A simple synthesis of the debrominated analogue of veranamine

Dawei Liang[a]*, Yueqiu Wang[a], Yanyan Wang[b] and Donghua Di[c]

[a]*Department of Pharmacy & Laboratory, Ya'an Vocational College, Ya'an 625000, Sichuan, P.R. China*

[b]*Department of Traditional Chinese Medicine (TCM), Lianyungang TCM Branch of Jiangsu Union Technical Institute, Lianyungang 222007, Jiangsu, P.R. China*

[c]*School of Pharmacy, Shenyang Pharmaceutical University, Shenyang 110016, Liaoning, P.R. China*

A facile synthesis of 4,5,5-trimethyl-5,6-dihydrobenzo[*c*][2,7]naphthyridine, the debrominated analogue of the marine alkaloid veranamine, has been achieved in three steps with a 38% overall yield. from the commercially available 2-bromoaniline. The key benzo[*c*][2,7]naphthyridine moiety was constructed using a Sonogashira coupling, a tandem Rupe rearrangement–Donnelly–Farrell cyclisation and a Diels–Alder reaction as the key steps. The synthetic strategy allows rapid access to various analogues of veranamine.

Keywords: facile synthesis, veranamine, benzo[*c*][2,7]naphthyridine, 2-bromoaniline, Sonogashira coupling

Natural products have played a substantial role in drug discovery in recent decades,[1] and some have shown striking biological activities[2–4] and have served as lead compounds for pharmaceutical development.[5] Veranamine (**2**, Fig. 1) was isolated by Hamann and co-workers from the marine sponge *Verongula rigida* harvested in the Florida Keys.[6] The evaluation of the compound by means of an *in vivo* assay known as a forced swim test, showed that veranamine had potent antidepressant and antianxiety activity when compared with the commercially available antidepressant drug, desipramine. Consequently, veranamine, including the aromatised benzo[*c*][2,7]naphthyridine ring system, represented a promising heterocyclic lead in antidepressant drug discovery.[7]

In spite of the particularly important pharmacological properties, only a few synthetic routes of veranamine and their analogues have been reported. Most recently, Araujo completed the first total synthesis of veranamine (**2**) in a seven-step process and an overall yield of 20% starting from the commercially available 3-bromoaniline. Veranamine (**2**) was subjected to a reductive dehalogenation using $PdCl_2$(dppf) to afford its debrominated analogue (**1**) in 70% yield. The key step in the synthesis is a novel vinylogous Pictet–Gams reaction to assemble the dihydronaphthyridine scaffold of the natural product.[8] As part of our approach towards the total synthesis of veranamine analogues, we were interested in developing an alternative synthetic route to construct the key benzo[*c*][2,7]naphthyridine core skeleton.

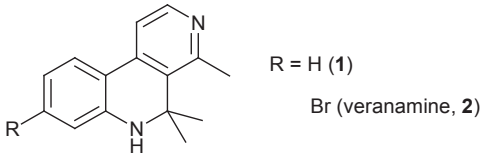
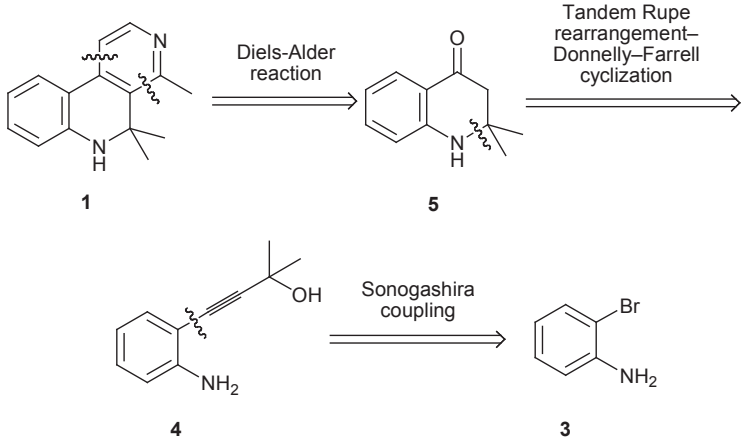


Fig. 1 Structure of veranamine (**2**) and its debrominated analogue (**1**).

Results and discussion

The retrosynthetic analysis is outlined in Scheme 1. It was envisioned that the target compound **1** could be obtained from compound **5** by establishing the 5,6-dihydrobenzo[*c*][2,7]naphthyridine core skeleton through a Diels–Alder reaction. In turn, the quinolin-4-one **5** could be synthesised from the intermediate **4** utilising a tandem Rupe rearrangement–Donnelly–Farrell cyclisation. Compound **4** could be obtained from the commercially available 2-bromoaniline (**3**).

We began the study with the preparation of the key intermediate **5**. The commercially available starting material, 2-bromoaniline (**3**) was coupled with 2-methyl-3-butyn-2-ol *via* the Sonogashira coupling in the presence of $Pd(PPh_3)_2Cl_2$ (0.05 equiv.) and CuI (0.05 equiv.), to afford the intermediate **4** in 95% yield. Cyclisation of the resulting **4** in concentrated



Scheme 1 Retrosynthetic analysis of 4,5,5-trimethyl-5,6-dihydrobenzo[*c*][2,7]naphthyridine (**1**).

* Correspondent. E-mail: ldawei@yahoo.com

HCl–H_2O (1 : 1, v/v) at 120 °C for 1.5 h, followed by a basic workup to give the key intermediate **5** in 75% yield. Compound **5** was characterised by its ^{1}H NMR spectrum which revealed the appearance of methylene protons (2H) at δ 2.60 ppm as a single peak (s, 2H). It was also characterised by the ^{13}C NMR spectrum with the appearance of the carbonyl carbon at δ 193.9 ppm. The mass spectrum exhibited the mass value of *m/z* 176.1071 $(M+H)^+$ was in agreement with the structure. The possible mechanism may be considered for the tandem Rupe rearrangement–Donnelly–Farrell cyclisation reaction which was outlined by Pisaneschi *et al.*[9–13] With the key intermediate **5** in hand, we then turned our attention to construction of the benzo[*c*][2,7]naphthyridine ring. A catalytic Diels–Alder reaction of 1,2,4-triazine with *in situ* generated pyrrolidine enamines under mild conditions was recently used in the development of new procedures for the synthesis of biologically active heterocyclic isoquinoline derivatives.[14] Following this precedent, we undertook the simple catalytic Diels–Alder reaction of quinolin-4-one **5** with corresponding 3-methyl-1,2,4-triazine[15] in refluxing dichloromethane under N_2(g) for 2 days to afford the potentially bioactive 4,5,5-trimethyl-5,6-dihydrobenzo[*c*][2,7]naphthyridine (**1**) and its regional isomer **6** (Scheme 2). These two isomers **1** and **6** were separated by column chromatography in 53% and 14% yields, respectively. The ^{1}H NMR results, showed that the isomer **1** was the target product due to the appearance of a signal characteristic for the methyl group (C-4) at δ 2.69 ppm while in the isomer **6** the methyl proton appeared at δ 2.28 ppm. The ^{1}H NMR, ^{13}C NMR and HRMS results of compound **1** were in agreement with those reported in the literature.[8] Moreover, in the NOE difference experiments for the isomer **1** and **6** (Fig. 2). Selective irradiation of the methyl protons (C-4) in compound **1** at δ 2.69 ppm produced an enhancement of 4.3% in the signal of the dimethyl protons (C-5), which revealed that the methyl group was close to the dimethyl group on one side of the naphthyridine ring. In contrast, the irradiation of the methyl group (C-1) in the isomer **6** at δ 2.28 ppm enhanced the signal intensity (12.7%) of the aromatic proton (C-10), and thus confirmed their regio-relationship. This synthetic method is regarded as an efficient procedure from the viewpoint of the number of steps and the overall yields, and has a great potential to be utilised extensively in the synthesis of the veranamine derivatives.

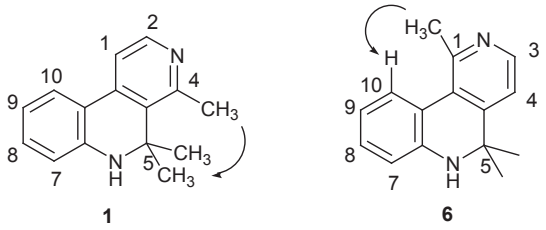


Fig. 2 Observed NOE differences for the isomer **1** and **6**.

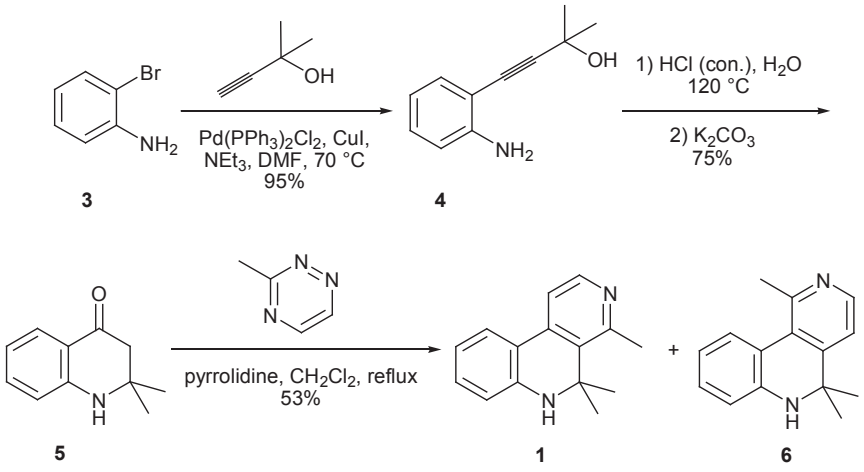
Conclusion

In conclusion, a facile synthesis of 4,5,5-trimethyl-5,6-dihydrobenzo[*c*][2,7]naphthyridine (**1**) *via* a 3-step process was achieved with 38% overall yield starting from the commercially available 2-bromoaniline (**3**). The Rupe rearrangement–Donnelly–Farrell cyclisation led to the quinolin-4-one moiety, and the catalytic Diels–Alder reaction afforded the benzo[*c*][2,7]naphthyridine ring were the key steps. The newly synthetic strategy allows rapid access to various analogues of veranamine.

Experimental

Melting points were determined on an X–5 digital microscope melting point apparatus (Yuhua, China) and are uncorrected. Some commercially available solvents were dried by standard procedures before use: DMF (CaH_2), Et_3N (KOH). Other commercial materials were analytical grade and used without further purification. IR spectra were run as KBr discs (and neat for liquid samples) on a PerkinElmer 120–000A apparatus (υ_{max} in cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker ARX–400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) spectrometer using TMS as an internal standard (chemical shifts in δ values, *J* in Hz). 1D selective NOESY measurements were performed at 25.0 °C using the standard Bruker pulse program (selnogp). High–resolution MS data were obtained on Agilent–6520 QTOF LC/MSD spectrometer, using ESI ionisation. Column chromatography was performed on silica gel (200–300 mesh, Qingdao Haiyang Chemical Co., Ltd, Qingdao, China). Analytical TLC was performed on plates precoated with silica gel (GF254, 0.25 mm, Qingdao Haiyang Chemical Co., Ltd, Qingdao, China) and iodine vapour was used to develop colour on the plates.

4-(2-Aminophenyl)-2-methyl-but-3-yn-2-ol (**4**): 2-Methyl-but-3-yn-2-ol (1.01 g, 12 mmol) was added at room temperature to a stirred solution of 2-bromoaniline (**3**) (1.72 g, 10 mmol) in DMF (15 mL) and Et_3N (5 mL). Then $Pd(PPh_3)_2Cl_2$ (0.35 g, 0.5 mmol) and CuI (0.10 g, 0.05 mmol) were added to the reaction mixture under a nitrogen atmosphere and the mixture was stirred at 70 °C for 5 h. After completion of the reaction (monitored by TLC) the reaction mixture was cooled and quenched with H_2O (50 mL). The resulting mixture



Scheme 2 Synthesis of 4,5,5-trimethyl-5,6-dihydrobenzo[*c*][2,7]naphthyridine (**1**).

was extracted with dichloromethane (3 × 20 mL). The combined organic phase was washed with brine (3 × 10 mL) and dried over anhydrous $MgSO_4$, and then concentrated *in vacuo*. The residue was chromatographed on silica gel using 20% EtOAc/petroleum ether, affording **4** 1.66 g (95%) as a brown solid. m.p. 40–42 °C (lit.[16] 39–41 °C); IR (KBr): 3357, 2979, 2925, 2213, 1614, 1490, 1156, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.0 Hz, 1H), 7.12–7.09 (m, 1H), 6.69 (t, *J* = 7.2 Hz, 2H), 4.20 (s, 2H), 1.64 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 132.1, 129.1, 118.0, 115.7, 113.5, 97.9, 80.2, 66.0, 31.5; HRMS (ESI) calcd for $C_{11}H_{13}NO$ $(M+H)^+$: 176.1075, found: 176.1081.

2,2-Dimethyl-2,3-dihydro-1H-quinolin-4-one (**5**): A solution of 4-(2-aminophenyl)-2-methyl-but-3-yn-2-ol (**4**) (1.75 g, 10 mmol) in concentrated HCl–H_2O (30 mL) (1 : 1, v/v) was heated at 120 °C for 1.5 h. When the reaction was complete, the reaction mixture was then concentrated *in vacuo*. H_2O (30 mL) was added and followed by K_2CO_3 to pH = 11. The mixture was extracted twice with CH_2Cl_2 and the combined organic phases were washed water, saturated brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by using 40% EtOAc/petroleum ether, affording 1.31 g (75%) of **5** as a light yellow oil. IR (KBr): 3330, 2923, 2849, 1657, 1610, 1480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (dd, *J* = 1.4 and 7.9 Hz, 1H), 7.33–7.26 (m, 1H), 6.70–6.65 (m, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 4.17 (s, 1H), 2.60 (s, 2H), 1.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 149.7, 135.2, 127.1, 118.0, 117.5, 115.7, 53.5, 50.5, 27.6; HRMS (ESI) calcd for $C_{11}H_{13}NO$ $(M+H)^+$: 176.1075, found: 176.1071.

4,5,5-Trimethyl-5,6-dihydrobenzo[c][2,7]naphthyridine (**1**) *and its isomer* (**6**): A solution of 3-methyl-1,2,4-triazine (0.95 g, 10 mmol) in dichloromethane (15 mL) under N_2 (g) was treated sequentially with 2,2-dimethyl-2,3-dihydro-1*H*-quinolin-4-one (**5**) (1.75 g, 10 mmol) and pyrrolidine (0.71 g, 10 mmol). Active 4 Å molecular sieve (2.0 g) was added, and then the reaction mixture was heated to reflux for 2 days. Then, the solvent was removed *in vacuo* and the resulting mixture was purified by using 10% EtOAc/petroleum ether to afford 1.19 g (53%) of **1** and 0.32 g (14%) of the isomer **6**. Compound **1** was isolated as a brown solid; m.p. 141–143 °C (lit.[8] 143–144 °C); IR (KBr): 3247, 2960, 1610, 1595, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, *J* = 5.0 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.40 (d, *J* = 5.0 Hz, 1H), 7.15–7.10 (m, 1H), 6.79–6.72 (m, 1H), 6.58 (dd, *J* = 7.2, 1.0 Hz, 1H), 3.76 (s, 1H), 2.69 (s, 3H), 1.60 (d, *J* = 1.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 147.1, 144.2, 139.2, 134.1, 130.7, 124.4, 119.0, 118.7, 115.2, 115.0, 54.0, 29.5, 26.7; HRMS (ESI) calcd for $C_{15}H_{16}N_2$ $(M+H)^+$: 225.1391, found: 225.1387. Compound **6** was isolated as a brown solid; m.p. 145–147 °C; IR (KBr): 3250, 2961, 1610, 1597, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J* = 5.0 Hz, 1H), 7.80 (d, *J* = 5.0 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.25–7.19 (m, 1H), 7.07–7.01 (m, 1H), 6.65 (dd, *J* = 7.2, 1.0 Hz, 1H), 2.87 (s, 1H), 2.28 (s, 3H), 1.58 (d, *J* = 1.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 153.9, 152.5, 151.7, 139.1, 127.9, 121.8, 121.0, 116.3, 107.8, 107.3, 57.2, 29.1, 25.9; HRMS (ESI) calcd for $C_{15}H_{16}N_2$ $(M+H)^+$: 225.1391, found: 225.1387.

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