, 60.0 (q, J_{C-F} = 36.6 Hz), 29.5.

IR (KBr): ν_{max} 3389, 2917, 2819, 1688, 1580, 1521, 1431, 1285, 1246, 1155, 1093, 954 cm^{-1}

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{10}H_{11}F_3NO_2^+$ 234.0736, found 234.0737.

4.2.4 *Synthesis of compound **9*** To a stirred solution of silyltriflate

4a (486.6 mg, 1.00 mmol) and compound **8** (244.8 mg, 1.05 mmol) in DME (10 mL) was added CsF (455.7 mg, 3.00 mmol). The solution was stirred at 80 °C for 24 h, then cooled to room temperature, filtered over silica gel (CH_2Cl_2 eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (80/1 PE/EtOAc) afforded compound **9** (409.8 mg, 82%) as a pale yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.42–7.28 (m, 6H), 7.02 (d, J = 8.4 Hz, 1H), 6.99–6.95 (m, 1H), 6.37 (d, J = 10.0 Hz, 1H), 6.27 (d, J = 2.4 Hz, 1H), 6.15 (d, J = 2.4 Hz, 1H), 5.42 (d, J = 10.0 Hz, 1H), 4.93 (s, 2H), 4.35 (q, J = 8.4 Hz, 2H), 3.20 (s, 3H), 1.38 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 159.9, 155.4, 150.1, 147.4, 136.7, 132.9, 131.2, 128.5, 127.9, 127.6, 127.1, 123.1 (q, J_{C-F} = 277.5 Hz), 121.7, 120.7, 120.6, 119.2, 110.2, 103.1, 98.8, 75.6, 70.0, 60.2 (q, J_{C-F} = 36.1 Hz), 42.4, 27.3.

IR (KBr): ν_{max} 3448, 2917, 2365, 1734, 1630, 1601, 1476, 1442, 1274, 1232, 1134 cm^{-1}

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{27}F_3NO_4^+$ 498.1887, found 498.1885.

4.2.5 *Synthesis of compound **4c*** 7-(Benzyloxy)-2,2-dimethyl-5-(trimethylsilyl)-2*H*-chromen-6-ol (3.52 g, 9.93 mmol) was dissolved in CH_2Cl_2 (40 mL) and cooled to 0 °C. TsCl (1.98 g, 10.4 mmol) and Et_3N (2.07 mL, 14.9 mmol) were added successively, and the mixture was then warmed to room temperature and stirred for 36 h. Saturated $NaHCO_3$ (aq.) was added to quench the reaction, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (40 mL x 3). The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure afforded the crude product, which was further purified by flash chromatography (100/1 PE/EtOAc) afforded compound **4c** (4.14 g, 82%) as a white solid.

m.p.114.0–114.8 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 2H), 7.35–7.31 (m, 3H), 7.19–7.16 (m, 2H), 6.92 (d, J = 8.4 Hz, 2H), 6.58 (d, J = 10.0 Hz, 1H), 6.34 (s, 1H), 5.55 (d, J = 10.0 Hz, 1H), 4.51 (s, 2H), 2.28 (s, 3H), 1.40 (s, 6H), 0.47 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4, 151.0, 144.1, 136.2, 136.1, 133.6, 133.6, 128.9, 128.5, 128.2, 127.8, 127.3, 127.2, 122.8, 118.8, 103.3, 75.4, 70.0, 27.4, 21.5, 1.9.

IR (ATR): ν_{max} 2927, 1589, 1443, 1382, 1352, 1249, 1193, 1154, 1090, 1008, 933, 917, 840, 770, 664 cm^{-1}

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{33}O_5SSi^+$ 509.1812, found 509.1810.

4.2.6 *Synthesis of compound **5** and compound **10*** To a stirred solution of precursor **4c** (508.7 mg, 1.00 mmol) and methyl 2-(methylamino)benzoate (**3**) (173.4 mg, 1.05 mmol) in DME (10 mL) was added CsF (455.7 mg, 3.00 mmol). The solution was stirred at 80 °C for 24 h, then cooled to room temperature, filtered over silica gel (CH_2Cl_2 eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (120/1 → 80/1 → 40/1 PE/EtOAc) afforded compound **5** (60.7 mg, 14%) as a white solid and compound **10** (363.0 mg, 83%) as a white solid.

*Characterization data of compound **10*** m.p. 88.8–89.3 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.4 Hz, 2H), 7.34–7.32 (m, 3H), 7.24–7.21 (m, 2H), 7.07 (d, J = 8.4 Hz, 2H), 6.92 (s, 1H), 6.34 (s, 1H), 6.21 (d, J = 10.0 Hz, 1H), 5.51 (d, J = 10.0 Hz, 1H), 4.76 (s, 2H), 2.35 (s, 3H), 1.41 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 151.2, 144.6, 136.0, 133.0, 131.8, 129.2, 128.7, 128.5, 128.3, 127.9, 127.1, 121.5, 113.9, 102.3, 70.4, 27.9, 21.6.

IR (KBr): ν_{max} 3439, 2971, 1617, 1502, 1443, 1254, 1181, 1049, 787 cm^{-1}

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{25}O_5S^+$ 437.1417, found 437.1417.

4.2.7 *Synthesis of compound **10*** To a stirred solution of precursor **4c** (508.7 mg, 1.00 mmol) in DME (10 mL) was added CsF (455.7 mg, 3.00 mmol). The solution was stirred at 80 °C for 10 h, then cooled to room temperature, filtered over silica gel (CH_2Cl_2 eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (30/1 PE/EtOAc) afforded compound **10** (402.5 mg, 92%) as a white solid.

4.2.8 *Gram-scale synthesis of compound **5***. To a stirred solution of silyltriflate **4a** (7.79 g, 16.00 mmol) and methyl 2-(methylamino) benzoate (**3**) (2.78 g, 16.80 mmol) in DME (160 mL) was added CsF (7.29 g, 48.00 mmol). The solution was stirred at 80 °C for 24 h, then cooled to room temperature, filtered over silica gel (CH_2Cl_2 eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (120/1 → 100/1 PE/EtOAc) afforded compound **5** (6.27 g, 91%) as a white solid.

4.2.9 *Synthesis of compound **11*** To a solution of compound **5** (5.03 g, 11.7 mmol) in MeOH/THF/H_2O (130 mL, 5:5:1) was added $LiOH\cdot H_2O$ (4.91 g, 117.1 mmol). The resulting mixture was heated under reflux for 24 h. The reaction mixture was subsequently allowed to cool at room temperature and acidified with 2 N HCl (aq). After separating both layers, the aqueous layer was extracted with EtOAc (80 mL x 3). The combined organic layers were dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. Purification of the residue by flash column chromatography (3/1 PE/EtOAc) provided compound **11** (4.72 g, 97%) as a yellow solid.

m.p.53.7–54.9 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.91 (brs, 1H), 8.26 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.46–7.39 (m, 4H), 7.37–7.29 (m, 1H), 6.98 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 6.37 (d, J = 2.4 Hz, 1H), 6.07 (d, J = 10.0 Hz, 1H), 5.31 (d, J = 10.0 Hz, 1H), 5.04 (s, 2H), 3.13 (s, 3H), 1.21 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 159.5, 155.6, 151.9, 145.1, 136.3, 134.2, 132.6, 128.6, 128.1, 128.0, 127.6, 125.9, 124.5, 124.0, 117.4, 108.8, 101.9, 99.2, 75.6, 70.1, 44.8, 27.1.

IR (KBr): ν_{max} 3427, 2973, 1720, 1688, 1605, 1568, 1485, 1453, 1248, 1139, 1038, 825 cm^{-1}

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{26}NO_4^+$ 416.1856, found 416.1850.

4.2.10 *Synthesis of Noracronycine **1*** To a solution of compound **11** (2.08 g, 5.00 mmol) in anhydrous CH_2Cl_2 (50 mL) at −20 °C was added a solution of oxalyl chloride (2 M in CH_2Cl_2, 2.75 mL, 5.50 mmol) dropwise over 5 min. The resulting mixture was stirred at −20 °C for 6 h before quenched with MeOH/CH_2Cl_2 (1:5, 12 mL). The mixture was warmed to room temperature, and the solvent was evaporated under reduced pressure. The residue was dissolved in MeOH (45 mL) and EtOAc (15 mL), and 20% Pd/C (266.1 mg, 0.50 mmol) was added. The mixture was placed under an atmosphere of hydrogen, stirred for 2 h at room temperature, and then filtered over celite (CH_2Cl_2 eluent). Evaporation of the solvent under reduced pressure, and the residue was further purified by flash chromatography (4/1 → 1/1 PE/CH_2Cl_2) afforded compound **1** (1.23 g, 80%) as a yellow solid.

m.p.216.8–217.7 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 14.72 (s, 1H), 8.30 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.69–7.65 (m, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 9.6 Hz, 1H), 6.22 (s, 1H), 5.48 (d, J = 9.6 Hz, 1H), 3.87 (s, 3H), 1.52 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.9, 165.1, 161.4, 144.6, 144.2, 133.8, 125.9, 122.7, 121.9, 121.6, 121.5, 116.0, 106.7, 100.8, 97.6, 76.3, 43.5, 26.8.

IR (KBr): ν_{max} 3449, 2965, 1778, 1590, 1477, 1422, 1332, 1273, 1146, 893 cm^{-1}

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{18}NO_3^+$ 308.1281, found

308.1285.

4.2.11 *Gram-scale synthesis of compound* ***7***. To a stirred solution of silyltriflate **4b** (3.28 g, 8.00 mmol) and methyl 2-(methylamino) benzoate (**3**) (1.39 g, 8.40 mmol) in DME (80 mL) was added CsF (3.65 g, 24.00 mmol). The solution was stirred at 80 °C for 24 h, then cooled to room temperature, filtered over silica gel (CH_2Cl_2 eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (80/1 → 60/1 PE/EtOAc) afforded compound **7** (2.54 g, 90%) as a white solid.

4.2.12 *Synthesis of compound* ***12*** To a solution of compound **7** (1.46 g, 4.13 mmol) in MeOH/THF/H_2O (45 mL, 5:5:1) was added $LiOH\cdot H_2O$ (1.73 g, 41.3 mmol). The resulting mixture was heated under reflux for 24 h. The reaction mixture was subsequently allowed to cool at room temperature and acidified with 2 N HCl (aq). After separating both layers, the aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic layers were dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. Purification of the residue by flash column chromatography (4/1 PE/EtOAc) provided compound **12** (1.32 g, 96%) as a yellow solid.

m.p.58.8–60.1 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.87 (brs, 1H), 8.25 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.46 (ddd, J = 8.4 Hz, 7.2 Hz, 1.6 Hz, 1H), 7.30 (td, J = 7.6 Hz, 1.2 Hz, 1H), 6.99 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 6.42 (d, J = 2.4 Hz, 1H), 6.28 (d, J = 2.4 Hz, 1H), 6.07 (d, J = 10.0 Hz, 1H), 5.30 (d, J = 10.0 Hz, 1H), 3.80 (s, 3H), 3.15 (s, 3H), 1.29 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 160.4, 155.7, 152.0, 145.0, 134.3, 132.7, 128.0, 126.2, 124.7, 124.1, 117.4, 108.6, 101.2, 98.4, 75.6, 55.4, 44.9, 27.2.

IR (KBr): ν_{max} 2971, 1726, 1687, 1606, 1568, 1485, 1375, 1360, 1247, 1200, 1138, 1046, 957 cm^{-1}

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{22}NO_4^+$ 340.1543, found 340.1546.

4.2.13 *Synthesis of Acronycine* ***2*** To a solution of compound **12** (814.5 mg, 2.40 mmol) in anhydrous CH_2Cl_2 (24 mL) at −20 °C was added a solution of oxalyl chloride (2 M in CH_2Cl_2, 1.32 mL, 2.64 mmol). The resulting mixture was stirred at −20 °C for 6 h before quenched with MeOH/CH_2Cl_2 (1:5, 6 mL). The mixture was warmed to room temperature, and the solvent was evaporated under reduced pressure. The residue was further purified by flash chromatography (3/1 → 2/1 PE/Acetone) afforded compound **2** (624.9 mg, 81%) as a yellow solid.

^{1}H NMR (400 MHz, Acetone-d_6) δ 8.20 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.67–7.63 (m, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.24–7.20 (m, 1H), 6.71 (d J = 9.6 Hz, 1H), 6.32 (s, 1H), 5.60 (d, J = 9.6 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 1.51 (s, 6H).

^{13}C NMR (101 MHz, Acetone-d_6) δ 176.4, 163.5, 159.8, 147.5, 145.4, 133.1, 126.9, 126.0, 123.5, 122.5, 122.1, 117.4, 110.9, 103.8, 94.7, 76.8, 56.1, 44.5, 26.7.

4.2.14 *Synthesis of compound* ***13*** To a solution of compound **5** (1.47 g, 3.42 mmol) in THF (34 mL) was added 20% $Pd(OH)_2/C$ (102.2 mg, 0.171 mmol). The mixture was placed under an atmosphere of hydrogen, stirred for 16 h at 40 °C, and then filtered over celite (EtOAc eluent). Evaporation of the solvent under reduced pressure, and the residue was further purified by flash chromatography (10/1 PE/EtOAc) afforded compound **13** (1.16 g, 99%) as a pale yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 7.35–7.31 (m, 1H), 6.96–6.90 (m, 2H), 6.17 (d, J = 2.4 Hz, 1H), 6.11 (d, J = 2.4 Hz, 1H), 5.97 (s, 1H), 3.59 (s, 3H), 3.19 (s, 3H), 2.24 (t, J = 6.4 Hz, 2H), 1.64 (t, J = 6.4 Hz, 2H), 1.24 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 155.8, 155.2, 149.4, 149.2, 132.0, 130.6, 123.9, 120.4, 108.9, 103.2, 100.2, 74.1, 51.8, 42.0, 32.7, 26.6, 19.0.

IR (ATR): ν_{max} 3392, 2969, 1702, 1613, 1579, 1431, 1293, 1119, 1104, 1027, 879, 841, 763, 753 cm^{-1}

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{24}NO_4^+$ 342.1700, found 342.1704.

4.2.15 *Synthesis of compound* ***14*** Phenol **13** (471.0 mg, 1.38 mmol) was dissolved in CH_2Cl_2 (13.8 mL) and cooled to 0 °C. BzCl (193 μL, 1.66 mmol), Et_3N (268 μL, 1.93 mmol) and DMAP (33.7 mg, 0.276 mmol) were added successively, and the mixture was then warmed to room temperature and stirred for 3 h. Saturated $NaHCO_3$ (aq.) was added to quench the reaction, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (15 mL x 3). The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure afforded the crude product, which was further purified by flash chromatography (15/1 PE/EtOAc) afforded compound **14** (535.9 mg, 87%) as a yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.16 (m, 2H), 7.63–7.56 (m, 2H), 7.49 (t, J = 8.0 Hz, 2H), 7.36–7.32 (m, 1H), 7.00–6.95 (m, 2H), 6.51 (d, J = 2.4 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 3.68 (s, 3H), 3.25 (s, 3H), 2.28 (t, J = 6.4 Hz, 2H), 1.66 (t, J = 6.4 Hz, 2H), 1.25 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 165.0, 155.7, 150.1, 149.4, 149.0, 133.4, 132.0, 130.7, 130.1, 129.7, 128.5, 124.6, 121.5, 121.1, 114.1, 108.0, 106.5, 74.2, 51.9, 42.4, 32.4, 26.6, 19.4.

IR (ATR): ν_{max} 2977, 1738, 1723, 1585, 1470, 1447, 1432, 1292, 1256, 1116, 1101, 1059, 1025, 758, 703 cm^{-1}

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{28}NO_5^+$ 446.1962, found 446.1966.

4.2.16 *Synthesis of compound* ***15*** Phenol **13** (700.8 mg, 2.05 mmol) was dissolved in DMF (8.2 mL) and cooled to 0 °C. Prenyl bromide (284 μL, 2.46 mmol) and K_2CO_3 (850.0 mg, 6.15 mmol) were added successively, and the mixture was then warmed to room temperature and stirred for 2 h. Water and EtOAc were added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure afforded the crude product, which was further purified by flash chromatography (15/1 PE/EtOAc) afforded compound **15** (756.4 mg, 90%) as a yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.34–7.29 (m, 1H), 6.95–6.92 (m, 2H), 6.27 (d, J = 2.4 Hz, 1H), 6.19 (d, J = 2.4 Hz, 1H), 5.49–5.46 (m, 1H), 4.42 (d, J = 6.8 Hz, 2H), 3.64 (s, 3H), 3.21 (s, 3H), 2.23 (t, J = 6.4 Hz, 2H), 1.77 (s, 3H), 1.70 (s, 3H), 1.64 (t, J = 6.4 Hz, 2H), 1.24 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 158.3, 155.6, 149.6, 149.2, 137.9, 131.8, 130.7, 124.1, 120.9, 120.6, 119.7, 108.9, 103.3, 98.2, 73.9, 64.6, 51.6, 42.3, 32.7, 26.5, 25.7, 18.9, 18.0.

IR (ATR): ν_{max} 2973, 1722, 1577, 1477, 1447, 1432, 1295, 1254, 1150, 1029, 879, 757, 704 cm^{-1}

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{32}NO_4^+$ 410.2326, found 410.2330.

4.2.17 *Gram-scale synthesis of compound* ***16***.2-Amino-5-bromobenzoic acid (8.79 g, 40.70 mmol) was dissolved in dry THF (85 mL) before triphosgene (4.03 g, 13.57 mmol) was added. The mixture was heated for 18 h at 50 °C. The solvent was removed and crude 6-bromo-1*H*-benzo[*d*] [1,3]oxazine-2,4-dione was obtained as an off-white solid, which was used immediately in the next step.

NaH (2.44 g, 60% suspension in mineral oil, 61.05 mmol) was washed with petroleum ether, and covered with DMF (81 mL). To the stirred mixture was added crude 6-bromo-1*H*-benzo[*d*] [1,3] oxazine-2,4-dione in portions followed by MeI (2.79 mL, 44.77 mmol). The mixture was stirred for 18 h, then poured into ice/water. The precipitate which formed was collected, washed with water and dried in *vacuo*. 6-Bromo-1-methyl-1*H*-benzo[*d*] [1,3] oxazine-2,4-dione was obtained as an off-white solid, which was used immediately in the next step.

Crude 6-bromo-1-methyl-1*H*-benzo[*d*] [1,3]oxazine-2,4-dione

was dissolved in DMF (41 mL) and MeOH (12 mL) before DMAP (994.5 mg, 8.14 mmol) was added. The mixture was heated for 4 h at 50 °C. Upon cooling, water and EtOAc were added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (60 mL x 3). The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure afforded the crude product, which was further purified by flash chromatography (50/1 PE/EtOAc) afforded compound **16** (7.41 g, 75%, 3 steps) as a pale yellow solid.

m.p. 67.8–68.8 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 2.4 Hz, 1H), 7.61 (brs, 1H), 7.24 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 6.55 (d, J = 8.8 Hz, 1H), 3.85 (s, 3H), 2.88 (s, 3H).

4.2.18 *Gram-scale synthesis of compound **17***To a stirred solution of silyltriflate **4a** (4.87 g, 10.00 mmol) and compound **16** (2.56 g, 10.50 mmol) in DME (100 mL) was added CsF (4.56 g, 30.00 mmol). The solution was stirred at 80 °C for 24 h, then cooled to room temperature, filtered over silica gel (CH_2Cl_2 eluent). Evaporation under reduced pressure afforded the crude product, which was further purified by flash chromatography (100/1 → 80/1 PE/EtOAc) afforded compound **17** (4.40 g, 86%) as a pale yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 2.4 Hz, 1H), 7.42 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.38–7.29 (m, 5H), 6.87 (d, J = 8.8 Hz, 1H), 6.37 (d, J = 9.6 Hz, 1H), 6.32 (d, J = 2.4 Hz, 1H), 6.12 (d, J = 2.4 Hz, 1H), 5.45 (d, J = 9.6 Hz, 1H), 4.93 (s, 2H), 3.54 (s, 3H), 3.16 (s, 3H), 1.39 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 159.9, 155.5, 148.4, 147.1, 136.7, 134.6, 133.5, 128.5, 127.9, 127.5, 127.4, 125.3, 121.6, 119.1, 112.6, 110.3, 103.3, 91.1, 75.7, 70.0, 51.9, 42.2, 27.5.

IR (ATR): ν_{max} 2972, 1718, 1603, 1477, 1432, 1388, 1288, 1243, 1133, 1111, 1027, 812, 732, 695 cm^{-1}

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{27}BrNO_4^+$ 510.1098, found 510.1102.

4.2.19 *Synthesis of compound **18*** To a Schlenk flask were added compound **17** (325.0 mg, 0.639 mmol), 3-thiopheneboronic acid (245.3 mg, 1.917 mmol) and $(Ph_3P)_2PdCl_2$ (22.5 mg, 0.032 mmol). The flask was degassed with N_2 for 3 times, then Na_2CO_3 (2 M aqueous, 1.28 mL, 2.56 mmol) and dioxane (15 mL) were added to the flask, and then stirred for 18 h at 100 °C. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with water. The mixture was extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography (30/1 PE/EtOAc) afforded compound **18** (286.1 mg, 87%) as a pale yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 2.0 Hz, 1H), 7.58 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.39–7.28 (m, 8H), 7.03 (d, J = 8.8 Hz, 1H), 6.42 (d, J = 10.0 Hz, 1H), 6.27 (d, J = 2.0 Hz, 1H), 6.17 (d, J = 2.0 Hz, 1H), 5.43 (d, J = 10.0 Hz, 1H), 4.94 (s, 2H), 3.57 (s, 3H), 3.22 (s, 3H), 1.39 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.5, 159.9, 155.4, 148.2, 147.6, 141.0, 136.7, 129.7, 128.9, 128.5, 128.4, 127.9, 127.5, 127.0, 126.2, 125.9, 124.1, 120.5, 119.4, 110.2, 103.1, 98.7, 75.6, 69.9, 51.8, 42.4, 27.4.

IR (ATR): ν_{max} 2943, 1713, 1603, 1565, 1486, 1434, 1296, 1236, 1134, 1112, 1029, 777, 695 cm^{-1}

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{30}NO_4S^+$ 512.1890, found 512.1897.

4.2.20 *Synthesis of compound **19*** To a Schlenk flask were added compound **17** (440.2 mg, 0.866 mmol), 4-methoxyphenylboronic acid (394.8 mg, 2.598 mmol) and $(Ph_3P)_2PdCl_2$ (30.4 mg, 0.043 mmol). The flask was degassed with N_2 for 3 times, then Na_2CO_3 (2 M aqueous, 1.73 mL, 3.46 mmol) and dioxane (20 mL) were added to the flask, and then stirred for 16 h at 100 °C. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with water. The mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography (20/1 PE/EtOAc) afforded compound **19** (372.6 mg, 80%) as a pale yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 2.4 Hz, 1H), 7.55 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.39–7.29 (m, 5H), 7.06 (d, J = 8.8 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 6.43 (d, J = 10.0 Hz, 1H), 6.26 (d, J = 2.4 Hz, 1H), 6.18 (d, J = 2.4 Hz, 1H), 5.43 (d, J = 10.0 Hz, 1H), 4.95 (s, 2H), 3.84 (s, 3H), 3.58 (s, 3H), 3.23 (s, 3H), 1.39 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.7, 159.9, 158.9, 155.4, 148.0, 147.7, 136.8, 133.2, 132.4, 129.9, 129.1, 128.5, 127.9, 127.6, 127.0, 124.3, 127.0, 124.3, 120.7, 119.4, 116.0, 114.7, 114.2, 110.2, 103.1, 98.6, 75.6, 70.0, 55.3, 51.8, 42.5, 27.4.

IR (ATR): ν_{max} 2957, 1697, 1605, 1558, 1486, 1435, 1343, 1240, 1135, 1111, 1034, 825, 739, 696 cm^{-1}

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{34}NO_5^+$ 536.2431, found 536.2436.

4.2.21 *Synthesis of compound **20*** To a Schlenk flask were added compound **17** (325.0 mg, 0.639 mmol), potassium vinyltrifluoroborate (256.8 mg, 1.917 mmol) and $(Ph_3P)_2PdCl_2$ (22.5 mg, 0.032 mmol). The flask was degassed with N_2 for 3 times, then Na_2CO_3 (2 M aqueous, 1.28 mL, 2.56 mmol) and dioxane (15 mL) were added to the flask, and then stirred for 16 h at 100 °C. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with water. The mixture was extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography (30/1 PE/EtOAc) afforded compound **20** (255.5 mg, 88%) as a pale yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 2.4 Hz, 1H), 7.42–7.30 (m, 6H), 6.96 (d, J = 8.8 Hz, 1H), 6.64 (dd, J = 17.6 Hz, 10.8 Hz, 1H), 6.39 (d, J = 10.0 Hz, 1H), 6.26 (d, J = 2.4 Hz, 1H), 6.14 (d, J = 2.4 Hz, 1H), 5.65 (d, J = 17.6 Hz, 1H), 5.43 (d, J = 10.0 Hz, 1H), 5.17 (d, J = 10.8 Hz, 1H), 4.94 (s, 2H), 3.55 (s, 3H), 3.20 (s, 3H), 1.39 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.6, 159.9, 155.4, 148.7, 147.5, 136.7, 135.5, 130.1, 129.5, 129.0, 128.5, 127.9, 127.5, 127.1, 123.8, 120.0, 119.3, 112.5, 110.3, 103.2, 98.8, 75.6, 70.0, 51.8, 42.5, 27.4.

IR (ATR): ν_{max} 2964, 1715, 1604, 1493, 1434, 1350, 1295, 1243, 1197, 1133, 1114, 1030, 827, 696 cm^{-1}

HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{29}H_{30}NO_4^+$ 456.2169, found 456.2176.

4.2.22 *Synthesis of compound **21*** To a solution of compound **19** (425.8 mg, 0.80 mmol) in MeOH/THF/H_2O (8.8 mL, 5/5/1) was added $LiOH \cdot H_2O$ (335.7 mg, 8.0 mmol). The resulting mixture was heated under reflux for 12 h. The reaction mixture was subsequently allowed to cool at room temperature and acidified with 2 N HCl (aq). After separating both layers, the aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layers were dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. Purification of the residue by flash column chromatography (4/1 PE/EtOAc) provided compound **21** (402.6 mg, 97%) as a yellow solid.

m.p.75.9–77.0 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.98 (brs, 1H), 8.45 (d, J = 1.6 Hz, 1H), 7.63 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.45–7.38 (m, 4H), 7.36–7.32 (m, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.51 (d, J = 2.4 Hz, 1H), 6.38 (d, J = 2.4 Hz, 1H), 6.13 (d, J = 10.0 Hz, 1H), 5.34 (d, J = 10.0 Hz, 1H), 5.04 (s, 2H), 3.84 (s, 3H), 3.15 (s, 3H), 1.31 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 159.6, 159.6, 155.7, 150.3, 145.1, 138.7, 136.4, 132.0, 131.3, 130.5, 128.6, 128.3, 128.2, 128.0,

127.6, 125.1, 124.3, 117.4, 114.3, 108.9, 101.9, 99.4, 75.7, 70.2, 55.3, 45.0, 27.2.

IR (ATR): ν_{max} 2969, 1684, 1603, 1567, 1482, 1432, 1244, 1134, 1027, 821, 736, 696, 527 cm^{-1}

HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{33}H_{31}NO_5^+$ 521.2197, found 521.2211.

4.2.23 *Synthesis of Compound* ***22*** To a solution of compound **21** (104.3 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (4.0 mL) at −20 °C was added a solution of oxalyl chloride (2 M in CH_2Cl_2, 200 μL, 0.40 mmol). The resulting mixture was stirred at −20 °C for 6 h before quenched with MeOH (2.0 mL). The mixture was warmed to room temperature, and the solvent was evaporated under reduced pressure. The residue was further purified by flash chromatography (8/2/1 PE/EtOAc/CH_2Cl_2) afforded compound **22** (81.8 mg, 81%) as a yellow syrup.

Note: Since the physical state of compound ***22*** *is a very viscous syrup, the residual ethyl acetate (EtOAc) cannot be removed completely. According to the* ^{1}*H NMR spectrum, the content of EtOAc is 6% (wt.), and the corrected yield is 76%.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.69 (d, J = 7.2 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.38 (d, J = 8.8 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 6.52 (d, J = 9.2 Hz, 1H), 6.37 (s, 1H), 5.49 (d, J = 9.2 Hz, 1H), 5.27 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 1.52 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.2, 161.8, 159.2, 159.1, 146.7, 143.3, 136.7, 134.2, 132.4, 131.0, 128.6, 127.9, 127.5, 126.7, 125.5, 124.3, 123.0, 121.8, 116.5, 114.2, 110.7, 103.2, 95.7, 76.3, 70.6, 55.3, 44.2, 26.8.

IR (KBr): ν_{max} 2925, 2602, 2496, 1714, 1621, 1593, 1559, 1496, 1443, 1377, 1238, 1173, 1099, 1026, 885, 811, 736, 697, 680 cm^{-1}

HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{33}H_{29}NO_4^+$ 503.2091, found 503.2100.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132273.

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