# Approaches to pseudopeptidic ergopeptines. Part 3.[1] Consequences of the incorporation of an α-azaphenylalanine residue into the ergotamine oxa-cyclolic system

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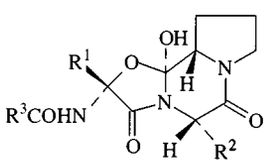
**In the context of a research program aimed at synthesizing pseudopeptidic ergopeptines, the incorporation of an α-azaPhe residue into the peptidic moiety of ergotamine has been studied. Acylation of cyclo(-azaPhe-Pro-) 6 with (+)-(*S*)-2-benzyloxy-2-methylmalonyl monoethyl ester monochloride 5 gives the (*E*)-isoimide 7 as the predominant reaction product; contrary to expectation the conversion of 7 into the desired imide isomer 8 proceeds with difficulty and is accompanied by decomposition. Hydrogenolysis of 8 leads stereospecifically to the pseudopeptidic oxa-cyclol ethyl ester 9. Subsequent rearrangement of the corresponding oxa-cyclol acyl-azide 11 in the presence of benzyl alcohol fails to give the pseudopeptidic ergotamine oxa-cyclol. The new stable pseudopeptidic aza-cyclol 12 containing the residue of the didehydroalanine has been isolated together with a comparable amount of the imino aza-cyclol derivative 13. The mechanism of the formation of the new products 12 and 13 and the unexpected stability of the (*E*)-isoimide 7 are discussed.**

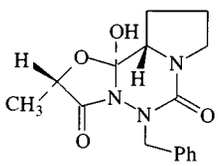
The free hydroxy group of a stable tetrahedral intermediate and the residue of an α-hydroxy-α-amino acid are the characterizing structural features of the peptidic portion of ergot alkaloids **1**. This unusual cyclotripeptide system contributes to the selective affinity of ergopeptines towards a variety of neurotransmitter receptors and modulates the pharmacokinetic properties of ergopeptines providing at the same time the main site for metabolic attack.[2–5]

In the context of a research programme aimed at studying backbone-modified ergot-like pseudopeptide systems we have recently examined the synthesis and properties of models containing an α-aza-amino acid residue;[1,6] attention was focused on the consequences of chemical modification on the properties of the resulting tetrahedral adduct and its prototropic forms. When the native phenylalanine was replaced with the α-azaphenylalanine (azaPhe) residue into a peptide model related to ergotamine, the tetrahedral adduct **2** was isolated as main reaction product.[6] However, the introduction of the α-azaproline (azaPro) residue in place of the native proline in an analogous model gave rather than the four-heteroatom tetrahedral adduct, the corresponding prototropic forms **3** and **4**.[1]

On the basis of the above results and in furtherance of our programme designed to synthesize pseudopeptidic ergopeptines, we report here results concerning the attempted synthesis of the azaPhe-containing peptide portion of ergotamine. The strategy adopted follows the classic scheme for ergopeptine synthesis elaborated by the Sandoz group.[4,7] Scheme 1 reports the first step of the synthesis consisting in the preparation of the *N*-acylcyclo(-azaPhe-Pro-) **8** by acylation of cyclo(-azaPhe-Pro-) **6** with (+)-(*S*)-2-benzyloxy-2-methylmalonyl monoethyl ester monochloride **5**. In contrast to previous results on the acylation of dioxopiperazines with $C^{\alpha}$-tetrasubstituted acyl chlorides[4,7] and cyclo(-azaPhe-Pro-) **6** with *O*-benzyl lactoyl chloride,[6] the synthesis of **8** proved to be difficult because of the predominant or exclusive formation of the α-aza-isoimide analogue (hydrazidoyl carboxylate) **7**.[8] As the result of a Mumm rearrangement,[9,10] which involves a rapid 1,3-acyl migration from oxygen to nitrogen, isoimides and related hydrazidoyl carboxylates are quite rare in organic chemistry and practically confined to the forms of *Z*-configuration (*i.e.* forms with a *trans* arrangement of the *O*-acyl group relative to the electron lone-pair on the neighbouring unsaturated nitrogen).[8,11] In the present context the *Z*-isomer cannot be formed; however, contrary to expectations, the (*E*)-isoimide **7** was found to be stable and its rearrangement to the desired *N*-acyl isomer **8**, under a variety of equilibration conditions, was only partial (*ca.* 20%) and accompanied by decomposition. It is worth noting, however, that **7** was formed neatly and in almost quantitative yields when molecular sieves were used as a neutral HCl scavenger under the very mild conditions adopted for the *N*-acylation of amides.[12] The nearly co-planar arrangement of

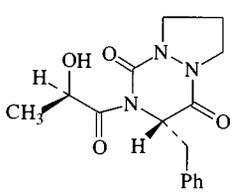


**1**

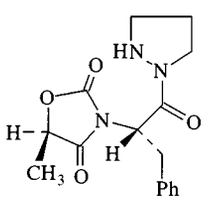


**2**

azaPhe analogue



**3**



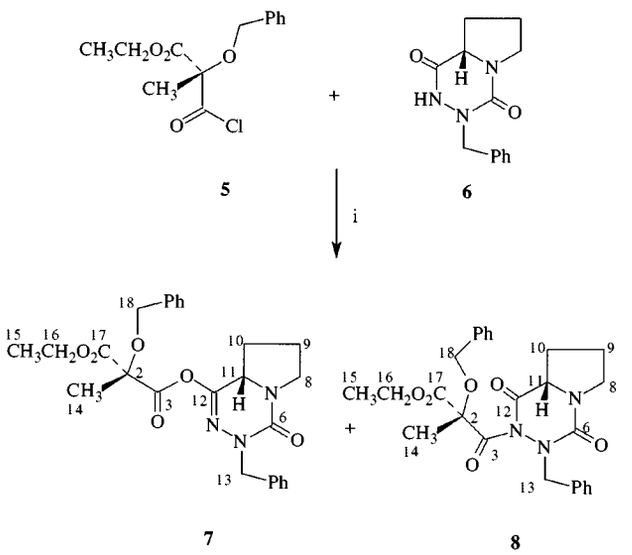
**4**

azaPro analogues

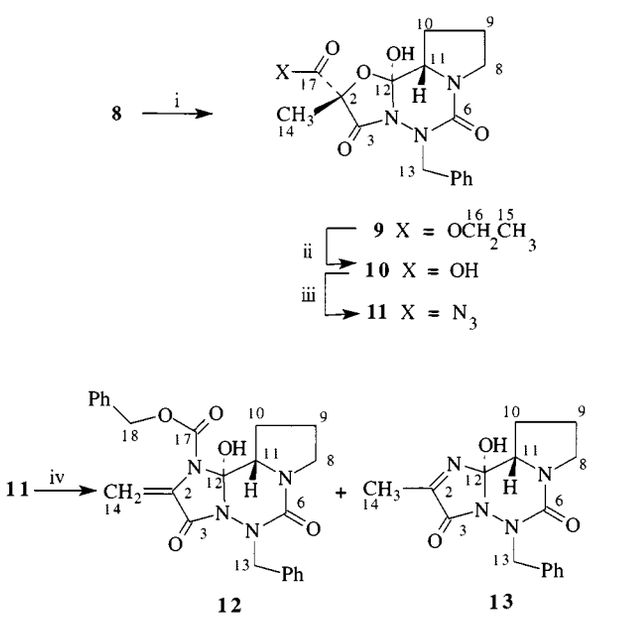
**Table 1** $^{1}$H NMR data[a,b] for compounds **7**, **8**, **9**, **12** and **13**

| Carbon no. | 7 | 8 | 9 | 12 | 13 |
|---|---|---|---|---|---|
| 8 | 3.4–3.7m | 3.2m | 3.5–3.7m | 3.4m | 3.5–3.7m |
| 9, 10 | 1.7–2.2m | 1.7–2.1m | 1.7–2.1m | 1.6–2.0m | 1.8–2.2m |
| 11 | 4.45m | 3.45m | 3.55m | 3.55m | 3.15m |
| 13 | 4.65, 4.9 | 4.3, 5.15 | 4.6, 5.5 | 4.6, 5.35 | 4.55, 5.55 |
| | ABq (15.0) | ABq (15.0) | ABq (14.5) | ABq (15.0) | ABq (14.5) |
| 14 | 1.8s | 1.75s | 1.6s | 5.55 (2.5) | 2.3s |
| 15 | 1.3t (7.0) | 1.25t (7.0) | 1.3t (7.0) | | |
| 16 | 4.25q | 4.2q | 4.2q | | |
| 18 | 4.65, 4.75 | 4.3, 4.8 | | 5.2 | |
| | ABq (12.0) | ABq (11.0) | | ABq (12.0) | |
| 12-OH | | | 3.85d (2.0) | 3.8br s | 2.4s |

[a] See structures for numbering scheme. [b] Solvent $CDCl_3$, $\delta$ (ppm) from tetramethylsilane. Coupling constants (in parentheses, Hz) for mutually coupled protons are given only once, at their first occurrence in the Table.




**Scheme 1** *Reagents and conditions*: i, pyridine, dioxane, 85 °C, 24 h




**Scheme 2** *Reagents and conditions*: i, $H_2$, 10% Pd–C, AcOH, room temp., 7 h; ii, 1 mol $dm^{-3}$ aq. NaOH, MeOH, room temp., 1.5 h; iii, isobutyl chloroformate, *N*-methylmorpholine, THF, −10 °C, 20 min; then $NaN_3$, water, −10 °C, 30 min; iv, benzyl alcohol, $CHCl_3$, 60 °C, 30 min; then reflux, 1 h

the benzylic side-chain, relative to the acylating carbonyl bearing the bulky tetrasubstituted $C^{\alpha}$ carbon atom, seems the main factor which destabilizes the imide form and disfavours the four-membered cyclic transition state involved in the intramolecular transfer of the acyl group from oxygen to nitrogen.[11] Although the hydrazidic nature of the system can play a role in stabilizing the isoimidic form, this does not seem relevant since the acylation of cyclo(-azaPhe-Pro-) with *O*-benzyl lactoyl chloride[6] does not involve the formation of a stable *O*-acyl intermediate.

The NMR spectra of **7** and **8** (see Tables 1 and 2) are in accordance with the assigned structures and, in general, very similar. Significant differences concern, as expected, the resonances of the $H^{\alpha}$ and the carboxylic carbon atom of the Pro residue; the first appears at $\delta$ 4.45 and 3.45, the second at $\delta$ 144.6 and 166.6 for **7** and **8**, respectively. The $^{13}$C NMR spectrum of the *O*-acyl isomer **7** is complicated by the observation of rotational isomerism; this problem manifests itself by doubling several resonances signals as can be deduced by Table 2. The location of the paired resonances indicates the 2-benzyloxy-2-methylmalonyl moiety as the locus of the isomerisation and the peak height ratios suggest a *ca.* 1:1 mixture. These data can be interpreted in terms of slow (*E*)-*syn*/(*E*)-*anti* isoimide interconversion due to hindered rotation about the bond connecting the exocyclic oxygen to the C=N carbon atom.[8]

The *N*-acyl isomer **8**, carefully isolated by the reaction mixture or recovered by the equilibration of **7**, was hydrogenolyzed to give stereospecifically the pseudopeptidic oxa-cyclol ester **9** in good yields (Scheme 2); all the properties of this tetrahedral adduct are in agreement with the assigned structure and with the spectral data of the previously studied lactoyl model.[6]

Aqueous alkaline hydrolysis of **9** was followed by carboxy activation *via* a mixed anhydride with isobutyl chloroformate; reaction of the activated species with sodium azide gave the acyl azide **11** in high yield. Curtius degradation of **11**, in the presence of benzyl alcohol, under the reaction conditions adopted by the Sandoz group during the total synthesis of ergot peptide alkaloids,[4,13] failed to give the expected benzyloxycarbonylamino derivative. Changes in the reaction conditions (solvent, temperature, presence of catalytic amounts of acids or bases) failed to give the expected rearrangement product; it should be considered, however, that exploration of the reaction conditions was limited by the low availability of the starting *N*-acyl isomer **8** caused by the above reported synthetic difficulties. Column chromatography of the reaction mixture revealed two main products (16 and 12% yield, respectively) in addition to small amounts (2–5%) of a third component identified as the benzyl ester of the starting oxa-cyclol **10**. Structures **12** and **13** were assigned to the minor and the major component, respectively. Both the assignments, including the stereochemistry at the newly formed chiral centre, were confirmed by X-ray crystallographic analysis (Figs. 1 and 2). $^{1}$H and $^{13}$C NMR spectral data of **12** and **13** are reported in Tables 1 and 2 and are in accordance with their structures. Characteristic features in the NMR spectra of **13** are represented by the $CH_3$ protons which appear as a deshielded singlet at $\delta$ 2.3 and by the unsaturated imine carbon atom found at $\delta$ 171.1. Compound **12** shows signals for

**Table 2** $^{13}$C NMR data[a,b] for compounds **7**, **8**, **9**, **12** and **13**

| Carbon no. | **7**[c] | **8** | **9** | **12** | **13** |
|---|---|---|---|---|---|
| 2 | 81.9 (82.0) | 83.6 | 82.4 | 131.5 | 171.1 |
| 3 | 168.2 (167.3) | 168.6[d] | 159.5 | 151.5[e] | 157.0 |
| 6 | 151.0 | 155.8 | 151.6 | 151.6[e] | 151.9 |
| 8 | 45.6 | 44.3 | 47.3 | 46.6 | 47.1 |
| 9 | 22.4 | 23.2 | 22.8 | 22.6 | 22.8 |
| 10 | 28.9 | 27.1 | 26.6 | 29.8 | 27.5 |
| 11 | 55.7 | 58.6 | 65.3 | 66.4 | 64.6 |
| 12 | 144.6 | 166.6[d] | 100.2 | 89.8 | 94.6 |
| 13 | 52.7 | 52.8 | 48.7 | 50.4 | 49.9 |
| 14 | 20.1 (21.3) | 20.5 | 19.1 | 100.7 | 15.0 |
| 15 | 14.0 | 14.0 | 14.0 | | |
| 16 | 62.2 (62.4) | 61.6 | 63.6 | | |
| 17 | 171.8 (169.2) | 170.5 | 170.1 | 155.5 | |
| 18 | 68.9 (68.5) | 67.6 | | 68.6 | |

[a] See structures for numbering scheme. [b] Solvent $CDCl_3$, $\delta$ (ppm) from tetramethylsilane. The assignments for proton-bearing carbons were confirmed by APT experiments. [c] Values in parentheses are due to the minor conformer. [d,e] Assignments may be interchanged.

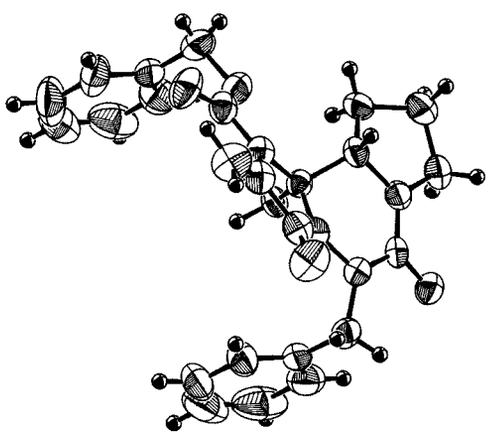


**Fig. 1** ORTEP diagram of the molecular structure of **12**

olefinic protons at $\delta$ 5.55 and the two olefinic carbon atoms at $\delta$ 131.5 and 100.7. The tetrahedral carbon atom bearing the aza-cyclolic hydroxy group is found at $\delta$ 89.8 and 94.6 in **12** and **13**, respectively. In accordance with previous results, these values are at higher field as compared with those exhibited by the corresponding tetrahedral carbons of the oxa-cyclolic forms[14] (*e.g.* $\delta$ 100.2 for oxa-cyclol **9**).

The results reported in Scheme 3 show that the pseudopeptidic acylazide **11**, under the adopted reaction conditions, rearranges to give stable aza-cyclol systems containing an imidazolinone or an imidazolidinone ring replacing the characteristic oxazolidin-4-one which is present in ergotamine and all related ergopeptines. Formation of the imino aza-cyclol **13** resembles the side reaction observed during the total synthesis of ergotamine and derives probably by intramolecular addition of the C-12 hydroxy to the intermediate isocyanate.[13] The formation of the didehydroalanine-containing aza-cyclol **12** from an oxa-cyclol system is not precedented and shows that the intermediate isocyanate can be intercepted by the benzyl alcohol to give the desired benzyloxycarbonylamino group; the product formed, however, undergoes further rearrangements leading eventually to the stable tetrahedral adduct **12**. The cyclolic hydroxy and the L-Pro α-CH of this new product exhibit the same *trans* stereochemistry found in natural ergopeptines, thus showing that the stereospecific course of cyclolization[15] is maintained in the pseudopeptidic skeleton. In

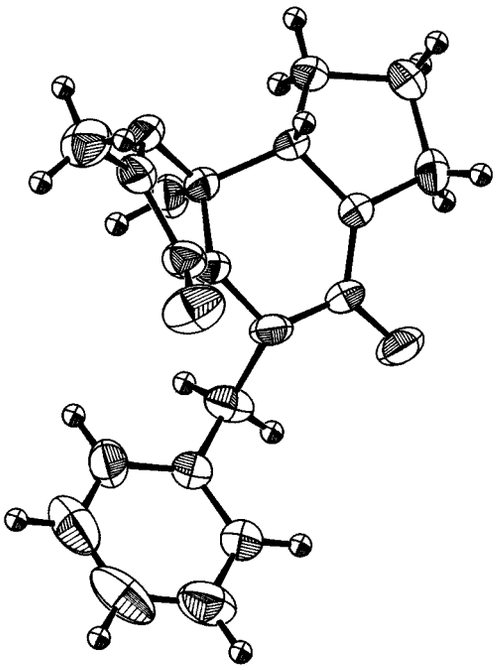


**Fig. 2** ORTEP diagram of the molecular structure of **13**

this connection it is worth mentioning that *cis*-arrangement involving the L-Pro $C^{\alpha}H$ and the cyclolic hydroxy group is quite rare in the chemistry of ergot-like cyclols and has been evidenced only in special cases.[16,17] The involvement of a resonance-stabilized bidentate carbocation during the rearrangement leading to **12** is supported by the observation that the distribution of the two reaction products **12** and **13** is altered in favour of **12** when the acyl–azide rearrangement is performed in the presence of a catalytic quantity of acids. A resonance-stabilized intermediate analogous to that reported in Scheme 3 has been proposed by Ott and co-workers for the well-known acid-catalyzed isomerization of the peptide moiety of ergopeptines.[18]

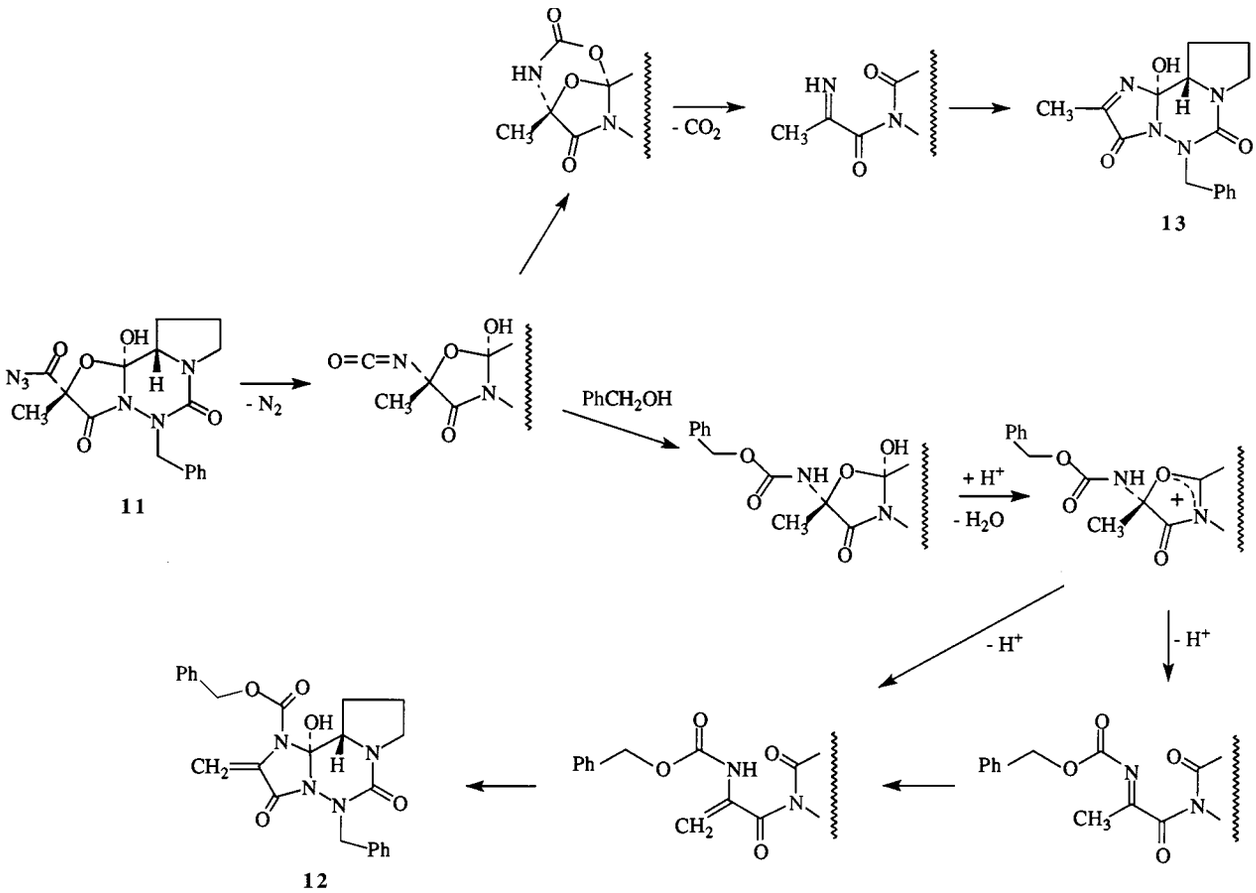
It is well known that an interplay of conformational and stereoelectronic factors are crucial for the stability and reactivity of the tetrahedral adducts;[19,20] a specific anomeric effect, involving the rotameric state of the free hydroxy group, should also play an important role.[6,21] In this context, detailed information on the conformation of the newly formed pseudopeptidic aza-cyclols and the hybridization state of the involved nitrogen atoms can help us to understand the influence of the α-aza residue on the course of the observed rearrangements. Further studies are in progress to examine this point.

## Experimental

Mps were determined on a Kofler hot-stage and are uncorrected. Optical rotations were taken at 20 °C with a Schmidt-Haensch Polartronic D polarimeter and are measured in units of $10^{-1}$ deg cm$^2$ g$^{-1}$. IR spectra were recorded in $CHCl_3$ on a Perkin–Elmer 983 spectrophotometer. $^1$H (300 MHz) and $^{13}$C (75.43 MHz) NMR spectra were determined in $CDCl_3$ solutions with tetramethylsilane as internal standard using a Varian XL-300 instrument; *J* values are given in Hz. The data concerning the X-ray structure determination of compounds **12** and **13** will be reported elsewhere.

### Compounds 7 and 8

A mixture of (+)-(*S*)-2-benzyloxy-2-methylmalonyl monoethyl ester monochloride **5** (33.1 g, 122.4 mmol) and cyclo(-azaPhe-Pro-) **6** (5.0 g, 20.4 mmol) in 1,4-dioxane (450 cm$^3$) containing dry pyridine (12.1 g, 153.0 mmol) was heated for 24 h at 85 °C. After cooling of the reaction mixture, the precipitate was



**Scheme 3**

filtered off and the resulting solution evaporated to dryness under reduced pressure. A chloroform solution of the residue was washed with 0.5 mol $dm^{-3}$ aq. HCl, saturated aq. $NaHCO_3$ and water, dried and evaporated to give a residue which was purified by column chromatography on silica gel using $CHCl_3$–ether (95:5) as eluent.

The main component isolated as an oil from column chromatography was the *O*-acyl derivative **7** (6.45 g, 66%) (Found: C, 65.0; H, 5.9; N, 8.6. $C_{26}H_{29}N_3O_6$ requires C, 65.1; H, 6.1; N, 8.8%); $[\alpha]_D$ +68.0 (*c* 1.00, $CHCl_3$); $\nu_{max}/cm^{-1}$ 1780, 1745 and 1670.

The minor fraction collected from column chromatography gave the isomeric *N*-acyl derivative **8** as an oil (1.95 g, 20%) (Found: C, 64.8; H, 6.3; N, 8.6. $C_{26}H_{29}N_3O_6$ requires C, 65.1; H, 6.1; N, 8.8%); $[\alpha]_D$ −106.0 (*c* 0.50, $CHCl_3$); $\nu_{max}/cm^{-1}$ 1750, 1725 and 1690.

### Compound 8 (from 7)

To a solution of the *O*-acyl derivative **7** (6.0 g, 12.5 mmol) in 1,4-dioxane (280 $cm^3$) was added a solution of dry pyridine (5.9 g, 75.0 mmol) in 1,4-dioxane (20 $cm^3$) and the stirred mixture was heated at 85 °C for 24 h. The residue obtained after removal of the solvent was chromatographed on silica gel using $CHCl_3$–ether (95:5) as the eluent to give title compound **8** (20%).

### Oxa-cyclol ester 9

Compound **8** (4.4g, 9.2 mmol) was hydrogenated in glacial acetic acid (220 $cm^3$) in the presence of 10% Pd on activated charcoal (1.76 g). After the mixture had been vigorously stirred for 7 h the catalyst was filtered off and the filtrate evaporated to dryness. The oily residue was purified by column chromatography using $CHCl_3$–ether (95:5) as eluent to yield title compound **9** as an oil (1.72 g, 48%) (Found: C, 53.4; H, 6.1; N, 9.6 $C_{19}H_{23}N_3O_6{\cdot}2H_2O$ requires C, 53.6; H, 6.4; N, 9.9%); $[\alpha]_D$ +120.0 (*c* 0.50, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3440br, 1725 and 1665.

### Oxa-cyclol acid 10

To a cooled solution of the above reported ethyl ester **9** (1.6 g, 4.1 mmol) in MeOH (3 $cm^3$) 1 mol $dm^{-3}$ aq. NaOH (5.1 $cm^3$) was added in portions with stirring. After 1.5 h at room temperature, the solution was evaporated under reduced pressure and the residue taken up in water. The aqueous alkaline solution was washed with ether, acidified with $KHSO_4$ and extracted with $CHCl_3$. The extract was dried and evaporated to give the oxa-cyclol acid **10** as a vitreous compound, pure by NMR and TLC (1.4 g, 94%), which was used without further purification. An analytical sample was purified by preparative TLC using $CHCl_3$–MeOH–$H_2O$ (65:25:4) as eluent (Found: C, 56.3; H, 5.2; N, 11.4. $C_{17}H_{19}N_3O_6$ requires C, 56.5; H, 5.3; N, 11.6%); $[\alpha]_D$ +110.0 (*c* 0.50, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3390br, 1730 and 1665; $\delta_H$ 1.65 (3 H, s, $CH_3$), 1.7–2.1 (4 H, m, β- and γ-$H_2$ Pro), 3.5–3.7 (3 H, m, δ-$H_2$ and α-H Pro), 4.7 and 5.45 (2 H, 2 AX d, *J* 15.5, $NCH_2$) and 7.15–7.35 (5 H, m, ArH); $\delta_C$ 19.25 ($C^{14}$), 22.74 ($C^9$), 26.42 ($C^{10}$), 47.40 ($C^8$), 49.26 ($C^{13}$), 65.63 ($C^{11}$), 82.29 ($C^2$), 99.94 ($C^{12}$), 128.43, 128.52, 129.88, 135.53 (aromatics), 152.30 ($C^6$), 160.17 ($C^3$) and 171.16 ($C^{17}$).

### Oxa-cyclol azide 11

Isobutyl chloroformate (1.06 g, 7.8 mmol) and *N*-methylmorpholine (0.79 g, 7.8 mmol) were added to a stirred solution cooled at −10 °C of the oxa-cyclol acid **10** (2.8 g, 7.8 mmol) in tetrahydrofuran (15 $cm^3$). Stirring was continued at −10 °C for 20 min after which a cold solution of $NaN_3$ (2.0 g, 31.2 mmol) in water (4 $cm^3$) was added to the mixture. After an additional 30 min at −10 °C with vigorous stirring the reaction mixture was taken up in $CH_2Cl_2$ and the resulting solution washed with water, dried and evaporated to give title compound **11** (2.35 g, 78%) as an unstable foam which was used immediately for the subsequent Curtius rearrangement; $\nu_{max}/cm^{-1}$ 3460br, 2145, 1720 and 1660.

**Aza-cyclols 12 and 13**

Compound **11** (2.35 g, 6.1 mmol) was dissolved in $CHCl_3$ (20 $cm^3$) containing saturated aq. HCl (1 drop in 100 $cm^3$ of $CHCl_3$) and benzyl alcohol (1.3 g, 12.2 mmol). The resulting solution was heated at 60 °C for 30 min, during which time gas was evolved. After an additional 1 h under reflux, the reaction mixture was evaporated to dryness and the residue chromatographed on silica gel.

The first fraction isolated by column chromatography using $CHCl_3$–ether (9:1) as eluent afforded compound **12**, further purified by crystallization from ethyl acetate (0.33 g, 12%), mp 177–178 °C (Found: C, 64.1; H, 5.2; N, 12.4. $C_{24}H_{24}N_4O_5$ requires C, 64.3; H, 5.4; N, 12.5%); $[\alpha]_D$ +80.0 (*c* 0.50, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3525, 1730, 1660 and 1415.

The main component obtained from chromatography by eluting with $CHCl_3$–ether (1:1) was collected and crystallized from ethyl acetate to give the aza-cyclol **13** (0.3 g, 16%), mp 229–230 °C (Found: C, 61.0; H, 5.5; N, 17.6. $C_{16}H_{18}N_4O_5$ requires C, 61.1; H, 5.8; N, 17.8%); $[\alpha]_D$ +86.0 (*c* 0.50, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3555, 1740 and 1660.

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