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# Total Synthesis of the Indole Alkaloid (±)-Tacamine [1]

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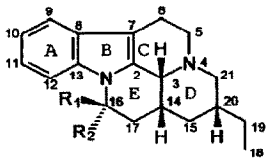
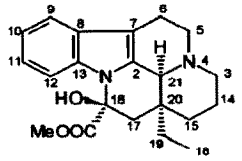
**Abstract:** The mixture of pentacyclic intermediates (**4**) was successfully converted into the pharmacologically interesting indole alkaloid (±)-tacamine (**1**). In a similar manner, the two unnatural isomers of **1**, (±)-14-epitacamine (**9**) and (±)-14-epi-16-epitacamine (**10**), were obtained from intermediate **7**. The key reaction, an acid-catalyzed displacement of the dimethylamino group with the hydroxyl group, is believed to take place *via* an iminium intermediate.

Little has been published[2] on the synthesis of tacamine (**1**), an indole alkaloid of pseudovincamine type[3] found in *Tabernaemontana eglandulosa*[4] and also as a minor constituent in *T. pandacaqui*.[5] Tacamine is structurally closely related to the widely-used potent cerebral vasodilator vincamine (**2**), but the lack of plant or synthetic material has prevented tests for its presumed pharmacological activities.



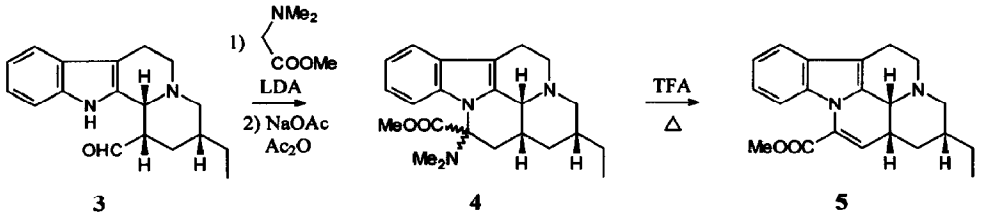
**1** ($R_1$ = COOMe, $R_2$ = OH)
**6** ($R_1$ = OH, $R_2$ = COOMe)



**2**

There are several methods for the synthesis of vincamine-type alkaloids *via* aldehyde intermediates.[3] In a recent paper[6] we reported our studies on the preparation and epimerization behaviour of aldehydes suitable for the synthesis of **1**. Starting from methyl 5-ethylnicotinate, we were able to prepare aldehyde **3** in a few simple steps, although it could not be characterized in totally pure form due to its easy epimerization.

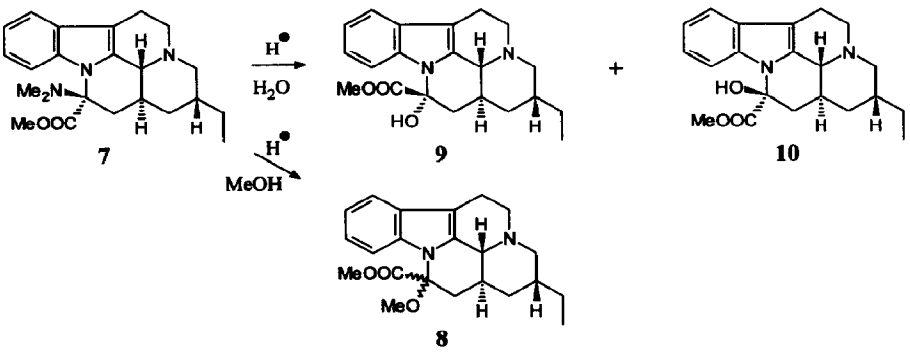
The epimeric mixture **4** was obtained from aldehyde **3** *via* successive condensation with an LDA-enolate of methyl *N,N*-dimethylglycinate and dehydration/cyclization with $NaOAc/Ac_2O$. Upon non-aqueous and non-nucleophilic acid treatment, **4** afforded (±)-apotacamine (**5**), the naturally occurring 16,17-anhydro derivative of **1**[4b] (Scheme 1).




**3** **4** **5**

**Scheme 1**

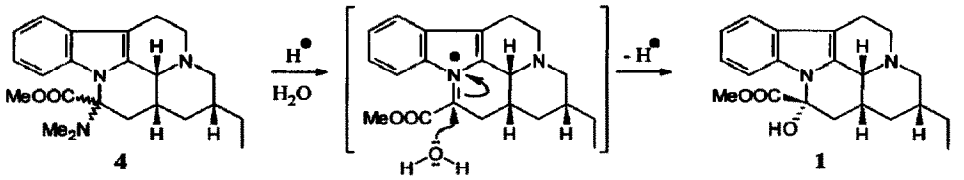
While optimizing the conditions of the above dehydration we assumed that a direct conversion of **4** into tacamine (**1**) and/or 16-epitacamine (**6**) might be possible. A promising sign of this possibility was obtained in preliminary studies with pentacycle **7**.[6] Refluxing this compound in methanol saturated with HCl gas produced significant amounts of compounds (mixture of 16-epimers) (**8**)[7] where the dimethylamino group was displaced by the methoxy group (Scheme 2). A method for the introduction of other nucleophiles, including water, into the 16-position seemed thus to be at hand. Indeed, under similar conditions, but with a small amount of water added to the acid solution, the two unnatural, previously unknown isomers of tacamine, namely (±)-14-epitacamine (**9**) and its 16-epimer, (±)-14-epi-16-epitacamine (**10**), were formed in good yield (Scheme 2). The two isomers were readily separated by column chromatography.[8] It should be noted that refluxing pentacycle **7** in either 30% aqueous HCl or $H_2SO_4$ did not yield 14-epitacamines.




**7** **9** **10** **8**

**Scheme 2**

(±)-Tacamine (**1**) was obtained in good yield when the epimeric mixture **4** was treated with a saturated MeOH/$HCl_g$ solution where a small amount of water was added.[9] A mechanism for this reaction, which probably proceeds *via* an iminium intermediate, is depicted in Scheme 3. After protonation of the dimethylamino group, cleavage of dimethylamine leads to the iminium intermediate, which is then susceptible to nucleophilic attack by water.




**Scheme 3**

In addition to small amounts of apotacamine (**5**), tacamine (**1**) was the major compound formed in this reaction. Only trace amounts of 16-epitacamine (**6**), one more major constituent of *T. eglandulosa*[4b], were detected. It has been pointed out earlier[4b] that the 16-epimer (**6**) is unstable and easily converted to tacamine (**1**).

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7. Selected spectral data of the mixture of (±)-14-epi-16-*O*-methyltacamines (**8**): MS (EI, *m/z*): 368 (95), 367 (100), 336 (30), 309 (65), 276 (30), 252 (53); $^1$H NMR (400 MHz, $CDCl_3$): 3.79 (3H, s, COOMe), 3.61 (3H, s, COOMe), 3.29 (3H, s, OMe), 3.09 (3H, s, OMe), 0.94 (3H, t, Me), 0.92 (3H, t, Me).

8. Selected spectral data of (±)-14-epitacamine (**9**): MS (EI, *m/z*): 354 (88), 353 (100), 293 (29), 252 (68), 223 (43); $^1$H NMR (400 MHz, $CDCl_3$): 3.89 (3H, s, COOMe), 0.94 (3H, t, Me); $^{13}$C NMR (100 MHz, $CDCl_3$): 174.0 (C=O), 135.4 (C-13), 134.3 (C-2), 129.3 (C-8), 121.5 (C-11), 120.4 (C-10), 118.7 (C-9), 110.4 (C-12), 106.2 (C-7), 82.8 (C-16), 64.4 (C-3), 58.5 (C-21), 54.1 (OMe), 53.0 (C-5), 41.7 (C-17), 36.4 (C-20), 33.7 (C-15), 28.2 (C-14), 25.0 (C-19), 21.4 (C-6), 12.7 (C-18).
Selected spectral data of (±)-14-epi-16-epitacamine (**10**): MS (EI, *m/z*): 354 (85), 353 (100), 293 (22), 252 (73), 223 (45); $^1$H NMR (400 MHz, $CDCl_3$): 3.59 (3H, s, COOMe), 0.92 (3H, t, Me); $^{13}$C NMR (100 MHz, $CDCl_3$): 173.3 (C=O), 136.4 (C-13), 134.8 (C-2), 121.5 (C-11), 120.3 (C-10), 118.3 (C-9), 111.0 (C-12), 106.1 (C-7), 83.4 (C-16), 64.0 (C-3), 58.3 (C-21), 53.9 (OMe), 52.9 (C-5), 42.3 (C-17), 36.2 (C-20), 34.1 (C-15), 30.9 (C-14), 25.3 (C-19), 21.3 (C-6), 12.6 (C-18).

9. The epimeric mixture **4** (10 mg, 0.26 mmol) was dissolved in saturated MeOH/$HCl_g$ (6 ml), and 3 ml of $H_2O$ was added. The reaction mixture was stirred at 50°C for 24 h. (This temperature and time gave the best yield of tacamine, but not without the formation of apotacamine starting to compete.) Basic work-up and chromatography on silica yielded 6 mg (65%) of (±)-tacamine (**1**), the spectral characteristics of which were in full agreement with the published data (Ref. 4).

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