Research on Chemical Intermediates
https://doi.org/10.1007/s11164-019-03977-z

A combined pathway for the synthesis of nitidine family alkaloids

Gangaram Pallikonda[1] · Chang-Yu Hsieh[1] · Haw-Lih Su[2] · Jen-Chieh Hsieh[1]

Received: 26 April 2019 / Accepted: 28 June 2019

Abstract
Three related alkaloids, oxynitidine, nitidine and 5,6-dihydronitidine, have been afforded by the new synthetic protocols. In this approach, the Ni-catalyzed annulation reaction is indicated as the key step to construct the isoquinolinone core structure. The subsequent transformations lead to the target alkaloids.

Keywords Alkaloids · Benzo[*c*]phenanthridine · Nitidine · Oxynitidine · 5, 6-Dihydronitidine

Introduction

The benzo[*c*]phenanthridine alkaloids are important isoquinoline-type alkaloids. So far, over than eighty alkaloids with this core structure have been identified and isolated from *papaveraceous*, *Rutaceae* and *Fumariaceae* plants [1]. Because of their significant pharmacological properties, the benzo[*c*]phenanthridine alkaloids have attracted considerable attention from the synthetic and the pharmaceutical chemists [2, 3]. Among them, the nitidine salt and its structural analogs have been extremely often reported and studied for a long time. In 1958, Arthur first isolated the nitidine hydroxide salt from the roots of *Zanthoxylum nitidum*, and it was later isolated from a variety of *Fagura* species [4]. The nitidine salt with chloride as counter anion has been found to possess several bioactivities, including inhibition of yeast respiration [5], cardiovascular activity [6, 7], activity for the anti-inflammatory [8] and analgesic activities [9, 10]. In addition, because of the strong inhibition of DNA topoisomerase I, nitidine and its derivatives have been familiar as promising anti-tumor drug candidates [11–13]; this inhibition also makes them exhibit strong anti-leukemic activity in the leukemia L-1210 and P-388 systems [14].

✉ Jen-Chieh Hsieh
jchsieh@mail.tku.edu.tw

[1] Department of Chemistry, Tamkang University, New Taipei City 25137, Taiwan, ROC

[2] Central Laboratories Unit, Qatar University, Doha, Qatar

Published online: 20 September 2019

The unique structural features of benzo[*c*]phenanthridine alkaloids with remarkable biological properties and their limited availability from natural resources made them as intriguing targets for total synthesis. Owing to the wide applications, the design and development of simple and efficient strategies for their construction remains a challenge for the synthetic community. Thus, much effort has been focused on the development of facile and straightforward route for the synthesis of benzo[*c*]phenanthridines.

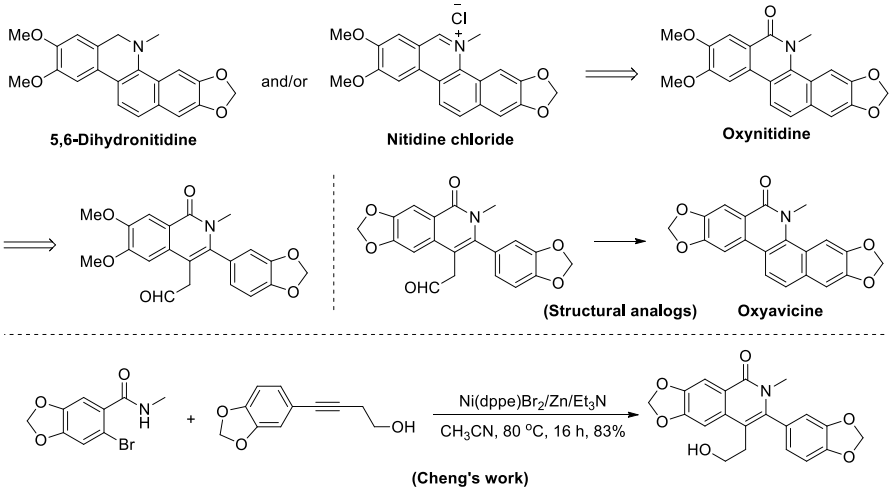
The reported literature for the synthesis of benzo[*c*]phenanthridine structures includes (1) Pd-catalyzed coupling of azabicyclic alkene with *o*-iodobenzene followed by tandem cyclization [15], (2) domino arylation of aryl triflates [16], (3) imine–toluamide condensation [17], (4) cycloaddition of the lithiated toluamide–benzonitrile [18, 19] and (5) condensation of homophthalic ester with imine [20]. Although a lot of methods are known for the construction of benzo[*c*]phenanthridine alkaloids by either classical or modern pathways, most of them can only proceed in harsh reaction conditions or use expensive catalysts with poor yields. In this concern, Cheng has reported the synthesis of substituted isoquinolinone derivatives through the Ni-catalyzed annulation reaction under mild condition with satisfied yields, and applied this reaction to synthesize the oxyavicine as well [21]. Inspired by Cheng's work, and also due to our continuous interest in the synthesis of heterocyclic compounds and natural alkaloids [22–33], we tried to follow their strategy to approach oxynitidine and extended the synthetic steps to synthesize two other related *Rutaceae* alkaloids, nitidine chloride and 5,6-dihydronitidine.

Herein, we reported the combined steps for the synthesis of three nitidine family alkaloids by using the Ni-mediated annulation as the key step to construct the isoquinolinone core structure.

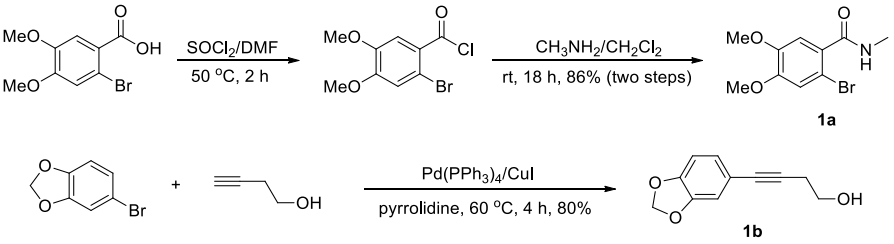
Result and discussion

Our study started from the retro-synthetic analysis, which mainly relies on two transformations. The first one is the reduction of oxynitidine to generate either the 5,6-dihydronitidine or the nitidine chloride; the second one is the formation of oxynitidine through the Friedel–Crafts reaction followed by the dehydration, which can fully refer to Cheng's work for the synthesis of oxyavicine (Scheme 1). According to their report, formation of the precursor of oxyavicine can be accomplished through the Ni-catalyzed cyclization of *o*-bromobenzamide with alkyne. Thus, we tried to synthesize the required substrates for the construction of our isoquinolinone core structure.

The preparation of starting substrates depends on the amidation and the Sonogashira coupling reaction (Scheme 2). As indicated, 2-bromo-4,5-dimethoxy-*N*-methylbenzamide (**1a**) could be obtained simply by the treatment of 2-bromo-4,5-dimethoxybenzoic acid with $SOCl_2$ followed by methyl amine in 86% yield. And the 4-(benzo[*d*][1,3]dioxol-5-yl)but-3-yn-1-ol (**1b**) could be generated through the typical Sonogashira coupling reaction of 5-bromobenzo[*d*][1,3]dioxole with 3-butyne-1-ol in 78% yield. After we got the required substrates **1a** and **1b**, we explored the



Scheme 1 Retrosynthetic pathway of oxynitidine, nitidine chloride and 5,6-dihydronitidine



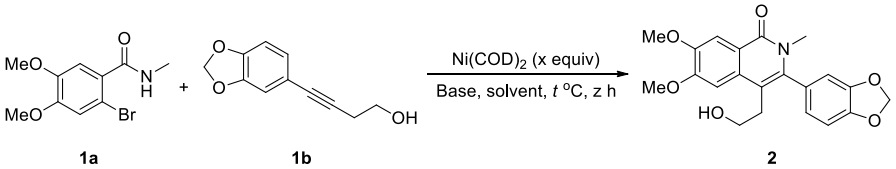
Scheme 2 Synthesis of substrates

cyclization for the construction of our desired isoquinolinone core structure (**2**, Table 1).

To optimize the reaction condition, we tried to use the Ni(dppe)Br_2/Zn as the catalytic system in the beginning. However, this catalytic system is only able to efficiently construct our desired structure in small scale (0.2 mmol). Larger reaction scale (over than 0.4 mmol) would cause a significantly lower yield. In addition, the unstable reaction yields in the big reaction scale also made us explore other suitable reaction protocol. Thus, we selected the easily handled Ni$(COD)_2$ as our requisite catalyst for further study.

We proceeded our further survey by using the stoichiometric amount of Ni$(COD)_2$ to investigate the effect of every factor. As revealed in Table 1, when we used **1a** and **1b** as the substrates in the presence of 1.0 equivalent of Ni$(COD)_2$ with 2.0 equivalent of Et_3N under CH_3CN at 80 °C, the reaction was able to be completed within 2 h, and the desired product **2** was provided in 82% yield (entry 1). Changing the base or the solvent did not improve the reaction yields (entries 2–9), while changing the reaction temperature and the amount of base also did not significantly affect

Table 1 Optimization of the reaction conditions for the cyclization



1a **1b** **2**

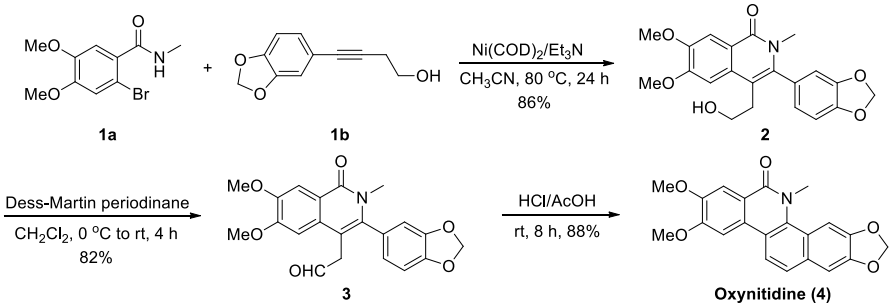
Entry	*x*	Base (*y* equiv)	Solvent	*z* (h)	*t* (°C)	Yield (%)[a]
1	1.0	Et_3N (2)	CH_3CN	2	80	82
2	1.0	Et_3N (2)	MeOH	2	80	54
3	1.0	Et_3N (2)	THF	2	80	68
4	1.0	Et_3N (2)	Toluene	2	80	77
5	1.0	Et_3N (2)	DMF	2	80	74
6	1.0	K_2CO_3 (2)	CH_3CN	2	80	40
7	1.0	Na_2CO_3 (2)	CH_3CN	2	80	35
8	1.0	NaOMe (2)	CH_3CN	2	80	51
9	1.0	DIPEA (2)	CH_3CN	2	80	73
10	1.0	Et_3N (2)	CH_3CN	2	60	78
11	1.0	Et_3N (2)	CH_3CN	2	90	82
12	1.0	Et_3N (1)	CH_3CN	2	80	80
13	1.0	Et_3N (3)	CH_3CN	2	80	75
14	1.0	Et_3N (4)	CH_3CN	2	80	73
15	0.4	Et_3N (2)	CH_3CN	8	80	84
16	0.2	Et_3N (2)	CH_3CN	13	80	83
17	0.1	Et_3N (2)	CH_3CN	24	80	86
18	0.05	Et_3N (2)	CH_3CN	> 30	80	6

Reaction condition: **1a** (0.4 mmol, 1.0 equiv), **1b** (0.44 mmol, 1.1 equiv), $Ni(COD)_2$ (*x* equiv), base (*y* equiv), solvent (2.0 mL), indicated temperature, under N_2, *z* h

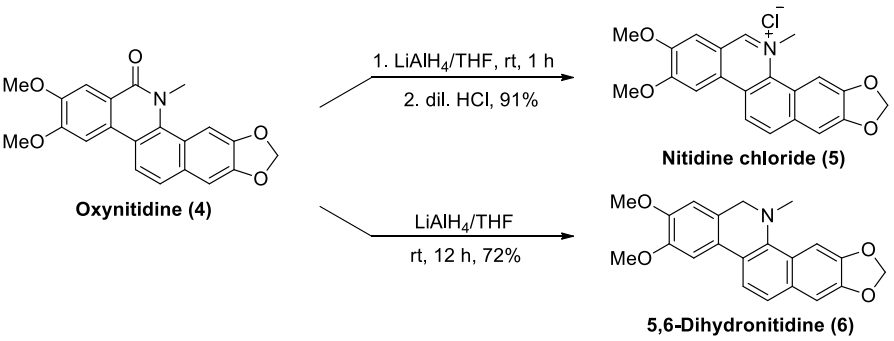
[a]Isolated yields

the yields (entries 10–14). We then reduced the amount of $Ni(COD)_2$ and carefully monitored the reaction. It was found that while the amount of $Ni(COD)_2$ decreasing, the reaction time increased, but the yields did not have obvious change except 5 mol% $Ni(COD)_2$ (entries 15–18). Therefore, we selected the 10 mol% $Ni(COD)_2$ with 2.0 equivalent of Et_3N under CH_3CN at 80 °C for 24 h as our condition for the synthesis of the isoquinolinone core structure **2**.

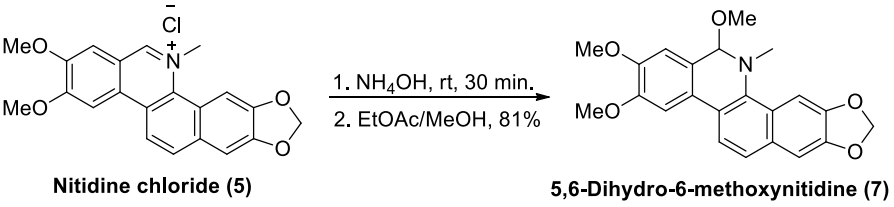
After getting the optimized condition for the Ni-catalyzed cyclization to form the isoquinolinone core structure **2**, we then proceeded the further transformations to furnish our desired alkaloids, and thus, the subsequent four steps have been conducted (Schemes 3, 4). Compound **3** could be obtained from compound **2** through the Dess–Martin periodinane (**DMP**) oxidation by using CH_2Cl_2 as solvent at 0 °C to ambient temperature in 82% yield. Our first targeted alkaloid oxynitidine (**4**)



Scheme 3 Procedure for the synthesis of oxynitidine



Scheme 4 Synthesis of nitidine chloride and 5,6-dihydronitidine



Scheme 5 Synthesis of 5,6-dihydro-6-methoxynitidine

could be generated through the acid-catalyzed ring-closure/dehydration reaction of compound **3** in 88% yield. Reduction of the oxynitidine (**4**) by $LiAlH_4$ followed by the treatment with diluted HCl leads to the second alkaloid nitidine chloride (**5**) in 91% yield (Scheme 4). When the reduction was conducted with excess $LiAlH_4$, the third targeted alkaloid 5,6-dihydronitidine (**6**) could be also provided smoothly in 72% yield.

An additional related alkaloids 5,6-dihydro-6-methoxynitidine (**7**) could be also furnished via the reported procedure by treating nitidine chloride with ammonium hydroxide at room temperature and then the methoxylation by hot methanol (Scheme 5) [34].

The overall yields from the substrates **1a** and **1b** to oxynitidine, nitidine and 5,6-dihydronitidine are 60%, 55% and 40%, respectively. Including the preparation of **1a** and **1b** from the commercial sources, the overall yields would be calibrated to around 80% of the above numbers.

Conclusion

In conclusion, we have provided a simple and concise strategy for the synthesis of *Rutaceae* alkaloids oxynitidine, nitidine and 5,6-dihydronitidine from the easily synthesized starting substrates employing the Ni-assisted annulation reaction as the key step. This strategy contained a combined pathway of the previous reports but with different reaction protocols, which provided the targeted three alkaloids in satisfied overall yields from the commercial sources. Further studies to explore the possibility to synthesize the alkaloids with structural similarity by using the present pathway are currently underway.

Experimental section

***Procedure for the synthesis of 2-bromo-4,5-dimethoxy-N-methylbenzamide* (1a)** 2-Bromo-4,5-dimethoxybenzoic acid (520 mg, 2 mmol, 1.0 equiv) stirring in $SOCl_2$ (1.25 mL) was added DMF (0.01 mL, 0.1 mmol, 10 mol%) and kept stirring at 50 °C for 2 h. The resulted mixture was concentrated in vacuo and then dissolved in CH_2Cl_2 (10 mL). A methylamine solution (40% in H_2O, 20 mL) was then added to the residue/CH_2Cl_2 solution and kept stirring at room temperature for 18 h. Upon completion of the reaction as observed by TLC, the mixture was diluted with water (15 mL) and extracted with EtOAc (4 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography [$R_f = 0.5$ (20% ethyl acetate in hexanes)] to give compound **1a** as white solid (464 mg, 85%); mp: 146 °C; IR (KBr): 1502, 1647, 2939 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.01 (d, $J = 4.8$ Hz, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 6.28 (s, br, 1H), 6.98 (s, 1H), 7.21 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8, 56.1, 56.3, 109.7, 113.0, 115.7, 129.1, 148.4, 150.8, 167.5; HRMS [(EI), (M^+)]:273.0004 (cal. for $C_{10}H_{12}BrNO_3$ 273.0001).

***Procedure for the synthesis of 4-(benzo[d][1,3]dioxol-5-yl)but-3-yn-1-ol* (1b)** To a solution of 1-bromo-3,4-(methylenedioxy)benzene (2.05 mL, 17 mmol, 1.0 equiv) in ultra pure water (35 mL) was added but-3-yn-1-ol (1.54 mL, 20.4 mmol, 1.2 equiv), pyrrolidine (1.40 mL, 17 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (982 mg, 0.85 mmol, 5 mol%) and CuI (324 mg, 1.7 mmol, 10 mol%) under nitrogen atmosphere. The reaction mixture was kept stirring at 60 °C for 4 h and cooled to the room temperature. The aqueous layer was extracted with EtOAc (100 mL × 2), and the organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography [$R_f = 0.4$ (25% ethyl acetate in hexanes)] to give compound **1b** as brownish oil (2.59 g, 80%); IR

(KBr): 1038, 1260, 1275, 1643, 3005 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.64 (t, $J=6.0$ Hz, 2H), 3.78 (t, $J=6.0$ Hz, 2H), 5.94 (s, 2H), 6.71 (d, $J=7.8$ Hz, 1H), 6.85 (d, $J=1.2$ Hz, 1H), 6.92 (dd, $J=8.4$, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 61.1, 82.1, 84.6, 101.2, 108.3, 111.6, 116.5, 126.0, 147.3, 147.5; HRMS [(EI), (M^+)]: 190.0627 (cal. for $C_{11}H_{10}O_3$ 190.0630).

***Procedure for the synthesis of 3-(Benzo[d][1,3]dioxol-5-yl)-4-(2-hydroxyethyl)-6,7-dimethoxy-2-methylisoquinolin-1(2H)-one* (2)** In an nitrogen-filled glove box, a 4-mL vial equipped with a magnetic stirrer bar was charged sequentially with compound **1a** (109 mg, 0.4 mmol, 1.0 equiv), compound **1b** (84 mg, 0.44 mmol, 1.1 equiv), $Ni(COD)_2$ (11 mg, 0.04 mmol, 10 mol%) and Et_3N (0.11 mL, 0.8 mmol, 2.0 equiv), followed by the addition of CH_3CN (2.0 mL). The vial was closed and removed from the glove box, and the reaction mixture was kept stirring at 80 °C for 24 h. Upon cooling to room temperature, the mixture was diluted with CH_2Cl_2 (10 mL) and filtered through a Celite pad with additional CH_2Cl_2 (10 mL) as an eluent. The organic solution was concentrated under reduced pressure, and the residue was purified through flash column chromatography [$R_f=0.2$ (75% ethyl acetate in hexanes)] to give the compound **2** as white solid (127 mg, 83%); mp: 237 °C; IR (KBr): 1034, 1240, 1636, 2875 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.73–2.82 (m, 2H), 3.26 (s, 3H), 3.72 (t, $J=7.2$ Hz, 2H), 4.01 (s, 3H), 4.03 (s, 3H), 6.07 (s, 2H), 6.73–6.74 (m, 2H), 6.93 (d, $J=8.4$ Hz, 1H), 7.11 (s, 1H), 7.90 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.9, 34.0, 56.1, 56.2, 62.5, 101.5, 103.7, 108.2, 108.8, 109.7, 110.9, 119.6, 123.1, 128.9, 131.7, 140.2, 148.0, 148.2, 149.1, 153.4, 161.7; HRMS [(EI), (M^+)]: 383.1363 (cal. for $C_{21}H_{21}NO_6$ 383.1369).

***Procedure for the synthesis of 2-(2-(Benzo[d][1,3]dioxol-5-yl)-6,7-dimethoxy-4-oxo-3,4-dihydronaphthalen-1-yl)acetaldehyde* (3)** Compound **2** (115 mg, 0.3 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (10 mL) and stirred at 0 °C in an ice bath. The solution was added Dess–Martin periodinane (191 mg, 0.45 mmol, 1.5 equiv) in one portion, and the reaction was kept stirring at room temperature for 4 h. The reaction was quenched at 0 °C by stirring with a solution of $Na_2S_2O_3$ (0.2 g in 5 mL water) and $NaHCO_{3(aq)}$ (saturated, 5 mL) for 10 min to quench the unreacted Dess–Martin reagent. The reaction mixture was diluted with CH_2Cl_2 and extracted by aqueous $NaHCO_3$. The combined organic layer was collected, dried over the $MgSO_4$ and concentrated in vacuo. The residue was purified through flash column chromatography [$R_f=0.5$ (40% ethyl acetate in hexanes)] to give the compound **3** as pale yellow solid (94 mg, 82%); mp: 223 °C; IR (KBr): 1035, 1274, 1514, 1638, 1716, 3005 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.30 (s, 3 H), 3.50–3.51 (m, 2H), 3.93 (s, 3H), 3.99 (s, 3 H), 6.05 (s, 2H), 6.70–6.72 (m, 2H), 6.75 (s, 1H), 6.91 (d, $J=8.4$ Hz, 1H), 7.87 (s, 1H), 9.56 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.2, 44.4, 56.0, 56.2, 101.6, 103.3, 106.0, 108.3, 109.0, 109.3, 119.4, 122.9, 128.4, 131.4, 141.6, 148.3, 148.4, 149.2, 153.5, 161.8, 199.6; HRMS [(EI), (M^+)]: 381.1216 (cal. for $C_{21}H_{19}NO_6$ 381.1212).

***Procedure for the synthesis of oxynitidine* (4)** To a solution of compound **3** (114 mg, 0.3 mmol, 1.0 equiv) in acetic acid (4 mL) was added 10% hydrochloric acid (0.2 mL) at room temperature. After stirring the reaction for 8 h, acetic acid was removed in vacuo. The resulted solid was then dissolved in CH_2Cl_2 and extracted by aqueous $NaHCO_3$. The combined organic layer was collected, dried over the $MgSO_4$ and concentrated in vacuo. The residue was purified through flash column chromatography [$R_f = 0.59$ (70% ethyl acetate in hexanes)] to give oxynitidine as white solid (96 mg, 88%); mp: 279 °C; IR (KBr): 1041, 1274, 1637, 3005 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.98 (s, 3H), 4.06 (s, 3H), 4.10 (s, 3H), 6.10 (s, 2H), 7.18 (s, 1H), 7.56 (d, $J = 9.0$ Hz, 1H), 7.59 (s, 1H), 7.64 (s, 1H), 7.93 (s, 1H), 7.99 (d, $J = 9.0$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.2, 56.1, 56.3, 101.5, 102.6, 102.8, 104.8, 108.6, 116.7, 118.3, 119.1, 121.0, 123.2, 128.9, 131.8, 135.9, 147.0, 147.5, 149.7, 153.5, 164.3; HRMS [(EI), (M^+)]: 363.1110 (cal. for $C_{21}H_{17}NO_5$ 363.1107).

***Procedure for the synthesis of nitidine chloride* (5)** $LiAlH_4$ (11 mg, 0.3 mmol, 1.0 equiv) was added to a solution of oxynitidine (109 mg, 0.3 mmol, 1.0 equiv) in dry THF (5 mL) and kept stirring at room temperature for 60 min. EtOAc was then added to quench the excess hydride. Filter and concentrated, the reaction residue was then treated with 10% HCl (5 mL) at room temperature. The resulting precipitates were collected by filtration to afford nitidine chloride as yellow solid (95 mg, 91%); mp: 280 °C; IR (KBr): 1260, 1275, 1636 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 4.03 (s, 3H), 4.22 (s, 3H), 4.89 (s, 3H), 6.33 (s, 2H), 7.76 (s, 1H), 7.91 (s, 1H), 8.27 (d, $J = 9.0$ Hz, 1H), 8.30 (s, 1H), 8.35 (s, 1H), 8.89 (d, $J = 9.0$ Hz, 1H), 9.87 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.2, 56.1, 56.3, 101.5, 102.7, 102.8, 104.8, 108.7, 116.7, 118.4, 119.2, 121.0, 123.2, 128.9, 131.9, 135.9, 147.0, 147.5, 149.7, 153.5, 164.3; HRMS [(FAB), (M^+)]: 348.1236 (cal. for $C_{21}H_{18}NO_4^+$ 348.1230).

***Procedure for the synthesis of 5,6-dihydronitidine* (6)** $LiAlH_4$ (22 mg, 0.6 mmol, 2.0 equiv) was added to a solution of oxynitidine (109 mg, 0.3 mmol, 1.0 equiv) in dry THF (5 mL) and kept stirring at room temperature for 12 h. The reaction mixture was diluted by CH_2Cl_2 and extracted by water. The organic layer was collected, dried over the $MgSO_4$ and concentrated in vacuo. The residue was purified through flash column chromatography [$R_f = 0.5$ (100% CH_2Cl_2)] to give 5,6-dihydronitidine as yellow solid (75 mg, 72%); mp: 213 °C; IR (KBr): 1032, 1463, 1641 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.60 (s, 3H), 3.95 (s, 3H), 4.00 (s, 3H), 4.14(s, 2H), 6.05 (s, 2H), 6.80 (s, 1H), 7.12 (s, 1H), 7.31 (s, 1H), 7.50 (d, $J = 8.4$ Hz, 1H), 7.66 (s, 1H), 7.69 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.0, 54.8, 56.0, 56.2, 100.6, 101.0, 104.3, 106.4, 110.1, 119.9, 123.8, 124.4, 124.5, 124.9, 126.4, 130.7, 142.8, 147.4, 148.1, 148.6, 148.8; HRMS [(EI), (M^+)]: 349.1319 (cal. for $C_{21}H_{19}NO_4$ 349.1314).

Acknowledgements We thank the Ministry of Science and Technology of Taiwan (ROC) for the financial support of this research (MOST 107-2113-M-032-006) and the fellowship for Gangaram Pallikonda (MOST 107-2811-M-032-002).

References

1. B.D. Krane, M.O. Fagbule, M. Shamma, B. Gözler, J. Nat. Prod. **47**, 1 (1984)
2. J.-P. Eun, G.Y. Koh, Biochem. Biophys. Res. Commun. **317**, 618 (2004)
3. H. Fuchino, M. Kawano, K. Mori-Yasumoto, S. Sekita, M. Satake, T. Ishikawa, F. Kiuchi, N. Kawahara, Chem. Pharm. Bull. **58**, 1047 (2010)
4. K.-Y. Zee-Cheng, C.C. Cheng, J. Heterocycl. Chem. **10**, 85 (1973)
5. R.H. Vallejos, O.A. Roveri, Biochem. Pharmacol. **21**, 3179 (1972)
6. I. Addae-Mensah, R. Munenge, A.N. Guantai, Phytother. Res. **3**, 165 (1989)
7. P. Li, S. Yan, X. Dong, Z. Li, Y. Qiu, C. Ji, J. Zang, M. Ji, W. Li, H. Wang, Z. Liu, X.L. Wang, J. Ye, D. Ma, Med. Chem. **14**, 60 (2018)
8. Z. Wang, W. Jiang, Z. Zhang, M. Qian, B. Du, J. Ethnopharmacol. **144**, 145 (2012)
9. M. Kang, H. Ou, R. Wang, W. Liu, A. Tang, J. BUON **19**, 130 (2014)
10. A.K. Larsen, L. Grondard, J. Couprie, B. Desoize, L. Comoe, J.-C. Jardillier, J.-F. Riou, Biochem. Pharmacol. **46**, 1403 (1993)
11. L. Guo, X. Liu, K. Nishikawa, W. Plunkett, Mol. Cancer Ther. **6**, 1501 (2007)
12. T. Onda, E. Toyoda, O. Miyazaki, C. Seno, S. Kagaya, K. Okamoto, K. Nishikawa, Cancer Lett. **259**, 99 (2008)
13. Z. Taira, M. Matsumoto, S. Ishida, T. Ichikawa, Y. Sakiya, Chem. Pharm. Bull. **42**, 1556 (1994)
14. R.K.-Y. Zee-Cheng, C.C. Cheng, J. Med. Chem. **18**, 66 (1975)
15. P. Lv, K. Huang, L. Xie, X. Xu, Org. Biomol. Chem. **9**, 3133 (2011)
16. M. Blanchot, D.A. Candito, F. Larnaud, M. Lautens, Org. Lett. **13**, 1486 (2011)
17. R.D. Clark, Jahangir, J. Org. Chem. **53**, 2378 (1988)
18. T.N. Le, S.G. Gang, W.-J. Cho, J. Org. Chem. **69**, 2768 (2004)
19. T.N. Le, S.G. Gang, W.-J. Cho, Tetrahedron Lett. **45**, 2763 (2004)
20. M. Cushman, L. Cheng, J. Org. Chem. **43**, 286 (1978)
21. C.-C. Liu, K. Parthasarathy, C.-H. Cheng, Org. Lett. **12**, 3518 (2010)
22. L.-H. Yeh, H.-K. Wang, G. Pallikonda, Y.-L. Ciou, J.-C. Hsieh, Org. Lett. **21**, 1730 (2019)
23. W.-L. Chen, Y.-Y. Jhang, J.-C. Hsieh, Res. Chem. Intermed. **43**, 3517 (2017)
24. W.-L. Chen, C.-Y. Chen, Y.-F. Chen, J.-C. Hsieh, Org. Lett. **17**, 1613 (2015)
25. Y.-F. Chen, J.-C. Hsieh, Org. Lett. **16**, 4642 (2014)
26. Y.-F. Chen, Y.-S. Wu, Y.-H. Jhan, J.-C. Hsieh, Org. Chem. Front. **1**, 253 (2014)
27. J.-C. Wan, J.-M. Huang, Y.-H. Jhan, J.-C. Hsieh, Org. Lett. **15**, 2742 (2013)
28. J.-C. Hsieh, A.-Y. Cheng, J.-H. Fu, T.-W. Kang, Org. Biomol. Chem. **10**, 6404 (2012)
29. J.-C. Hsieh, Y.-C. Chen, A.-Y. Cheng, H.-C. Tseng, Org. Lett. **14**, 1282 (2012)
30. M.-H. Chen, J.-C. Hsieh, Y.-H. Lee, C.-H. Cheng, ACS Catal. **8**, 9364 (2018)
31. Y.-Y. Jhang, T.-T. Fan-Chiang, J.-M. Huang, J.-C. Hsieh, Org. Lett. **18**, 1154 (2016)
32. C.-C. Liu, J.-C. Hsieh, R.P. Korivi, C.-H. Cheng, Chem. Eur. J. **21**, 9544 (2015)
33. Y.-H. Jhan, T.-W. Kang, J.-C. Hsieh, Tetrahedron Lett. **54**, 1155 (2013)
34. M.E. Wall, M.C. Wani, H. Taylor, J. Nat. Prod. **50**, 1095 (1987)