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TOTAL SYNTHESES OF ZWITTERIONIC INDOLE ALKALOIDS, FLAVOCARPINE AND DIHYDROVINCARPINE, BY EXTENDED METHOD FOR SUBSTITUTED PYRIDINE SYNTHESIS THROUGH AZAELECTROCYCLIZATION

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Dedicated to Professor Isao Kuwajima on the occasion of his 77th birthday

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Abstract – The total syntheses of flavocarpine (**1**) and dihydrovincarpine (**2**) have been accomplished through the common intermediate, 2,4,5-trisubstituted pyridine compound **3** which was prepared by the accelerated 6π-azaelectrocyclization of 4-alkoxycarbonylazatriene **4** followed by aromatization of the resulting dihydropyridine derivative.

Flavocarpine (**1**) and its dihydroderivative, dihydrovincarpine (**2**), were isolated from stem bark of *Pleiocarpa mutica* Benth. and *Vinca major* L. var. *elegantissima* Hort. by Büchi's group and Pakrashi's group in 1962 and 1976, respectively (Figure 1).[1,2] These naturally occurring compounds are unique zwitterionic indole alkaloids possessing the indolo[2,3-*a*]quinolizine ring system including a 1,2,4,5-tetrasubstituted pyridinium core. The total synthesis of flavocarpine (**1**) has been reported by two groups,[1,3] but the synthesis of dihydrovincarpine (**2**) has not yet.

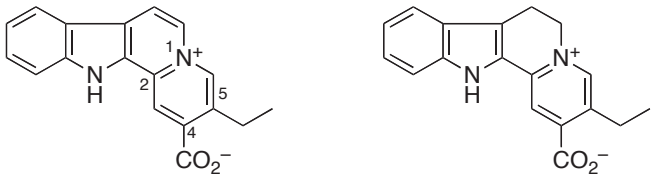


Figure 1

In 2000, we have developed the novel synthetic method for 2,4-disubstituted pyridines through the accelerated 6π-azaelectrocyclization followed by aromatization due to the remarkable substituent effect of the Schiff base prepared from (*E*)-3-alkoxycarbonyl-2,4,6-trienal and the appropriate amine.[4] Furthermore, the method was extended to the more efficient one-pot variant for 2-arylpyridine synthesis.[5,6] We now describe the concise total syntheses of zwitterionic indole alkaloids **1** and **2** by further extension of the previous method to 2,4,5-trisubstituted pyridine synthesis featured by the accelerated 6π-azaelectrocyclization.

The synthetic strategy of these alkaloids is outlined in Figure 2. The target molecules **1** and **2** could be synthesized from the common intermediate, 2,4,5-trisubstituted pyridine derivative **3,** through the construction of the zwitterionic indolo[2,3-*a*]quinolizine ring system. The key intermediate **3** would be obtained via 6π-azaelectrocyclization followed by aromatization of the azatriene **4**, which could be prepared by Schiff base formation between the aldehyde **5** and appropriate amine. Aldehyde **5** could be synthesized by the Migita-Kosugi-Stille coupling of the tetrasubstituted vinyl iodide **6**[7] with vinylstannane **7**.

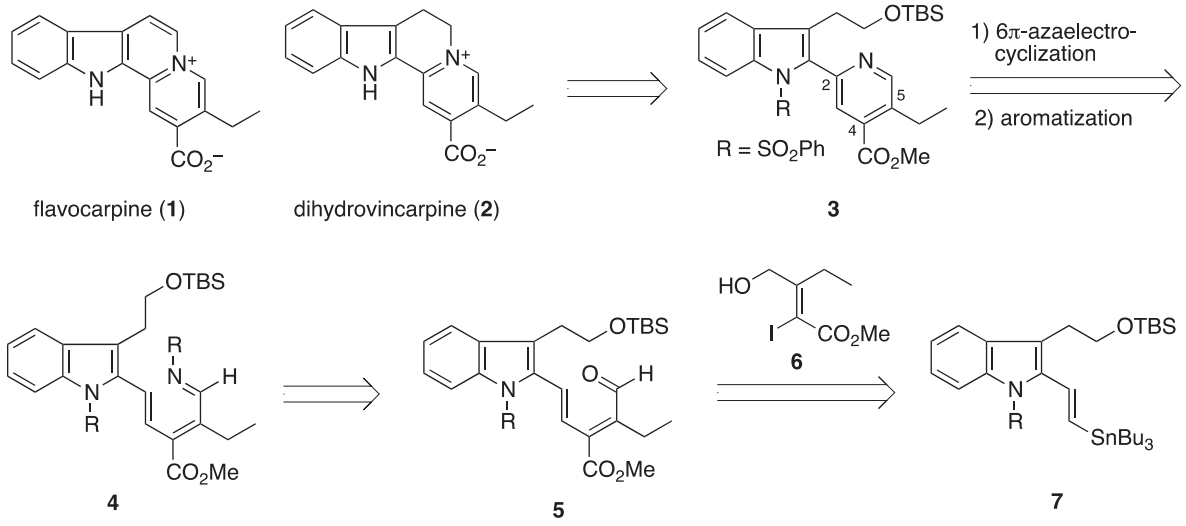
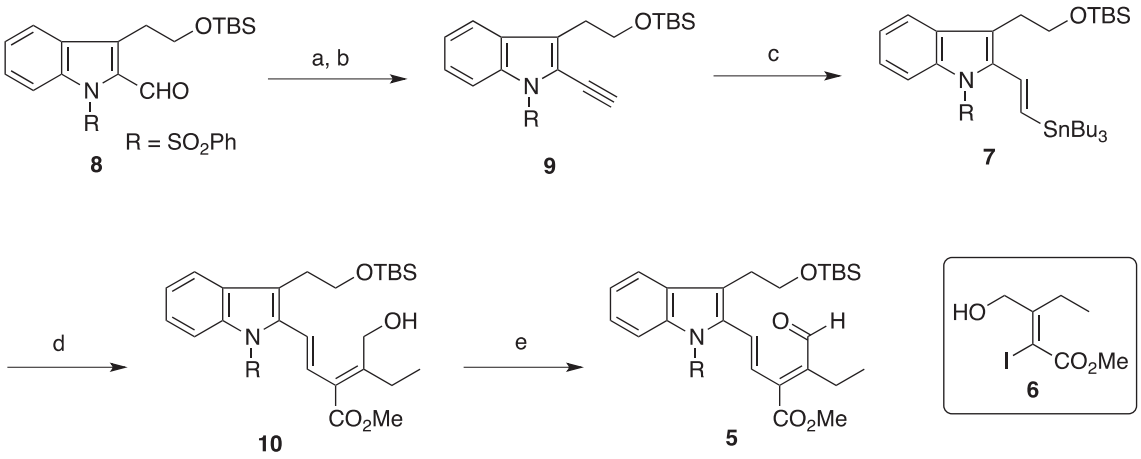


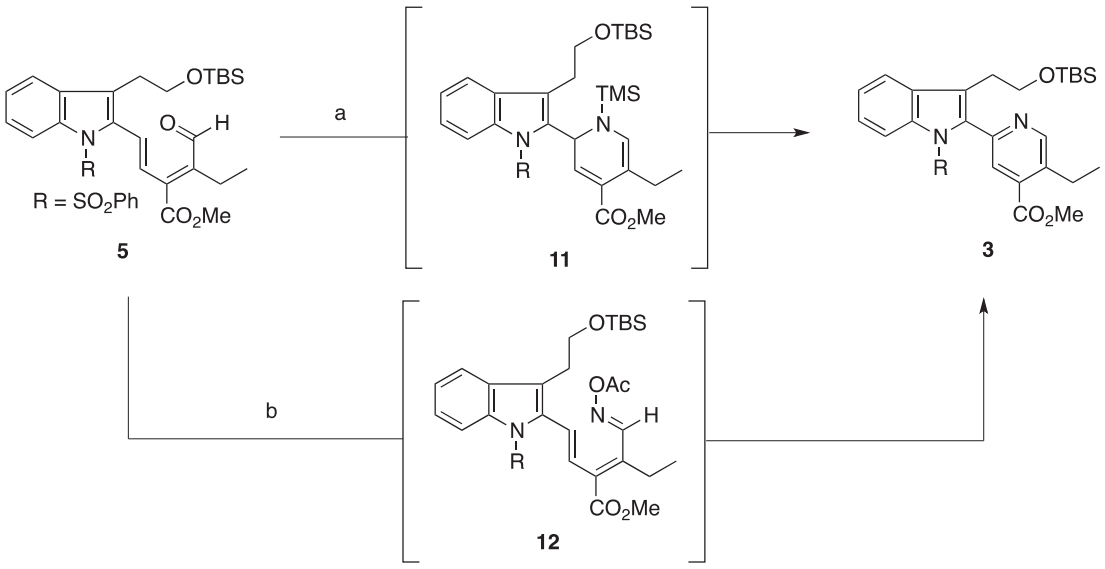
Figure 2. Retrosynthesis of flavocarpine (**1**) and dihydrovincarpine (**2**)

The synthesis of aldehyde **5**, the precursor of 6π-azaelectrocyclization, is shown in Scheme 1. The known 2-indolecarbaldehyde derivative **8**[8] was reacted with carbon tetrabromide and tripheylphosphine[9] to produce the corresponding dibromide in 81% yield, which was successively treated with lithium bis(trimethylsilyl)amide and then *n*-butyllithium to give the desired acetylene **9** in 95% yield. The regio- and stereo-selective hydrostannylation of **9** produced the (*E*)-vinylstannane **7** in 89% yield. The Migita-Kosugi-Stille coupling of **7** with **6**[7] afforded the corresponding coupling product **10** in 70% yield, which was followed by oxidation with manganese dioxide to give the desired aldehyde **5**[10] in 85% yield (Scheme 1).



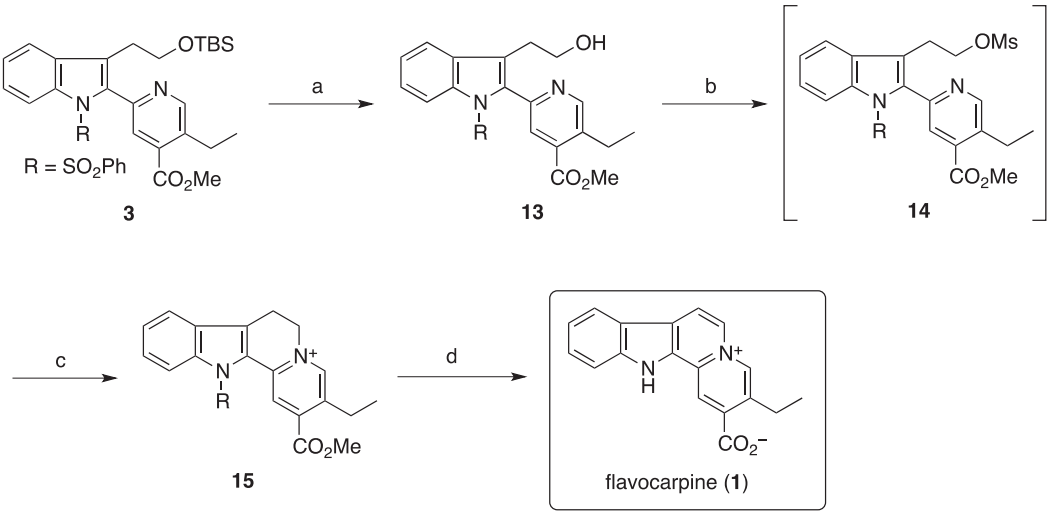
Scheme 1. Reagents and conditions: (a) CBr_4, PPh_3, CH_2Cl_2, –78 °C, 15 min, 81%; (b) LHMDS, THF, –78 °C, 15 min, then *n*-BuLi, THF, –78 °C, 10 min, 95%: (c) *n*-Bu_3SnH, AIBN, toluene, reflux, 6 h, 89%; (d) **6**, $PdCl_2(PPh_3)_2$, CuI, DMF, 80 °C, 3 h, 70%; (e) MnO_2, CH_2Cl_2, rt, 30 min, 85%

With the key aldehyde **5** in hand, we next examined the construction of the 2,4,5-trisubstituted pyridine skeleton by our two methods that were previously developed for 2,4-disubstitued pyridine synthesis.[4] First, the treatment of aldehyde **5** with lithium bis(trimethylsilyl)amide in THF at room temperature unexpectedly gave no desired dihydropyridine derivative **11** and the starting material **5** was only admitted by TLC. When the reaction mixture was refluxed in THF, **11** was detected by TLC and the mixture was successively treated with DDQ at room temperature, however, a trace amount of the desired trisubstituted pyridine derivative **3** was obtained. In this case, the 6π-azaelectrocyclization of the resulted Schiff base of aldehyde **5** did not proceed at room temperature due to its increased steric hindrance, and the intermediary **11** produced under reflux would not be stable for DDQ treatment. Since the condition via Peterson olefination gave unsatisfactory results, we next attempted the oxime route.[4] Thus, aldehyde **5** was reacted with hydroxylamine in pyridine for 15 min, and the produced oxime derivative was continuously treated with acetyl chloride at 50 °C for 2 hour to successfully provide the desired 2,4,5-trisubstituted pyridine compound **3**[11] in 86% yield (Scheme 2). In this case, both 6π-azaelectrocyclization and aromatization proceeded smoothly under the reaction conditions.



Scheme 2. Reagents and conditions: (a) LHMDS, THF, reflux, 1 h then DDQ, rt, 1h, trace; (b) NH_2OH•HCl, pyridine rt, 15 min then AcCl, 50 °C, 2 h, 86%

As the key intermediate **3** was obtained, our attention was turned to the construction of the indolo[2,3-*a*]quinolizine ring system for the syntheses of zwitterionic indole alkaloids **1** and **2**. Hydrolysis of the TBS group of **3** led to alcohol **13**[12] in 94% yield, the hydroxyl group of which was then converted into a mesyl group, and the resulting mesylate **14** was treated with SiO_2 to successfully provide the cyclized product **15** in 86% yield for 2 steps. Finally, treatment of **15** with aqueous NaOH solution in methanol at 60 °C resulted in the hydrolysis of both *N*-phenylsulfonyl and methyl ester groups, that accompanied by the aromatization to directly produce the desired flavocarpine (**1**)[13] in 79% yield (Scheme 3).



Scheme 3. Reagents and conditions: (a) 2 M HCl, THF, rt, 1 h, 94%; (b) MsCl, Et_3N, THF, 0 °C, 30 min; (c) SiO_2 $CHCl_3$/MeOH, rt, over night, 86% for 2 steps (d) 2 M NaOH, MeOH, 60 °C, 4 h, 79%

In the final pathway from **15** to **1**, the aromatization would proceed through deprotonation at the C-6 position followed by elimination of the *N*-phenylsulfonyl protecting group as depicted in Figure 3.

Therefore, for the synthesis of dihydrovincarpine (**2**), cleavage of the *N*-phenylsulfonyl protecting group must be prior to the construction of the indolo[2,3-*a*]quinolizine ring system.

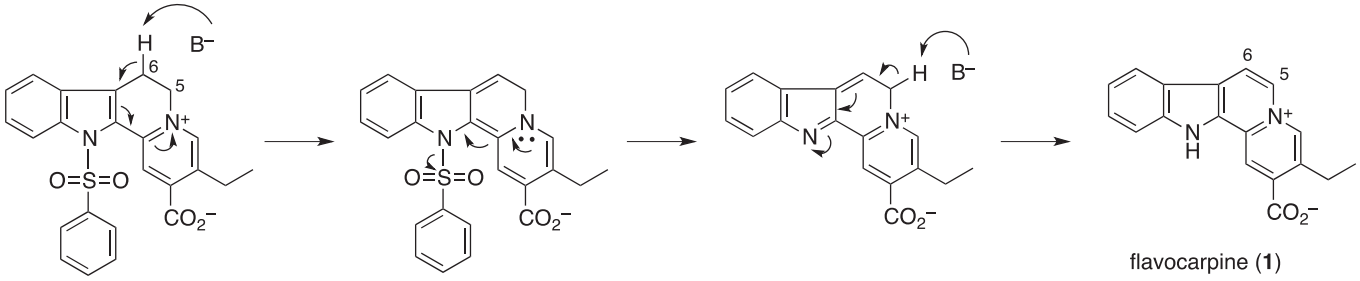
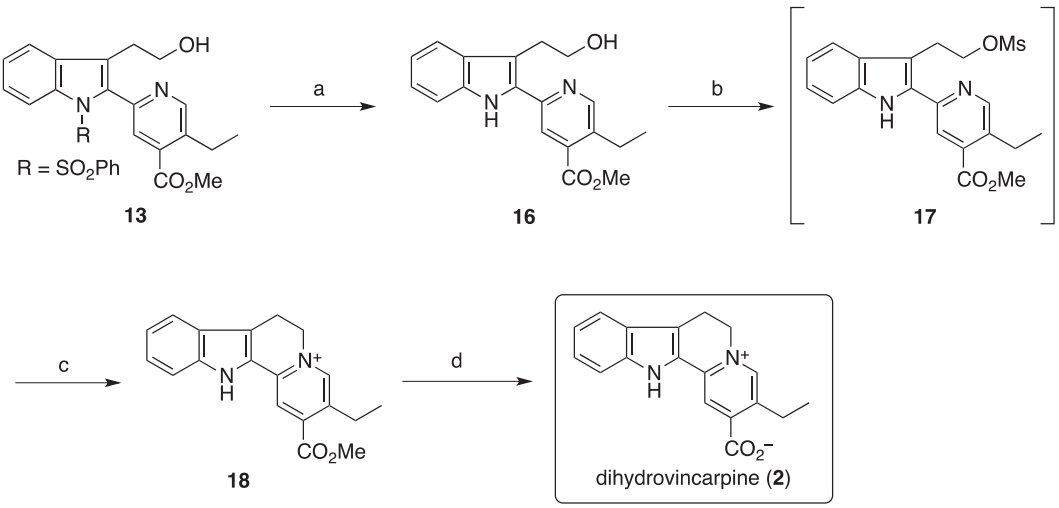


Figure 3. plausible reaction mechanism of aromatization

The synthesis of dihydrovincarpine (**2**) is shown in Scheme 4. After several trials, the cleavage of the *N*-phenylsulfonyl protecting group was achieved by hydrogenolysis of **13** with Raney Ni as a catalyst and the desired compound **16**[14] was obtained in 73% yield. Mesylation of **16** followed by cyclization with SiO_2 afforded the expected 5,6-dihydroindolo[2,3-*a*]quinolizine derivative **18** in 73% yield for 2 steps. Finally, hydrolysis of the methyl ester in **18** provided dihydrovincarpine (**2**)[15] in 85% yield without aromatization as expected.



Scheme 4. Reagents and conditions: (a) H_2, Raney Ni, THF, rt, 3 h, 73%; (b) MsCl, Et_3N, THF, 0 °C, 30 min; (c) SiO_2 $CHCl_3$/MeOH, rt, over night, 73% for 2 steps (d) 2 M NaOH, MeOH, 60 °C, 4 h, 85%

In conclusion, we achieved the total syntheses of both flavocarpine (**1**) and dihydrovincarpine (**2**) by applying the accelerated 6π-azaelectrocyclization followed by the aromatization protocol for 2,4,5-trisubstituted pyridine synthesis. The present syntheses clearly demonstrate that the accelerated 6π-azaelectrocyclization is a powerful method for the synthesis of alkaloids possessing the polysubstituted pyridine nucleus.

ACKNOWLEDGEMENTS

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10. **5**: IR (KBr disk, cm^{-1}) 2984, 2855, 1732, 1667, 1449, 1366, 1217, 1090; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.3 (s, 1H), 8.29 (d, 1H, *J* = 8.4 Hz), 7.80 (d, 1H, *J* = 16.8 Hz), 7.74 (d, 2H, *J* = 8.0 Hz), 7.54-7.25 (m, 7H), 4.04 (s, 3H), 3.93 (t, 2H, *J* = 6.4 Hz), 2.99 (t, 2H, *J* = 6.4 Hz), 2.36 (q, 2H, *J* = 7.2 Hz), 1.10 (t, 3H, *J* = 7.6 Hz), 0.69 (s, 9H), –0.38 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 168.0, 145.9, 139.3, 138.3, 136.9, 134.5, 133.8, 130.8, 129.1, 127.1, 126.8, 126.0, 124.0, 123.3, 122.5, 119.7, 115.2, 62.6, 52.6, 28.7, 25.8, 22.1, 18.3, 13.7, –5.8; ESI-HRMS *m/z* calcd for $C_{31}H_{39}NNaO_6SSi$ $[M+Na]^+$ 604.2165, found 604.2167.
11. **3**: IR (KBr disk, cm^{-1}) 3450, 2992, 1736, 1473, 1370, 1179; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.17 (d, 1H, *J* = 8.8 Hz), 7.98 (s, 1H), 7.68 (dd, 1H, *J* = 1.2, 7.6 Hz), 7.51 (d, 1H, *J* = 7.2 Hz), 7.47-7.23 (m, 6H), 3.95 (s, 3H), 3.67 (t, 2H, *J* = 7.2 Hz), 3.08 (q, 2H, *J* = 7.6 Hz), 2.81 (t, 2H, *J* = 7.2 Hz), 1.35 (t, 3H, *J* = 7.2 Hz), 0.77 (s, 9H), –0.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 151.1, 149.6, 138.6, 136.9, 136.8, 135.8, 135.6, 133.4, 131.3, 128.6, 127.1, 127.0, 125.5, 12 4.1, 123.8, 120.0, 115.9, 62.8, 52.4, 28.0, 25.86, 25.82, 24.7, 15.5, –5.5; ESI-HRMS *m/z* calcd for $C_{31}H_{38}N_2NaO_5SSi$ $[M+Na]^+$ 601.2168, found 601.2150.
12. **13**: IR (KBr disk, cm^{-1}) 3400, 2900, 1734, 1449, 1370, 1179; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s,

1H), 8.22 (d, 1H, *J* = 8.4 Hz), 8.20 (s, 1H), 7.45-7.05 (m, 8H), 5.68 (brs, 1H), 3.97 (s, 3H), 3.76 (brs, 2H), 3.09 (q, 2H, *J* = 8.0 Hz), 2.81 (brt, 2H, *J* = 5.2 Hz), 1.35 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.1, 149.6, 148.1, 139.1, 138.3, 136.8, 136.4, 135.2, 133.7, 132.9, 131.5, 128.5, 128.1, 126.9, 126.2, 124.9, 119.4, 117.2, 61.2, 52.6, 26.9, 24.8, 15.5; ESI-HRMS *m/z* calcd for $C_{25}H_{24}N_2NaO_4S$ $[M+Na]^+$ 487.1304, found 487.1298.

13. Flavocarpine (**1**): IR (KBr disk, cm^{-1}) 3100, 2926, 2450, 1900, 1595, 1527, 1466, 1390, 1080, 845, 793; ^{1}H NMR (400 MHz, CD_3OD/TFA) 9.38 (s, 1H), 9.22 (s, 1H), 8.87 (d, 1H, *J* = 7.2 Hz), 8.78 (d, 1H, *J* = 6.8 Hz), 8.40 (d, 1H, *J* = 8.4 Hz), 7.84 (d, 1H, *J* = 8.8 Hz), 7.77 (t, 1H, *J* = 6.8 Hz), 7.51 (t, 1H, *J* = 6.8 Hz), 3.31 (q, 2H, *J* = 7.2 Hz), 1.43 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, CD_3OD/TFA) δ 166.7, 143.8, 139.0, 138.6, 137.1, 133.2, 132.1, 131.5, 128.3, 126.3, 124.7, 123.6, 123.2, 122.4, 119.3, 114.0, 25.8, 15.1; ESI-HRMS *m/z* calcd for $C_{18}H_{15}N_2O_2$ $[M+H]^+$ 291.1134, found 291.1146.

14. **16**: IR (KBr disk, cm^{-1}) 3300, 2932, 1732, 1601, 1437, 1275, 1096; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (brs, 1H), 8.46 (s, 1H), 8.00 (s, 1H), 7.57 (d, 1H, *J* = 8.0 Hz), 7.30 (d, 1H, *J* = 8.4 Hz), 7.19 (t, 1H, *J* = 8.4 Hz), 7.08 (t, 1H, *J* = 7.2 Hz), 4.07 (t, 2H, *J* = 6.0 Hz), 3.96 (s, 3H), 3.32 (t, 2H, *J* = 6.0 Hz), 2.93 (q, 2H, *J* = 7.6 Hz), 1.25 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 160.0, 148.9, 137.4, 137.2, 136.2, 132.9, 129.2, 123.5, 120.6, 119.8, 119.1, 113.1, 63.4, 63.3, 52.6, 27.6, 24.6, 15.5; ESI-HRMS *m/z* calcd for $C_{19}H_{20}N_2NaO_3$ $[M+Na]^+$ 347.1372, found 347.1365.

15. Dihydrovincarpine (**2**): IR (KBr disk, cm^{-1}) 3500, 3150, 1650, 1581, 1421, 1366, 1142; ^{1}H NMR (400 MHz, CD_3OD/TFA) δ 8.77 (s, 1H), 8.46 (s, 1H), 7.69 (d, 1H, *J* = 8.4 Hz), 7.50 (d, 1H, *J* = 8.4 Hz), 7.39 (t, 1H, *J* = 7.2 Hz), 7.20 (t, 1H, *J* = 7.2 Hz), 4.94 (t, 2H, *J* = 7.2 Hz), 3.47 (t, 2H, *J* = 8.0 Hz), 3.11 (q, 2H, *J* = 7.6 Hz), 1.36 (t, 3H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, CD_3OD/TFA) δ 166.5, 148.0, 147.3, 143.8, 141.8, 140.1, 128.1, 126.4, 126.0, 122.5, 122.0, 121.5, 119.5, 113.7, 57.6, 25.3, 20.4, 15.1; ESI-HRMS *m/z* calcd for $C_{18}H_{17}N_2O_2$ $[M+H]^+$ 293.1290, found 293.1296.