TOTAL SYNTHESIS OF N_a,*O*-DI-BOC-5β-CYANO-*Z*-GEISSOSCHIZINE AND N_a-BOC-21α-CYANOTETRAHYDROALSTONINE, THE LATTER A SYNTHETIC EQUIVALENT OF N_a-BOC-CATHENAMINE

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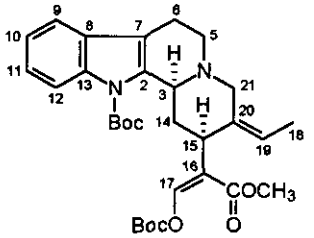
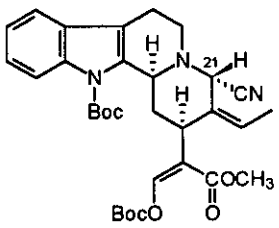
Abstract - Modified Polonovski reaction of the synthetically prepared N_a,*O*-di-Boc-*Z*-geissoschizine *cis*-N_b-oxide (**6**), followed by cyano trapping of the formed iminium intermediates, led to four compounds (**1**), (**5a**), (**7**), and (**8a**) [and to two secondary products, (**9**) and (**10**)]. The most important of these compounds were N_a,*O*-di-Boc-5β-cyano-*Z*-geissoschizine (**5a**) and N_a-Boc-21α-cyanotetrahydroalstonine (**8a**) [synthetic equivalent of N_a-Boc-cathenamine (**8b**)]. Change in the reaction temperature caused one ($\Delta^{4(21)}$) of the intermediate iminium ions to be strongly favoured, leading to the nearly exclusive formation of compound (**8a**) at the expense of compounds (**5a**), (**7**), (**9**), and (**10**).

The Claisen rearrangement of an appropriate indolo[2,3-*a*]quinolizidine vinyl allyl ether, followed by $(Boc)_2O$ treatment, permits an easy access to N_a,*O*-di-Boc-*Z*-geissoschizine (**1**).[1,2]



1

This compound seemed to us to be ideally suited for a rapid preparation of N_a,*O*-di-Boc-21α-cyano-*Z*-geissoschizine (**2**) and/or an N_a-Boc-21α-cyanoheteroyohimbine structure [*e.g.* N_a-Boc-21α-cyanorauniticine (**3**) or N_a-Boc-21α-cyano-19-epiajmalicine (**4**)] (*vide infra*).



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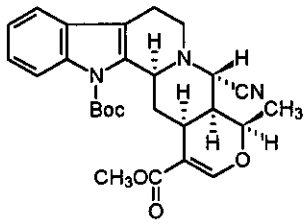

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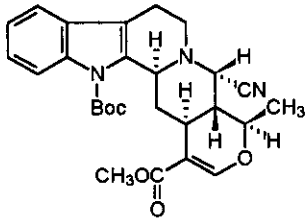

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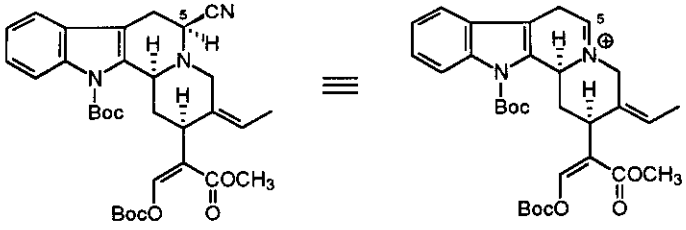
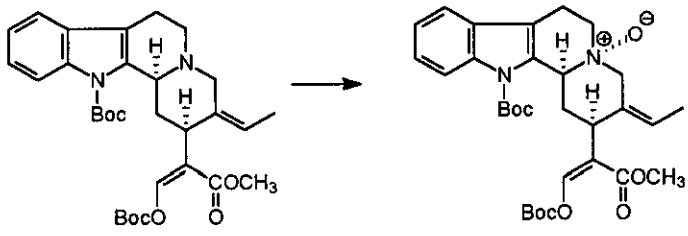
Moreover, the di-Boc derivative (**1**) might possibly lead to N_a,O-di-Boc-5β-cyano-*Z*-geissoschizine (**5a**) [equivalent to N_a,O-di-Boc-*Z*-geissoschizine $\Delta^{4(5)}$-iminium ion (**5b**)], a possible intermediate in the preparation of sarpagine/ajmaline derivatives (*vide infra*).



5a **5b**

RESULTS AND DISCUSSION

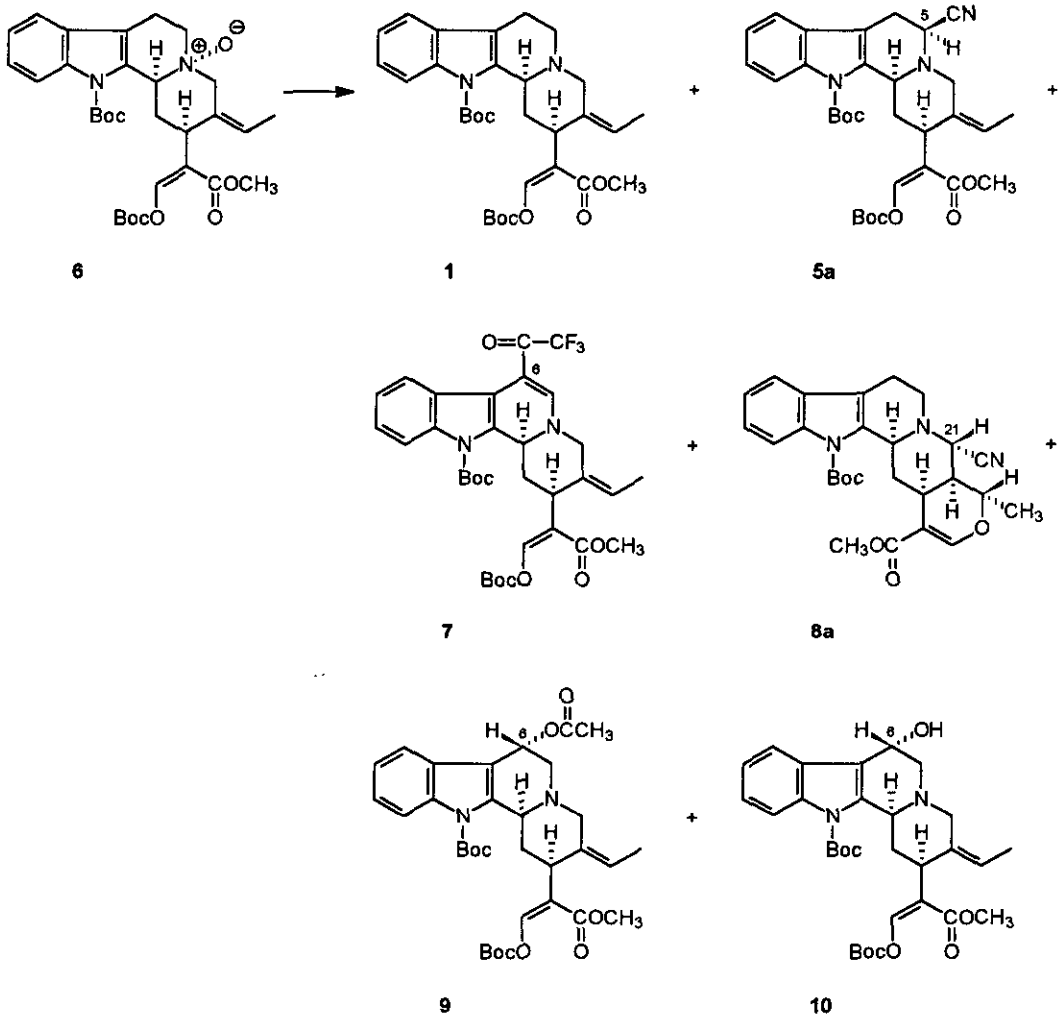
Oxidation of N_a,*O*-di-Boc-*Z*-geissoschizine (**1**) with *m*-chloroperbenzoic acid (*m*-CPBA) led to the corresponding N_a,*O*-di-Boc-*Z*-geissoschizine *cis*-N_b-oxide (**6**) (Scheme 1).



1 **6**

Scheme 1.

The modified Polonovski reaction (Polonovski-Potier reaction)[3-5] carried out on the N_a,*O*-di-Boc-*Z*-geissoschizine *cis*-N_b-oxide (**6**), followed by KCN treatment (*cf.* Experimental), afforded a mixture from which four compounds were isolated and identified: N_a,*O*-di-Boc-*Z*-geissoschizine (**1**), N_a,*O*-di-Boc-5β-cyano-*Z*-geissochizine (**5a**), N_a,*O*-di-Boc-6-trifluoroacetyl-5,6-didehydro-*Z*-geissochizine (**7**), and N_a-Boc-21α-cyanotetrahydroalstonine (**8a**). Small amounts of N_a,*O*-di-Boc-6α-acetoxy-*Z*-geissoschizine (**9**) and N_a,*O*-di-Boc-6α-hydroxy-*Z*-geissoschizine (**10**), due to secondary reactions of the formed intermediates,[6] were also isolated (Scheme 2).



Scheme 2.

Change in the reaction temperature caused one ($\Delta^{4(21)}$) of the intermediate iminium ions to be strongly favoured, allowing nearly exclusive preparation of N_a-Boc-21α-cyanotetrahydroalstonine (**8a**) at the expense of compounds (**5a**), (**7**), (**9**), and (**10**) (*cf.* Experimental).

Comparison of the chemical shifts found for compounds (**5a**), (**6**), (**8a**), (**9**), and (**10**) with the data of similar compounds, taking into account the conformational considerations relevant for indolo[2,3-*a*]quinolizidines in general, provided clear evidence for the stereostructures depicted in the formulae.[7-10] The ^{1}H-nmr data of compounds (**5a**), (**6**), (**9**), and (**10**) are given in Table 1 (*cf.* refs. 11-13) and the ^{13}C-nmr data of compounds (**5a**), (**6**), (**7**), (**8a**), (**9**), and (**10**) in Figure 1.

Table 1. ^{1}H-Nmr data of compounds (**5a**), (**6**), (**9**), and (**10**).

	5a	**6**	**9**	**10**
H-3	4.26 dd	5.11 dd	4.89 dd	4.79 dd
H-5α	4.19 dd	3.23 ddd	2.88 dd	2.91 dd
H-5β	-	4.03 ddd	3.55 dd	3.52 dd
H-6α	3.03 dd	3.5 m	-	-
H-6β	3.29 dd	2.86 ddd	6.20 dd	4.87 dd
H-9	7.39 d	7.44 d	7.49 d	7.66 d
H-10	7.24 t	7.23 t	7.23 t	7.26 t
H-11	7.31 t	7.28 t	7.29 t	7.29 t
H-12	8.14 d	8.08 d	8.16 d	8.14 d
H-14α	2.2 m	2.51 ddd	1.90 ddd	1.94 ddd
H-14β	2.2 m	2.41 ddd	2.42 ddd	2.44 ddd
H-15	3.8 m	3.9 m	3.8 m	3.82 dd
H-17	8.11 s	8.23 s	8.15 s	8.16 s
H-18	1.69 d	1.75 d	1.65 d	1.66 d
H-19	5.13 q	5.33 q	5.16 q	5.18 q
H-21α	3.34 br d	4.09 br d	3.62 br d	3.58 br d
H-21β	4.04 d	4.65 d	3.96 d	3.97 d
CO_2Me	3.71 s	3.71 s	3.71 s	3.71 s
***O*-Boc**	1.53 s	1.54 s	1.52 s	1.53 s
N_a-Boc	1.66 s	1.68 s	1.68 s	1.69 s

Table 1 (continued). Coupling constants:

Compound (**5a**)

$J_{3,14\alpha} \approx 6$ Hz; $J_{3,14\beta} \approx 6$ Hz; $J_{5\alpha,6\alpha} = 3.5$ Hz; $J_{5\alpha,6\beta} = 5.5$ Hz; $J_{6\alpha,6\beta} = 15.5$ Hz; $J_{18,19} = 6.5$ Hz; $J_{21\alpha,21\beta} = 13.5$ Hz

Compound (**6**)

$J_{3,14\alpha} = 4$ Hz; $J_{3,14\beta} = 12$ Hz; $J_{5\alpha,5\beta} = 12$ H; $J_{5\alpha,6\alpha} = 7$ Hz; $J_{5\alpha,6\beta} \approx 1$ Hz; $J_{5\beta,6\alpha} \approx 12$ Hz; $J_{5\beta,6\beta} = 5$ Hz; $J_{6\alpha,6\beta} = 16$ Hz; $J_{14\alpha,14\beta} = 12$ Hz; $J_{14\alpha,15} = 4.5$ Hz; $J_{14\beta,15} \approx 11$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 14$ Hz

Compound (**9**)

$J_{3,14\alpha} \approx 3$ Hz; $J_{3,14\beta} = 12$ Hz; $J_{5\alpha,5\beta} = 13$ Hz; $J_{5\alpha,6\beta} \approx 2$ Hz; $J_{5\beta,6\beta} \approx 3$ Hz; $J_{14\alpha,14\beta} = 13$ Hz; $J_{14\alpha,15} \approx 4$ Hz; $J_{14\beta,15} \approx 11$ Hz; $J_{18,19} = 6.5$ Hz; $J_{21\alpha,21\beta} = 15$ Hz

Compound (**10**)

$J_{3,14\alpha} = 3$ Hz; $J_{3,14\beta} = 12$ Hz; $J_{5\alpha,5\beta} = 12.5$ Hz; $J_{5\alpha,6\beta} \approx 2$ Hz; $J_{5\beta,6\beta} = 3$ Hz; $J_{14\alpha,14\beta} = 13$ Hz; $J_{14\alpha,15} \approx 4$ Hz; $J_{14\beta,15} \approx 11$ Hz; $J_{18,19} = 6.5$ Hz; $J_{21\alpha,21\beta} = 15$ Hz

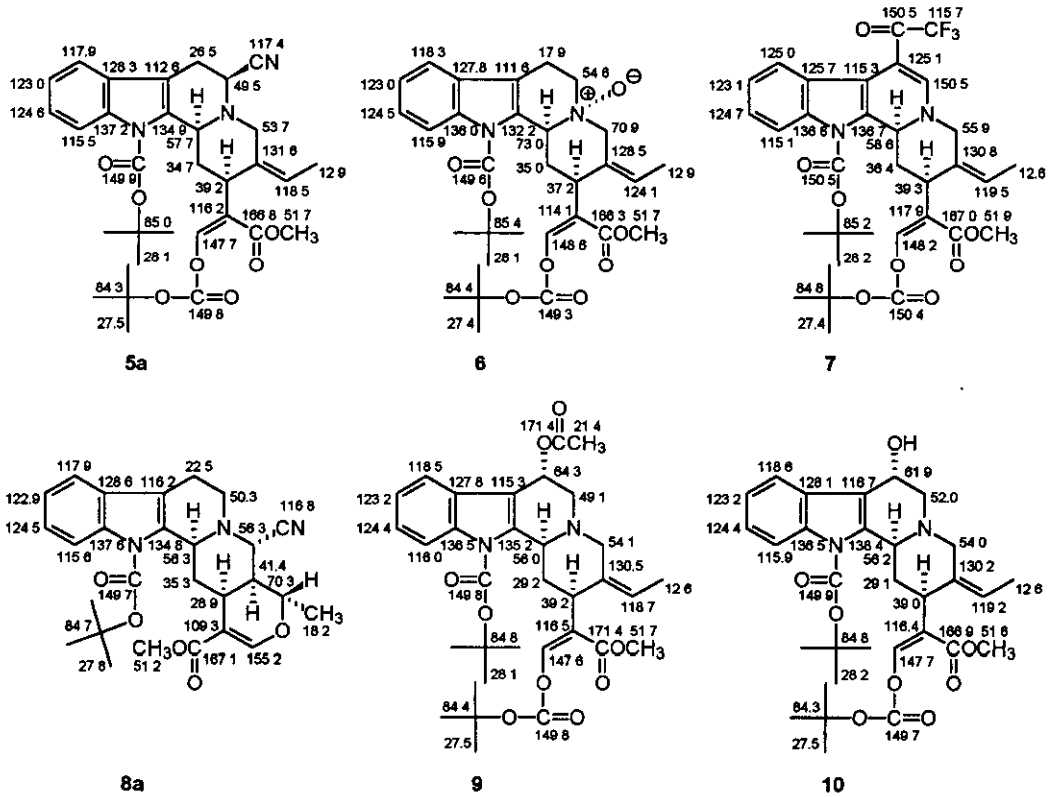
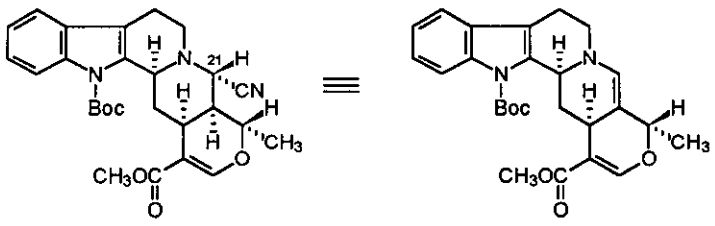


Figure 1. ^{13}C-Nmr data of compounds (**5a**), (**6**), (**7**), (**8a**), (**9**), and (**10**).

The N_a-Boc-21α-cyanotetrahydroalstonine (**8a**) synthesized here proved to be identical with the recently described N_a-Boc-21α-cyanotetrahydroalstonine,[14] which we prepared from commercially available tetrahydroalstonine.[15]

CONCLUSIONS

Cathenamines are key intermediates in the biosynthetic formation of heteroyohimbine alkaloids.[16-20] Our short synthesis of N_a-Boc-21α-cyanotetrahydroalstonine (**8a**) [equivalent to N_a-Boc-cathenamine (**8b**)] represents the first easy access to these important structures without the use of natural products as starting materials.

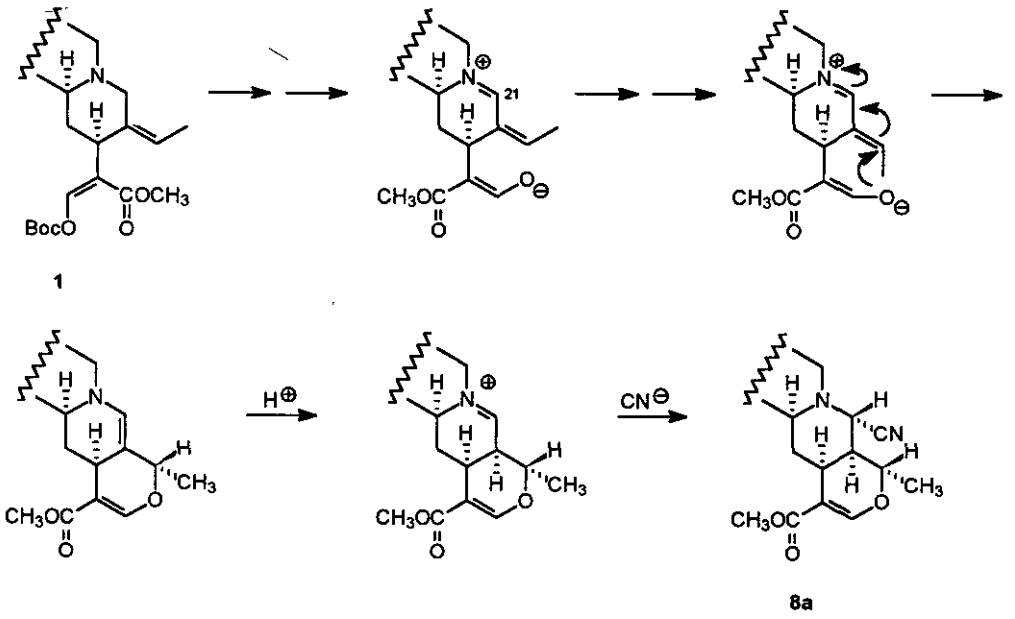


8a **8b**

The formation of an N_a-Boc-21α-cyanoheteroyohimbine structure (*vide supra*) from compound (**1**) can be presented mechanistically as the formation of a $\Delta^{4(21)}$ iminium ion followed by a Michael addition, protonation, and cyano trapping (Scheme 3). The stereochemical conditions are such that the Michael addition can take place only from the β-face.[21] This should lead in the case of a *Z*-ethylidene side-chain to the 19αH stereochemistry [and after cyano trapping to N_a-Boc-21α-cyanorauniticine (**3**) and/or N_a-Boc-21α-cyano-19-epiajmalicine (**4**) (*vide supra*)]. In the case of an *E*-ethylidene side-chain, compounds possessing the 19βH stereochemistry should be formed. Since the only N_a-Boc-21α-cyanoheteroyohimbine structure formed is N_a-Boc-21βH-cyanotetrahydroalstonine (**8a**), which possesses the 19βH stereochemistry, the isomerization of the *Z*-ethylidene side-chain to the *E*-ethylidene side-chain must have taken place before the cyclization (*cf.* ref. 22).

Moreover, our synthesis of N_a,*O*-di-Boc-5β-cyano-*Z*-geissoschizine (**5a**) furnishes a rapid route to a compound that might turn out to be important in the preparation of sarpagine/ajmaline structures.[7,8,23-27]

It is of considerable significance that change in the reaction temperature (*cf.* Experimental), influences the competitive formation of different products, especially, between compounds (**5a**) and (**8a**).



Scheme 3.

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 in $CDCl_3$ either with a Varian Gemini-200 spectrometer working at 199.975 MHz (^1H-nmr) and 50.289 MHz (^{13}C-nmr) or a Varian Unity-400 NMR spectrometer working at 399.952 MHz (^1H-nmr) and 100.577 MHz (^{13}C-nmr). Chemical shifts are given in ppm by reference to TMS (^1H-nmr; δ_H=0.0 ppm) and $CDCl_3$ (^{13}C-nmr; δ_C=77.0 ppm). Signal assignments were confirmed by H,H-COSY and H,C-COSY experiments. Abbreviations s, d, t, q, m, and br are used to designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. For the ^{13}C-nmr data, see Figure 1. Mass spectrometry (EIms and HRms) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of N_a,O-di-Boc-Z-geissoschizine cis-N_b-oxide (6):

A solution of N_a,O-di-Boc-Z-geissoschizine (**1**)[1] (423 mg, 0.77 mmol) and *m*-chloroperbenzoic acid (*m*-CPBA, 25% H_2O) (186 mg, 1.4 equiv.; dried with Na_2SO_4) in dry CH_2Cl_2 (7 ml) was stirred at room temperature for 3 h (Ar atm). Normal work-up and purification by column chromatography (alumina, CH_2Cl_2/MeOH:98/2) yielded compound (**6**).

Compound (**6**): Y. 363 mg (83%). Amorphous material. Ir: 1730 br (3 x C=O). For the ^1H-nmr data, see

Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 552 (M^+-16, <1%), 452, 395, 337, 251, 169 (100%), 156. HRms found: (M^+-16) 552.2845. Calcd for $C_{31}H_{40}N_2O_7$: 552.2836.

Formation of N_a,O-di-Boc-Z-geissoschizine (1), N_a,O-di-Boc-5αH-cyano-Z-geissoschizine (5a), N_a,O-di-Boc-6-trifluoroacetyl-5,6-didehydro-Z-geissoschizine (70), and N_a-Boc-21βH-cyanotetrahydroalstonine (8a) [and secondary products N_a,O-Di-Boc-6α-acetoxy-Z-geissoschizine (9), and N_a,O-Di-Boc-6α-hydroxy-Z-geissoschizine (10)]:

The cis-N_b-oxide (**6**) (115 mg, 0.20 mmol) was dissolved in dry CH_2Cl_2 (4 ml) and the mixture cooled to -17°C with an ice/salt bath. Freshly distilled trifluoroacetic anhydride (TFAA) (0.07 ml, 2.5 equiv.) was added with a syringe during 5 min and stirring was continued for 2 h, with the temperature kept at -17°C with an ice/salt bath (*vide infra*). During one further hour the temperature of the reaction mixture was allowed to rise to -3°C, whereafter the bath was taken away. KCN (40 mg, 3 equiv.) in H_2O (2 ml) was added, and the pH of the aqueous layer was adjusted to pH 5 by addition of solid NaOAc. The mixture was stirred for 45 min at room temperature, basified to pH 10 with 10% Na_2CO_3, and extracted with CH_2Cl_2. Normal work-up and purification by flash chromatography (silica gel) gave compounds (**5a**), (**7**), and (**8a**) [CH_2Cl_2/hexane:90/10, separated by repeated tlc (silica gel, CH_2Cl_2)], compound (**9**) (CH_2Cl_2/MeOH:99/1) and compounds (**1**) and (**10**) [CH_2Cl_2/MeOH:98/2, separated by tlc (silica gel, CH_2Cl_2/MeOH:95/5)].

Compound (**1**): Y. 10 mg (9 %). For analytical data, see ref. 1.

Compound (**5a**): Y. 12 mg (12 %). Amorphous material. Ir: 2350 (CN), 1730 br (3 x C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 577 (M^+), 550, 477, 450, 420 (100%), 394, 377, 293, 213, 169, 168. HRms found: 577.2766. Calcd for $C_{32}H_{39}N_3O_7$: 577.2788.

Compound (**7**): Y. 8 mg (6%). Amorphous material. Ir: 1720 br (4 x C=O). ^{1}H-Nmr: 1.50 (9H, s, -*O*-Boc), 1.70 (9H, s, -N_a-Boc), 1.73 (3H, d, J=7 Hz, =CHC<u>H</u>$_3$), 3.72 (3H, s, -OC<u>H</u>$_3$), 4.54 (1H, d, J= 14 Hz, H-21β), 5.23 (1H, q, J=7 Hz, =C<u>H</u>CH$_3$), 5.62 (1H, br d, J=11 Hz, H-3), 7.21-7.30 (2H, m, H-10, H-11), 7.58 (1H, s, H-5), 8.10 (1H, d, J=7 Hz, H-12), 8.12 (1H, s, H-17), 8.45 (1H, d, J=7 Hz, H-9). For the ^{13}C-nmr data, see Figure 1. Ms: 646 (M^+), 590, 546, 544, 490, 343 (100%), 265. HRms found: 646.2479. Calcd for $C_{33}H_{37}F_3N_2O_8$: 646.2502.

Compound (**8a**): Y. 20 mg (21 %). For analytical data, see Figure 1 and ref. 14.

Compound (**9**): Y. 4 mg (3 %). Amorphous material. Ir: 1730 br (4 x C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 610 (M^+), 595, 554, 510, 453, 450, 395, 394, 365, 293, 213, 169, 168 (100%), 167. HRms found: 610.2867. Calcd for $C_{33}H_{42}N_2O_9$: 610.2890.

Compound (**10**): Y. 3 mg (3 %). Amorphous material. Ir: 3400 br (OH), 1730 br (3 x C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 568 (M^+), 512, 468, 456, 439, 411 (100%), 395, 379, 367, 311, 169, 168, 167. HRms found: 568.2797. Calcd for $C_{31}H_{40}N_2O_8$: 568.2785.

In a similar experiment, where the only difference was that the reaction mixture was allowed to warm to room temperature immediately after TFAA addition and stirred thereafter 2 h at room temperature before the KCN addition (*vide supra*), the reaction led to a mixture of compounds (**1**) and (**8a**), which were separated and purified as above.

Compound (**1**): Y. 16 mg (13 %). For analytical data, see ref. 1.

Compound (**8a**): Y. 38 mg (36 %). For analytical data, see Figure 1 and ref. 14.

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