GENERAL STRATEGIES IN THE PREPARATION OF ANTIRHINE-TYPE INDOLE ALKALOIDS

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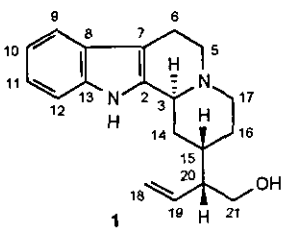
Abstract - Preparation of dimethyl malonyl-substituted indolo[2,3-*a*]quinolizidine derivative (**9**), which is a potential synthon in the antirhine (**1**) series, has been studied. Routes passing through intermediates (**22**) or (**26**) are superior to the route passing *via* intermediate (**7**),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



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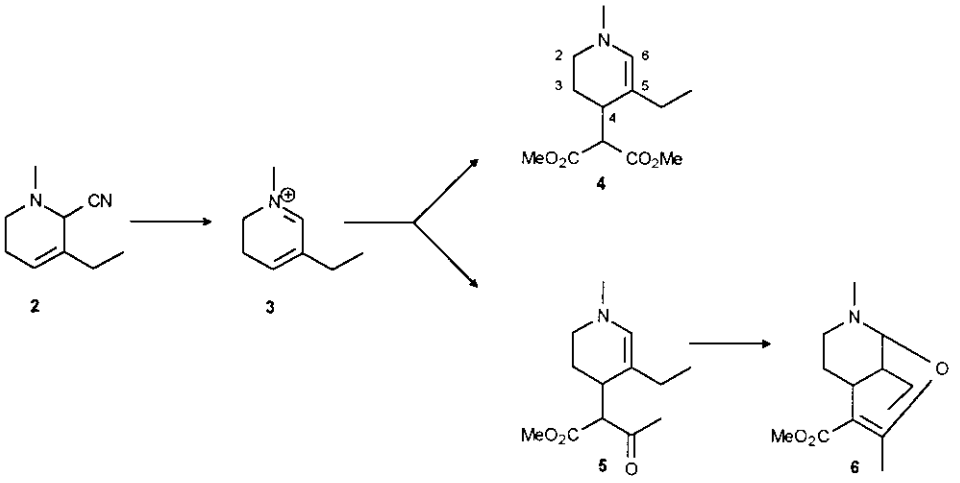
In many synthetic routes to indole alkaloids of indoloquinolizidine type, the most tedious and intellectually least attractive part of the work is the preparation of pyridine derivatives appropriately substituted at β- and γ-positions. Methods that permit direct introduction of substituents into simpler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

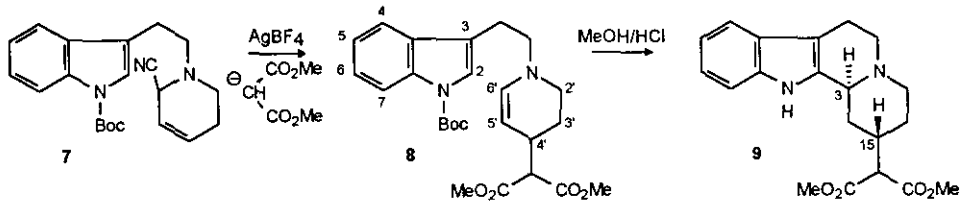
Continuing our synthetic efforts towards antirhine analogues[6,7] we became interested in the application of the above principle to the preparation of indolo[2,3-*a*]quinolizidine derivatives possessing an appropriate substituent [*e.g.* CH_3-CO-CH(CO_2Me)-CO_2Me or -$CH(CO_2Me)_2$] at the C(2) position [corresponding to the C(15) position in the biogenetic numbering[2]].

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).



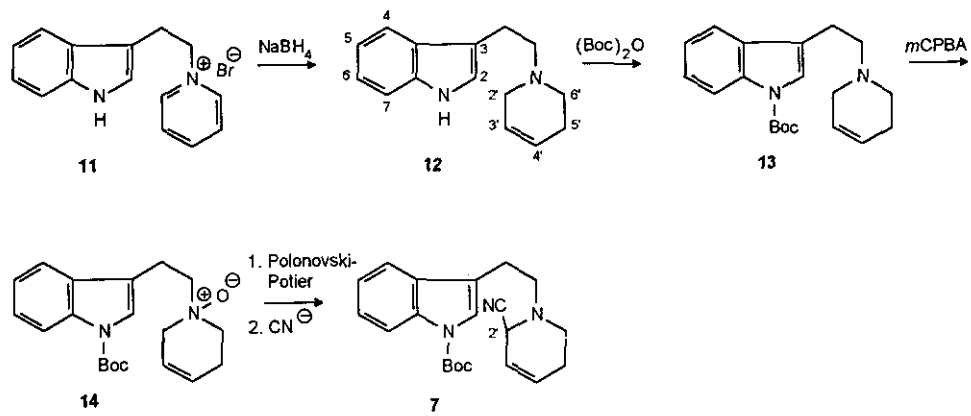
Scheme 1. Preparation of *N*-methyl-1,2,3,4-tetrahydropyridines (**4**) and (**5**) (and/or **6**).

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-$\Delta^{3'}$-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 numbering[2]], and the whole procedure [(**7**)→(**8**)→(**9**)] was reported to result in 45% overall yield (Scheme 2).[13]



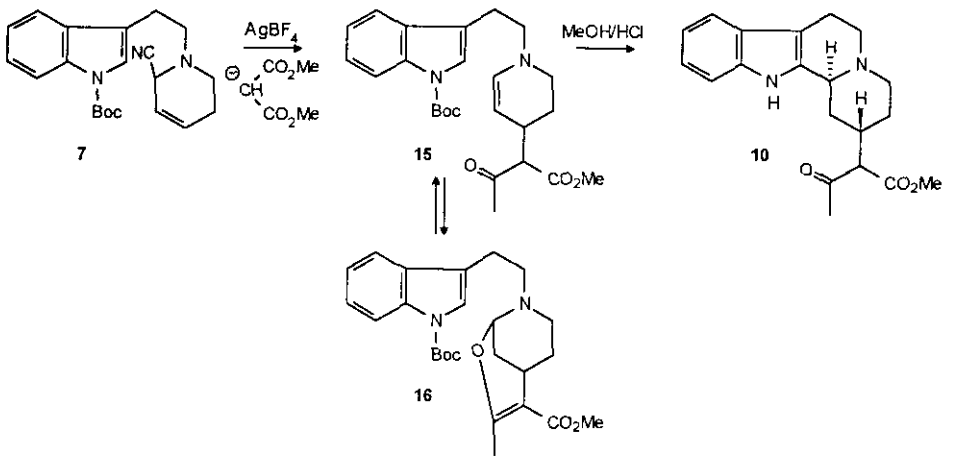
Scheme 2. Reported[13] preparation of compound (**9**).

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 [$(Boc)_2O$] 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 reaction[16-18] and subsequent addition of $CN^{\ominus}$ ions (Fry cyano-trapping method[19,20]) yielded the 2'-cyano-$\Delta^{3'}$-piperideine (**7**) (Scheme 3).



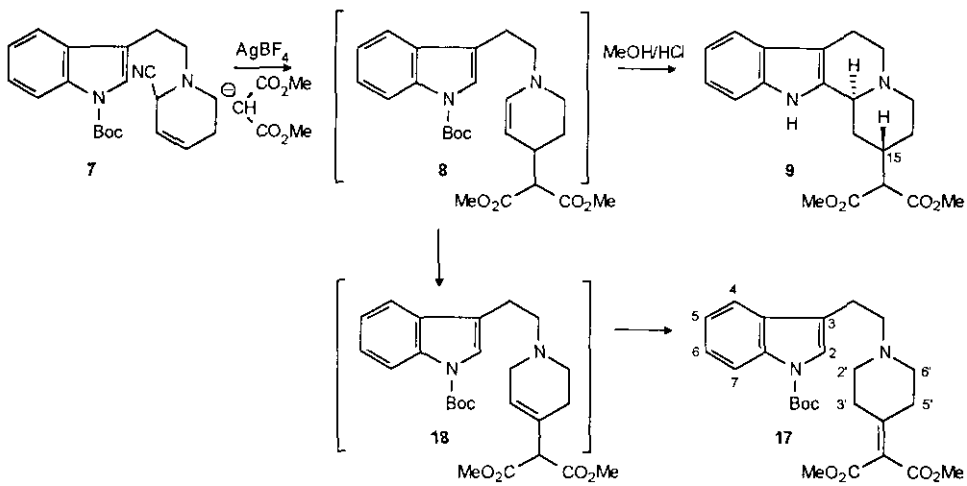
Scheme 3. Transformation of compound (**11**) to compound (**7**) *via* compounds (**12**, **13**, and **14**).

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-$\Delta^{3'}$-piperideine (**7**) with β-dicarbonyl anions (*vide supra*). For this purpose we decided to utilize exactly the same anion [*i. e.* $^{\ominus}CH(CO_2Me)_2$] as Husson *et al.*[13] Thus, our above-described 2'-cyano-$\Delta^{3'}$-piperideine (**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).

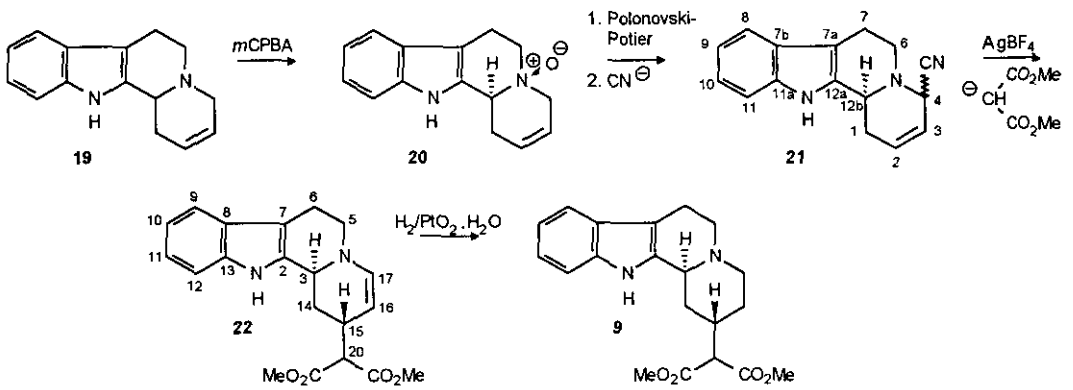


Scheme 5. Attempt to prepare compound (**9**) from compound (**7**). Formation of compound (**17**).

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

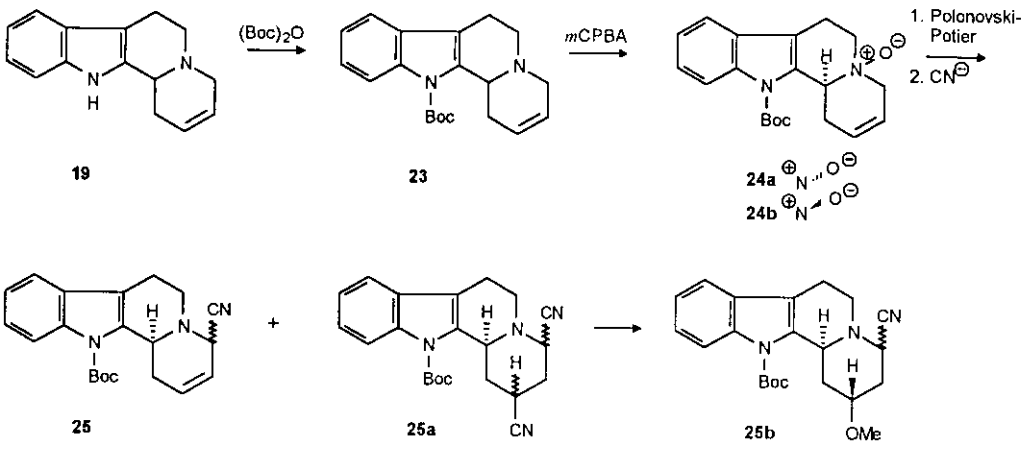
It thus turned out that, at least in our hands, the preparation of the 15-substituted compound (**9**) (and/or **10**) by the described route is not the *méthode de choix*. The desethyl analogue and its derivatives seem to be more unstable than the corresponding ethyl analogue and make the reaction path 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 $CN^{\ominus}$ trapping, afforded 4-cyanoindolo[2,3-*a*]quinolizidine (**21**) (IUPAC numbering[23]). Treatment of compound (**21**) with sodium dimethyl malonate in the presence of $AgBF_4$ yielded, *via* the corresponding iminium salt, compound (**22**), albeit in low yield. Catalytic hydrogenation (H_2, $PtO_2 \cdot H_2O$) of compound (**22**) yielded compound (**9**) (Scheme 6).



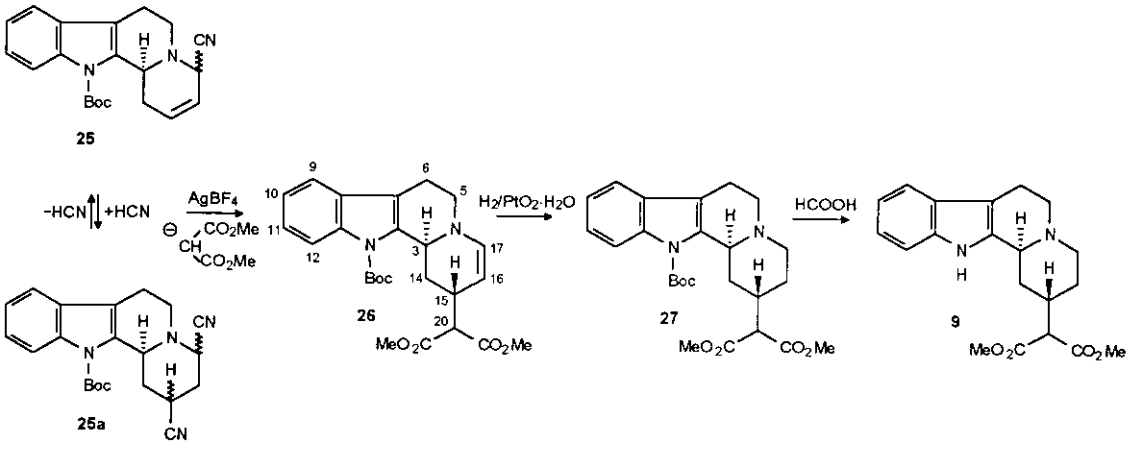
Scheme 6. Formation of compound (**9**) from compound (**19**) *via* compounds (**20**, **21**, and **22**).

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 $CN^{\ominus}$ 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, $PtO_2 \cdot H_2O$) 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**).

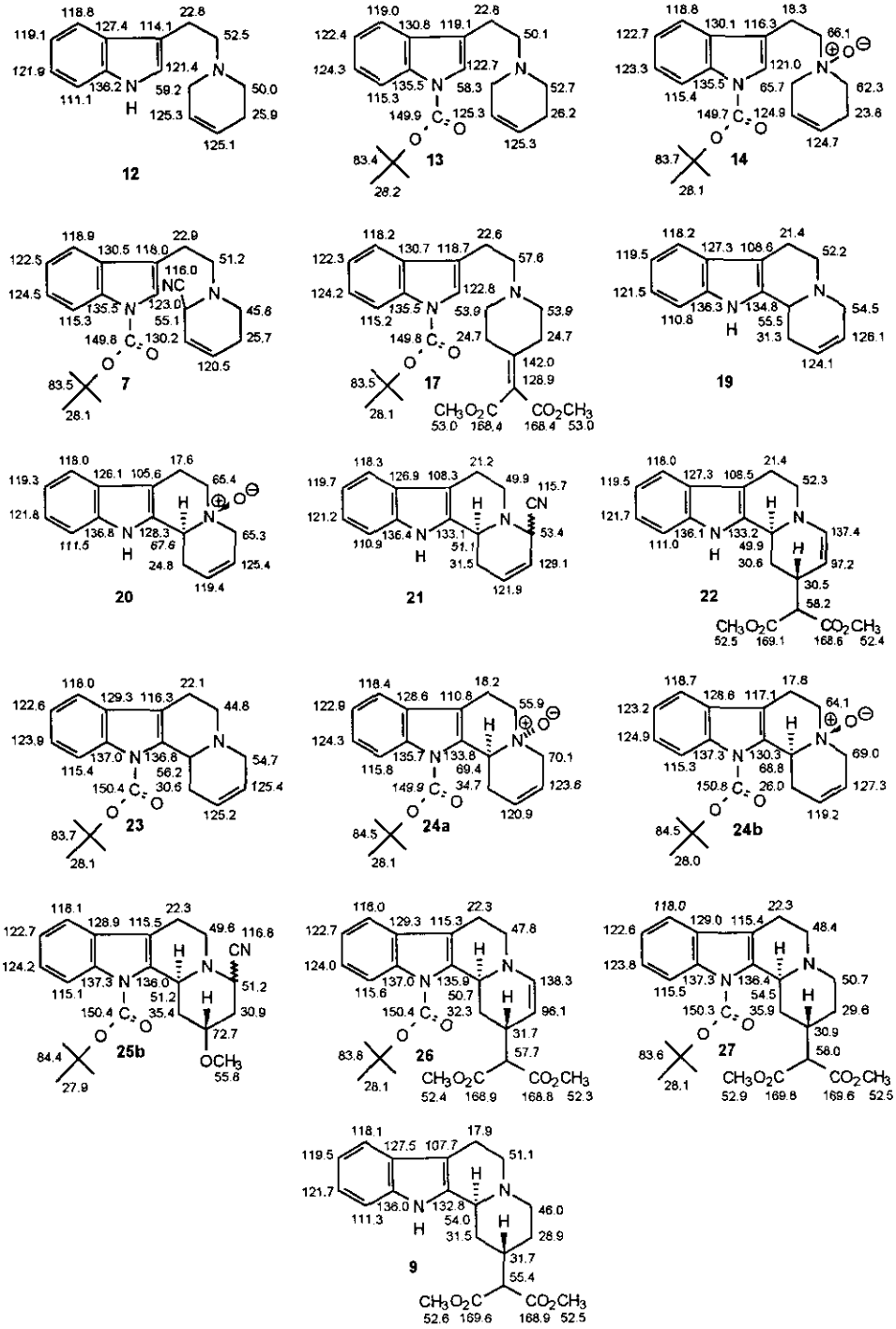


Chart 1. ^{13}C NMR data of compounds (**7**, **9**, **12-14**, **17**, **19-27**). The values for compound (**24a**) are taken from the spectrum of the 2:1 mixture of compounds (**24a**) and (**24b**) (*cf.* Experimental). The influence of the *endocyclic homoallylic effect* is easily identifiable in 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**), earlier[13] 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}). ^{1}H- and ^{13}C-NMR spectra were measured with a Varian Gemini-200 NMR spectrometer working at 199.975 MHz (^{1}H-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 (^{1}H-NMR; δ_H=0.00 ppm) and $CDCl_3$ (^{13}C-NMR; δ_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_b-tryptophylpyridinium salt (11)

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

Preparation of N_b-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). ^{1}H-NMR ($CDCl_3/CD_3OD$: 70/1): 2.25 (2H, m, H-5'), 2.70 (2H, t, J = 6 Hz, -C*H*$_2$CH$_2$N<), 2.79 (2H, m, -CH$_2$C*H*$_2$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 $C_{15}H_{18}N_2$: 226.1470. Found: 226.1456. Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.40; H. 7.88; N, 12.26.

Preparation of N_a-Boc-N_b-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 CH_2Cl_2 (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, CH_2Cl_2/MeOH; 99.8/0.2) to give compound (**13**).

Compound (**13**): 386.6 mg (73%). Amorphous (lit.,[13] colorless oil). IR: 1735 (C=O). ^{1}H-NMR ($CDCl_3$): 1.67 [9H, s, -C(CH_3)$_3$], 2.24 (2H, m, H-5'), 2.68 (2H, t, J = 6 Hz, -CH_2CH_2N<), 2.78 (2H, m, -CH_2CH_2N<), 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 $C_{20}H_{25}N_2O_2$: 326.1994. Found: 326.1986. Anal. Calcd for $C_{20}H_{25}N_2O_2$: C, 73.82; H, 7.74; N, 8.61. Found: C, 73.56; H, 7.82; N, 8.46.

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

Compound (**13**) (375.0 mg, 1.15 mmol) was dissolved in CH_2Cl_2 (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 colum chromatography (alumina, CH_2Cl_2/MeOH; 99/1) to give compound (**14**).

Compound (**14**): 377.0 mg (96%). Amorphous (lit.,[13] colorless foam). IR: 1730 (C=O). ^{1}H-NMR ($CDCl_3$): 1.67 [9H, s, -C(CH_3)$_3$], 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 $C_{20}H_{25}N_2O_3$: 342.1943. Found: 342.1932. Anal. Calcd for $C_{20}H_{25}N_2O_3$: C, 70.36; H, 7.38; N, 8.20. Found: C, 70.26; H, 7.26; N, 8.08.

Preparation of N_a-Boc-N_b-tryptophyl-2'-cyano-$\Delta^{3'}$-piperideine (7)

Compound (**14**) (56.0 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (30 mL), and trifluoroacetic anhydride (TFAA) (40 µL, 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 H_2O (12 mL) was added, and stirring was continued for 45 min 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 crude product was purified by flash chromatography (silica gel, CH_2Cl_2/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). ^{1}H-NMR ($CDCl_3$): 1.67 [9H, s, -C(CH_3)$_3$], 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, J_1 = 7 Hz, J_2 = 2

Hz, H-4), 8.13 (1H, br d, J = 7 Hz, H-7). MS: 351 (M^+), 251, 144, 143, 130, 121 (100%). HRMS: Calcd for $C_{21}H_{25}N_3O_2$: 351.1947. Found: 351.1939. Anal. Calcd for $C_{21}H_{25}N_3O_2$: 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)]

$AgBF_4$ (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 $NaHCO_3$ solution was added and the reaction mixture was extracted with CH_2Cl_2 and the extract was dried with anhydrous Na_2SO_4. 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)

$AgBF_4$ (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 $NaHCO_3$ 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, which did not contain compound (**8**) in detectable amount (no ^1H NMR signals between 4.5 - 7.2 ppm), was purified by CH_2Cl_2/hexane extraction to give compound (**17**).

Compound (**17**): 8.6 mg (58%). Amorphous. IR: 1730 (C=O). ^1H-NMR ($CDCl_3$): 1.67 [9H, s, $-C(CH_3)_3$], 3.69 (6H, s, 2 x $-CO_2CH_3$), 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 $C_{25}H_{32}N_2O_6$: 456.2260. Found: 456.2246. Anal: Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.06; N, 6.14. Found: C, 65.52; H, 7.14; N, 6.04.

In a similar procedure, where $AgBF_4$ was replaced by a small amount (0.1 equiv.) of anhydrous $ZnCl_2$,[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 CH_2Cl_2 (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, CH_2Cl_2/MeOH; 99/1) to give compound (**20**).

Compound (**20**): 211.8 mg (60%). Amorphous. ^{1}H-NMR ($CDCl_3$/CD_3OD; 13/1): 4.44 (1H, dd, J_1 = 10 Hz, J_2 = 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, J_1 = 7.5 Hz, J_2 = 2.5 Hz, H-11), 7.49 (1H, dd, J_1 = 7.5 Hz, J_2 = 2.5 Hz, H-8). MS: 240 (M^+, < 1%), 239, 224 (100%), 197, 170, 169. HRMS: Calcd for $C_{15}H_{16}N_2O$: 240.1263. Found 240.1242. Anal. Calcd for $C_{15}H_{16}N_2O$: 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 CH_2Cl_2 (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 H_2O (12 mL) was added, and stirring was continued for 45 min 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 crude product was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH; 99/1) to give compound (**21**).

Compound (**21**): 20 mg (7.5%). Amorphous. ^{1}H-NMR ($CDCl_3$): 2.31 (1H, ddd, J_1 = 10.5 Hz, J_2 = 4 Hz, J_3 = 2 Hz, H-1α), 2.54 (1H, ddd, J_1 = 17 Hz, J_2 = 4.5 Hz, J_3 = 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, J_1 = 11 Hz, J_2 = 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 $C_{21}H_{23}N_3O_2$: 349.1790. Found: 349.1778. Anal. Calcd for $C_{21}H_{23}N_3O_2$: 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)

$AgBF_4$ (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 $NaHCO_3$ 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 flash chromatography (silica gel, CH_2Cl_2/MeOH; 99.8/0.2) to give compound (**22**).

Compound (**22**): 14.8 mg (52%). Amorphous. IR: 1730 (C=O). ^{1}H-NMR ($CDCl_3$): 3.75 (3H, s, $-CO_2CH_3$), 3.80 (3H, s, $-CO_2CH_3$), 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 $C_{20}H_{22}N_2O_4$: 354.1580. Found: 354.1558. Anal. Calcd for $C_{20}H_{22}N_2O_4$: 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, $PtO_2 \cdot H_2O$, 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, CH_2Cl_2/MeOH; 95/5) to give compound (**9**).

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

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

Compound (**19**) (184.7 mg, 0.825 mmol), $(Boc)_2O$ (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, CH_2Cl_2/MeOH; 99/1) to give compound (**23**).

Compound (**23**): 248.6 mg (93%). Amorphous. IR: 1730 (C=O). ^{1}H-NMR ($CDCl_3$): 1.66 [9H, s, $-C(CH_3)_3$], 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 $C_{20}H_{24}N_2O_2$: 324.1838. Found: 324.1826. Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.63. Found: C, 74.16; H, 7.32; N, 8.46.

Preparation of N_a-Boc-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine N_b-*cis*-oxide (24a) and N_a-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, CH_2Cl_2/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 $C_{20}H_{24}N_2O_2$ ($C_{20}H_{24}N_2O_3$ - O) = 324.1838. Found: 324.1828. For the ^{1}H-NMR spectrum and elemental analysis of compound (**24b**), see below.

Attempt to prepare N_a-Boc-1,4,6,7,12,12b-hexahydro-4ξ-cyanoindolo[2,3-*a*]quinolizine (25); Formation of N_a-Boc-1,4,6,7,12,12b-hexahydro-2α-methoxy-4α-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, CH_2Cl_2/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}H-NMR ($CDCl_3$): 1.47 (1H, ddd, J_1 = 13 Hz, J_2 = 12.5 Hz, J_3 = 2.5 Hz, H-1β), 1.69 [9H, s, -C(CH_3)$_3$], 3.49 (3H, s, -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 $C_{22}H_{27}N_3O_3$: 381.2052. Found: 381.2038. Anal. Calcd for $C_{22}H_{27}N_3O_3$: 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_a-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, CH_2Cl_2/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}H-NMR ($CDCl_3$): 1.66 [9H, s, -C(CH_3)$_3$], 3.75 (6H, s, 2 x -CO_2CH_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%). ^{1}H-NMR ($CDCl_3$): 1.66 [9H, s, -C(CH_3)$_3$], 3.94 (1H, br d, J = 15.5 Hz, H-4α), 4.20 (1H, dd, J_1 = 15.5 Hz, J_2 = 2 Hz, H-4β), 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). ^{1}H-NMR ($CDCl_3$): 1.65 [9H, s, -C(CH_3)$_3$], 2.17 (1H, br d, J = 15 Hz, H-14α), 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). ^{1}H-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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14. The ^{1}H-NMR data, few in number, given in Ref. 13 for compound (**8**) (compound (**24**) in Ref. 13) are confusing: δ 2.52 [9H, s, -C(CH_3)$_3$], 4.15 (1H, dd, $J_1 \approx 10$ Hz, $J_2 \approx 4$ Hz, H-3; corresponding to H-6' in our numbering), no chemical shift value is given (1H, dd, $J_1 = 10$ Hz, $J_2 \approx 1.5$ Hz, H-14; corresponding to H-5' in our numbering).
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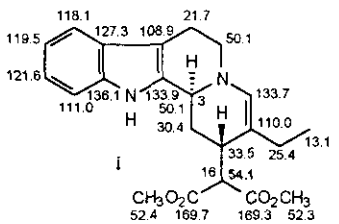

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