

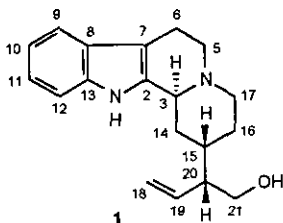
GENERAL STRATEGIES IN THE PREPARATION OF ANTIRHINE-TYPE INDOLE ALKALOIDS

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Abstract - Preparation of dimethyl malonyl-substituted indolo[2,3-*a*]quinolizidine derivative (**9**), which is a potential synthon in the antirhine (**1**) series, has been studied. Routes passing through intermediates (**22**) or (**26**) are superior to the route passing *via* intermediate (**7**), earlier preconized for that purpose.

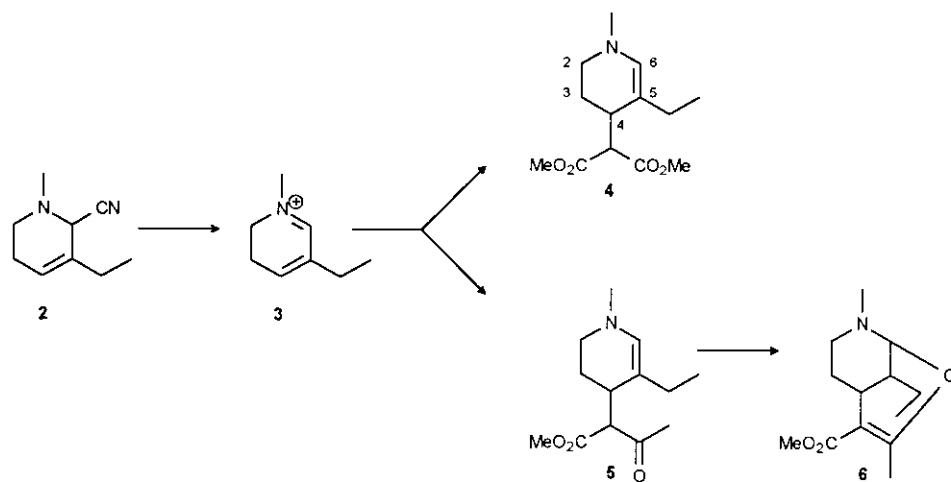
Antirhine (**1**) and its derivatives form a small group of indole alkaloids of *Corynanthé-Strychnos* type without a C(16) substituent.^{1,2} In most cases, the C(3)H-C(15)H relationship is *trans* (biogenetic formation^{3,4}), although some derivatives with the *cis* relationship are known as well.⁵



In many synthetic routes to indole alkaloids of indoloquinolizidine type, the most tedious and intellectually least attractive part of the work is the preparation of pyridine derivatives appropriately substituted at β - and γ -positions. Methods that permit direct introduction of substituents into simpler and more easily accessible intermediates are thus an attractive alternative.

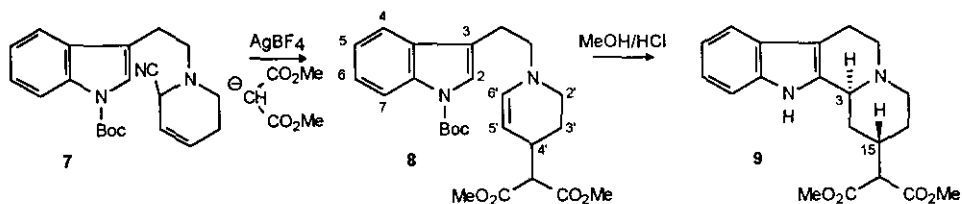
Continuing our synthetic efforts towards antirrhine analogues^{6,7} we became interested in the application of the above principle to the preparation of indolo[2,3-*a*]quinolizidine derivatives possessing an appropriate substituent [*e.g.* CH₃-CO-CH-CO₂Me or -CH(CO₂Me)₂] at the C(2) position [corresponding to the C(15) position in the biogenetic numbering²].

About 15 years ago Husson and his research group^{8,9} and Lounasmaa and his research group^{10,11} independently described the use of 2-cyano-3-ethyl- Δ^3 -piperideines as synthons in a general synthetic approach to complex alkaloid structures. *N*-Methyl-3-ethyl-5,6-dihydropyridinium salt (**3**), regenerated *in situ* from *N*-methyl-2-cyano-3-ethyl- Δ^3 -piperideine (**2**), was condensed with sodium dimethyl malonate or sodium methyl acetoacetate (both generating a β -dicarbonyl anion) to yield *N*-methyl-1,2,3,4-tetrahydropyridines (**4**) and (**5**) (and/or **6**),¹² respectively (Scheme 1).



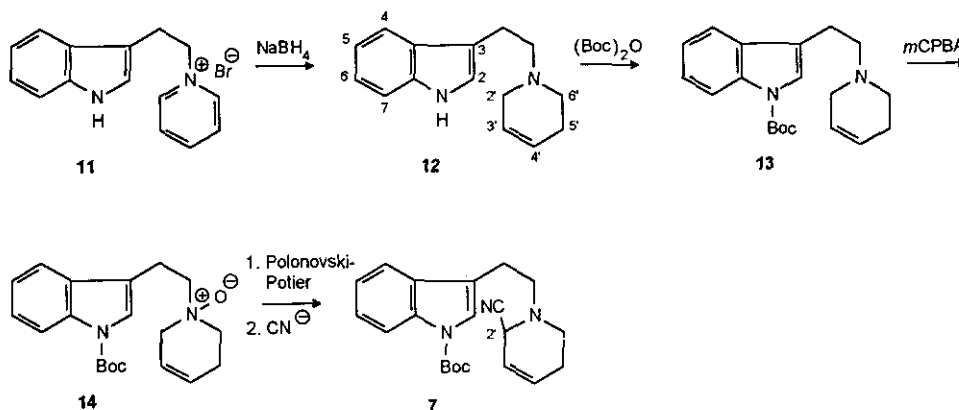
Scheme 1. Preparation of *N*-methyl-1,2,3,4-tetrahydropyridines (**4**) and (**5**) (and/or **6**).

A little later Husson and his group replaced the *N*-methyl-2-cyano-3-ethyl- Δ^3 -piperideine (**2**) with *N*_a-Boc-*N*_b-tryptophyl-2'-cyano- Δ^3 -piperideine (**7**).¹³ Condensation of (**7**) with sodium dimethyl malonate was reported to afford *N*_a-Boc-*N*_b-tryptophyl-1',2',3',4'-tetrahydropyridine (**8**) in quantitative yield.^{13,14} Subsequent deprotection at *N*_a and ring closure, initiated with MeOH/HCl_{gas}, was described as leading to compound (**9**) [C(3)H-C(15)H *trans*, biogenetic numbering²], and the whole procedure [(**7**)→(**8**)→(**9**)] was reported to result in 45% overall yield (Scheme 2).¹³



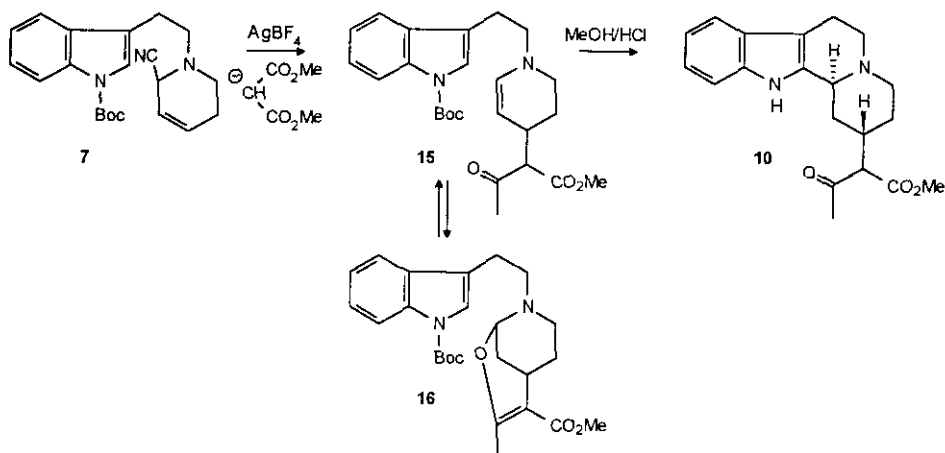
Scheme 2. Reported¹³ preparation of compound (9).

As the procedure seemed to be well suited for our present purposes and the reported overall yield (45%) reasonable, we decided to apply it in the preparation of indolo[2,3-*a*]quinolizidine derivative (10) (*vide infra*). Thus, the easily obtainable N_b -tryptophylpyridinium salt (11)¹⁵ was reduced with NaBH_4 to 1',2',5',6'-tetrahydropyridine (12), which by $[(\text{Boc})_2\text{O}]$ treatment was transformed to the corresponding N_a -Boc-protected compound (13). Oxidation of compound (13) with *m*CPBA afforded the corresponding N_b -oxide (14). Polonovski-Potier reaction¹⁶⁻¹⁸ and subsequent addition of CN^\ominus ions (Fry cyano-trapping method^{19,20}) yielded the 2'-cyano- Δ^3 '-piperidine (7) (Scheme 3).



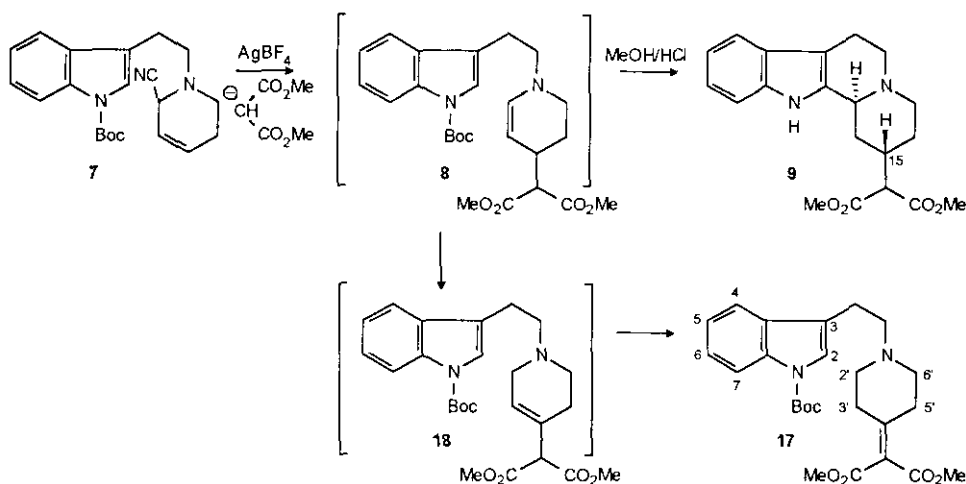
Scheme 3. Transformation of compound (11) to compound (7) via compounds (12, 13, and 14).

Reaction of compound (7) with sodium methyl acetoacetate in the presence of AgBF_4 was expected to yield 1',2',3',4'-tetrahydropyridine (15) (and/or bicyclic compound (16); see Refs. 8 and 10), which would then be transformable to compound (10) with MeOH/HCl treatment. However, we failed to find either 1',2',3',4'-tetrahydropyridine (15) or bicyclic derivative (16) in the reaction mixture (Scheme 4).



Scheme 4. Attempt to prepare compound (**10**) *via* compound (**15**) (and/or **16**).

These disappointing results incited us to investigate the reliability of the earlier reports;¹³ *i. e.* the reaction of 2'-cyano- Δ^3 -piperidine (**7**) with β -dicarbonyl anions (*vide supra*). For this purpose we decided to utilize exactly the same anion [*i. e.* $^-\text{CH}(\text{CO}_2\text{Me})_2$] as Husson *et al.*¹³ Thus, our above-described 2'-cyano- Δ^3 -piperidine (**7**) was reacted with sodium dimethyl malonate in the presence of AgBF_4 or ZnCl_2 . Despite our repeated efforts no 1',2',3',4'-tetrahydropyridine (**8**) was found in the reaction mixture.^{13,14} Thus, the anticipated acid induced cyclization of compound (**8**) to compound (**9**) could not be carried through. Instead, piperidine derivative (**17**) was isolated in 58% yield. One explanation for the formation of (**17**) and the absence of compound (**8**) in the reaction mixture might be that compound (**8**) was indeed formed but rapidly transformed [*e.g.* *via* intermediate (**18**)] to compound (**17**) (Scheme 5).

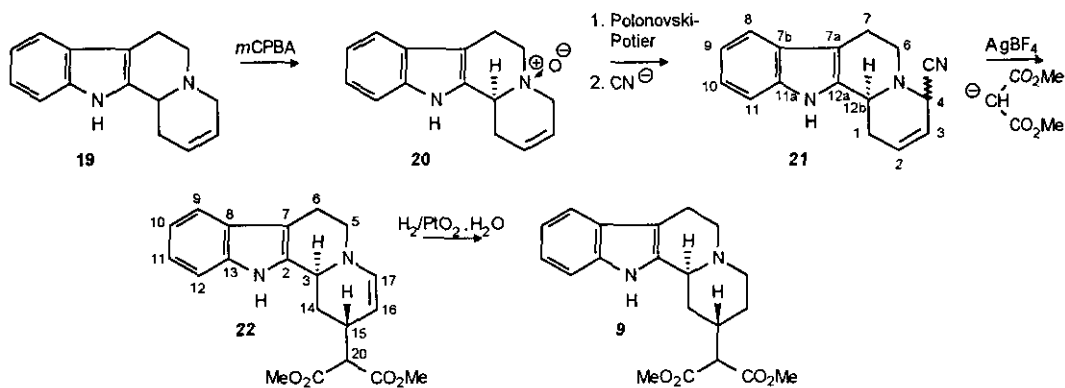


Scheme 5. Attempt to prepare compound (**9**) from compound (**7**). Formation of compound (**17**).

Attempts to transform compound (7) directly to compound (9), without isolation of the hypothetical intermediate (8) [(7)→(8)→(9)], did not give better results.

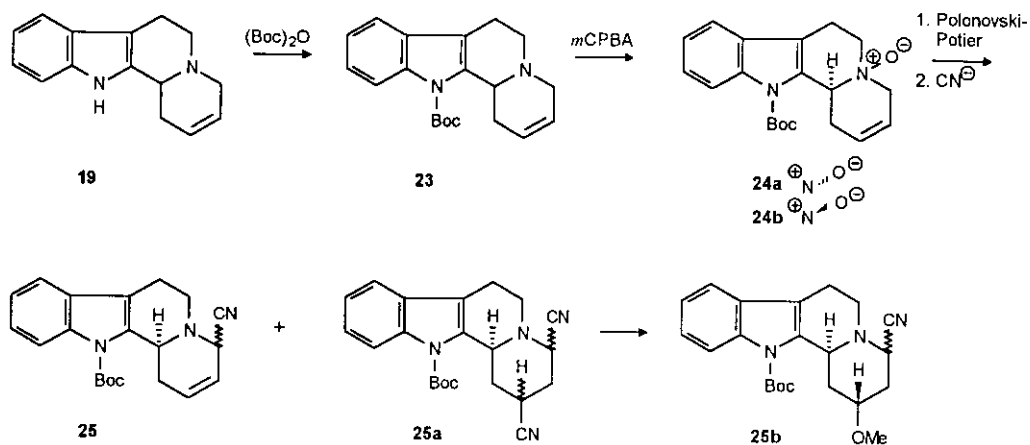
It thus turned out that, at least in our hands, the preparation of the 15-substituted compound (9) (and/or 10) by the described route is not the *méthode de choix*. The desethyl analogue and its derivatives seem to be more unstable than the corresponding ethyl analogue and make the reaction path more unreliable (*vide supra*). Accordingly, we switched our attention to the alternative route that we recently developed for our hirsutine synthesis.²¹

The easily obtainable compound (19)²² was oxidized with *m*CPBA to *N*_b-oxide (20). Polonovski-Potier reaction, followed by CN[⊖] trapping, afforded 4-cyanoindolo[2,3-*a*]quinolizidine (21) (IUPAC numbering²³). Treatment of compound (21) with sodium dimethyl malonate in the presence of AgBF₄ yielded, *via* the corresponding iminium salt, compound (22), albeit in low yield. Catalytic hydrogenation (H₂, PtO₂·H₂O) of compound (22) yielded compound (9) (Scheme 6).



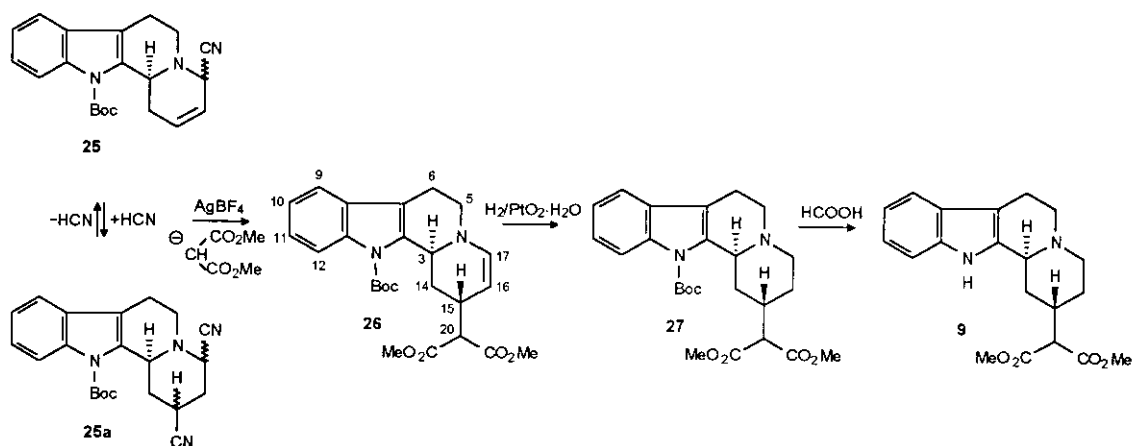
Scheme 6. Formation of compound (9) from compound (19) *via* compounds (20, 21, and 22).

As the total yield of the above procedure was relatively low, mainly due to resinification, compound (19)²² was transformed by (Boc)₂O treatment to the corresponding *N*_a-Boc protected compound (23), which was oxidized with *m*CPBA to a mixture of *N*_b-oxides (24a) and (24b). Polonovski-Potier reaction, followed by CN[⊖] trapping, yielded the crude product as a complex mixture containing at least two cyano derivatives, 4-monocyano compound (25) (minor) and 2,4-dicyano compound (25a) (major). The crude product was submitted to TLC purification, which led to the isolation of compound (25b), formed during the purification procedure (Scheme 7).



Scheme 7. Formation of compounds (**25**) and (**25a**), and their transformation to compound (**25b**) during the purification.

To avoid the undesired substitution product (**25b**), we treated the crude product of the Polonovski-Potier reaction and CN^\ominus trapping directly with sodium dimethyl malonate in the presence of AgBF_4 . In this way compound (**26**) was obtained, after fractionation, in reasonable yield. Catalytic hydrogenation (H_2 , PtO_2 , H_2O) of compound (**26**) afforded compound (**27**), which was Boc deprotected in acidic conditions, yielding compound (**9**) (Scheme 8).



Scheme 8. Transformation of the mixture of compounds (**25**) and (**25a**) to compound (**9**) via compounds (**26**) and (**27**).

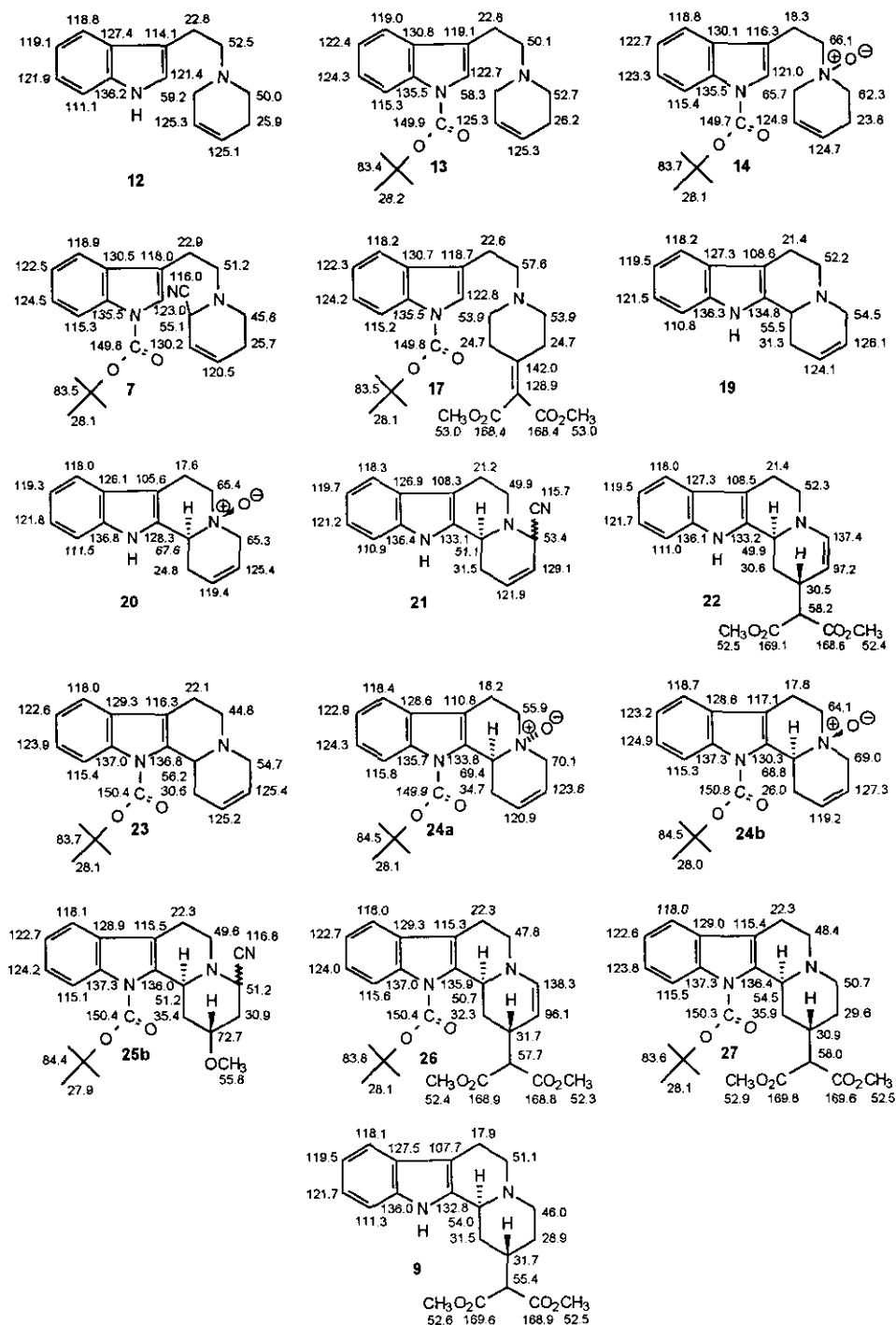


Chart 1. ^{13}C NMR data of compounds (7, 9, 12-14, 17, 19-27). The values for compound (24a) are taken from the spectrum of the 2:1 mixture of compounds (24a) and (24b) (*cf.* Experimental). The influence of the *endocyclic homoallylic effect* is easily identifiable in most of the cases [compounds (7, 12-14, 19-26)].^{24,25}

CONCLUSIONS

We have shown that for the preparation of dimethyl malonyl-substituted indolo[2,3-*a*]quinolizidine derivative (**9**), a potential synthon in the antirhine (**1**) series, intermediates (**21**) and (**25**) [and eventually intermediate (**25a**)] are superior to intermediate (**7**), earlier¹³ preconized for that purpose. However, in all cases examined the total yields are relatively low. Thus, it seems to us recommended that the use of the desethyl derivatives (present case) is much more delicate than that of ethyl derivatives described earlier.⁸⁻¹⁰

EXPERIMENTAL

IR spectra were recorded with a Perkin-Elmer 700 IR spectrophotometer using CHCl_3 as solvent. IR absorption bands are expressed in reciprocal centimetres (cm^{-1}). ^1H - and ^{13}C -NMR spectra were measured with a Varian Gemini-200 NMR spectrometer working at 199.975 MHz (^1H -NMR) and at 50.289 MHz (^{13}C -NMR) using CDCl_3 as solvent if not otherwise stated. Chemical shifts are given in ppm by reference to TMS (^1H -NMR; $\delta_{\text{H}}=0.00$ ppm) and CDCl_3 (^{13}C -NMR; $\delta_{\text{C}}=77.00$ ppm). Signal assignments were confirmed by APT and HETCOR (partly) experiments. Abbreviations s, d, t, q, m, def, and br are used to designate singlet, doublet, triplet, quartet, multiplet, deformed, and broad, respectively. For the ^{13}C -NMR data, see Chart 1. Mass spectrometry (EI and HRMS) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of N_6 -tryptophylpyridinium salt (**11**)

For the preparation and analytical data of compound (**11**), see Ref. 26 [compound (**1**) in Ref. 26].

Preparation of N_6 -tryptophyl-1',2',5',6'-tetrahydropyridine (**12**)

Compound (**11**) (200.0 mg, 0.662 mmol) was dissolved in MeOH (20 mL), and NaBH_4 (50.1 mg, 1.32 mmol) was added during 10 min to the cooled stirred solution. Stirring was continued for 0.5 h at rt (Ar atm) after which H_2O was added and MeOH evaporated. The reaction mixture was extracted with CH_2Cl_2 and the extract was dried with anhydrous Na_2SO_4 and evaporated to give essentially pure compound (**12**). Compound (**12**): 112.2 mg (75%). Amorphous (lit.,⁹ colorless solid). ^1H -NMR ($\text{CDCl}_3/\text{CD}_3\text{OD}$: 70/1): 2.25 (2H, m, H-5'), 2.70 (2H, t, $J = 6$ Hz, $-\text{CH}_2\text{CH}_2\text{N}<$), 2.79 (2H, m, $-\text{CH}_2\text{CH}_2\text{N}<$), 3.01 (2H, m, H-6'), 3.11 (2H, m, H-2'), 5.76 (2H, m, H-3', H-4'), 7.02 (1H, s, H-2), 7.15 (2H, m, H-5, H-6), 7.36 (1H, d, $J = 8$ Hz, H-7), 7.62 (1H, d, $J = 8$ Hz, H-4), 8.35 (1H, br s, NH). MS: 226 (M^+ , 100%), 144, 143, 130, 96. HRMS: Calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2$: 226.1470. Found: 226.1456. Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.40; H, 7.88; N, 12.26.

Preparation of N_α -Boc- N_β -tryptophyl-1',2',5',6'-tetrahydropyridine (13)

Compound (12) (366.3 mg, 1.621 mmol), (Boc)₂O (97%) (389.1 mg, 1.73 mmol), and DMAP (19.8 mg, 0.162 mmol) were dissolved in CH₂Cl₂ (50 mL). The reaction mixture was stirred for 2.5 h at rt (Ar atm), after which the solvent was evaporated and the crude product was purified by column chromatography (silica gel, CH₂Cl₂/MeOH; 99.8/0.2) to give compound (13).

Compound (13): 386.6 mg (73%). Amorphous (lit.,¹³ colorless oil). IR: 1735 (C=O). ¹H-NMR (CDCl₃): 1.67 [9H, s, -C(CH₃)₃], 2.24 (2H, m, H-5'), 2.68 (2H, t, J = 6 Hz, -CH₂CH₂N<), 2.78 (2H, m, -CH₂CH₂N<), 2.95 (2H, m, H-6'), 3.10 (2H, m, H-2'), 5.76 (2H, m, H-3', H-4'), 7.26 (2H, m, H-5, H-6), 7.41 (1H, s, H-2), 7.55 (1H, d, J = 8 Hz, H-4), 8.12 (1H, d, J = 8 Hz, H-7). MS: 326 (M⁺, 100%), 269, 144, 143, 130, 96. HRMS: Calcd for C₂₀H₂₅N₂O₂: 326.1994. Found: 326.1986. Anal. Calcd for C₂₀H₂₅N₂O₂: C, 73.82; H, 7.74; N, 8.61. Found: C, 73.56; H, 7.82; N, 8.46.

Preparation of N_α -Boc- N_β -tryptophyl-1',2',5',6'-tetrahydropyridine N_β -oxide (14)

Compound (13) (375.0 mg, 1.15 mmol) was dissolved in CH₂Cl₂ (30 mL), and *m*CPBA (90%) (238.2 mg, 1.24 mmol) was added to the stirred solution. Stirring was continued for 2 h at rt (Ar atm), after which the solvent was evaporated and the crude product was purified by column chromatography (alumina, CH₂Cl₂/MeOH; 99/1) to give compound (14).

Compound (14): 377.0 mg (96%). Amorphous (lit.,¹³ colorless foam). IR: 1730 (C=O). ¹H-NMR (CDCl₃): 1.67 [9H, s, -C(CH₃)₃], 3.97 (2H, t, def, H-2'), 5.67 (1H, br d, J = 10 Hz, H-4'), 5.93 (1H, br d, J = 10 Hz, H-3'), 7.29 (2H, m, H-5, H-6), 7.46 (1H, s, H-2), 7.61 (1H, d, J = 7 Hz, H-4), 8.13 (1H, d, J = 7 Hz, H-7). MS: 342 (M⁺, <1%), 326, 243, 187, 156, 143 (100%). HRMS: Calcd for C₂₀H₂₅N₂O₃: 342.1943. Found: 342.1932. Anal. Calcd for C₂₀H₂₅N₂O₃: C, 70.36; H, 7.38; N, 8.20. Found: C, 70.26; H, 7.26; N, 8.08.

Preparation of N_α -Boc- N_β -tryptophyl-2'-cyano- Δ^3 -piperidine (7)

Compound (14) (56.0 mg, 0.16 mmol) was dissolved in CH₂Cl₂ (30 mL), and trifluoroacetic anhydride (TFAA) (40 μ L, 0.28 mmol) was added to the solution during 5 min. The reaction mixture was stirred for 2 h at rt (Ar atm), after which KCN (45.6 mg, 0.70 mmol) in H₂O (12 mL) was added, and stirring was continued for 45 min at rt (Ar atm). The reaction mixture was neutralized with saturated NaHCO₃ solution, extracted with CH₂Cl₂, and the extract was dried with anhydrous Na₂SO₄. The crude product was purified by flash chromatography (silica gel, CH₂Cl₂/MeOH; 99/1) to give compound (7).

Compound (7): 11.5 mg (20%). Amorphous (lit.,¹³ colorless oil which turned to foam under vacuum). IR: 1730 (C=O). ¹H-NMR (CDCl₃): 1.67 [9H, s, -C(CH₃)₃], 4.26 (1H, br s, H-2'), 5.68-5.77 (1H, m, H-4'), 6.00-6.07 (1H, m, H-3'), 7.21-7.37 (2H, m, H-5, H-6), 7.46 (1H, s, H-2), 7.56 (1H, dd, J₁ = 7 Hz, J₂ = 2

H_z, H-4), 8.13 (1H, br d, J = 7 Hz, H-7). MS: 351 (M⁺), 251, 144, 143, 130, 121 (100%). HRMS: Calcd for C₂₁H₂₅N₃O₂: 351.1947. Found: 351.1939. Anal. Calcd for C₂₁H₂₅N₃O₂: C, 68.64; H, 6.86; N, 11.44. Found: C, 68.52; H, 6.68; N, 11.56.

Attempt to prepare methyl acetoacetyl-substituted *N*_a-Boc-*N*_b-tryptophyl-1',2',3',4'-tetrahydropyridine (15) [and/or bicyclic piperidine derivative (16)]

AgBF₄ (24.7 mg, 0.127 mmol) was added to the stirred solution of compound (7) (37.1 mg, 0.106 mmol) in THF (2 mL). Stirring was continued for 5 min at rt (Ar atm). Sodium methyl acetoacetate [NaH (60%, 6.7 mg, 0.167 mmol) and methyl acetoacetate (15 μL, 0.139 mmol) in THF (1 mL)] was added to the solution and the reaction mixture was stirred for 20 h at rt. Saturated NaHCO₃ solution was added and the reaction mixture was extracted with CH₂Cl₂ and the extract was dried with anhydrous Na₂SO₄. NMR and mass spectral examination of the crude product did not indicate the presence of any detectable amount of compound 15 (and/or compound 16) in the mixture.

Attempt to prepare dimethyl malonyl-substituted *N*_a-Boc-*N*_b-tryptophyl-1',2',3',4'-tetrahydropyridine (8); Formation of piperidine derivative (17)

AgBF₄ (7.0 mg, 0.036 mmol) was added to the stirred solution of compound (7) (11.5 mg, 0.033 mmol) in THF (1 mL). Stirring was continued for 5 min at rt (Ar atm). Sodium dimethyl malonate [NaH (60%, 4.2 mg, 0.105 mmol) and dimethyl malonate (10 μL, 0.088 mmol) in THF (0.5 mL)] was added to the solution and the reaction mixture was stirred for 15 h at rt. Saturated NaHCO₃ solution was added and the reaction mixture was extracted with CH₂Cl₂ and the extract was dried with anhydrous Na₂SO₄. The crude product, which did not contain compound (8) in detectable amount (no ¹H NMR signals between 4.5 - 7.2 ppm), was purified by CH₂Cl₂/hexane extraction to give compound (17).

Compound (17): 8.6 mg (58%). Amorphous. IR: 1730 (C=O). ¹H-NMR (CDCl₃): 1.67 [9H, s, -C(CH₃)₃], 3.69 (6H, s, 2 x -CO₂CH₃), 7.2-7.6 (3H, m, H-4, H-5, H-6), 7.31 (1H, d, J = 1 Hz, H-2), 8.13 (1H, d, J = 8 Hz, H-7). MS: 456 (M⁺), 226 (100%), 144, 143, 130. HRMS: Calcd for C₂₅H₃₂N₂O₆: 456.2260. Found: 456.2246. Anal. Calcd for C₂₅H₃₂N₂O₆: C, 65.77; H, 7.06; N, 6.14. Found: C, 65.52; H, 7.14; N, 6.04.

In a similar procedure, where AgBF₄ was replaced by a small amount (0.1 equiv.) of anhydrous ZnCl₂,¹³ compound (8) was not detected.

Preparation of 1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (19)

For the preparation and analytical data of compound (19), see Ref. 22 [compound (3a) in Ref. 22].

Preparation of 1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine *N*_b-*trans*-oxide (20)

Compound (19) (331.9 mg, 1.482 mmol) was dissolved in CH₂Cl₂ (20 mL) and *m*CPBA (90%) (319.5 mg, 1.67 mmol) was added to the stirred solution. Stirring was continued for 3 h at rt (Ar atm), after which the solvent was evaporated and the crude product was purified by column chromatography (alumina, CH₂Cl₂/MeOH; 99/1) to give compound (20).

Compound (20): 211.8 mg (60%). Amorphous. ¹H-NMR (CDCl₃/CD₃OD; 13/1): 4.44 (1H, dd, J₁ = 10 Hz, J₂ = 6 Hz, H-12b), 5.65 (1H, br d, J = 12 Hz, H-2), 5.88 (1H, br d, J = 12 Hz, H-3), 7.0-7.2 (2H, m, H-9, H-10), 7.28 (1H, dd, J₁ = 7.5 Hz, J₂ = 2.5 Hz, H-11), 7.49 (1H, dd, J₁ = 7.5 Hz, J₂ = 2.5 Hz, H-8). MS: 240 (M⁺, < 1%), 239, 224 (100%), 197, 170, 169. HRMS: Calcd for C₁₅H₁₆N₂O: 240.1263. Found 240.1242. Anal. Calcd for C₁₅H₁₆N₂O: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.06; H, 6.56; N, 11.42.

Preparation of 1,4,6,7,12,12b-hexahydro-4-cyanoindolo[2,3-*a*]quinolizine (21)

Compound (20) (377.1 mg, 1.57 mmol) was dissolved in CH₂Cl₂ (30 mL) and trifluoroacetic anhydride (TFAA)(310 μL, 2.19 mmol) was added to the solution during 5 min. The reaction mixture was stirred for 2 h at rt (Ar atm), after which KCN (306.9 mg, 4.71 mmol) in H₂O (12 mL) was added, and stirring was continued for 45 min at rt (Ar atm). The reaction mixture was neutralized with saturated NaHCO₃ solution, extracted with CH₂Cl₂, and the extract was dried with anhydrous Na₂SO₄. The crude product was purified by flash chromatography (silica gel, CH₂Cl₂/MeOH; 99/1) to give compound (21).

Compound (21): 20 mg (7.5%). Amorphous. ¹H-NMR (CDCl₃): 2.31 (1H, ddd, J₁ = 10.5 Hz, J₂ = 4 Hz, J₃ = 2 Hz, H-1α), 2.54 (1H, ddd, J₁ = 17 Hz, J₂ = 4.5 Hz, J₃ = 4.5 Hz, H-6β), 2.82 (1H, m, H-7α), 3.0-3.1 (2H, m, H-6α, H-7β), 3.98 (1H, dd, J₁ = 11 Hz, J₂ = 3.5 Hz, H-12b), 4.38 (1H, br dd, J = 12 Hz, H-4), 5.79-5.84 (1H, m, H-2), 6.04-6.08 (1H, m, H-3), 7.12 (1H, t, J = 7 Hz, H-9), 7.17 (1H, t, J = 7 Hz, H-10), 7.32 (1H, d, J = 7 Hz, H-11), 7.50 (1H, d, J = 7 Hz, H-8), 7.80 (1H, br s, NH). MS: 249 (M⁺), 221, 170 (100%), 169. HRMS: Calcd for C₂₁H₂₃N₃O₂: 349.1790. Found: 349.1778. Anal. Calcd for C₂₁H₂₃N₃O₂: C, 72.18; H, 6.63; N, 12.03. Found: C, 72.26; H, 6.52; N, 11.84.

Preparation of dimethyl malonyl-substituted indolo[2,3-*a*]quinolizidine derivative (22)

AgBF₄ (18.8 mg, 0.096 mmol) was added to the stirred solution of compound (21) (20.0 mg, 0.080 mmol) in THF (2 mL). Stirring was continued for 5 min at rt (Ar atm). Sodium dimethyl malonate [NaH (60%, 7.7 mg, 0.19 mmol) and dimethyl malonate (20 μL, 0.175 mmol) in THF (1 mL)] was added to the solution and the reaction mixture was stirred for 16 h at rt. Saturated NaHCO₃ solution was added and the reaction mixture was extracted with CH₂Cl₂, and the extract was dried with anhydrous Na₂SO₄. The crude product was purified by flash chromatography (silica gel, CH₂Cl₂/MeOH; 99.8/0.2) to give compound (22).

Compound (**22**): 14.8 mg (52%). Amorphous. IR: 1730 (C=O). $^1\text{H-NMR}$ (CDCl_3): 3.75 (3H, s, $-\text{CO}_2\text{CH}_3$), 3.80 (3H, s, $-\text{CO}_2\text{CH}_3$), 4.26 (1H, br d, $J = 8$ Hz, H-3), 4.34 (1H, br dd, $J_1 = 8$ Hz, $J_2 \approx 4$ Hz, H-16), 6.08 (1H, dd, $J_1 = 8$ Hz, $J_2 = 1.5$ Hz, H-17), 7.10 (1H, t-like, $J = 8$ Hz, H-10), 7.15 (1H, t-like, $J = 8$ Hz, H-11), 7.34 (1H, d, $J = 8$ Hz, H-12), 7.47 (1H, d, $J = 8$ Hz, H-9), 7.92 (1H, br s, NH). MS: 354 (M^+), 223 (100%), 170, 169. HRMS: Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4$: 354.1580. Found: 354.1558. Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.62; H, 6.38, N, 7.72.

Preparation of dimethyl malonyl-substituted indolo[2,3-*a*]quinolizidine derivative (9) from compound (22)

Catalytic hydrogenation (H_2 , $\text{PtO}_2 \cdot \text{H}_2\text{O}$, 15 mg, 1 atm, 1 h) of compound (**22**) (8.9 mg, 0.025 mmol) in MeOH (3 mL) afforded the crude product, which was purified by TLC (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$; 95/5) to give compound (**9**).

Compound (**9**): 3.1 mg (35%). Amorphous. For the analytical data, see below.

Preparation of N_α -Boc-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (23)

Compound (**19**) (184.7 mg, 0.825 mmol), $(\text{Boc})_2\text{O}$ (97%) (265.5 mg, 1.18 mmol), and DMAP (10.2 mg, 0.0835 mmol) were dissolved in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 1 h at rt (Ar atm), after which the solvent was evaporated and the crude product was purified by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$; 99/1) to give compound (**23**).

Compound (**23**): 248.6 mg (93%). Amorphous. IR: 1730 (C=O). $^1\text{H-NMR}$ (CDCl_3): 1.66 [9H, s, $-\text{C}(\text{CH}_3)_3$], 4.14 (1H, dd, $J_1 = 10$ Hz, $J_2 = 3$ Hz, H-12b), 5.79 (2H, m, H-2, H-3), 7.2-7.3 (2H, m, H-9, H-10), 7.43 (1H, dd, $J_1 = 7$ Hz, $J_2 = 2$ Hz, H-8), 8.07 (1H, dd, $J_1 = 7$ Hz, $J_2 = 2$ Hz, H-11). MS: 324 (M^+), 268, 267, 214, 170, 169 (100%). HRMS: Calcd for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2$: 324.1838. Found: 324.1826. Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2$: C, 74.05; H, 7.46; N, 8.63. Found: C, 74.16; H, 7.32; N, 8.46.

Preparation of N_α -Boc-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine N_b -*cis*-oxide (24a) and N_α -Boc-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine N_b -*trans*-oxide (24b)

Compound (**23**) (216.3 mg, 0.668 mmol) was dissolved in CH_2Cl_2 (15 mL) and *m*CPBA (90%) (172.4 mg, 0.899 mmol) was added to the stirred solution. Stirring was continued for 3 h at rt (Ar atm), after which the solvent was evaporated and the crude product was purified by column chromatography (alumina, $\text{CH}_2\text{Cl}_2/\text{MeOH}$; 99/1) to give compounds (**24a**) (*cis*) and (**24b**) (*trans*) as ~2:1 mixture.

The 2:1 mixture of compounds (**24a**) and (**24b**): 219.8 mg (97%). Amorphous. IR: 1730 (C=O). MS: 340 (M^+ , <1%), 324, 268, 267, 252, 221, 170, 169 (100%). HRMS: Calcd for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2$ ($\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3 - \text{O}$) = 324.1838. Found: 324.1828. For the $^1\text{H-NMR}$ spectrum and elemental analysis of compound (**24b**), see below.

Attempt to prepare N_α -Boc-1,4,6,7,12,12b-hexahydro-4 ξ -cyanoindolo[2,3-*a*]quinolizine (25); Formation of N_α -Boc-1,4,6,7,12,12b-hexahydro-2 α -methoxy-4 α -cyanoindolo[2,3-*a*]quinolizine (25b)

The mixture of compounds (24a) and (24b) (135.8 mg, 0.400 mmol) was dissolved in CH_2Cl_2 (2 mL), and trifluoroacetic anhydride (TFAA) (140 μL , 0.991 mmol) was added to the solution during 5 min. The reaction mixture was stirred for 1 h at rt (Ar atm), after which KCN (52.7 mg, 0.809 mmol) in H_2O (2 mL) was added, the pH was adjusted to pH 4 (NaOAc), and stirring was continued for 1 h at rt (Ar atm). The reaction mixture was neutralized with saturated NaHCO_3 solution, extracted with CH_2Cl_2 , and the extract was dried with anhydrous Na_2SO_4 . The complex crude product mixture, containing (according to MS) two cyano derivatives [monocyano derivative (25) (minor)(M^+ at m/z 349) and dicyano compound (25a) (major)(M^+ at m/z 376)], was submitted to TLC purification (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$; 99/1). This led to the isolation of compound (25b), formed by substitution during purification.

Compound (25b): 19.2 mg (13%). Amorphous. IR: 1730 (C=O). $^1\text{H-NMR}$ (CDCl_3): 1.47 (1H, ddd, $J_1 = 13$ Hz, $J_2 = 12.5$ Hz, $J_3 = 2.5$ Hz, H-1 β), 1.69 [9H, s, $-\text{C}(\text{CH}_3)_3$], 3.49 (3H, s, $-\text{OCH}_3$), 4.61 (1H, br d, $J = 12.5$ Hz, H-12b), 7.2-7.3 (2H, m, H-9, H-10), 7.42 (1H, dd, $J_1 = 6$ Hz, $J_2 = 2$ Hz, H-8), 8.05 (1H, dd, $J_1 = 6$ Hz, $J_2 = 2$ Hz, H-11). MS: 381 (M^+), 324, 281, 265, 241, 221 (100%), 197, 169. HRMS: Calcd for $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_3$: 381.2052. Found: 381.2038. Anal. Calcd for $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_3$: C, 69.27; H, 7.13; N, 11.02. Found: C, 69.08; H, 7.02; N, 10.86.

Preparation of dimethyl malonyl-substituted N_α -Boc-indolo[2,3-*a*]quinolizidine derivative (26)

The mixture of compounds (24a) and (24b) (178.6 mg, 0.525 mmol) was dissolved in CH_2Cl_2 (4 mL), and trifluoroacetic anhydride (TFAA) (110 μL , 0.779 mmol) was added during 5 min. The reaction mixture was stirred for 1 h at rt (Ar atm), after which KCN (39.1 mg, 0.600 mmol) in H_2O (4 mL) was added, the pH was adjusted to pH 4 (NaOAc), and stirring was continued for 0.5 h at rt (Ar atm). The reaction mixture was neutralized with saturated NaHCO_3 solution, extracted with CH_2Cl_2 , and the extract was dried with anhydrous Na_2SO_4 . AgBF_4 (102.3 mg, 0.525 mmol) was added to the stirred solution of crude product (165.6 mg) in THF (4 mL). Stirring was continued for 5 min at rt (Ar atm). Sodium dimethyl malonate [NaH (60%, 47.2 mg, 1.181 mmol) and dimethyl malonate (90 μL , 0.787 mmol) in THF (3 mL)] was added to the solution and the reaction mixture was stirred for 17 h at rt. Saturated NaHCO_3 solution was added and the reaction mixture was extracted with CH_2Cl_2 and the extract was dried with anhydrous Na_2SO_4 . The crude product was purified by column chromatography (alumina, $\text{CH}_2\text{Cl}_2/\text{MeOH}$; 99.9/0.1, 99.5/0.5, 99/1) to give compounds (23, 26, and 24b).

Compound (23): 14.5 mg (9%). For the spectral data, see above.

Compound (26): 28.6 mg (12%). Amorphous. IR: 1730 (C=O). $^1\text{H-NMR}$ (CDCl_3): 1.66 [9H, s, $-\text{C}(\text{CH}_3)_3$], 3.75 (6H, s, 2 x $-\text{CO}_2\text{CH}_3$), 4.29 (1H, br dd, $J_1 = 8$ Hz, $J_2 \approx 4$ Hz, H-16), 4.57 (1H, dd, $J_1 = 10$ Hz, $J_2 =$

2.5 Hz, H-3), 6.17 (1H, dd, $J_1 = 8$ Hz, $J_2 = 1.5$ Hz, H-17), 7.20-7.29 (2H, m, H-10, H-11), 7.41 (1H, dd, $J_1 = 8$ Hz, $J_2 = 2$ Hz, H-9), 7.93 (1H, dd, $J_1 = 8$ Hz, $J_2 = 2$ Hz, H-12). MS: 454 (M^+), 398, 340, 324, 284, 267 (100%), 214, 170, 169. HRMS: Calcd for $C_{25}H_{30}N_2O_6$: 454.2104. Found: 454.2092. Anal. Calcd for $C_{25}H_{30}N_2O_6$: C, 66.06; H, 6.65; N, 6.16. Found: C, 65.88; H, 6.42; N, 6.02.

Compound (**24b**): 36.2 mg (20%). 1H -NMR ($CDCl_3$): 1.66 [9H, s, $-C(CH_3)_3$], 3.94 (1H, br d, $J = 15.5$ Hz, H-4 α), 4.20 (1H, dd, $J_1 = 15.5$ Hz, $J_2 = 2$ Hz, H-4 β), 4.79 (1H, br d, $J = 10$ Hz, H-12b), 5.68 (1H, br d, $J = 10$ Hz, H-3), 6.08 (1H, m, H-2), 7.21-7.34 (2H, m, H-9, H-10), 7.48 (1H, dd, $J_1 = 7$ Hz, $J_2 = 2$ Hz, H-8), 7.94 (1H, dd, $J_1 = 7$ Hz, $J_2 = 2$ Hz, H-11). For the other spectral data, see above. Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23. Found: C, 70.72; H, 7.208; N, 8.36.

Preparation of indolo[2,3-*a*]quinolizidine derivative (**27**)

Catalytic hydrogenation (H_2 , $PtO_2 \cdot H_2O$, 30 mg, 1 atm, 1 h) of compound (**26**) (22.4 mg, 0.049 mmol) in MeOH (5 mL) afforded the crude product, which was purified by TLC (silica gel, $CH_2Cl_2/MeOH$; 95/5) to give compound (**27**).

Compound (**27**): 10.1 mg (45%). Amorphous. IR: 1730 (C=O). 1H -NMR ($CDCl_3$): 1.65 [9H, s, $-C(CH_3)_3$], 2.17 (1H, br d, $J = 15$ Hz, H-14 α), 3.75 (3H, s, $-CO_2CH_3$), 3.81 (3H, s, $-CO_2CH_3$), 3.98 (1H, d, $J = 11.5$ Hz, H-20), 4.27 (1H, br d, $J = 9$ Hz, H-3), 7.17-7.28 (2H, m, H-10, H-11), 7.41 (1H, dd, $J_1 = 7$ Hz, $J_2 = 3$ Hz, H-9), 7.92 (1H, dd, $J_1 = 7$ Hz, $J_2 = 3$ Hz, H-12). MS: 456 (M^+), 399 (100%), 355, 283, 269, 223, 170, 169. HRMS: Calcd for $C_{25}H_{32}N_2O_6$: 456.2260. Found: 456.2252. Anal. Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.06; N, 6.14. Found: C, 65.62; H, 7.18; N, 6.02.

Preparation of indolo[2,3-*a*]quinolizidine derivative (**9**) from compound (**27**)

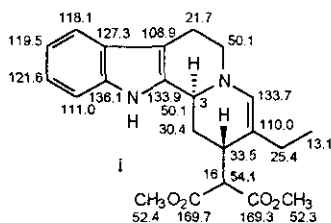
Compound (**27**) (9.2 mg, 0.020 mmol) was dissolved in HCOOH (3 mL) and the reaction mixture was stirred at rt for 20 h (Ar atm). HCOOH was evaporated, the residue was dissolved in CH_2Cl_2 , neutralized with $NaHCO_3$, and the extract was dried with anhydrous Na_2SO_4 . The solution was evaporated to yield crude compound (**9**), which was purified by flash chromatography (alumina, $CH_2Cl_2/MeOH$; 99/1).

Compound (**9**): 6.8 mg (95%). Amorphous (lit.,⁹ pale yellow oil). IR: 1730 (C=O). 1H -NMR ($CDCl_3$): 3.39 (1H, d, $J = 10$ Hz, H-20), 3.71 (3H, s, $-CO_2CH_3$), 3.80 (3H, s, $-CO_2CH_3$), 4.30 (1H, br, H-3), 7.11 (1H, ddd, $J_1 = 7$ Hz, $J_2 = 7$ Hz, $J_3 = 1.5$ Hz, H-10), 7.18 (1H, ddd, $J_1 = 7$ Hz, $J_2 = 7$ Hz, $J_3 = 1.5$ Hz, H-11), 7.41 (1H, dd, $J_1 = 7$ Hz, $J_2 = 1.5$ Hz, H-12), 7.49 (1H, dd, $J_1 = 7$ Hz, $J_2 = 1.5$ Hz, H-9), 8.05 (1H, br s, NH). MS: 356 (M^+ , 100%), 355, 341, 325, 297, 225, 223, 197, 169. HRMS: Calcd for $C_{20}H_{24}N_2O_4$: 356.1736. Found: 356.1728. Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.32; H, 6.58; N, 7.66.

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