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Studies on the Biomimetic Preparation of the Sarpagan Ring System. Attempts to Apply the Spontaneous "Biogenetic-type Cyclization" of van Tamelen to Bond Formation between C-5 and C-16 in the Corynantheine Series

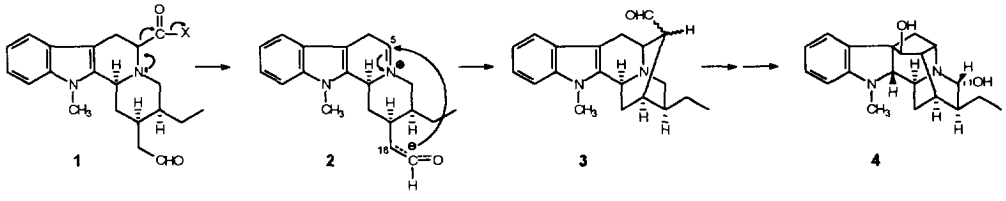
Mauri Lounasmaa* and Pirjo Hanhinen

Laboratory for Organic and Bioorganic Chemistry,
Technical University of Helsinki,
FIN-02150 Espoo, Finland

Abstract - Attempts were made to apply the spontaneous "biogenetic-type cyclization" of van Tamelen to the preparation of the sarpagan ring system by utilizing indolo[2,3-*a*]quinolizidines **10**, **11**, **12**, and **14**. The fact that the spontaneous "biogenetic-type cyclization" did not take place casts some doubt on the correctness of the earlier results.

About twenty five years ago van Tamelen and Oliver presented a synthetic work, which they claimed to lead *via* a sarpagan ring system ("deoxyajmalal system") to the six-ring indole alkaloid ajmaline **4** and which they called "The Biogenetic-Type Total Synthesis of Ajmaline".[1,2]

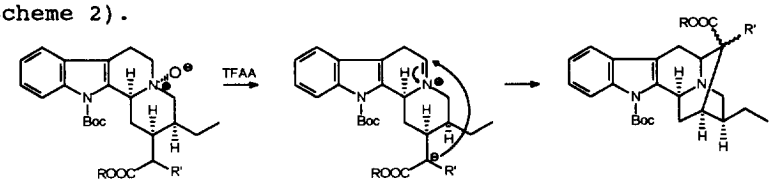
The "crucial steps" in the van Tamelen approach to the sarpagan ring system were the regioselective formation of the $\Delta^{4(5)}$ iminium ion **2** (realized by decarbonylation; **1**→**2**), followed by spontaneous bond formation between C-5 and C-16 (spontaneous "biogenetic-type cyclization"; **2**→**3**) (Scheme 1).



Scheme 1.

In connection with our recent studies on the application of the Polonovski-Potier reaction to the formation of iminium ions, we developed a method that permits the generation of $\Delta^{4(5)}$ iminium ions from Boc-protected indolo[2,3-*a*]quinolizidines.[3-7] Thus, it seemed that application of this

method, in combination with the spontaneous "biogenetic-type cyclization" of van Tamelen,[1,2] to suitable indolo[2,3-*a*]quinolizidines, would permit an easy access to the sarpagan (**5** → **6** → **7**)(and eventually to the ajmalan) ring systems (Scheme 2).



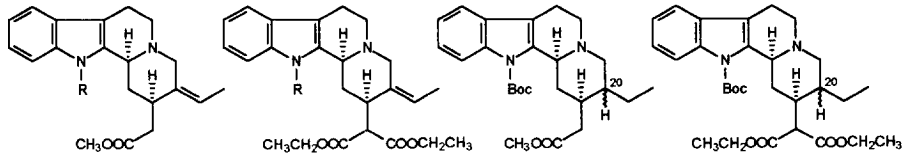
5 **6** **7**

Scheme 2.

We have earlier shown that an analogous cyclization reaction takes place in the monocyclic series.[8]

RESULTS AND DISCUSSION

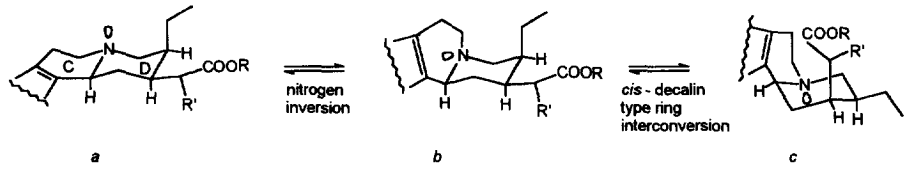
For starting materials we chose our recently described compounds **8** and **9**,[9,10] which were transformed by $(Boc)_2O$ treatment to the corresponding N_a-Boc analogues **10** and **11**, respectively. Catalytic hydrogenation of one part each of compounds **10** and **11** afforded mixtures of compounds **12** (*allo*) and **13** (*normal*), and **14** (*allo*) and **15** (*normal*), respectively. The mixtures were easily fractionated by flash chromatography (*Cf.* Experimental).



8 R= H **9** R= H **12** H-20 α **14** H-20 α
10 R= Boc **11** R= Boc **13** H-20 β **15** H-20 β

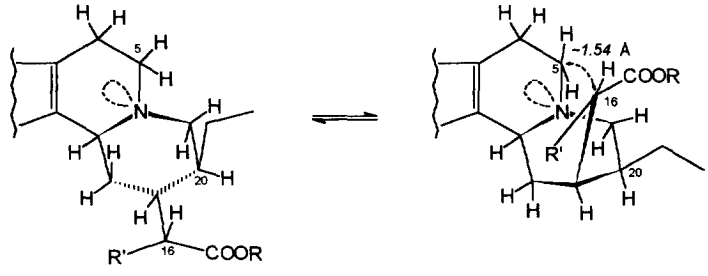
In considering which of the above-mentioned compounds would be the most interesting for the present work (*vide infra*), we came to the conclusion that for a successful bond formation between C-5 and C-16 at least the following two conditions could be taken as *sine qua non* (See Schemes 3 and 4):

Primo: Presence of conformation *b* in sufficient amount in the conformational equilibrium of the indolo[2,3-*a*]quinolizidines in question (Scheme 3). This is favoured by the presence of the N_a-Boc group.[3,4,11] For a more detailed discussion on these conformations, see Refs. 12 and 13 and references therein.



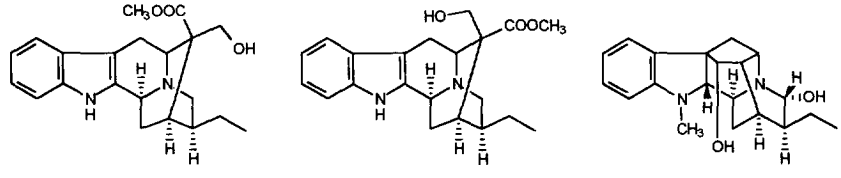
Scheme 3. Conformational equilibrium of indolo[2,3-*a*]quinolizidines.

Secundo: Existence of ring D (*Cf.* Scheme 3) of the indolo[2,3-*a*]quinolizidines in conformation *b* in sufficient amount in the boat conformation in the conformational equilibrium between the chair and boat conformations, in order to permit C-5 and C-16 to be close enough for bond formation (*vide infra*). This is favoured in the all *cis* isomers **12** and **14** because it permits the C-20 ethyl group to occupy the energetically more favourable pseudoequatorial position (Scheme 4).



Scheme 4. Equilibrium between the chair and boat conformations of ring D of the indolo[2,3-*a*]quinolizidines in conformation *b* (*vide supra*). Approximate distance between C-16 and C-5 in the boat conformation is 1.54 Å.

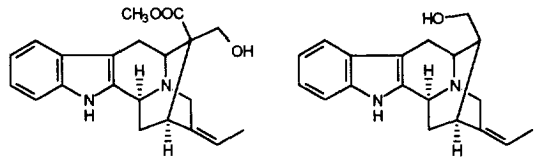
An attractive aspect of the stereostructures of compounds **12** and **14** is that they correspond to the C-3, C-15, C-20 arrangement in 19,20-dihydrosarpagine derivatives (*e.g.* 19,20-dihydroakuammidine **16** and 19,20-dihydropolyneuridine **17**) and in most compounds in the ajmaline series with the C-20 ethyl side chain (*e.g.* ajmaline **4** and sandwicine **18**).[14,15]



16 **17** **18**

Compounds **10** and **11**, on the other hand, would be appropriate for the direct preparation of sarpagine derivatives possessing a 19-*Z*-ethylidene

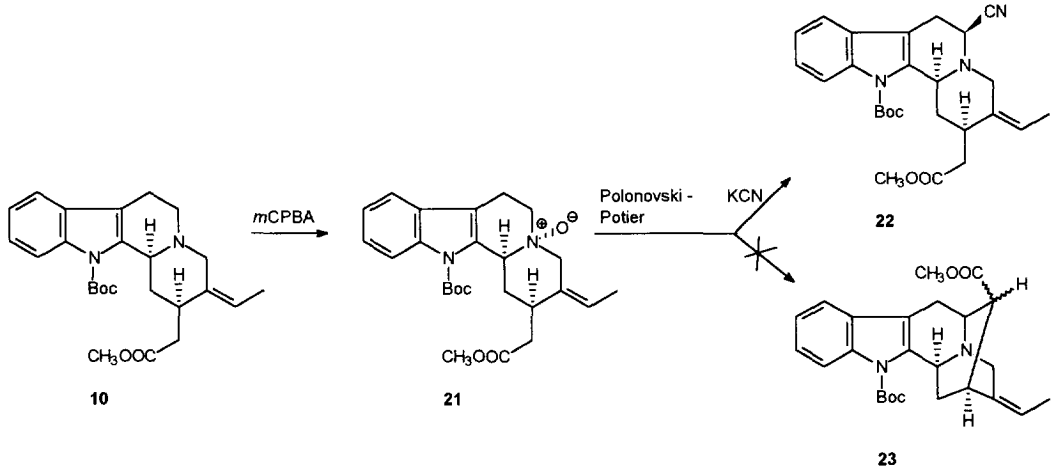
side chain (*e.g.* 19-*Z*-akuammidine **19** and koumidine **20**).[16,17]



19 **20**

Based on the above considerations, we chose among compounds **8** - **15**, first compounds **10** and **12**, and then compounds **11** and **14**, for further examination.

We have shown earlier[9] that Boc-protected compound **10** can be transformed *via* *cis*-N_b-oxide **21** to compound **22** by utilizing the Polonovski-Potier reaction and CN^- trapping at -17°C (Scheme 5).

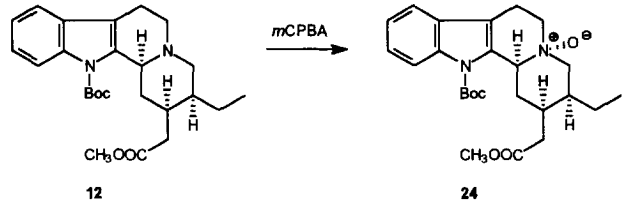


Scheme 5.

Although the formation of compound **22** clearly indicated the formation of a $\Delta^{4(5)}$ iminium ion under the reaction conditions, no spontaneous "biogenetic-type cyclization" (bond formation between C-16 and C-5) was found to take place in either the presence or absence of CN^- ions (no formation of compound **23**) (Scheme 5).[18,19]

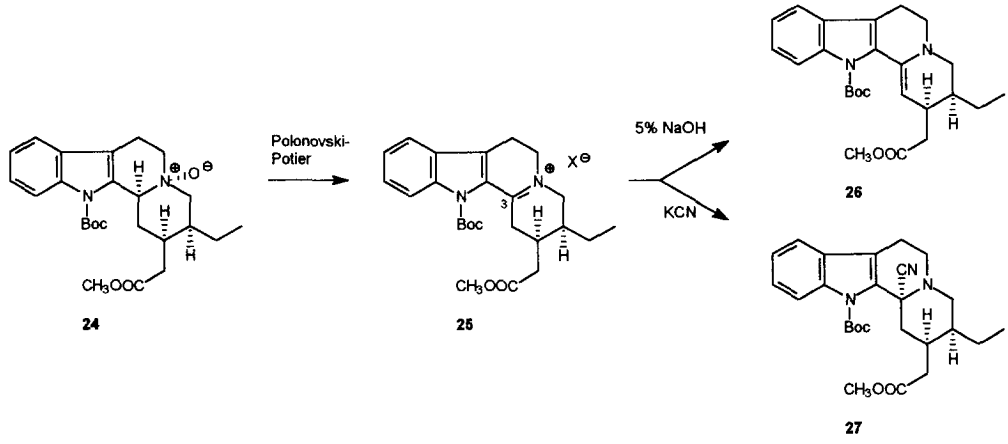
In view of the preconditions mentioned (*vide supra*) for a successful cyclization, compound **12**, where the C-20 ethylidene side chain is reduced, seemed to be more promising. Oxidation of compound **12** with *m*CPBA afforded

the corresponding *cis*-N_b-oxide **24** (Scheme 6).



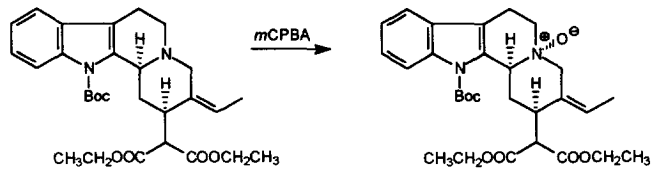
Scheme 6.

Treatment of compound **24** under the Polonovski-Potier reaction conditions at -17°C, followed by normal work-up ($NaHCO_3$), afforded the surprisingly stable iminium salt **25**. This could be transformed to the enamine **26** with 5% NaOH solution. When the iminium salt **25** was treated with KCN, the only α-aminonitrile that could be isolated and identified was compound **27** (Scheme 7). This furnished a supplementary evidence that the intermediate iminium salt **25** is the $\Delta^{3(4)}$ iminium salt and not the desired $\Delta^{4(5)}$ one. As was expected, no bond formation between C-16 and C-5 was detected.



Scheme 7.

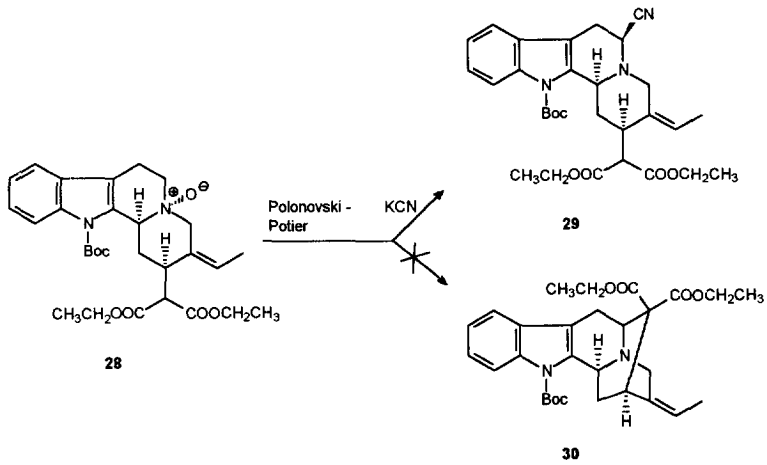
We next considered that perhaps the C-16 position in compounds **10** and **12** was not sufficiently activated to permit the spontaneous "biogenetic-type cyclization" to take place.[20] To investigate this possibility, we looked at compound **11**, where the C-16 position is activated by two alkoxycarbonyl groups. Oxidation of compound **11** with *m*CPBA afforded *cis*-N_b-oxide **28** (Scheme 8).



11 28

Scheme 8.

Treatment of compound **28** under the Polonovski-Potier reaction conditions at -17°C easily produced the desired $\Delta^{4(5)}$ iminium ion, as shown by CN^- trapping (compound **29**)(Scheme 9). However, to our disappointment, no bond formation between C-16 and C-5 (spontaneous "biogenetic-type cyclization", *vide supra*) was found, either with or without the presence of CN^- ions (no formation of compound **30**).[19]

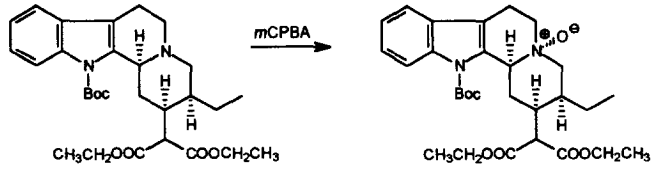


28 29 30

Scheme 9.

Finally, we looked at compound **14** (*vide supra*), which should be the most favourable of our compounds for the spontaneous "biogenetic-type cyclization" (N_a-Boc; C-3-H, C-15-H, C-20-H all *cis*; C-16 activated by two alkoxycarbonyl groups).[20,21]

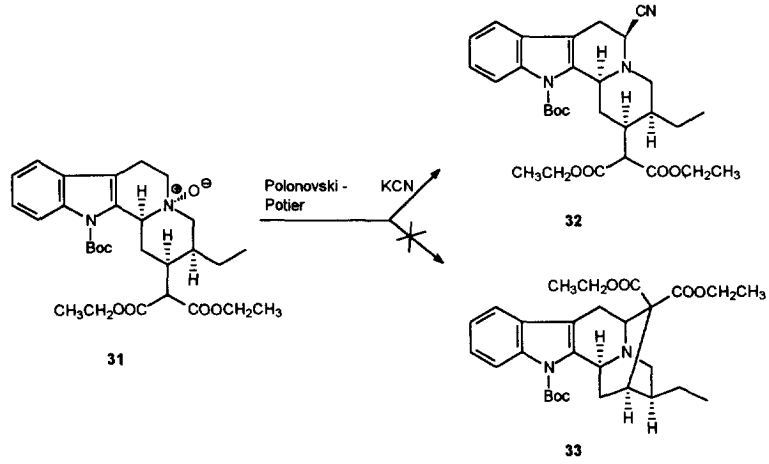
Oxidation of compound **14** with *m*CPBA afforded the *cis*-N_a-oxide **31** (Scheme 10).



14 31

Scheme 10.

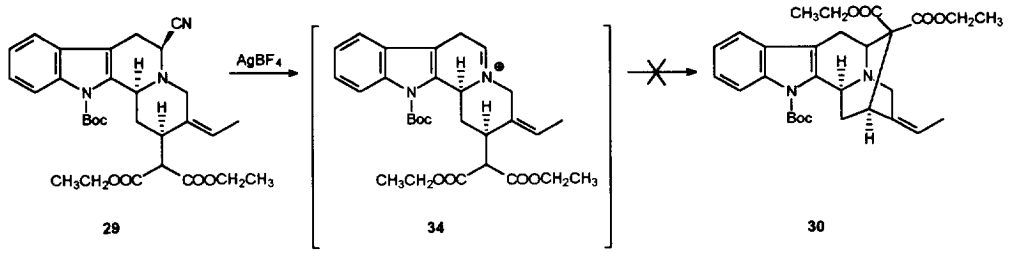
Although compound **31** under the Polonovski-Potier reaction conditions at -17°C, followed by CN^- treatment, readily produced the C-5β-cyano derivative **32**, no bond formation between C-16 and C-5 was detected (no formation of compound **33**)(Scheme 11).[19] Nor could bond formation be detected when the CN^- treatment was not applied (*Cf.* Experimental).



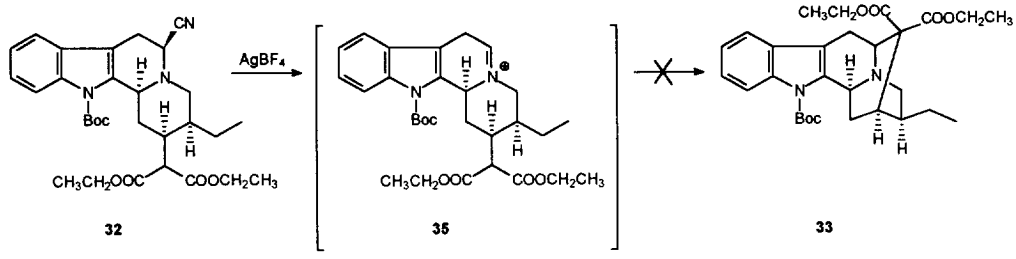
31 32 33

Scheme 11.

To complete the examination, compounds **29** and **32** were treated with $AgBF_4$ to enhance the leaving potential of the cyano group[22-25] and the regeneration of the corresponding iminium ions **34** and **35**, respectively. Even in these cases the spontaneous "biogenetic-type cyclization" was not found to take place (no formation of compound **30** or **33**)(Schemes 12 and 13). Moreover, the situation was not changed by the addition of an external base (*Cf.* Experimental).



Scheme 12.



Scheme 13.

^{13}C-Nmr data of all the compounds formed are given in Figure 1. Comparison of the measured chemical shifts with earlier results, taking into account the conformational considerations relevant for indolo[2,3-a]quinolizidines in general, provides clear evidence of the stereostructures depicted in the formulae.[26-32]

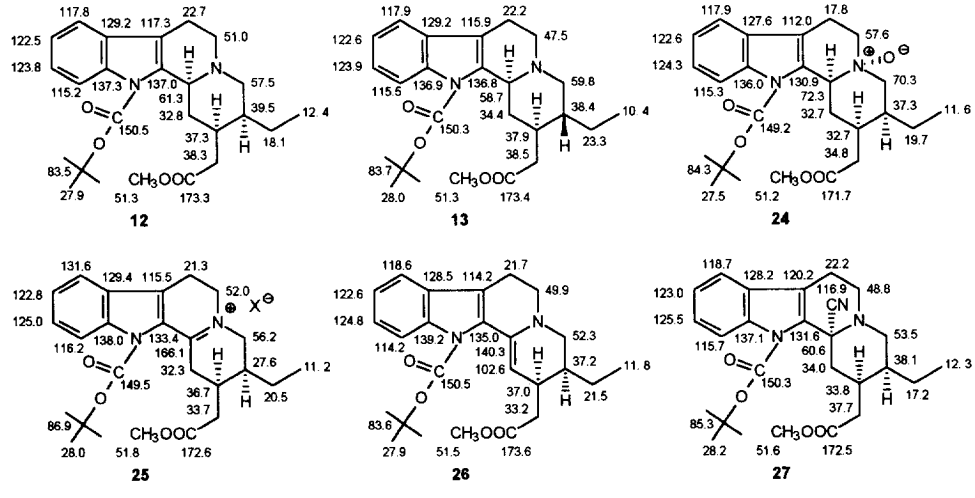


Figure 1. (continues next page).

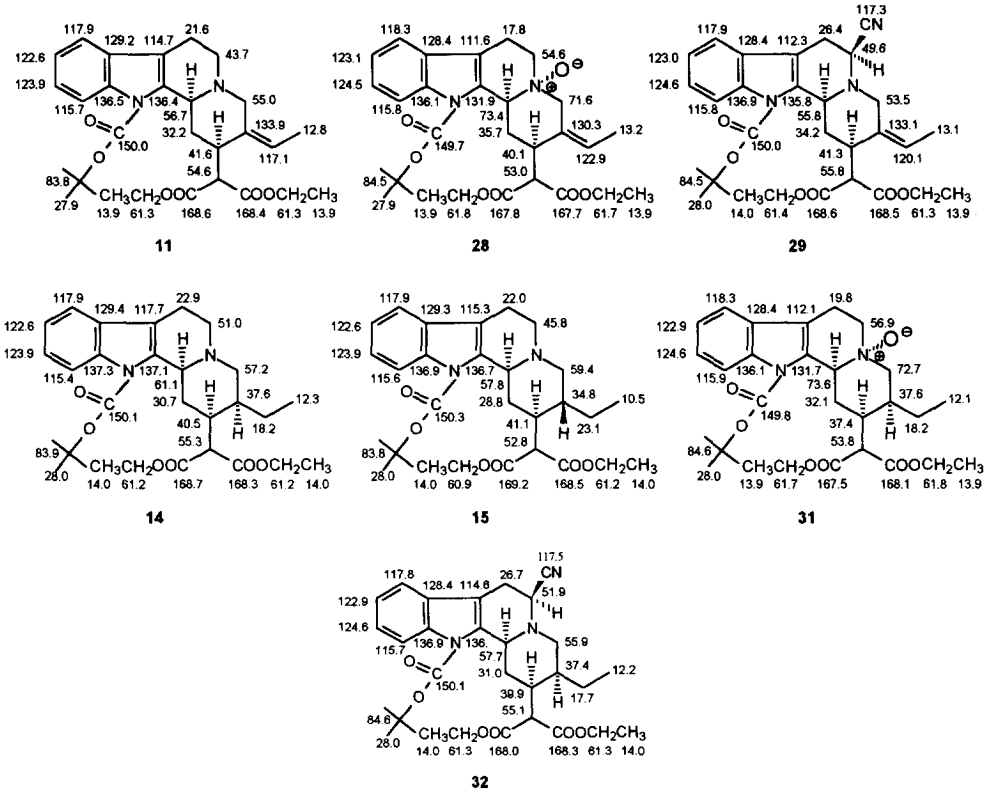


Figure 1 (cont.). ^{13}C-Nmr data of compounds **11 - 15, 24 - 29,** and **31 - 32.**

CONCLUSIONS

In contrast to van Tamelen and Oliver,[1,2] we were unable to detect a spontaneous "biogenetic-type cyclization" and were thus unable to cyclize compounds **10, 11, 12,** and **14** to the sarpagan skeleton. This casts some doubt on the correctness of the earlier results.[1,2] The fact that a similar cyclization reaction took place in the monocyclic series[8] is apparently due to greater flexibility of the monocyclic iminium intermediate.

It is noteworthy that, although the minimal distance between C-16 and C-5 when N_b is sp^3 hybridized is ~1.54 Å (*vide supra*), it increases to ~2.70 Å when N_b is sp^2 hybridized (iminium ion) (Figure 2).

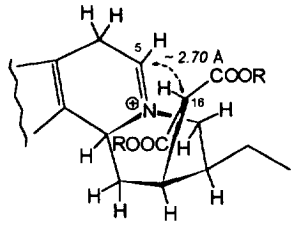


Figure 2. The $\Delta^{4(5)}$ iminium ion of compound **14** (ring D in boat conformation; *vide supra*). Approximate distance between C-16 and C-5 is 2.70 Å.

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 spectrophotometer, in $CHCl_3$. Ir absorption bands are expressed in reciprocal centimeters (cm^{-1}). ^1H- and ^{13}C-nmr spectra were measured in $CDCl_3$ with a Varian Gemini-200 spectrometer working at 199.975 MHz (^1H-nmr) and 50.289 MHz (^{13}C-nmr). Chemical shifts are given in ppm by reference to TMS (^1H-nmr; δ_H=0.0 ppm) and $CHCl_3$ (^{13}C-nmr; δ_C=77.0 ppm). Abbreviations s, d, t, q, m, def, and br are used to designate singlet, doublet, triplet, quartet, multiplet, deformed, and broad, respectively. Mass spectrometry (EIms and HRms) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of compound 10.
For the preparation and analytical data of compound **10**, see Ref. 9 (compound **2** in Ref. 9).

Preparation of *cis*-N_b-oxide 21.
For the preparation and analytical data of *cis*-N_b-oxide **21**, see Ref. 9 (compound **3** in Ref. 9).

Polonovski-Potier reaction of *cis*-N_b-oxide 21. Formation of compound 10.
A solution of *cis*-N_b-oxide **21** (60.0 mg, 0.136 mmol) in dry CH_2Cl_2 (10 ml) was cooled to -17°C and TFAA (30 μl, 0.21 mmol, 1.6 equiv.) was added (Ar atm). The reaction mixture was stirred for 2 h at -17°C after which the temperature was allowed to rise to -5°C during three more hours. The solvent was evaporated and 10% Na_2CO_3 solution was added. The mixture was extracted with CH_2Cl_2, dried with Na_2SO_4 and the solvent was evaporated. The crude,

tarry mixture was fractionated by plc (silica gel, CH_2Cl_2/MeOH : 95/5). The only identifiable product was compound **10**.
Compound **10**. Y. 2.3 mg (4%). For the analytical data, see above and Ref. 9.

Polonovski-Potier reaction of *cis*-N_b-oxide 21, followed by KCN treatment. Preparation of compound 22.
For the preparation and analytical data of compound **22**, see Ref. 9 (compound **4** in Ref. 9).

Catalytic hydrogenation of compound 10. Preparation of compounds 12 and 13.
Catalytic hydrogenation (MeOH, PtO_2, 0.5 h) of compound **10** (449,7 mg, 1.06 mmol), followed by purification by flash chromatography (silica gel) afforded compounds **12** (CH_2Cl_2/MeOH : 99.75/0.25) and **13** (CH_2Cl_2/MeOH : 99.5/0.5).
Compound **12**: Y. 84.0 mg (20%). Amorphous material. Ir: 1720 (2 x C=O). ^{1}H Nmr: 0.91 (3H, t, J=7 Hz, H-18), 1.65 [9H, s, $-C(CH_3)_3$], 3.67 (3H, s, $-COOCH_3$), 7.1-7.3 (2H, m, H-10, H-11), 7.39 (1H, d, J=7 Hz, H-9), 8.06 (1H, d, J=7 Hz, H-12). Ms: 426 (M^+), 369 (100%), 325, 297, 215, 169. HRms found: 426.2533. Calcd for $C_{25}H_{34}N_2O_4$: 426.2519.
Compound **13**: Y. 129.7 mg (30%). Amorphous material. Ir: 1725 (2 x C=O). ^{1}H Nmr: 0.92 (3H, t, J=7 Hz, H-18), 1.67 [9H, s, $-C(CH_3)_3$], 3.65 (3H, s, $-COOCH_3$), 4.04 (1H, br d, J=10 Hz, H-3), 7.1-7.3 (2H, m, H-10, H-11), 7.40 (1H, d, J=7 Hz, H-9), 8.11 (1H, d, J=7 Hz, H-12). Ms: 426 (M^+), 369 (100%), 325, 297, 215, 169. HRms found: 426.2533. Calcd for $C_{25}H_{34}N_2O_4$: 426.2552.

Preparation of *cis*-N_b-oxide 24.
Compound **12** (27.0 mg, 0.063 mmol), *m*CPBA (20.1 mg, 0.12 mmol, 1.8 equiv.) and CH_2Cl_2 (10 ml) were stirred for 4 h at room temperature (Ar atm). The crude product was purified by column chromatography (alumina, CH_2Cl_2/MeOH : 98/2) to give compound **24**.
Compound **24**. Y. 23.3 mg (83%). Amorphous material. Ir: 1730 (2 x C=O). ^{1}H Nmr: 1.02 (3H, t, J=7 Hz, H-18), 1.67 [9H, s, $-C(CH_3)_3$], 3.67 (3H, s, $-COOCH_3$), 5.02 (1H, br d, J=10 Hz, H-3), 7.1-7.3 (2H, m, H-10, H-11), 7.41 (1H, d, J=8 Hz, H-9), 8.07 (1H, d, J=8 Hz, H-12). Ms: 442 (M^+, <1%), 426, 369, 325 (100%), 295, 251, 169. HRms found: 426.2521. Calcd for $C_{25}H_{34}N_2O_4$: 426.2552.

Polonovski-Potier reaction of *cis*-N_b-oxide 24. Preparation of compound 25.
A solution of *cis*-N_b-oxide **24** (71.1 mg, 0.16 mmol) in dry CH_2Cl_2 (5 ml) was cooled to -15°C and TFAA (60 μl, 0.42 mmol, 2.6 equiv.) was added (Ar atm). The reaction mixture was stirred for 3 h at -15°C, after which the temperature was allowed to rise to 5°C during two more hours. $NaHCO_3$ was added, the solution was filtered and the solvent was evaporated. The crude product was purified by plc (silica gel, CH_2Cl_2/MeOH : 95/5) to give compound **25**.
Compound **25**. Y. 34.3 mg (50%). Amorphous material. Ir: 1730 (2 x C=O). ^{1}H Nmr: 1.03 (3H, t, J=7 Hz, H-18), 1.70 [9H, s, $-C(CH_3)_3$], 3.64 (3H, s, $-COOCH_3$), 7.39 (1H, t, J=8 Hz, H-10), 7.61 (1H, t, J=8 Hz, H-11), 7.69 (1H, d, J=8 Hz, H-9), 7.94 (1H, d, J=8 Hz, H-12). Ms: 424 (M^+), 295 (100%), 251. HRms found: 424.2360. Calcd for $C_{25}H_{32}N_2O_4$: 424.2362.

Treatment of compound 25 with NaOH. Preparation of compound 26.
Compound **25** (10.1 mg, 0.024 mmol), 5% NaOH (6 ml) and a few drops of CH_2Cl_2 were stirred for 2 h at room temperature (Ar atm). The mixture was extracted with CH_2Cl_2, dried with Na_2SO_4 and the solvent was evaporated to give compound **26**.
Compound **26**. Y. 7.6 mg (75%). Amorphous material. Ir: 1730 (2 x C=O). ^{1}H Nmr: 0.98 (3H, t, J=7 Hz, H-18), 1.63 [9H, s, $-C(CH_3)_3$], 3.70 (3H, s, $-COOCH_3$), 7.1-7.3 (2H, m, H-10, H-11), 7.41 (1H, d, J=8 Hz, H-9), 7.87 (1H, d, J=8 Hz, H-12). Ms: 424 (M^+), 295, 251 (100%). HRms found: 424.2369. Calcd for $C_{25}H_{32}N_2O_4$: 424.2362.

Treatment of compound 25 with KCN. Preparation of compound 27.
A solution of compound **25** (23.5 mg, 0.055 mmol) in dry CH_2Cl_2 (4 ml) was cooled to -17°C and KCN (10.8 mg, 0.17 mmol, 3 equiv.) was added (Ar atm). The reaction mixture was stirred for 2 h at -17°C, after which the temperature was allowed to rise to 0°C and KCN (10.8 mg, 0.17 mmol, 3 equiv.) in H_2O (2ml) was added. Stirring was continued one more hour and the temperature was allowed to rise to 4°C. 10% Na_2CO_3 was added, the mixture was extracted with CH_2Cl_2 and dried with Na_2SO_4 and the solvent was evaporated to give compound **27**.
Compound **27**. Y. 18.0 mg (72%). Amorphous material. Ir: 1725 (2 x C=O). ^{1}H Nmr: 0.90 (3H, t, J=7 Hz, H-18), 1.71 [9H, s, $-C(CH_3)_3$], 3.70 (3H, s, $-COOCH_3$), 7.2-7.3 (2H, m, H-10, H-11), 7.44 (1H, d, J=8 Hz, H-9), 8.02 (1H, d, J=8 Hz, H-12). Ms: 452 (M^+ + 1, <2%), 425, 324, 295, 251 (100%). HRms found: 425.2428. Calcd for $C_{25}H_{33}N_2O_4$ ($C_{26}H_{33}N_3O_4$ - CN): 425.2440.

Treatment of compound 9 with $(Boc)_2O$. Preparation of compound 11.
A solution of compound **9** (66.0 mg, 0.161 mmol), $(Boc)_2O$ (92.4 mg, 0.423 mmol, 2.6 equiv.), and DMAP (4.0 mg, 0.032 mmol, 0.2 equiv.) in dry CH_2Cl_2 (10 ml) was stirred for 4 h at room temperature (Ar atm). The crude product was purified by flash chromatography (silica gel) to give compound **11** (CH_2Cl_2/MeOH : 99.5/0.5).
Compound **11**. Y. 67.7 mg (82%). Amorphous material. Ir: 1720 (br, 3 x C=O). ^{1}H Nmr: 1.25 (6H, m, 2 x $-COOCH_2CH_3$), 1.68 [9H, s, $-C(CH_3)_3$], 3.46 (1H, br d, J=14 Hz, H-21α), 3.66 (1H, d, J=10 Hz, H-16), 3.95 (1H, d, J=14 Hz, H-21β), 4.18 (4H, m, 2 x $-COOCH_2CH_3$), 4.68 (1H, br d, J=10 Hz, H-3), 5.26 (1H, q, J=6 Hz, H-19), 7.2-7.3 (2H, m, H-10, H-11), 7.39 (1H, d, J=7 Hz, H-9), 8.14 (1H, d, J=7 Hz, H-12). Ms: 510 (M^+), 453 (100%), 295. HRms found: 510.2750. Calcd for $C_{29}H_{38}N_2O_6$: 510.2730.

Preparation of *cis*-N_b-oxide 28.
Compound **11** (94.2 mg, 0.18 mmol), *m*CPBA (64.0 mg, 0.37 mmol, 2 equiv.) and CH_2Cl_2 (15 ml) were stirred for 4 h at room temperature (Ar atm). The crude product was purified by column chromatography (alumina, CH_2Cl_2/MeOH : 99/1) to give compound **28**.
Compound **28**. Y. 88.1 mg (91%). Amorphous material. Ir: 1730 (br, 3 x C=O). ^{1}H Nmr: 1.26 (3H, t, J=7 Hz, $-COOCH_2CH_3$), 1.28 (3H, t, J=7 Hz, $-COOCH_2CH_3$), 1.68 [9H, s, $-C(CH_3)_3$], 1.80 (3H, d, J=7 Hz, H-18), 4.08 (1H, br d, J=14 Hz, H-21α), 4.20 (4H, q, J=7 Hz, 2 x $-COOCH_2CH_3$), 4.62 (1H, d, J=14 Hz, H-21β), 5.13 (1H, br d, J=12 Hz, H-3), 5.47 (1H, q, J=7 Hz, H-19), 7.2-7.3 (2H, m, H-10, H-11), 7.43 (1H, d, J=7 Hz, H-9), 8.08 (1H, d, J=7 Hz, H-12). Ms: 526 (M^+), 510, 453 (100%), 426, 409, 295. HRms found: 526.2709. Calcd for $C_{29}H_{38}N_2O_7$: 526.2679.

Polonovski-Potier reaction of *cis*-N_b-oxide 28. Formation of compound 11.
A solution of *cis*-N_b-oxide **28** (40.0 mg, 0.08 mmol) in dry CH_2Cl_2 (10 ml) was cooled to -17°C and TFAA (20 μl, 0.14 mmol, 1.9 equiv.) was added (Ar atm). The reaction mixture was stirred for 2 h at -17°C, after which the temperature was allowed to rise to -5°C during three more hours. The solvent was evaporated and 10% Na_2CO_3 solution was added. The mixture was extracted with CH_2Cl_2, dried with Na_2SO_4 and the solvent was evaporated. The crude, tarry mixture was fractionated by plc (silica gel, CH_2Cl_2/MeOH : 95/5). The only identifiable product was compound **11**.
Compound **11**: Y. 1.7 mg (4%). See above and Ref. 9.

Polonovski-Potier reaction of *cis*-N_b-oxide 28, followed by KCN treatment. Preparation of compound 29. Formation of compound 11.

A solution of compound **28** (27.4 mg, 0.052 mmol) in dry CH_2Cl_2 (3 ml) was cooled to -17°C and TFAA (15 µl, 0.106 mmol, 2.0 equiv.) was added (Ar atm). The reaction mixture was stirred for 1 h. The external cooling was interrupted and the stirring was continued for 1 h. KCN (20.4 mg, 0.31 mmol, 6 equiv.) in H_2O (1 ml) was added, followed by the buffer solution (citric acid/NaOH/NaCl; 3 ml; pH 4). Stirring was continued one more hour, after which the mixture was extracted with CH_2Cl_2 and dried with Na_2SO_4 and the solvent was evaporated to give a crude mixture. The mixture was fractionated by plc (silica, CH_2Cl_2/MeOH : 95/5) to give compounds **29** and **11**.

Compound **29**: Y. 7.6 mg (27%). Amorphous material. Ir: 1720 (3 x C=O), 2225 (-CN). ^{1}H Nmr: 1.2-1.3 (6H, m, 2 x $-COOCH_2\mathit{CH_3}$), 1.68 [9H, s, $-C(CH_3)_3$], 4.1-4.2 (4H, m, 2 x $-COO\mathit{CH_2}CH_3$), 5.34 (1H, q, J=6 Hz, H-19), 7.2-7.3 (2H, m, H-10, H-11), 7.40 (1H, d, J=7 Hz, H-9), 8.07 (1H, d, J=7 Hz, H-12). Ms: 535 (M^+), 508, 478, 452, 407, 379, 318, 293 (100%), 280, 276, 169, 168. HRms found: 535.2682. Calcd for $C_{30}H_{37}N_3O_6$: 535.2682.

Compound **11**: Y. 0.5 mg (4%). For the analytical data, see above and Ref. 9.

Catalytic hydrogenation of compound 11. Preparation of compounds 14 and 15.

Catalytic hydrogenation (MeOH, PtO_2, 3 h) of compound **11** (80,0 mg, 0.16 mmol), followed by purification by flash chromatography (silica gel) afforded compounds **14** (CH_2Cl_2/MeOH : 99.75/0.25) and **15** (CH_2Cl_2/MeOH : 99.5/0.5).

Compound **14**: Y. 15.1 mg (19%). Amorphous material. Ir: 1720 (3 x C=O). ^{1}H Nmr: 0.89 (3H, t, J=7 Hz, H-18), 1.27 (6H, t, J=7 Hz, $-COOCH_2\mathit{CH_3}$), 1.66 [9H, s, $-C(CH_3)_3$], 3.04 (1H, d, J=13 Hz, H-21α), 3.35 (1H, d, J=11 Hz, H-16), 3.74 (1H, br d, J=11 Hz, H-3), 4.19 (4H, q, J=7 Hz, 2 x $-COO\mathit{CH_2}CH_3$), 7.2-7.3 (2H, m, H-10, H-11), 7.40 (1H, d, J=8 Hz, H-9), 8.04 (1H, d, J=8 Hz, H-12). Ms: 512 (M^+), 455 (100%), 411. HRms found: 512.2897. Calcd for $C_{29}H_{40}N_2O_6$: 512.2886.

Compound **15**: Y. 15.5 mg (19%). Amorphous material. Ir: 1740 (3 x C=O). ^{1}H Nmr: 0.92 (3H, t, J=6 Hz, H-18), 1.26 (6H, m, $-COOCH_2\mathit{CH_3}$), 1.68 [9H, s, $-C(CH_3)_3$], 4.19 (4H, m, 2 x $-COO\mathit{CH_2}CH_3$), 4.04 (1H, br d, J=10 Hz, H-3), 7.2-7.3 (2H, m, H-10, H-11), 7.40 (1H, d, J=6 Hz, H-9), 8.10 (1H, d, J=6 Hz, H-12). Ms: 512 (M^+), 455 (100%), 411. HRms found: 512.2880. Calcd for $C_{29}H_{40}N_2O_6$: 512.2886.

Preparation of *cis*-N_b-oxide 31.

Compound **14** (39.8 mg, 0.078 mmol), *m*CPBA (40.2 mg, 0.23 mmol, 3 equiv.) and CH_2Cl_2 (10 ml) were stirred for 4 h at room temperature (Ar atm). The crude product was purified by column chromatography (alumina, CH_2Cl_2/MeOH : 99.5/0.5) to give compound **31**.

Compound **31**. Y. 22.8 mg (55%). Amorphous material. Ir: 1730 (3 x C=O). ^{1}H Nmr: 1.07 (3H, t, J=7 Hz, H-18), 1.28 (6H, t, J=7 Hz, $-COOCH_2CH_3$), 1.68 [9H, s, $-C(CH_3)_3$], 4.21 (4H, q, J=7 Hz, 2 x $-COOCH_2CH_3$), 5.02 (1H, br d, J=11 Hz, H-3), 7.2-7.3 (2H, m, H-10, H-11), 7.44 (1H, d, J=7 Hz, H-9), 8.05 (1H, d, J=7 Hz, H-12). Ms: 528 (M^+, <1%), 512, 455 (100%), 411, 295, 251. HRms found: 512.2886. Calcd for $C_{29}H_{40}N_2O_6$ [$C_{29}H_{40}N_2O_7$ - O]: 512.2886.

Polonovski-Potier reaction of *cis*-N_b-oxide 31. Formation of compound 14.

A solution of *cis*-N_b-oxide **31** (40.0 mg, 0.076 mmol) in dry CH_2Cl_2 (10 ml) was cooled to -17°C and TFAA (20 μl, 0.14 mmol, 1.9 equiv.) was added (Ar atm). The reaction mixture was stirred for 2 h at -17°C, after which the temperature was allowed to rise to -5°C during three more hours. The solvent was evaporated and 10% Na_2CO_3 solution was added. The mixture was extracted with CH_2Cl_2 and dried with Na_2SO_4 and the solvent was evaporated. The crude, tarry mixture was fractionated by plc (silica gel, CH_2Cl_2/MeOH : 95/5). The only identifiable product was compound **14**.

Compound **14**. Y. 2.0 mg (5%). For the analytical data, see above.

Polonovski-Potier reaction of *cis*-N_b-oxide 31, followed by KCN treatment. Preparation of compound 32. Formation of compound 14.

A solution of *cis*-N_b-oxide **31** (20.9 mg, 0.04 mmol) in dry CH_2Cl_2 (1 ml) was cooled to -17°C and TFAA (10 μl, 0.07 mmol, 1.8 equiv.) was added (Ar atm). The reaction mixture was stirred for 1 h. The external cooling was interrupted and the stirring was continued for 1 h. KCN (12.9 mg, 0.20 mmol, 5 equiv.) in H_2O (1 ml) was added, followed by the buffer solution (citric acid/NaOH/NaCl; 3 ml; pH 4). Stirring was continued one more hour, after which the mixture was extracted with CH_2Cl_2, dried with Na_2SO_4 and the solvent was evaporated. The crude product was purified by plc (CH_2Cl_2/MeOH : 95/5) to give compounds **32** and **14**.

Compound **32**: Y. 5.3 mg (25%). Amorphous material. Ir: 1725 (br, 3 x C=O), 2250 (-CN). ^{1}H Nmr: 0.86 (3H, t, J=7 Hz, H-18), 1.27 (6H, t, J=7 Hz, 2 x $-COOCH_2CH_3$), 1.68 [9H, s, $-C(CH_3)_3$], 3.33 (1H, d, J=12 Hz, H-21α), 4.1-4.2 (4H, m, 2 x $-COOCH_2CH_3$), 7.2-7.3 (2H, m, H-10, H-11), 7.38 (1H, d, J=8 Hz, H-9), 8.07 (1H, d, J=8 Hz, H-12). Ms: 537 (M^+), 510, 480, 454, 409, 295 (100%).

HRms found: 537.2829. Calcd for $C_{30}H_{39}N_3O_6$: 537.2829.
Compound **14**: Y. 0.5 mg (2%). For the analytical data, see above.

Treatment of compound 29 with $AgBF_4$.
A mixture of compound **29** (8.5 mg, 0.016 mmol) and $AgBF_4$ (4.6 mg, 0.024 mmol, 1.5 equiv.) in dry THF (2 ml) was stirred in dark for 3 h at room temperature (Ar atm). Dilute NH_4OH solution was added and the mixture was extracted with CH_2Cl_2 and dried with Na_2SO_4 and the solvent was evaporated. No identifiable products were isolated from the tarry mixture.
Alternatively, the dilute NH_4OH solution was slowly added under stirring. After 30 min the mixture was extracted with CH_2Cl_2, dried with Na_2SO_4 and the solvent was evaporated. The slow addition of the base to the reaction mixture did not give better results.

Treatment of compound 32 with $AgBF_4$.
A mixture of compound **32** (5.0 mg, 0.009 mmol) and $AgBF_4$ (2.7 mg, 0.014 mmol, 1.5 equiv.) in dry THF (2 ml) was stirred in dark for 3 h at room temperature (Ar atm). Dilute NH_4OH solution was added and the mixture was extracted with CH_2Cl_2 and dried with Na_2SO_4 and the solvent was evaporated. No identifiable products were isolated from the tarry mixture.
Alternatively, the dilute NH_4OH solution was slowly added under stirring. After 30 min the mixture was extracted with CH_2Cl_2, dried with Na_2SO_4 and the solvent was evaporated. The slow addition of the base to the reaction mixture did not give better results.

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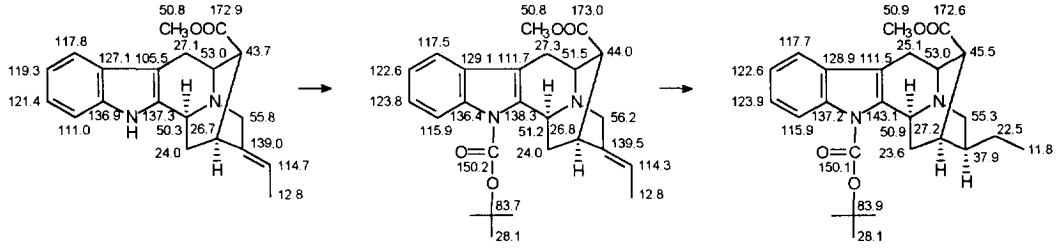
18. Neither could compound **23** be obtained from compound **22** by treatment with an external base.
19. In order to get useful ^{13}C-Nmr data for comparison, pericyclivine (**i**)[14,15,33] was transformed by $(Boc)_2O$ treatment to the corresponding N_a-Boc derivative (**ii**). Catalytic hydrogenation of compound (**ii**) afforded compound (**iii**). The ^{13}C-Nmr data of compounds (**i**), (**ii**), and (**iii**) are given below.



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21. However, Rapoport,[34] in his studies on intramolecular cyclization between an iminium salt and a nucleophilic carbon, has shown that in certain cases when the activating two ester groups in a malonate

nucleophile were replaced by a single, electron withdrawing group, the yields in the reversible cyclization process were higher because of decreasing steric strain in the product.

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32. The most characteristic signal indicating the presence of a cyano group at C-5β (compounds **29** and **32**) is that of C-6 at ~26.5 ppm (*Cf.* Figure 1).
33. **Note!** The formula given for pericyclivine (**i**)(*vide supra*) on p. 836 of Ref. 14 is erroneous.
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