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# Stereoselective Synthesis of Methyl 3α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine-1α-carboxylate: A Key Intermediate for the Preparation of Tacamine-Type Indole Alkaloids

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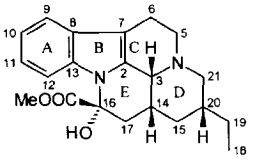
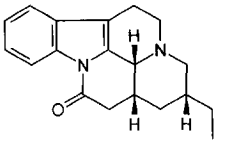
**Abstract:** Methyl 3α-ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine-1α-carboxylate (**6**), a key intermediate for the synthesis of tacamine-type indole alkaloids, was prepared in six simple steps from methyl 5-(1'-hydroxyethyl)nicotinate (**7**). The last step was the catalytic hydrogenation of the two ethylidene isomers **14** and **15**, both of which gave the target ester stereoselectively.

Synthetic efforts have recently been taken towards indole alkaloids of the tacamine (pseudovincamine) type, presumably because of their close relationship to the pharmacologically important eburnamine-vincamine group.[1] The principal compounds, tacamine (**1**) and tacamonine (**2**), obtained from *Tabernaemontana eglandulosa*[2], have been synthesised[3,4], even before their actual isolation.[3a,4a] The published methods offer some elegant examples of alkaloid synthesis, even an asymmetric approach[4c], but they all suffer from more or less poor stereoselectivity. The synthesis of all these compounds is complicated, however, by the seemingly trivial stereochemical feature: the relative configurational relationship at centres C-3, C-14 and C-20 (all hydrogens *cis*). The construction of this system remains the crucial step for an efficient synthesis of tacamine (**1**) and tacamonine (**2**) and their derivatives.



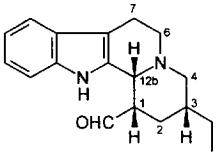

**1**



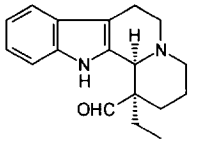

**2**

Our original method[3c,5] for the preparation of tacamine was based on the use of aldehyde **3**, which fulfils the above-mentioned stereochemical requirement and can easily be converted to tacamine and its derivatives. Aldehyde **3** is a close analogue of the renowned Oppolzer's aldehyde (**4**), which is an important

intermediate in the synthesis of the cerebral vasodilator vincamine (**5**).[1] Aldehyde **3** cannot, however, be prepared in satisfactory yield with use of our initial epimerization method.[3c] A search was therefore begun for an approach that would lead to the corresponding ester **6**. Relevant to this, we had already solved the problem concerning the relative stereochemistry at C-1 and C-12b in our aldehyde and ester intermediates.[4d,6] As this can be controlled by epimerization using either acid or base, only the stereochemistry at C-3 remained to be settled. One idea, we reasoned, would be to "remove" this centre and create it later in the synthesis, and perhaps the simplest way to accomplish this would be to replace the ethyl side chain with an ethylidene side chain. This would leave only two centres (C-1 and C-12b) in our intermediate, and catalytic hydrogenation could then produce the third (C-3). We thus turned our attention to the synthesis of the 3-ethylidene isomers of **6**.




**3**

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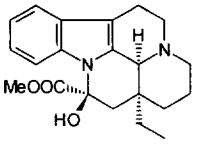
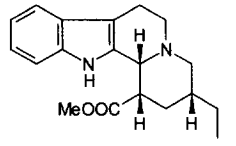


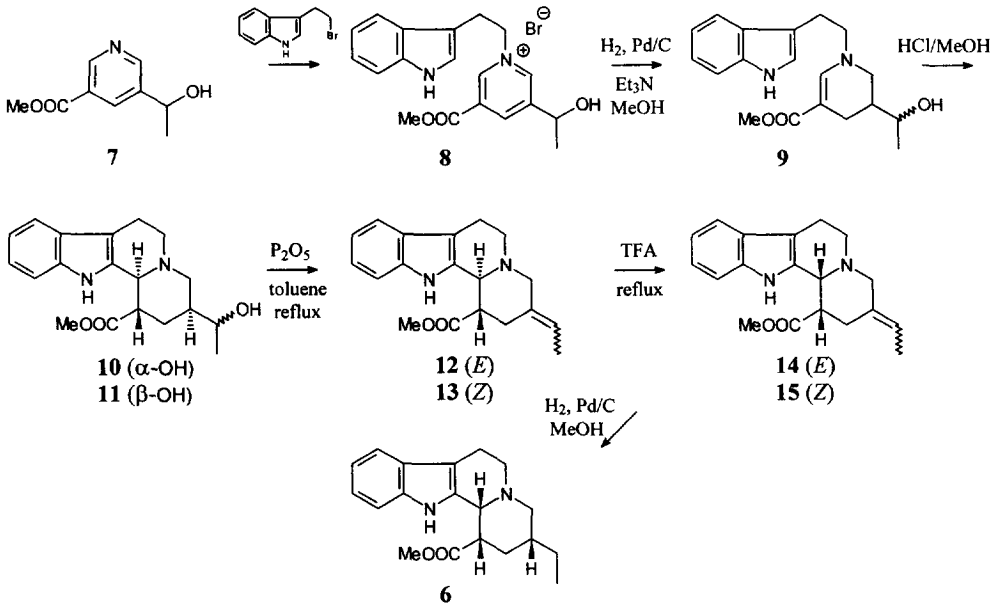

**5**




**6**

Synthesis was begun from methyl 5-(1'-hydroxyethyl)nicotinate (**7**)[7], which was prepared by reduction from methyl 5-acetylnicotinate.[8] Alkylation of **7** with tryptophyl bromide gave salt **8** (97%) (Scheme), which was subjected to catalytic hydrogenation under basic conditions to give the vinylogous urethane **9**[9] as an inseparable mixture of isomers (80%). Cyclization with HCl/MeOH furnished two alcohols, **10**[10] and **11**[11], in about 1:1 ratio (total yield 82%). Dehydration of these alcohols with $P_2O_5$ gave mainly the two ethylidene isomers **12**[12] and **13**[13] (in about 3:2 ratio) and a small amount of the corresponding vinyl derivative (total yield 50%). Separation of **12** and **13** proved to be laborious and it was more economical to perform the next step with the mixture of these isomers. Exposure of the mixture to trifluoroacetic acid (TFA) led, as expected, to the thermodynamically more stable (H-1 and H-12b *cis*) ethylidene isomers **14**[14] (*E*) and **15**[15] (*Z*) (3:2, total yield 58%), which could be separated relatively easily. The stereochemistry of the side chain was deduced by comparison with $^{13}C$ NMR data of similar compounds[16] and, unequivocally, by NOE difference spectroscopy.

Inspection of the models of esters **14** and **15** had already suggested that, in their hydrogenation, there could be preference for the approach of hydrogen from the desired face of the molecule. We first expected that the different geometrical isomers (*E* or *Z*) of the ethylidene esters would provide different ratios of hydrogenation products, but surprisingly the hydrogenation step was highly stereoselective, for both the (*E*)-isomer (**14**) and the (*Z*)-isomer (**15**). Hydrogenation of **14** or **15** separately, or more favourably their mixture, gave ester **6** (methyl 3α-ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine-1α-carboxylate)[17] in nearly quantitative yield (Scheme).




Scheme

The search for stereoselective syntheses of 1,3-disubstituted indolo[2,3-*a*]quinolizidines is intensifying.[18] We expect that ester **6** will provide an easy access to tacamine-type compounds and we believe that it is actually the first potentially significant intermediate for this group of indole alkaloids.

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9. Selected spectral data of compound **9** (mixture of epimers): MS (EI, *m/z*): 328 (48), 297 (12), 198 (100), 166 (77); $^1$H NMR (200 MHz, $CDCl_3$): 3.66 (3H, s, COOMe) and 3.65 (3H, s, COOMe), 1.26 (3H, d, $J$ = 6.3 Hz, Me) and 1.17 (3H, d, $J$ = 6.4 Hz, Me); $^{13}$C NMR (50 MHz, $CDCl_3$): 169.5 and 169.4 (C=O), 69.4 and 68.6 (-*C*(OH)Me), 21.2 and 20.0 (-C(OH)*Me*).
10. Selected spectral data of compound **10**: MS (EI, *m/z*): 328 (100), 327 (78), 283 (67), 184 (54); $^1$H NMR (400 MHz, $CDCl_3$): 4.22 (1H, dq, $J$ = 6.4 and 3.2 Hz, -C*H*(OH)Me), 3.85 (3H, s, COOMe), 3.82 (1H, d, $J$ = 10.8 Hz, H-12b), 1.24 (3H, d, $J$ = 6.4 Hz, -CH(OH)*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$): 177.7 (C=O), 72.7 (-*C*H(OH)Me), 21.0 (-CH(OH)*Me*).
11. Selected spectral data of compound **11**: MS (EI, *m/z*): 328 (100), 327 (85), 283 (63), 184 (98); $^1$H NMR (400 MHz, $CDCl_3$): 4.07 (1H, dq, $J$ = 6.4 and 2.4 Hz, -C*H*(OH)Me), 3.84 (3H, s, COOMe), 3.83 (1H, d, $J$ = 10.8 Hz, H-12b), 1.28 (3H, d, $J$ = 6.4 Hz, -CH(OH)*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$): 177.6 (C=O), 72.2 (-*C*H(OH)Me), 23.5 (-CH(OH)*Me*).
12. Selected spectral data of compound **12**: MS (EI, *m/z*): 310 (100), 309 (71), 170 (57), 169 (75); $^1$H NMR (400 MHz, $CDCl_3$): 5.46 (1H, q, $J$ = 6.8 Hz, =C*H*Me), 4.13 (1H, d, $J$ = 10.4 Hz, H-12b), 3.81 (3H, s, COOMe), 1.66 (3H, dt, $J$ = 6.8 and 1.6 Hz, =CH*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$): 177.0 (C=O), 120.4 (=*C*HMe), 12.7 (=CH*Me*).
13. Selected spectral data of compound **13**: MS (EI, *m/z*): 310 (100), 309 (64), 170 (54), 169 (78); $^1$H NMR (400 MHz, $CDCl_3$): 5.43 (1H, q, $J$ = 6.8 Hz, =C*H*Me), 4.12 (1H, d, $J$ = 10.2 Hz, H-12b), 3.78 (3H, s, COOMe), 1.68 (3H, dt, $J$ = 6.8 and 1.4 Hz, =CH*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$): 176.8 (C=O), 120.2 (=*C*HMe), 12.8 (=CH*Me*).
14. Selected spectral data of compound **14**: MS (EI, *m/z*): 310 (69), 309 (52), 170 (53), 169 (100); $^1$H NMR (400 MHz, $CDCl_3$): 5.49 (1H, q, $J$ = 6.4 Hz, =C*H*Me), 4.14 (1H, br s, H-12b), 3.60 (3H, s, COOMe), 1.65 (3H, d, $J$ = 6.4 Hz, =CH*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$): 173.7 (C=O), 120.4 (=*C*HMe), 12.7 (=CH*Me*).
15. Selected spectral data of compound **15**: MS (EI, *m/z*): 310 (67), 309 (52), 170 (50), 169 (100); $^1$H NMR (400 MHz, $CDCl_3$): 5.36 (1H, q, $J$ = 6.4 Hz, =C*H*Me), 4.29 (1H, br s, H-12b), 3.66 (3H, s, COOMe), 1.65 (3H, d, $J$ = 6.4 Hz, =CH*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$): 174.4 (C=O), 119.8 (=*C*HMe), 12.9 (=CH*Me*).
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17. Selected spectral data of ester **6**: MS (EI, *m/z*): 312 (42), 311 (41), 170 (100), 169 (80); $^1$H NMR (400 MHz, $CDCl_3$): 4.73 (1H, br s, H-12b), 3.85 (3H, s, COOMe), 0.86 (3H, t, $J$ = 7.2 Hz, Me); $^{13}$C NMR (100 MHz, $CDCl_3$): 176.6 (C=O), 16.9 (C-7), 11.3 ($CH_2CH_3$).
18. For a very recent approach, see Ihara, M.; Ishida, Y.; Tokunaga, Y.; Kabuto, C.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.*, **1995**, 2085-2086.


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