

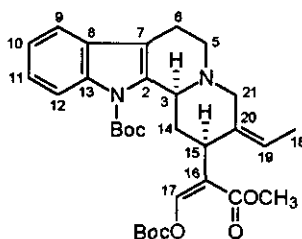
TOTAL SYNTHESIS OF N_a , O -DI-BOC-5 β -CYANO- Z -GEISSOSCHIZINE AND N_a -BOC-21 α -CYANOTETRAHYDROALSTONINE, THE LATTER A SYNTHETIC EQUIVALENT OF N_a -BOC-CATHENAMINE

Mauri Lounasmaa*, Minna Halonen, and Reija Jokela

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

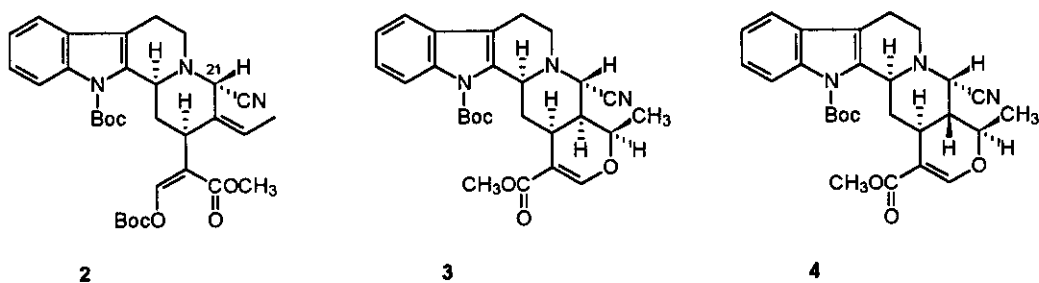
Abstract - Modified Polonovski reaction of the synthetically prepared N_a , O -di-Boc- Z -geissoschizine *cis*- N_b -oxide (6), followed by cyano trapping of the formed iminium intermediates, led to four compounds (1), (5a), (7), and (8a) [and to two secondary products, (9) and (10)]. The most important of these compounds were N_a , O -di-Boc-5 β -cyano- Z -geissoschizine (5a) and N_a -Boc-21 α -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}

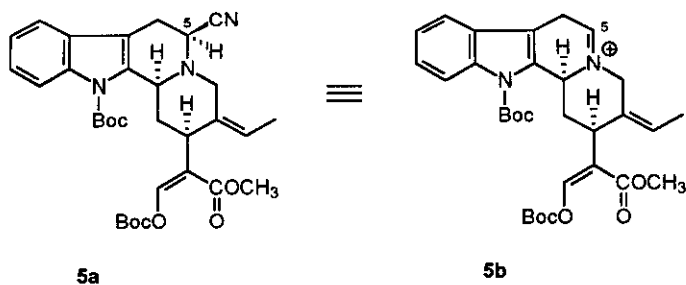


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This compound seemed to us to be ideally suited for a rapid preparation of N_a , O -di-Boc-21 α -cyano- Z -geissoschizine (2) and/or an N_a -Boc-21 α -cyanoheteroyohimbine structure [e.g. N_a -Boc-21 α -cyanoraunicine (3) or N_a -Boc-21 α -cyano-19-epiajmalicine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

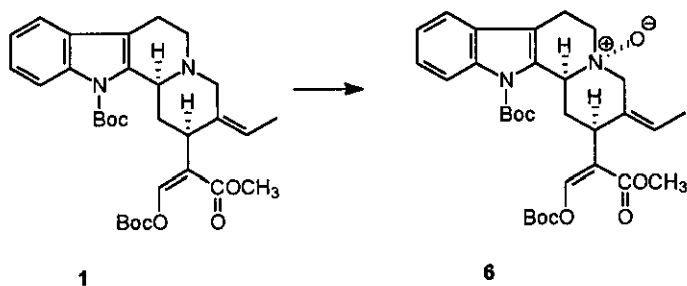


Moreover, the di-Boc derivative (1) might possibly lead to N_a,O -di-Boc-5 β -cyano-Z-geissoschizine (5a) [equivalent to N_a,O -di-Boc-Z-geissoschizine $\Delta^{4(5)}$ -iminium ion (5b)], a possible intermediate in the preparation of sarpagine/ajmaline derivatives (*vide infra*).



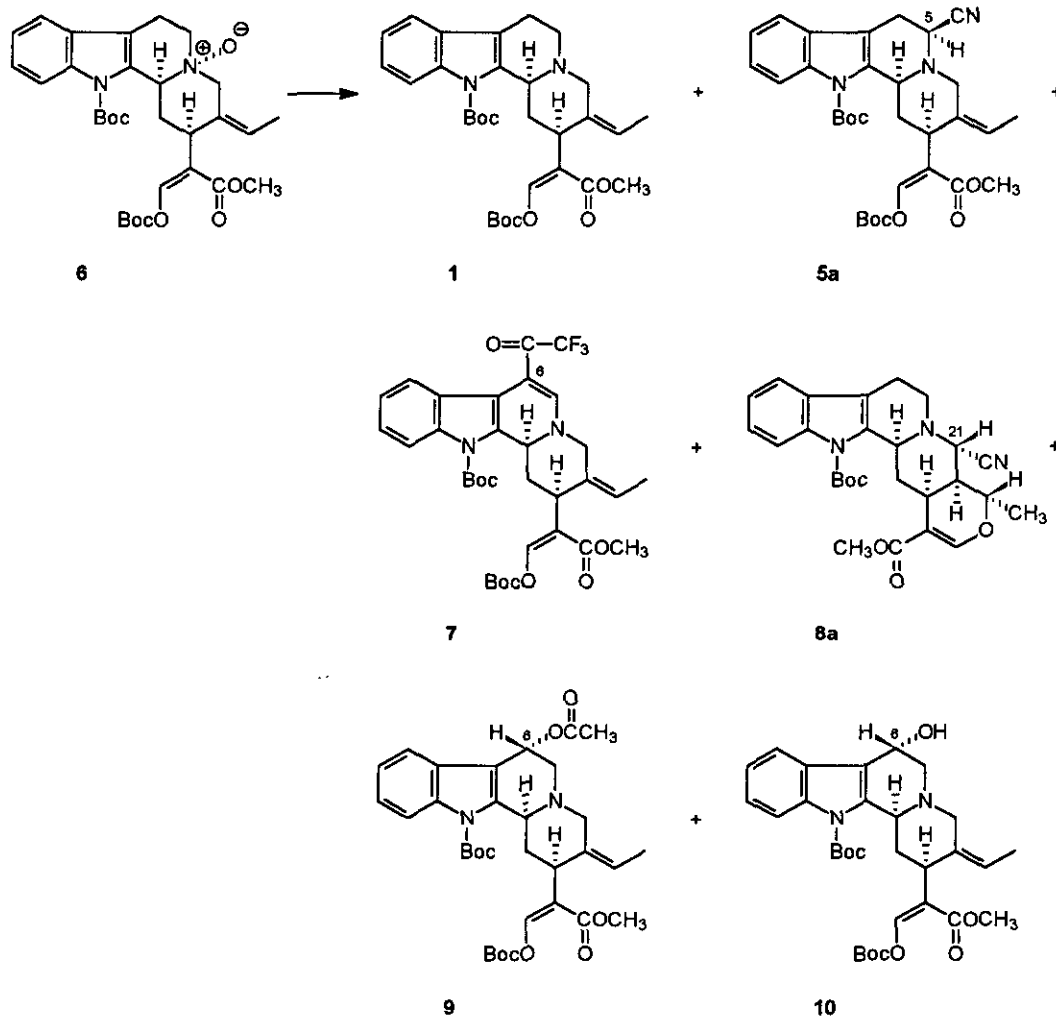
RESULTS AND DISCUSSION

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).



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-5 β -cyano-*Z*-geissoschizine (**5a**), N_a,O -di-Boc-6-trifluoroacetyl-5,6-didehydro-*Z*-geissoschizine (**7**), and N_a -Boc-21 α -cyanotetrahydroalstonine (**8a**). Small amounts of N_a,O -di-Boc-6 α -acetoxy-*Z*-geissoschizine (**9**) and N_a,O -di-Boc-6 α -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-21 α -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 ¹H-nmr data of compounds (5a), (6), (9), and (10) are given in Table 1 (*cf.* refs. 11-13) and the ¹³C-nmr data of compounds (5a), (6), (7), (8a), (9), and (10) in Figure 1.

Table 1. ¹H-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-5 α	4.19 dd	3.23 ddd	2.88 dd	2.91 dd
H-5 β	-	4.03 ddd	3.55 dd	3.52 dd
H-6 α	3.03 dd	3.5 m	-	-
H-6 β	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-14 α	2.2 m	2.51 ddd	1.90 ddd	1.94 ddd
H-14 β	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-21 α	3.34 br d	4.09 br d	3.62 br d	3.58 br d
H-21 β	4.04 d	4.65 d	3.96 d	3.97 d
CO ₂ Me	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 ₂ -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; $J_{5\alpha,5\beta} = 12$ Hz; $J_{5\alpha,6\alpha} = 7$ 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

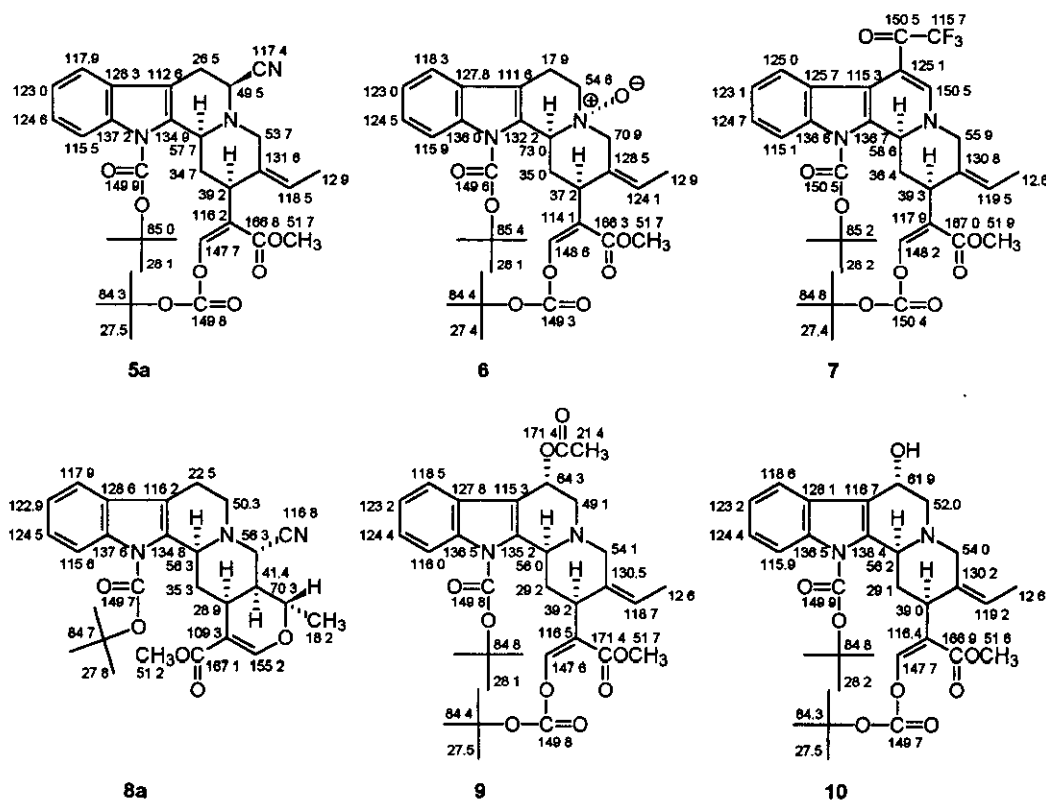
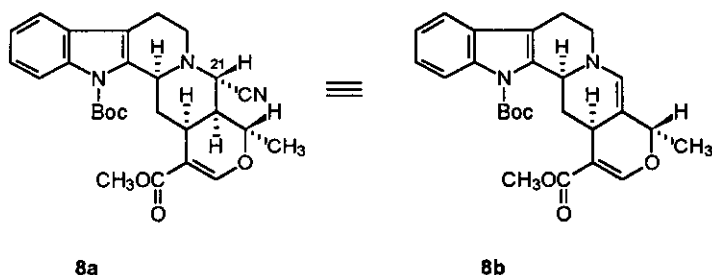


Figure 1. ^{13}C -Nmr data of compounds (5a), (6), (7), (8a), (9), and (10).

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

CONCLUSIONS

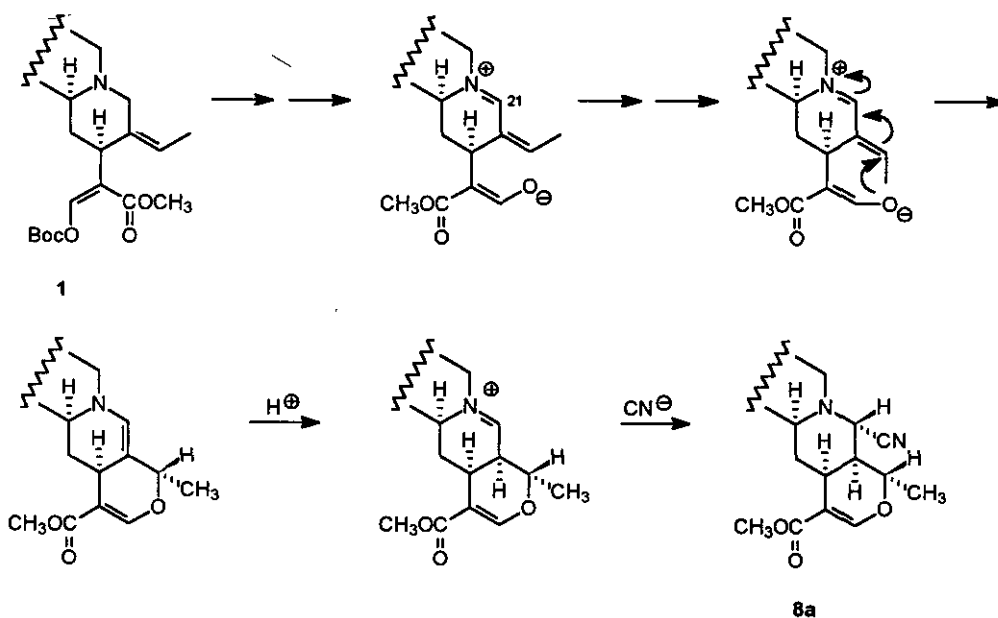
Cathenamines are key intermediates in the biosynthetic formation of heteroyohimbine alkaloids.¹⁶⁻²⁰ Our short synthesis of N_a -Boc-21 α -cyanotetrahydroalstonine (**8a**) [equivalent to N_a -Boc-cathenamine (**8b**)] represents the first easy access to these important structures without the use of natural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



The formation of an N_a -Boc-21 α -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 19 α H stereochemistry [and after cyano trapping to N_a -Boc-21 α -cyanoraunicine (3) and/or N_a -Boc-21 α -cyano-19-epiajmalicine (4) (*vide supra*)]. In the case of an *E*-ethylidene side-chain, compounds possessing the 19 β H stereochemistry should be formed. Since the only N_a -Boc-21 α -cyanoheteroyohimbine structure formed is N_a -Boc-21 β H-cyanotetrahydroalstonine (**8a**), which possesses the 19 β H 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-5 β -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; $\delta_{\text{H}}=0.0$ ppm) and CDCl_3 (^{13}C -nmr; $\delta_{\text{C}}=77.0$ 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_{α} ,O-di-Boc-Z-geissoschizine cis- N_{β} -oxide (6):

A solution of N_{α} ,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, $\text{CH}_2\text{Cl}_2/\text{MeOH}:98/2$) 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 ($\text{M}^+ - 16$, <1%), 452, 395, 337, 251, 169 (100%), 156. HRms found: ($\text{M}^+ - 16$) 552.2845. Calcd for $\text{C}_{31}\text{H}_{40}\text{N}_2\text{O}_7$: 552.2836.

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

The cis- N_6 -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 ^1H -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 $\text{C}_{32}\text{H}_{39}\text{N}_3\text{O}_7$: 577.2788.

Compound (7): Y. 8 mg (6%). Amorphous material. Ir: 1720 br (4 x C=O). ^1H -Nmr: 1.50 (9H, s, -O-Boc), 1.70 (9H, s, - N_α -Boc), 1.73 (3H, d, $J=7$ Hz, =CHCH $_3$), 3.72 (3H, s, -OCH $_3$), 4.54 (1H, d, $J=14$ Hz, H-21 β), 5.23 (1H, q, $J=7$ Hz, =CHCH $_3$), 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 $\text{C}_{33}\text{H}_{37}\text{F}_3\text{N}_2\text{O}_8$: 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 ^1H -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 $\text{C}_{33}\text{H}_{42}\text{N}_2\text{O}_9$: 610.2890.

Compound (10): Y. 3 mg (3 %). Amorphous material. Ir: 3400 br (OH), 1730 br (3 x C=O). For the ^1H -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 $\text{C}_{31}\text{H}_{40}\text{N}_2\text{O}_8$: 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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Received, 16th December, 1994