



## A new synthesis of the benzo[*c*]phenanthridines nornitidine, noravicine, and isodecarine, based on a microwave-assisted electrocyclic reaction of the aza 6 $\pi$ -electron system

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### ARTICLE INFO

#### Article history:

Received 22 October 2008

Revised 18 November 2008

Accepted 20 November 2008

Available online 24 November 2008

### ABSTRACT

A new and versatile synthetic route to a benzophenanthridine alkaloid was developed by a bond formation between C4b and N5 on the benzo[*c*]phenanthridine nucleus, using a microwave-assisted electrocyclic reaction of the aza 6 $\pi$ -electron system. This strategy was successfully used to synthesize nornitidine (**1b**), noravicine (**1d**), and isodecaline (**1f**).

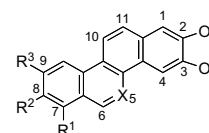
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New and more versatile synthetic routes to benzo[*c*]phenanthridines are in high demand,<sup>1–7</sup> because of their potent anti-tumor activity.<sup>8–17</sup> Among benzo[*c*]phenanthridines, nitidine (**1a**) and 7-hydroxy-8-methoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium hydrogen sulfate (NK109) (**1e**) are the most promising compounds, exhibiting significant anti-tumor activity against drug-resistant human tumor cell lines.<sup>18–21</sup> Nitidine (**1e**) is a potent inhibitor of topoisomerase II.<sup>21</sup>

In our laboratory, we have focused on the construction of fused pyridine ring systems, such as furoisoquinoline,<sup>22</sup> phenanthridine,<sup>23</sup>  $\beta$ -carboline,<sup>24</sup> and azaanthraquinone alkaloids,<sup>25</sup> using a microwave-assisted electrocyclic reaction of the aza 6 $\pi$ -electron system. Here, we describe a new and versatile synthesis of benzo[*c*]phenanthridine alkaloids, using the microwave-assisted electrocyclic reaction of the aza 6 $\pi$ -electron system to induce bond formation between the C4b and N5-positions<sup>13</sup> in the tetracyclic benzo[*c*]phenanthridine nucleus (Fig. 1).

We planned the syntheses of nornitidine (**1b**), noravicine (**1d**), and isodecarine (**1f**), derived from 11,12-dihydrobenzo[*c*]phenanthridines **2** as shown in retro-synthetic Scheme 1. Dihydro-compound **2** would be obtained from a 2-cycloalkenylbenzaldoxime methyl ether **3** through a microwave-assisted electrocyclic reaction. An oxime ether **3** could be prepared from 2-cycloalkenylbenzaldehyde **4**, which would be provided by the Suzuki–Miyaura reaction between 2-bromobenzaldehyde **5** and 2-(6,7-methylenedioxy-3,4-dihydronaphthyl)boronic acid pinacol ester **6**.

Initially, to obtain a required pinacol borate **6**, we attempted an alternative synthesis of 6,7-methylenedioxy- $\beta$ -tetralone (**7**) (Scheme 2). Treatment of 2-allyl-4,5-methylenedioxyphenol



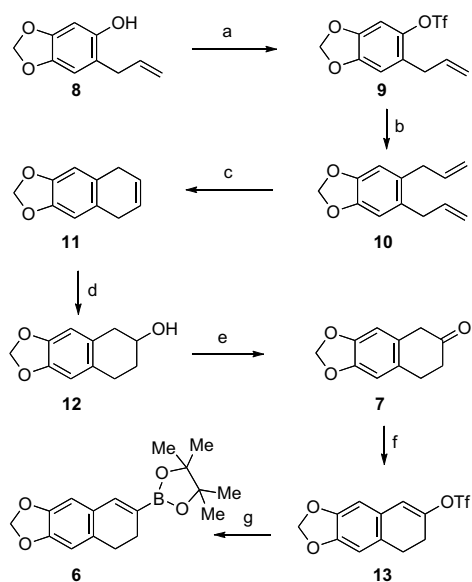
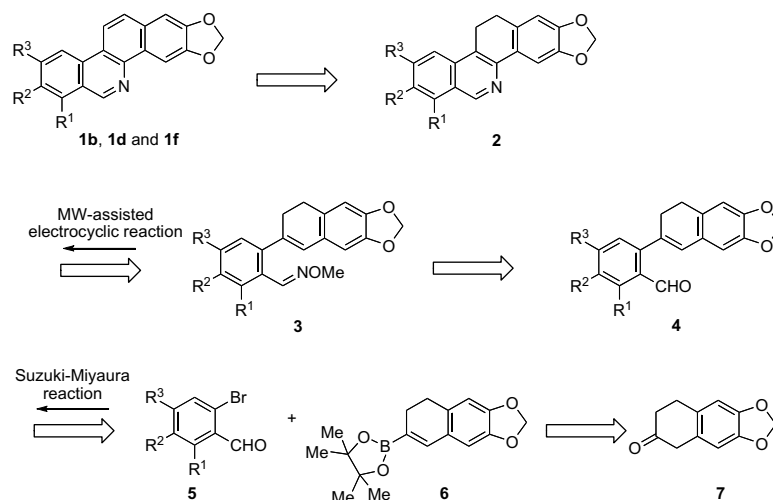
- 1a**: R<sup>1</sup> = H, R<sup>2</sup> = R<sup>3</sup> = OMe, X = \*N-Me (nitidine)  
**1b**: R<sup>1</sup> = H, R<sup>2</sup> = R<sup>3</sup> = OMe, X = N (nornitidine)  
**1c**: R<sup>1</sup> = H, R<sup>2</sup> + R<sup>3</sup> = OCH<sub>2</sub>O, X = \*N-Me (avicine)  
**1d**: R<sup>1</sup> = H, R<sup>2</sup> + R<sup>3</sup> = OCH<sub>2</sub>O, X = N (noravicine)  
**1e**: R<sup>1</sup> = OH, R<sup>2</sup> = OMe, R<sup>3</sup> = H, X = \*N-Me (NK109, fagaridine)  
**1f**: R<sup>1</sup> = OH, R<sup>2</sup> = OMe, R<sup>3</sup> = H, X = N (isodecaline)

Figure 1.

(**8**)<sup>26</sup> with trifluoromethanesulfonyl anhydride (Tf<sub>2</sub>O) and pyridine afforded the *O*-triflate **9**,<sup>27</sup> which was subjected to the Stille reaction with allyltributyltin in the presence of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and LiCl to give the diallylbenzene **10**. Olefin metathesis of diallylbenzene **10** with the Grubbs's I catalyst yielded 1,4-dihydronaphthalene **11**, which was subjected to hydroboration followed by oxidation to afford 2-hydroxytetrahydronaphthalene **12**. The alcohol **12** was subsequently oxidized by pyridinium chlorochromate (PCC) in CH<sub>2</sub>Cl<sub>2</sub> to give the known  $\beta$ -tetralone **7**.<sup>28</sup> The unstable tetralone **7** was immediately treated with *N*-phenylbis(trifluoromethanesulfonamide) (Tf<sub>2</sub>NPh) and LDA to obtain the triflate **13**, via a reaction with bis(pinacolate)diborane and PdCl<sub>2</sub>(dppf)<sup>29</sup> to afford the expected pinacol borate **6**.

Next, the Suzuki–Miyaura reaction of readily available 2-bromobenzaldehydes (**5b**, **5d**, and **5f**) with the prepared pinacol borate **6** smoothly proceeded in the presence of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> to give the 2-cycloalkenylbenzaldehydes **4b** and **4d**, or in the presence of PdCl<sub>2</sub>(dppf)<sup>30</sup> to give **4f**. The reaction of **5f** with **6**, however, yielded the deacetylated product **4f**.

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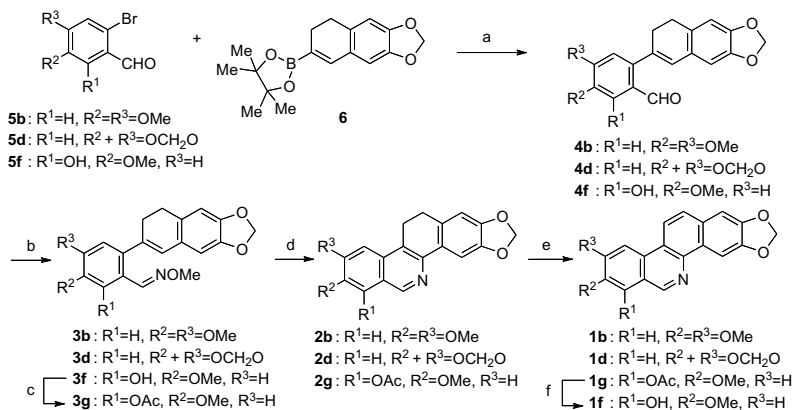


**Scheme 2.** Reagents and conditions: (a)  $\text{TiF}_4$ , pyridine,  $\text{CH}_2\text{Cl}_2$ , rt, 2 h, 93%; (b) allyltributyltin, LiCl,  $\text{PdCl}_2(\text{PPh}_3)_2$ , dppf, DMF, 180 °C, 2 h, 99%; (c) Grubbs's 1 catalyst,  $\text{CH}_2\text{Cl}_2$ , 50 °C, 1 h, 99%; (d) (i)  $\text{BH}_3$ , THF, 0 °C, 1 h, (ii) 28%  $\text{H}_2\text{O}_2$ , 3 M NaOH, 50 °C, 1 h, 86%; (e) PCC,  $\text{CH}_2\text{Cl}_2$ , rt, 1.5 h, 74%; (f) LDA,  $\text{TiF}_4$ , THF, -78 °C to rt, 4 h, 84%; (g) bis(pinacolate)diborane, AcOK,  $\text{PdCl}_2(\text{dppf})$ , DMSO, 70 °C, 1 h, 86%.

Subsequent treatment of **4** with hydroxylamine methyl ether afforded oximes (**3b**, **3d**, and **3f**). The oxime ether **3f** was converted to the acetyl compound **3g**, and then oximes **3b**, **3d**, and **3g** were subjected to a microwave-assisted electrocyclic reaction at 180 °C to give the tetracyclic 11,12-dihydrobenzo[*c*]phenanthridines (**2b**, **2d**, and **2g**) in good to excellent yield (Scheme 3).<sup>31,32</sup>

Finally, the dihydrobenzophenanthridines **2b**, **2d**, and **2g** were oxidized by refluxing with 10% Pd-C in 1,2-dichlorobenzene to give norniitidine (**1b**), noravicine (**1d**), and *O*-acetylisodecaline (**1g**), respectively. Hydrolysis of the acetyl group of **1g** with  $\text{KHCO}_3$  afforded isodecaline (**1f**). The physical and spectroscopic data of **1b**,<sup>32–34</sup> **1d**,<sup>32–34</sup> and **1f**<sup>34,35</sup> were identified by comparing them with those previously reported.<sup>36</sup>

In conclusion, an alternative synthesis of 6,7-methylenedioxy- $\beta$ -tetralone (**7**) was achieved in a five-step sequence, and the desired reagent of the Suzuki–Miyaura reaction, pinacol borate **6**, was derived in two steps. After the C–C bond connection between C9a and C9b by the Suzuki–Miyaura reaction, a new synthetic strategy for anti-tumor benzo[*c*]phenanthridines was established by inducing a bond formation between C4b and N5 using a microwave-assisted electrocyclic reaction of the aza  $6\pi$ -electron system. Formal total syntheses of nitidine (**1a**) and avicine (**1c**) were achieved. In addition, the total synthesis of isodecaline (**1f**) was completed. This new synthetic strategy will be an useful procedure for the synthesis of other benzo[*c*]phenanthridine alkaloids.



**Scheme 3.** Reagents and conditions: (a)  $\text{PdCl}_2(\text{PPh}_3)_2$ , or  $\text{PdCl}_2(\text{dppf})$  in the case of **4f**,  $\text{K}_2\text{CO}_3$ , MeOH, DMF, 80 °C, 0.5–1 h, 98% (**4b**), 78% (**4d**), 97% (**4f**); (b)  $\text{MeONH}_2 \cdot \text{HCl}$ , AcONa, EtOH, 80 °C, 1 h, 95% (**3b**), 98% (**3d**), 95% (**3f**); (c)  $\text{Ac}_2\text{O}$ ,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ , 80 °C, 1 h, 94%; (d) microwave, 1,2-dichlorobenzene, 180 °C, 84% (**2b**), 94% (**2d**), 77% (**2g**); (e) 10% Pd-C, 1,2-dichlorobenzene, 180 °C, 97% (**1b**), 74% (**1d**), 93% (**1g**); (f)  $\text{KHCO}_3$ , MeOH,  $\text{H}_2\text{O}$ , rt, 4 h, 74%.

## Acknowledgments

This work was supported in part by Grant-in Aid for Scientific Research (C) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

## References and notes

1. Simanek, V. In *The Alkaloids*; Brossi, A., Ed.; Academic Press Inc.: New York, 1985; Vol. 26, pp 185–240.
2. Suffness, M.; Cordell, G. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press Inc.: New York, 1985; Vol. 25, pp 178–189.
3. Ninomiya, I.; Naito, T. *Recent Dev. Chem. Nat. Carbon Comp.* **1984**, *10*, 9–90.
4. Dostal, J.; Potacek, M. *Collect. Czech. Chem. Commun.* **1990**, *55*, 2840–2873.
5. MacKay, S. P.; Meth-Cohn, O.; Waigh, R. D. *Adv. Heterocycl. Chem.* **1996**, *67*, 345–389.
6. Harayama, T. *Heterocycles* **2005**, *65*, 697–713. and related references cited therein.
7. Styskala, J.; Cankar, P.; Soural, M.; Hlavac, J.; Hradil, P.; Vicar, J.; Simanek, V. *Heterocycles* **2007**, *73*, 769–775. and related references cited therein.
8. Herbert, J. M.; Angereau, J. M.; Gleye, J.; Maffrand, J. P. *Biochem. Biophys. Res. Commun.* **1990**, *172*, 993–999.
9. Fang, S.-D.; Wang, L.-K.; Hecht, S. M. *J. Org. Chem.* **1993**, *58*, 5025–5027.
10. Vavreckova, C.; Gawlik, I.; Muller, K. *Planta Med.* **1996**, *62*, 397–401.
11. Schmeller, T.; Latz-Bruning, B.; Wink, M. *Phytochemistry* **1997**, *44*, 257–266.
12. Kanzawa, F.; Nishio, T.; Ishida, T.; Fukuda, M.; Kurokawa, H.; Fukumoto, H.; Nomoto, Y.; Fukuoka, K.; Bojanowski, K.; Saijo, N. *Br. J. Cancer* **1997**, *76*, 571–581.
13. Ishikawa, T.; Ishii, H. *Heterocycles* **1999**, *50*, 627–639.
14. Ishikawa, T. *Med. Res. Rev.* **2001**, *21*, 61–72.
15. Fleury, F.; Sukhanova, A.; Ianoul, A.; Devy, J.; Kudelina, I.; Duval, O.; Alix, A. J. P.; Jardillier, J. C.; Nabiev, I. *J. Biol. Chem.* **2000**, *275*, 3501–3509.
16. Caballero-George, C.; Vanderheyden, P. M. L.; Apers, S.; Van den Heuvel, H.; Solis, P. N.; Gupta, M. P.; Claeys, M.; Pieters, L.; Vauquelin, G.; Vlietinck, A. J. *Planta Med.* **2002**, *68*, 770–775.
17. Gonzaga, W. A.; Weber, A. D.; Giacomelli, S. R.; Dalcol, I. I.; Hoelzel, S. C. S.; Morel, A. F. *Planta Med.* **2003**, *69*, 371–374.
18. Nakanishi, T.; Suzuki, M. *J. Nat. Prod.* **1998**, *61*, 1263–1267.
19. Nakanishi, T.; Suzuki, M.; Saimoto, A.; Kabasawa, T. *J. Nat. Prod.* **1999**, *62*, 864–867.
20. Nakanishi, T.; Suzuki, M. *Org. Lett.* **1999**, *1*, 985–988.
21. Nakanishi, T.; Masuda, A.; Suwa, M.; Akiyama, Y.; Hoshino-Abe, N.; Suzuki, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2321–2323.
22. Kumemura, T.; Choshi, T.; Hirata, A.; Sera, M.; Takahashi, Y.; Nobuhiro, J.; Hibino, S. *Chem. Pharm. Bull.* **2005**, *53*, 393–397.
23. Kumemura, T.; Choshi, T.; Yukawa, J.; Hirose, A.; Nobuhiro, J.; Hibino, S. *Heterocycles* **2005**, *66*, 87–90.
24. Omura, K.; Choshi, T.; Watanabe, S.; Satoh, Y.; Nobuhiro, J.; Hibino, S. *Chem. Pharm. Bull.* **2008**, *56*, 237–238.
25. Choshi, T.; Kumemura, T.; Nobuhiro, J.; Hibino, S. *Tetrahedron Lett.* **2008**, *49*, 3725–3728.
26. Van, T. N.; Debenedetti, S.; De Kimpe, N. *Tetrahedron Lett.* **2003**, *44*, 4199–4201.
27. All new compounds have been characterized by physical and spectroscopic analyses.
28. Makhey, D.; Li, D.; Zhao, B.; Sim, S.-P.; Li, T.-K.; Liu, A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem.* **2003**, *11*, 1809–1820.
29. The pinacol borate **6** was prepared by the procedure of: Takahashi, K.; Takagi, J.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 126–127.
30. When the catalyst, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> was used in the C–C coupling reaction of **5f** with **6**, a yield of **4f** was 60%.
31. Yields of **2b**, **2d** and **2g** by the conventional method were 45% (12 h), 45% (12 h) and 49% (3 h), respectively.
32. Beugelmans, R.; Chastanet, J.; Ginsburg, H.; Quintero-Cortes, L.; Roussi, G. *J. Org. Chem.* **1985**, *50*, 4933–4938.
33. Geen, G. R.; Mann, I. S.; Mullane, M. V.; McKillop, A. *Tetrahedron* **1998**, *54*, 9875–9894.
34. Chen, J.-J.; Fang, H.-Y.; Duh, C.-Y.; Chen, I.-S. *Planta Med.* **2005**, *71*, 470–475.
35. Styskala, J.; Cankar, P.; Soural, M.; Hlavac, J.; Hradil, P.; Vicar, J.; Simanek, V. *Heterocycles* **2007**, *73*, 769–775.
36. Noritidine (**1b**) mp 278–281 °C (EtOAc–hexane) (Lit.,<sup>33</sup> mp 281–282 °C); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ: 3.97 (3H, s), 4.07 (3H, s), 6.20(2H, s), 7.50 (1H, s), 7.69 (1H, s), 7.95 (1H, d, *J* = 8.7 Hz), 8.15 (1H, s), 8.54 (1H, s), 8.62 (1H, d, *J* = 8.7 Hz), 9.29 (1H, s); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ: 55.7, 56.1, 101.0, 101.4, 102.4, 104.5, 107.7, 119.2, 119.7, 121.9, 126.3, 128.2, 128.3, 129.2, 139.5, 147.9, 148.0, 149.7, 149.9, 153.1; MS *m/z*: 333 (M<sup>+</sup>). HR-MS *m/z*: 333.1031 (Calcd for C<sub>20</sub>H<sub>15</sub>NO<sub>4</sub>: 333.1001). Noravicine (**1d**) mp 312 °C (EtOAc–hexane) (Lit.,<sup>33</sup> mp 325 °C (decomp.)); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ: 6.20 (2H, s), 6.27 (2H, s), 7.50 (1H, s), 7.67 (1H, s), 7.93 (1H, d, *J* = 8.8 Hz), 8.31 (1H, s), 8.52 (1H, d, *J* = 8.8 Hz), 8.53 (1H, s), 9.25 (1H, s); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ: 100.1, 101.1, 101.5, 102.1, 104.5, 104.8, 119.2, 120.2, 123.2, 126.5, 128.1, 129.3, 130.2, 139.9, 147.8, 148.0, 150.0, 151.5; MS *m/z*: 317 (M<sup>+</sup>). HR-MS *m/z*: 317.0674 (Calcd for C<sub>19</sub>H<sub>11</sub>NO<sub>4</sub>: 317.0688). Isodecarine (**1f**) mp 239–241 °C (CHCl<sub>3</sub>–hexane) (Lit.,<sup>34</sup> mp 225–227 °C, Lit.,<sup>35</sup> mp 265–268 °C); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ: 3.98 (3H, s), 6.20 (2H, s), 7.50 (1H, s), 7.74 (1H, d, *J* = 8.9 Hz), 7.95 (1H, d, *J* = 8.9 Hz), 8.27 (1H, d, *J* = 8.9 Hz), 8.52 (1H, s), 8.53 (1H, d, *J* = 8.9 Hz), 9.65 (1H, s), 9.98 (1H, s); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ: 56.8, 101.0, 101.4, 104.4, 113.2, 117.3, 118.6, 118.9, 119.7, 126.8, 127.1, 128.3, 129.3, 138.9, 142.7, 144.2, 146.6, 147.9, 148.1; MS *m/z*: 319 (M<sup>+</sup>). HR-MS *m/z*: 319.0819 (Calcd for C<sub>19</sub>H<sub>13</sub>NO<sub>4</sub>: 319.0845).