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## SYNTHESIS OF MACROCYCLIC LACTAMS FROM 2-( $\omega$ -AMINO-ALKYL)-2-BENZOYLAMINO-3-PHENYL-*N,N*-DIMETHYLPROPAN-AMIDES VIA DIRECT AMIDE CYCLIZATION

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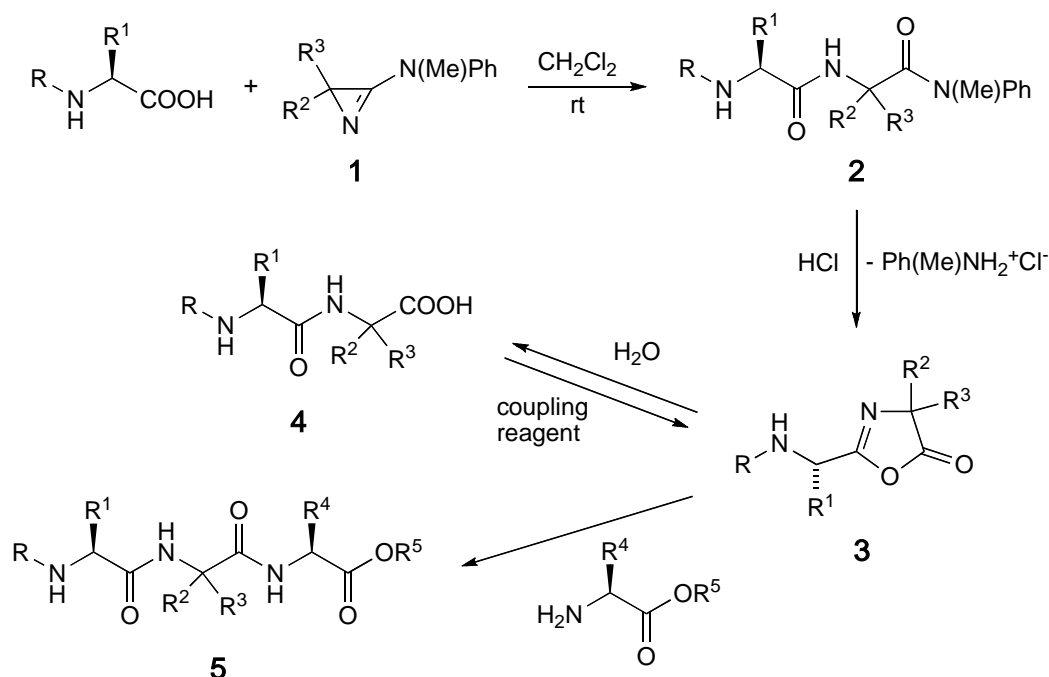
*Dedicated to the memory of Dr. John Daly*

**Abstract** – The alkylation of 4-benzyl-2-phenyl-1,3-oxazol-5(4*H*)-one (**11**) with  $\omega$ -azidoalkyl iodides (**12**) by deprotonation with LDA in THF/HMPT at –78 °C yielded mixtures of the 4,4-disubstituted 1,3-oxazol-5(4*H*)-ones (**13**) and the *O*-alkylated 1,3-oxazoles (**14**) in 65–50%, with **13** as the major product. The reaction of the latter with dimethylamine in acetonitrile at room temperature led to  $\omega$ -azido-2-benzamido-2-benzylalkane amides (**15**), which were reduced to give the corresponding  $\omega$ -amino derivatives (**16**). On treatment with HCl gas or BF<sub>3</sub> in boiling toluene, the macrocyclic 2-benzamido lactams (**18**) were formed in up to 27% yield via the intermediate formation of 1,3-oxazol-5(4*H*)-ones (**17**). The structures of the 14- and 15-membered lactams have been established by X-ray crystallography.

## INTRODUCTION

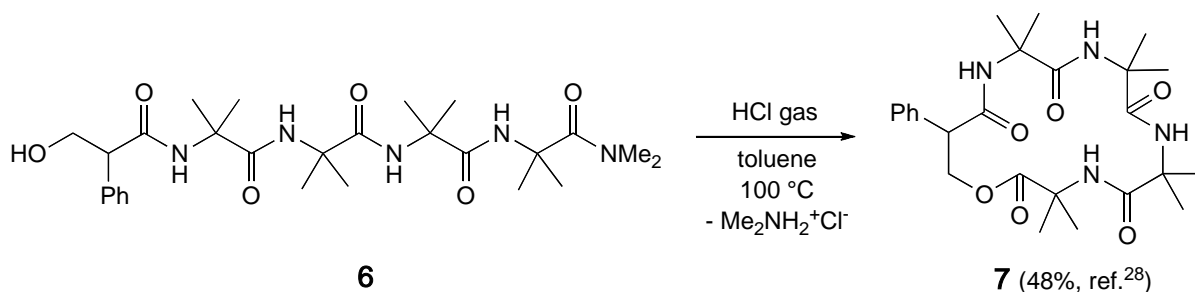
In the last couple of years, we have investigated extensively the use of 2,2-disubstituted 2*H*-azirin-3-amines (**1**) as synthons for  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acids in peptide synthesis.<sup>2,3,4,5,6,7,8,9,10,11,12,13,14,15,16</sup> The basic concept is the so-called ‘azirine/oxazolone method’,<sup>17,18,19,20,21,22</sup> in which both the selective hydrolysis of the terminal amide group of **2**, obtained *via* extension of the peptide chain by the reaction with the 2*H*-azirin-3-amine (**1**), to give **4**, and the coupling with the next amino acid or peptide segment to yield **5** occur *via* 1,3-oxazol-5(4*H*)-ones (azlactones, **3**) as intermediates (*Scheme 1*, see also refs.<sup>23,24</sup>). In a very recent study, *Brückner* and coworkers pointed to the high tendency of peptides containing  $\alpha$ -aminoisobutyric acid (Aib) to undergo acid-catalyzed cleavage of the peptide chain *via* the formation of 1,3-oxazol-5(4*H*)-ones.<sup>25</sup>

Scheme 1



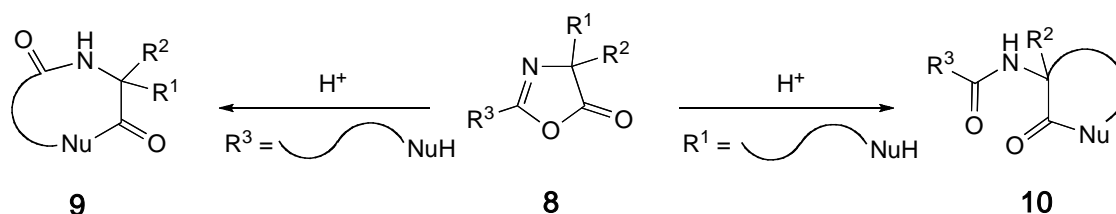
Furthermore, it has been shown that the cyclization of peptide-like compounds of type (6) by treatment with dry HCl gas in toluene at 100 °C proceeds smoothly ('direct amide cyclization'), and cyclic depsipeptides (7) are formed in astonishingly high yield (Scheme 2).<sup>9,26,27,28,29,30</sup> Again, the 'activated intermediates' are 1,3-oxazol-5(4*H*)-ones, which are formed *via* acid-catalyzed cyclization of the C-terminal acyl-Aib-NMe<sub>2</sub> unit.

Scheme 2



Under different reaction conditions, *i.e.*, by the treatment of penta to octapeptides containing  $\alpha,\alpha$ -disubstituted glycines and deprotected  $\text{H}_2\text{N}$ - and  $-\text{COOH}$  termini with peptide coupling reagents, the synthesis of the corresponding cyclopeptides could be achieved.<sup>3,12,13,14,31</sup> Also in these cases, 1,3-oxazol-5(4*H*)-ones are likely intermediates in the cyclization reaction.

The above ring closing reactions to cyclodepsipeptides and cyclopeptides can be characterized by the sequence **8**  $\rightarrow$  **9** (*Scheme 3*), in which the nucleophilic group in the side chain at C(2) of the 1,3-oxazol-5(4*H*)-one (**8**,  $R^3 = \text{HNu}\sim\sim$ ) attacks C(5) of **8**, followed by ring opening. The intermolecular version of this reaction, *e.g.*, the ring opening of 1,3-oxazol-5(4*H*)-ones *via* hydrolysis and methanolysis, is well known<sup>32,33,34,35,36</sup> (for some relevant examples, see refs.<sup>37,38,39,40,41</sup>). The preferred reaction mechanism is the nucleophilic attack at C(5), but, depending on steric and electronic effects of the substituents, the nucleophilic attack of  $\text{H}_2\text{O}$  can also occur at C(2), leading to the same product.<sup>42,43</sup> Similarly, the reactions of 1,3-oxazol-5(4*H*)-ones with N-nucleophiles lead to  $\alpha$ -(*N*-acylamino) alkanamides or peptides *via* attack at C(5).<sup>43,44,45</sup>

*Scheme 3*

Some years ago, we demonstrated that 1,3-oxazol-5(4*H*)-ones with an OH group in the side chain at C(4), *i.e.*, **8**,  $R^1 = \text{HO}\sim\sim$ , under acidic conditions (HCl, toluene, 110 °C) form 2-acylaminolactones *via* the nucleophilic addition to the C(5)=O group of the azlactone, followed by ring opening<sup>31,46</sup> (**8**  $\rightarrow$  **10**, *Scheme 3*).

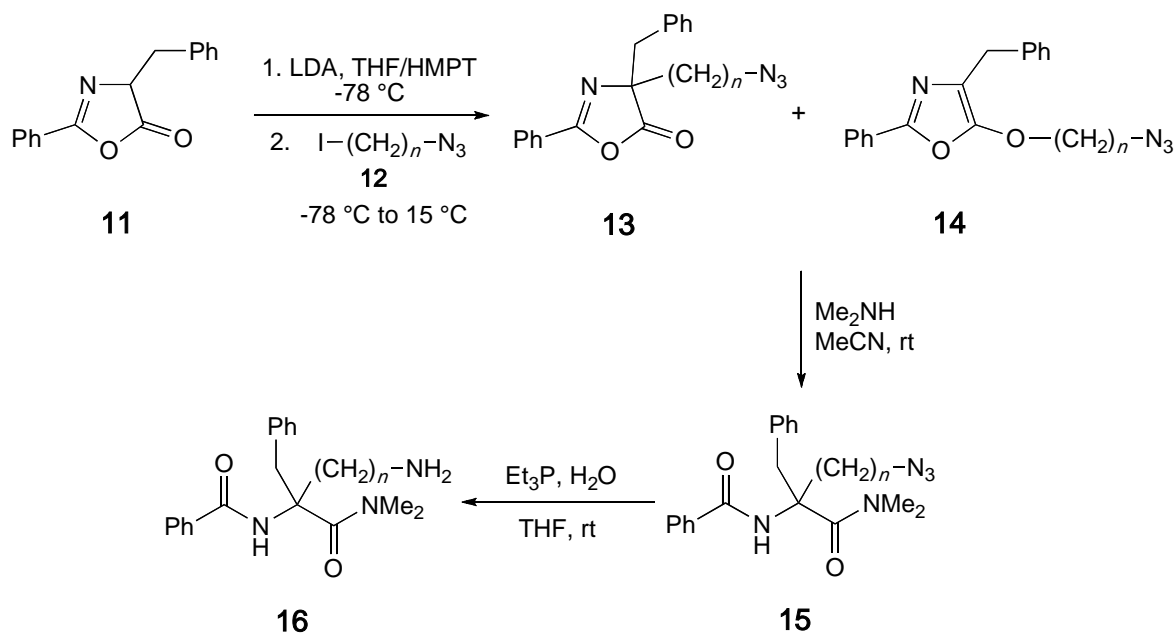
In the present paper, the results of lactam formations of the type **8**  $\rightarrow$  **10** ( $\text{HNu} = \text{NH}_2$ ) under acidic conditions ('direct amide cyclization') are reported.

## RESULTS AND DISCUSSION

We intended to prepare 1,3-oxazol-5(4*H*)-ones of type (**13**) with an  $\text{NH}_2$  group in the side chain as starting materials for the cyclization of type **8**  $\rightarrow$  **10** *via* the alkylation of the anion of 4-benzyl-2-phenyl-1,3-oxazol-5(4*H*)-one (**11**)<sup>47,48</sup> (*Scheme 4*). Whereas benzylations and allylations of azlactones are known to proceed smoothly by using *Hünig's* base,<sup>41,49,50</sup> alkylations occur more sluggishly. These reactions could be improved by variation of the reaction conditions, *e.g.*, the base and the solvent.<sup>38,45,46,51,52</sup> For this reason, alkyl iodides are the most promising reagents. The required alkyl iodides (**12**) with  $\text{N}_3$  as a masked amino group were prepared in a straightforward sequence starting with  $\omega$ -bromoalkanols, which were transformed into the corresponding  $\omega$ -azidoalkanols, respectively. These

products were treated with 2-fluoro-*N*-methylpyridinium tosylate (FMPT) and NaI<sup>53</sup> to give the desired  $\omega$ -azidoalkyl iodides (**12a–c**) in good yields (see experimental part).

*Scheme 4*



The alkylations of **11** were carried out in a mixture of THF/HMPT by deprotonation with LDA at ca.  $-78\text{ }^{\circ}\text{C}$  and reaction with **12a–c** at ca.  $15\text{ }^{\circ}\text{C}$ . In all cases, mixtures of the 4-alkylated oxazolones (**13**) and the *O*-alkylated oxazoles (**14**) were obtained with **13** as the major product (*Table 1*). All attempts to separate the two products were in vain.

Table 1. Alkylation of 4-benzyl-2-phenyl-1,3-oxazol-5(4H)-one (**11**)<sup>a)</sup>

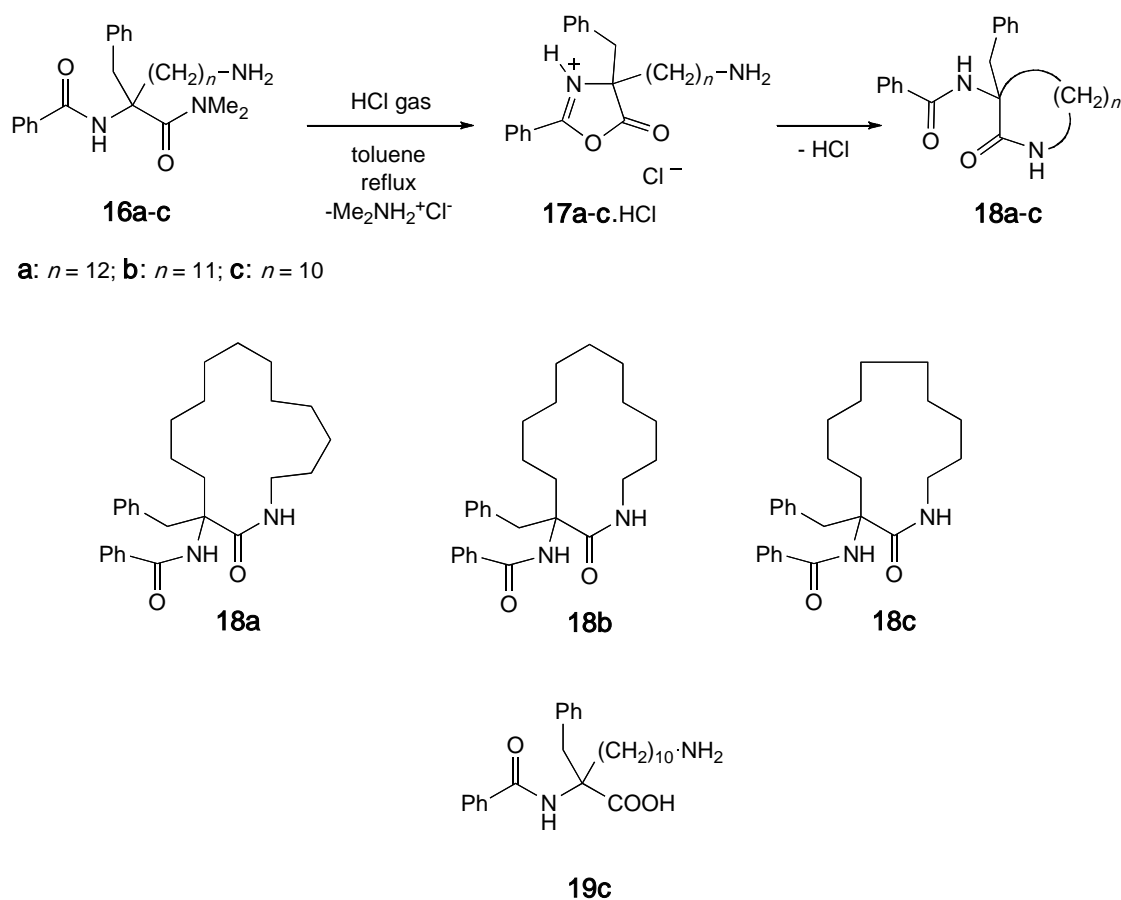
<i>n</i>	Alkyl iodide ( <b>12</b> )	Products <b>13</b> + <b>14</b> [%]	Ratio <b>13/14</b>	<b>15</b> [%]	<b>16</b> [%]
12	<b>a</b>	50	37 : 23	96	95
11	<b>b</b>	65	19 : 1	94	quant.
10	<b>c</b>	61	10 : 1	91	97

- a) Reaction conditions: i) addition of LDA to a solution of **11** in THF/HMPT at  $-78\text{ }^{\circ}\text{C}$ ; ii) addition of the iodide (**12**) at  $-78\text{ }^{\circ}\text{C}$ ; iii) increasing the temperature to  $15\text{ }^{\circ}\text{C}$ .

Furthermore, preliminary experiments ( $\text{H}_2$ , Pd/C;  $\text{LiAlH}_4$ ;  $\text{ZnCl}_2$  or  $\text{SnCl}_2$  in MeOH) showed that it was not possible to reduce the azido group of **13** without destroying the azlactone structure. Therefore, the mixtures **13/14** were treated with dimethylamine in acetonitrile to yield the azido amides (**15**), which subsequently were reduced in a *Staudinger* reaction<sup>54,55,56</sup> with triethylphosphine<sup>57</sup> and water to give the corresponding amines (**16**) in almost quantitative yields.<sup>58</sup>

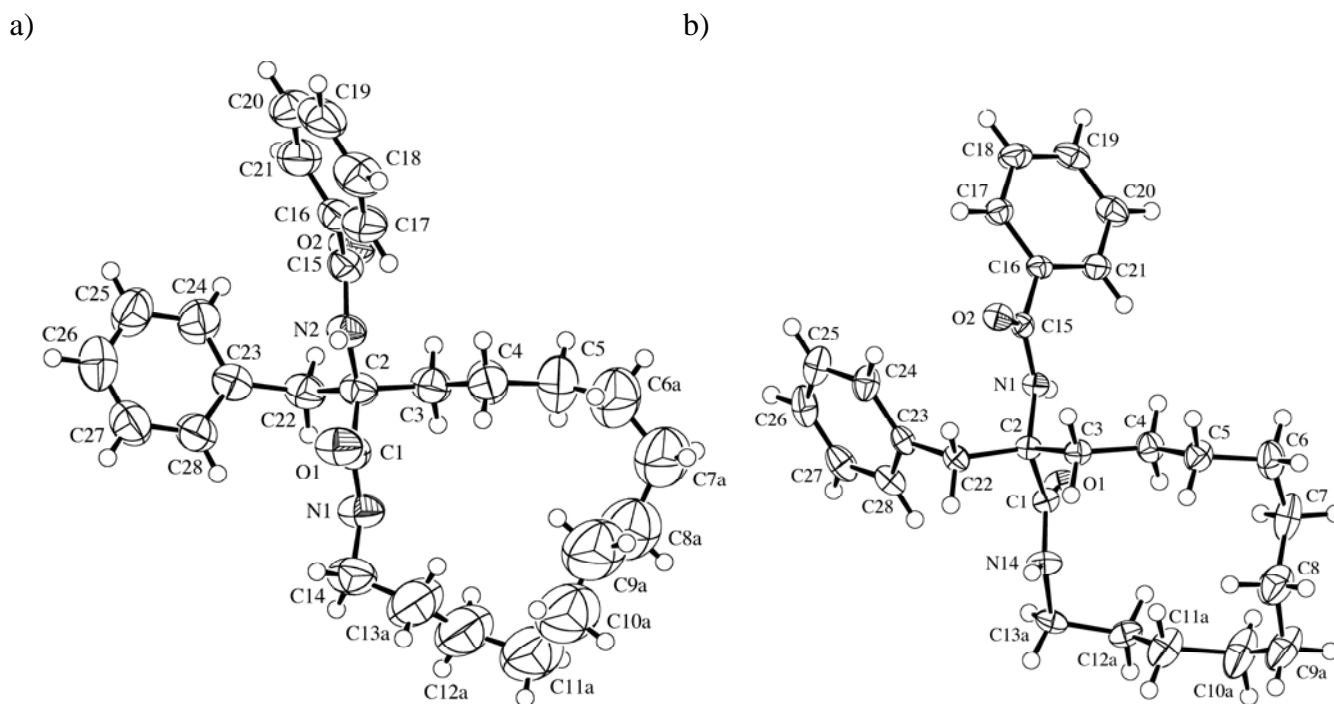
The  $\omega$ -aminoalkyl-substituted diamides (**16**) were exposed to the conditions of the ‘direct amide cyclization’,<sup>46</sup> *i.e.*, dry HCl gas was bubbled through a solution of **16** in boiling dry toluene for 1.5–2 h, and the mixture was kept boiling for 15 h. Then, toluene and excess HCl were evaporated and the residue was separated by ‘flash column chromatography’<sup>59</sup> ( $\text{SiO}_2$ ,  $\text{Et}_2\text{O}$ /hexane) to give the lactams **18a–c** in 27, 23, and 11% yield, respectively (*Scheme 5*). In an analogous experiment with **16c**, in which toluene had not been dried before its use, the corresponding carboxylic acid (**19c**) was obtained in 51% yield, indicating the intermediate formation of an oxazolonium ion of type (**17**).

*Scheme 5*



The spectroscopic data (MS, NMR, IR) of **18a–c** were in accordance with the lactam structures. Indicative were two IR absorptions at 1675–1670 and 1650–1645  $\text{cm}^{-1}$ ; the amide bands in the precursors (**16**) appeared at 1660 and 1625  $\text{cm}^{-1}$ . The  $^1\text{H}$ -NMR spectra showed the lactam NH ( $\text{CONH-CH}_2$ ) at 5.80–5.30 ppm as a multiplet or broadened signal, whereas the NH of the benzamide group absorbed as a singlet at 7.64–7.61 ppm. The corresponding absorptions in **16** were at ca. 1.95 ( $\text{NH}_2$ ) and 7.99 ppm ( $\text{PhCONH}$ ). On the other hand, the differences of the  $^{13}\text{C}$ -NMR absorptions for the amide and lactam  $\text{C=O}$  groups of **18** were not significant.

For this reason, the structures of **18a** and **18b** were established by X-ray crystal-structure determinations (*Figure 1*). Suitable crystals were grown from  $\text{Et}_2\text{O}$ /hexane/ $\text{CH}_2\text{Cl}_2$  and  $\text{CH}_2\text{Cl}_2$ /hexane, respectively, whereas no good crystals of **18c** could be obtained.



*Figure 1.* ORTEP plots<sup>60</sup> of the molecular structures of a) **18a** and b) **18b** (arbitrary numbering of the atoms; 50% probability ellipsoids)

Since the space groups of **18a** and **18b** are centrosymmetric, the compounds in the crystal are racemic. The macrocyclic ring of **18a** is severely disordered. The disorder is of the type common to such rings where the molecule can adopt a large number of slightly different conformations. The net effect is that the electron density of each atom is spread out over a wide region and it is very difficult to define a model, which closely fits the electron density. Two sets of positions were defined for seven consecutive  $\text{CH}_2$

groups. Furthermore, the crystals were very weakly diffracting, and only a small percentage of the reflections in the region with  $2\theta > 40^\circ$  had a measurable intensity. It was also necessary to record the data at room temperature, because the crystals were always damaged when the temperature was reduced. These factors, together with the disorder, have resulted in a poor agreement between the model and the observed data. This is reflected in the high *R*-factor and large estimated standard deviations for the atomic parameters. The model is the best one obtainable under the circumstances, but the nature of the disorder makes it extremely difficult to adequately account for the electron density distribution in the disordered region of the molecule. The refined model is therefore only an approximation to the large number of actual molecular conformations adopted in the crystal lattice. In the case of **18b**, the macrocyclic ring is disordered over two conformations. Two sets of positions were defined for five consecutive CH<sub>2</sub> groups. The N-H group of the 15- and 14-membered rings (in **18a** and **18b**, resp.) acts as a donor for intermolecular hydrogen bonds with the corresponding acceptor atom being the carbonyl O-atom of the side chain of a neighboring molecule. These interactions link the molecules into extended chains which run parallel to the [010] direction and can be described by a graph set motif<sup>61</sup> of C(7). The NH of the benzamide group is not involved in any intermolecular hydrogen bonds.

A possible explanation for the low yields of the cyclization reaction in comparison with analogous lactone formations<sup>46</sup> is the unfavorable strongly acidic reaction condition, which led to the preferred protonation of the amino group, and not only to that of the amide group in **16** or the intermediate oxazolone to give the activated **17**.<sup>62</sup> Therefore, we tried to substitute the *Brønsted* acid by a *Lewis* acid, *e.g.*, boron trifluoride (BF<sub>3</sub>).

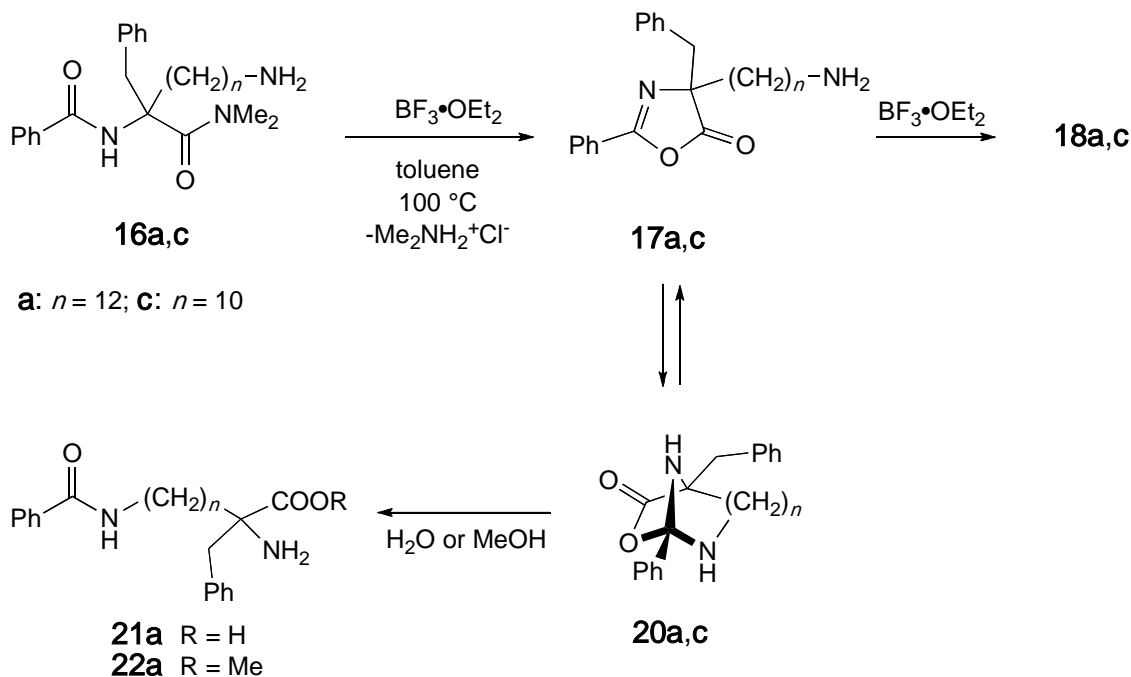
Treatment of a solution of **16a** and **16c** in toluene with BF<sub>3</sub>·Et<sub>2</sub>O at 100 °C and chromatographic workup led to the corresponding lactams (**18a**) and (**18c**), respectively, in only 7–8% yield. In addition, a labile product, for which we propose the structure **20a,c**, was obtained in 10 and 23% yield, respectively (*Scheme 6*). In the case of **20c**, it was possible to collect the spectroscopic data (see experimental part), which supported the structure, but the compound was not stable at room temperature and decomposed slowly to give at least three different products. The isolated homologous product (**20a**) rearranged within a few minutes into the azlactone (**17a**), which had also been isolated in 30% yield from the original reaction mixture. Furthermore, the linear ω-benzamido α-amino acid (**21a**) was obtained in 35% yield.

In an additional experiment, a solution of **16a** and BF<sub>3</sub>·Et<sub>2</sub>O in toluene was heated to reflux for 2 h. Then, 6 equivalents of methanol were added and the mixture was kept boiling for another 21 h. Chromatographic workup gave the ester (**22a**) in 80% yield, and a second product in *ca.* 6% yield, which rearranged quickly to give **22a**.

A likely reaction mechanism for the formation of **21a** and **22a** is shown in *Scheme 6*. Whereas, in the intermediate azlactones (**17**), the nucleophilic addition of the NH<sub>2</sub> group onto the C(5)=O group leads to

the lactams (**18**), the alternative addition onto C(2)<sup>42,43</sup> yields the bicyclic product (**20**). Hydrolysis and methanolysis of **20a** then give the linear  $\alpha$ -amino- $\omega$ -benzamido alcanoic acid (**21**) and ester (**22**), respectively.

Scheme 6



## CONCLUSIONS

The  $\alpha,\alpha$ -disubstituted  $\alpha$ -acylamino acid amides of type (**16**), which bear an amino group in the  $\omega$ -position, are conveniently accessible via alkylation of 4-benzyl-2-phenyl-1,3-oxazol-5(4*H*)-one (**11**) with  $\omega$ -azidoalkyl iodides (**12**), ring opening with dimethylamine, and reduction of the azido group. Treatment of **16** with dry HCl gas in boiling toluene leads to the corresponding  $\alpha$ -benzamido lactams (**18**), albeit in low yield. The analogous  $\text{BF}_3$ -catalyzed cyclization yields a mixture of different products with the lactams (**18**) in very low yield. We propose that the cyclization reactions occur via the intermediate formation of 1,3-oxazol-5(4*H*)-ones (azlactones, **17**), *i.e.*, the so-called ‘direct amide cyclization’. An indication for the appearance of azlactones as intermediates is the formation of the products (**19**) – (**22**), and in the  $\text{BF}_3$ -catalyzed reaction with **16a**, the corresponding azlactone **17a** could be isolated.

## EXPERIMENTAL

*General remarks.* TLC: silica gel 60 F<sub>254</sub> aluminium sheets (0.25 mm, Merck). Flash column chromatography<sup>59</sup> (FCC): silica gel 60 (40–60  $\mu\text{m}$ , Merck). Melting points: Mettler FP-5 apparatus, uncorrected. IR spectra: Perkin-Elmer 297 or Perkin-Elmer 781 IR spectrophotometer, in  $\text{CHCl}_3$  or KBr;



in  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR (300 MHz) and  $^{13}\text{C}$ -NMR (50 MHz) spectra: Varian XL-200, Bruker AC-300, and Bruker ARX-300 instrument, in  $\text{DMSO}-d_6$  or  $\text{CDCl}_3$ ; chemical shifts in ppm, coupling constants  $J$  in Hz; multiplicity of C atoms from DEPT spectra. EI-MS: MAT-112 instrument, 70 eV; CI-MS: MAT-90 instrument, isobutane or  $\text{NH}_3$  as carrier gas; ESI-MS: Finnigan TSQ-700 instrument.

*Starting materials.* 4-Benzyl-2-phenyl-1,3-oxazol-5(4*H*)-one (**11**) was prepared from 2-benzamido-3-phenylpropanoic acid according to ref.<sup>47</sup> All other reagents and solvents were commercially available (Fluka, Aldrich).

*Synthesis of  $\omega$ -azidoalkan-1-ols. General procedure.* A solution of a  $\omega$ -bromoalkan-1-ol (1 equiv.),  $\text{NaN}_3$  (2 equiv.), and  $\text{Bu}_4\text{NHSO}_4$  (0.1 equiv.) in THF/ $\text{H}_2\text{O}$  (2:1) was stirred for 60 h at 25–34 °C. Then, the mixture was poured into  $\text{H}_2\text{O}$  and extracted with  $\text{Et}_2\text{O}$  (3x). The organic phase was dried over  $\text{MgSO}_4$ , filtered, and evaporated. The crude products were directly used for the next reaction.

*12-Azidododecan-1-ol.* From 12-bromododecan-1-ol (3.03 g, 11.4 mmol) in THF (13 mL) and  $\text{H}_2\text{O}$  (7 mL),  $\text{NaN}_3$  (1.49 g, 22.9 mmol), and  $\text{Bu}_4\text{NHSO}_4$  (0.78 g, 2.3 mmol). Yield: 2.52 g (97%). Colorless oil. IR ( $\text{CHCl}_3$ ): 3620 *w*, 3450 *w* (br), 3000 *w*, 2930 *s*, 2860 *s*, 2100 *s*, 1470 *m*, 1460 *m*, 1390 *w*, 1350 *w*, 1290 *m*, 1255 *m* (br), 1050 *m* (br), 1015 *w*, 890 *w* (br).  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ): 3.64 (*t*-like,  $J \approx 5.2$ ,  $\text{CH}_2\text{O}$ ); 3.25 (*t*,  $J = 6.9$ ,  $\text{CH}_2\text{N}_3$ ); 1.65–1.50 (*m*, 3  $\text{CH}_2$ ); 1.45–1.25 (*m*, 7  $\text{CH}_2$ ).  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ): 62.8 (*t*,  $\text{CH}_2\text{O}$ ); 51.4 (*t*,  $\text{CH}_2\text{N}_3$ ); 32.7, 29.5 (2*t*, 2  $\text{CH}_2$ ); 29.4, 29.3 (2*t*, 4  $\text{CH}_2$ ); 29.0, 28.7, 26.6, 25.6 (4*t*, 4  $\text{CH}_2$ ). CI-MS ( $\text{NH}_3$ ): 245 (28,  $[\text{M}+18]^+$ ), 228 (7,  $[\text{M}+1]^+$ ), 200 (100,  $[\text{M}+1-\text{N}_2]^+$ ).

*11-Azidoundecan-1-ol.* From 11-bromoundecan-1-ol (3.98 g, 15.8 mmol) in THF (20 mL) and  $\text{H}_2\text{O}$  (10 mL),  $\text{NaN}_3$  (1.23 g, 19.0 mmol), and  $\text{Bu}_4\text{NHSO}_4$  (0.97 g, 2.9 mmol). Yield: 3.37 g (quant.). Colorless oil. IR ( $\text{CHCl}_3$ ): 3620 *m*, 3460 *w* (br), 3030 *w*, 3010 *m*, 2930 *s*, 2860 *s*, 2100 *s*, 1465 *m*, 1455 *m*, 1390 *w*, 1350 *m*, 1285 *m*, 1250 *m* (br), 1110 *w*, 1050 *m* (br), 1025 *m*, 890 *w* (br).  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ): 3.65 (*t*,  $J = 6.6$ ,  $\text{CH}_2\text{O}$ ); 3.26 (*t*,  $J = 6.9$ ,  $\text{CH}_2\text{N}_3$ ); 1.65–1.50 (*m*, 2  $\text{CH}_2$ ); 1.40–1.25 (*m*, 7  $\text{CH}_2$ ).  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ): 62.5 (*t*,  $\text{CH}_2\text{O}$ ); 51.3 (*t*,  $\text{CH}_2\text{N}_3$ ); 32.5, 29.4 (2*t*, 2  $\text{CH}_2$ ); 29.2 (*t*, 3  $\text{CH}_2$ ); 28.9, 28.6, 26.5, 25.6 (4*t*, 4  $\text{CH}_2$ ). CI-MS ( $\text{NH}_3$ ): 214 (6,  $[\text{M}+1]^+$ ), 186 (100,  $[\text{M}+1-\text{N}_2]^+$ ). Anal. Calcd for  $\text{C}_{11}\text{H}_{23}\text{N}_3\text{O}$ : C, 61.93; H, 10.87; N, 19.70. Found: C, 61.69; H, 10.66; N, 19.86.

*10-Azidodecan-1-ol.* From 10-bromodecan-1-ol (1.90 g, 8.0 mmol) in THF (10 mL) and  $\text{H}_2\text{O}$  (5 mL),  $\text{NaN}_3$  (0.63 g, 9.6 mmol), and  $\text{Bu}_4\text{NHSO}_4$  (0.49 g, 1.4 mmol). Yield: 1.58 g (99%). Colorless oil. IR ( $\text{CHCl}_3$ ): 3620 *w*, 3440 *w* (br), 3030 *w*, 2995 *w*, 2920 *s*, 2850 *s*, 2095 *s*, 1465 *s*, 1455 *w*, 1390 *w*, 1350 *w*, 1300 *m*, 1255 *m* (br), 1045 *m* (br), 1015 *w*, 915 *w*.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ): 3.65 (*t*,  $J = 6.6$ ,  $\text{CH}_2\text{O}$ ); 3.26 (*t*,  $J = 6.9$ ,  $\text{CH}_2\text{N}_3$ ); 1.70–1.50 (*m*, 2  $\text{CH}_2$ ); 1.50–1.20 (*m*, 6  $\text{CH}_2$ ).  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ): 62.8 (*t*,  $\text{CH}_2\text{O}$ ); 51.4 (*t*,  $\text{CH}_2\text{N}_3$ ); 32.6, 29.4 (2*t*, 2  $\text{CH}_2$ ); 29.3 (*t*, 2  $\text{CH}_2$ ); 29.0, 28.7, 26.6, 25.6 (4*t*, 4  $\text{CH}_2$ ). CI-MS ( $\text{NH}_3$ ): 217 (100,  $[\text{M}+18]^+$ ), 200 (9,  $[\text{M}+1]^+$ ), 172 (48,  $[\text{M}+1-\text{N}_2]^+$ ). Anal. Calcd for  $\text{C}_{10}\text{H}_{21}\text{N}_3\text{O}$ : C, 60.27; H, 10.62; N, 21.08. Found: C, 60.37; H, 10.45; N, 20.98.

*Synthesis of  $\omega$ -azidoalkyl iodides (12). General procedure.* To a solution of an  $\omega$ -azidoalkan-1-ol (1 equiv.) and triethylamine (TEA, 1.5 equiv.) in  $\text{CHCl}_3$  was added 2-fluoro-*N*-methylpyridinium tosylate (FMPT, 1.5–2.0 equiv.) and the mixture stirred for 2 h at 24 °C. After evaporation of the solvent, the residue was dissolved in acetone, NaI (2 equiv.) was added, and the mixture was heated to reflux for 18 h. The precipitate was filtered, the filtrate evaporated, and  $\text{Et}_2\text{O}$  added. Filtration, evaporation, and FCC ( $\text{SiO}_2$ ,  $\text{Et}_2\text{O}$ /hexane 1:9 to 2:1) gave the product and up to 50% recovered starting material.

*12-Azidododecyl iodide (12a).* From 12-azidododecan-1-ol (2.30 g, 10.1 mmol) in  $\text{CHCl}_3$  (55 mL), FMPT (4.29 g, 15.1 mmol), and TEA (1.54 g, 15.2 mmol), and then NaI (3.03 g, 20.2 mmol) in acetone (55 mL). Yield: 1.68 g (49%) of **12a**. Colorless oil. IR ( $\text{CHCl}_3$ ): 3000 $w$ , 2930 $s$ , 2860 $s$ , 2100 $s$ , 1465 $w$ , 1460 $w$ , 1370 $w$ , 1350 $w$ , 1290 $w$ , 1255 $w$  (br), 1170 $w$  (br).  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ): 3.19 ( $t$ ,  $J = 6.9$ ,  $\text{CH}_2\text{N}_3$ ); 3.12 ( $t$ ,  $J = 7.1$ ,  $\text{CH}_2\text{I}$ ); 1.75 ( $p$ ,  $J \approx 7.1$ ,  $\text{CH}_2$ ); 1.65–1.45 ( $m$ ,  $\text{CH}_2$ ); 1.40–1.15 ( $m$ , 8  $\text{CH}_2$ ).  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ): 51.4 ( $t$ ,  $\text{CH}_2\text{N}_3$ ); 33.5, 30.4 (2 $t$ , 2  $\text{CH}_2$ ); 29.4 ( $t$ , 3  $\text{CH}_2$ ); 29.3, 29.1, 28.8, 28.4, 26.6 (5 $t$ , 5  $\text{CH}_2$ ); 7.1 ( $t$ ,  $\text{CH}_2\text{I}$ ). CI-MS ( $\text{NH}_3$ ): 310 (14,  $[\text{M}+1-\text{N}_2]^+$ ), 182 (19), 151 (100). Anal. Calcd for  $\text{C}_{12}\text{H}_{24}\text{IN}_3$ : C, 42.74; H, 7.17; I, 37.63; N, 12.46. Found: C, 42.53; H, 7.02; I, 37.41, N, 12.38.

*11-Azidoundecyl iodide (12b).* From 11-azidoundecan-1-ol (2.21 g, 10.4 mmol) in  $\text{CHCl}_3$  (55 mL), FMPT (4.29 g, 15.1 mmol), and TEA (1.60 g, 15.8 mmol), and then NaI (3.03 g, 20.2 mmol) in acetone (50 mL). Yield: 1.78 g (53%) of **12b**. Colorless oil. IR ( $\text{CHCl}_3$ ): 3000 $w$ , 2930 $s$ , 2860 $m$ , 2100 $s$ , 1465 $w$ , 1455 $w$ , 1370 $w$ , 1350 $w$ , 1255 $w$  (br), 1170 $w$ .  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ): 3.26 ( $t$ ,  $J = 7.0$ ,  $\text{CH}_2\text{N}_3$ ); 3.19 ( $t$ ,  $J = 7.0$ ,  $\text{CH}_2\text{I}$ ); 1.82 ( $p$ ,  $J \approx 7.2$ ,  $\text{CH}_2$ ); 1.60 ( $p$ ,  $J \approx 7.3$ ,  $\text{CH}_2$ ); 1.45–1.25 ( $m$ , 7  $\text{CH}_2$ ).  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ): 51.4 ( $t$ ,  $\text{CH}_2\text{N}_3$ ); 33.5, 30.4 (2 $t$ , 2  $\text{CH}_2$ ); 29.30 ( $t$ , 2  $\text{CH}_2$ ); 29.27, 29.0, 28.8, 28.4, 26.6 (5 $t$ , 5  $\text{CH}_2$ ); 7.1 ( $t$ ,  $\text{CH}_2\text{I}$ ). CI-MS ( $\text{NH}_3$ ): 324 (14,  $[\text{M}+1]^+$ ), 296 (100,  $[\text{M}+1-\text{N}_2]^+$ ). Anal. Calcd for  $\text{C}_{11}\text{H}_{22}\text{IN}_3$ : C, 40.88; H, 6.86; I, 13.00; N, 39.26. Found: C, 40.86; H, 6.61; I, 12.82; N, 39.05.

*10-Azidodecyl iodide (12c).* From 10-azidodecan-1-ol (1.45 g, 7.3 mmol) in  $\text{CHCl}_3$  (35 mL), FMPT (4.22 g, 14.6 mmol), and TEA (1.52 g, 10.9 mmol), and then NaI (2.18 g, 14.6 mmol) in acetone (50 mL). Yield: 1.11 g (49%). Colorless oil. IR ( $\text{CHCl}_3$ ): 3000 $m$ , 2930 $s$ , 2860 $s$ , 2100 $s$ , 1465 $m$ , 1455 $m$ , 1430 $w$ , 1370 $w$ , 1350 $m$ , 1295 $m$ , 1285 $m$ , 1260 $m$  (br), 1175 $m$ , 1130 $w$ , 1100 $w$ , 890 $w$ .  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ): 3.26 ( $t$ ,  $J = 6.9$ ,  $\text{CH}_2\text{N}_3$ ); 3.19 ( $t$ ,  $J = 7.0$ ,  $\text{CH}_2\text{I}$ ); 1.90–1.75 ( $m$ ,  $\text{CH}_2$ ); 1.70–1.55 ( $m$ ,  $\text{CH}_2$ ); 1.40–1.25 ( $m$ , 6  $\text{CH}_2$ ).  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ): 62.8 ( $t$ ,  $\text{CH}_2\text{O}$ ); 51.4 ( $t$ ,  $\text{CH}_2\text{N}_3$ ); 33.5, 30.4, 29.3, 29.2, 28.4, 27.8, 26.6 (8 $t$ , 8  $\text{CH}_2$ ); 7.1 ( $t$ ,  $\text{CH}_2\text{I}$ ). CI-MS ( $\text{NH}_3$ ): 327 (12,  $[\text{M}+18]^+$ ), 282 (20,  $[\text{M}+1-\text{N}_2]^+$ ), 154 (100). Anal. Calcd for  $\text{C}_{10}\text{H}_{20}\text{IN}_3$ : C, 38.85; H, 6.52; I, 41.04; N, 13.59. Found: C, 39.08; H, 6.37; I, 40.71; N, 13.35.

*Alkylations of 1,3-oxazol-5(4H)-one (11) with  $\omega$ -azidoalkyl iodides (12). General procedure.* To a solution of LDA in a mixture of THF and HMPT between  $-110$  and  $-60$  °C was added a solution of **11** in THF. After addition of **12**, the temperature was increased to  $15$ – $20$  °C and the mixture stirred for  $5$ – $16$  h. Then, the mixture was extracted with cold water (3x) and Et<sub>2</sub>O, and the organic phase was dried over MgSO<sub>4</sub>. Filtration, evaporation, and FCC (SiO<sub>2</sub>, Et<sub>2</sub>O/hexane) gave mixtures of **13** and **14**.

*4-(12-Azidododecyl)-4-benzyl-2-phenyl-1,3-oxazol-5(4H)-one (13a) and 5-[(12-Azidododecyl)oxy]-4-benzyl-2-phenyl-1,3-oxazole (14a).* From **11** (1.00 g, 3.99 mmol) in THF (7 mL), LDA (4.4 mmol) in THF (7 mL) and HMPT (4 mL), and **12a** (1.50 g, 4.40 mmol) in THF (7 mL). FCC gave 0.44 g (24%) of **13a** and 0.57 g (26%) of a *ca.* 6:11 mixture of **13a** and **14a** as colorless oils. Data of **13a**: IR (CHCl<sub>3</sub>): 3060<sub>w</sub>, 3030<sub>w</sub>, 3010<sub>w</sub>, 2930<sub>s</sub>, 2860<sub>m</sub>, 2100<sub>s</sub>, 1815<sub>s</sub>, 1655<sub>s</sub>, 1605<sub>w</sub>, 1580<sub>w</sub>, 1495<sub>w</sub>, 1465<sub>w</sub>, 1450<sub>m</sub>, 1320<sub>m</sub>, 1290<sub>m</sub>, 1050<sub>m</sub>, 970<sub>m</sub>, 700<sub>s</sub>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.90–7.80 (*m*, 2 arom. H); 7.55–7.50 (*m*, 1 arom. H); 7.45–7.40 (*m*, 2 arom. H); 7.20–7.10 (*m*, 5 arom. H); 3.30–3.15 (*m*, CH<sub>2</sub>N<sub>3</sub>); 3.22, 3.14 (*AB*, *J* = 13.4, PhCH<sub>2</sub>); 2.05–1.95 (*m*, CH<sub>2</sub>); 1.65–1.50 (*m*, 2 CH<sub>2</sub>); 1.40–1.10 (*m*, 8 CH<sub>2</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 179.6 (*s*, CO); 159.6 (*s*, CN); 134.3 (*s*, 1 arom. C); 132.3 (*d*, 1 arom. CH); 130.0, 128.5, 127.9, 127.6 (4*d*, 2 arom. CH each); 127.0 (*d*, 1 arom. CH); 125.7 (*s*, 1 arom. C); 74.7 (*s*, C(4)); 51.3 (*t*, CH<sub>2</sub>N<sub>3</sub>); 43.7 (*t*, PhCH<sub>2</sub>); 37.3 (*t*, CH<sub>2</sub>); 29.3 (*t*, 5 CH<sub>2</sub>); 29.1, 29.0, 28.7, 26.6, 23.9 (5*t*, 5 CH<sub>2</sub>). CI-MS (NH<sub>3</sub>): 461 (100, [*M*+1]<sup>+</sup>), 433 (26, [*M*+1–N<sub>2</sub>]<sup>+</sup>).

Data of **14a** (from the mixture): <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.95–7.85 (*m*, 2 arom. H); 7.30–7.25 (*m*, 8 arom. H); 4.11 (*t*, *J* = 6.6, CH<sub>2</sub>O); 3.83 (*s*, PhCH<sub>2</sub>); 1.80–1.65 (*m*, CH<sub>2</sub>).

*4-(11-Azidoundecyl)-4-benzyl-2-phenyl-1,3-oxazol-5(4H)-one (13b) and 5-[(11-Azidoundecyl)oxy]-4-benzyl-2-phenyl-1,3-oxazole (14b).* From **11** (0.99 g, 3.94 mmol) in THF (7 mL), LDA (4.1 mmol) in THF (7 mL) and HMPT (4 mL), and **12b** (1.40 g, 4.33 mmol) in THF (7 mL). Yield: 1.14 g (65%) of an oily 19:1 mixture of **13b** and **14b**. Data of this mixture: IR (CHCl<sub>3</sub>): 3060<sub>w</sub>, 3030<sub>w</sub>, 3010<sub>w</sub>, 2930<sub>s</sub>, 2860<sub>s</sub>, 2100<sub>s</sub>, 1815<sub>s</sub>, 1655<sub>s</sub>, 1600<sub>w</sub>, 1580<sub>w</sub>, 1495<sub>m</sub>, 1465<sub>w</sub>, 1450<sub>m</sub>, 1320<sub>m</sub>, 1290<sub>s</sub>, 1255<sub>m</sub>, 1045<sub>m</sub>, 1025<sub>m</sub>, 970<sub>m</sub>, 895<sub>m</sub>, 700<sub>s</sub>. EI-MS: 446 (4, *M*<sup>+</sup>), 418 (5), 355 (12), 285 (100), 251 (32). Anal. Calcd for C<sub>27</sub>H<sub>34</sub>N<sub>4</sub>O: C, 72.62; H, 7.67; N, 12.55. Found: C, 72.40; H, 7.81; N, 12.81. Data of **13b** (from the mixture): <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.90–7.80 (*m*, 2 arom. H); 7.60–7.50 (*m*, 1 arom. H); 7.45–7.35 (*m*, 2 arom. H); 7.20–7.10 (*m*, 5 arom. H); 3.24 (*t*, *J* = 7.0, CH<sub>2</sub>N<sub>3</sub>); 3.22, 3.14 (*AB*, *J* = 13.3, PhCH<sub>2</sub>); 2.05–1.95 (*m*, CH<sub>2</sub>); 1.65–1.50 (*m*, CH<sub>2</sub>); 1.45–1.10 (*m*, 8 CH<sub>2</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 179.6 (*s*, CO); 159.6 (*s*, CN); 134.3 (*s*, 1 arom. C); 132.3 (*d*, 1 arom. CH); 130.0, 128.5, 127.9, 127.6 (4*d*, 2 arom. CH each); 127.0 (*d*, 1 arom. CH); 125.7 (*s*, 1 arom. C); 74.7 (*s*, C(4)); 51.3 (*t*, CH<sub>2</sub>N<sub>3</sub>); 43.7 (*t*, PhCH<sub>2</sub>); 37.3 (*t*, CH<sub>2</sub>); 29.2 (*t*, 4 CH<sub>2</sub>); 29.1, 29.0, 28.7, 26.6, 23.9 (5*t*, 5 CH<sub>2</sub>).

Data of **14b** (from the mixture):  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 7.95–7.90 (*m*, 2 arom. H); 7.30–7.25 (*m*, 8 arom. H); 4.11 (*t*,  $J = 6.6$ ,  $\text{CH}_2\text{O}$ ); 3.84 (*s*,  $\text{PhCH}_2$ ); 2.75–2.65 (*m*,  $\text{CH}_2$ ); 2.50–2.35 (*m*,  $\text{CH}_2$ ).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 128.0, 127.7, 127.0 (3*d*, 2 arom. CH each); 38.4 (*t*,  $\text{CH}_2$ ).

*4-(10-Azidodecyl)-4-benzyl-2-phenyl-1,3-oxazol-5(4H)-one* (**13c**) and *5-[(10-Azidodecyl)oxy]-4-benzyl-2-phenyl-1,3-oxazole* (**14c**). From **11** (1.00 g, 3.98 mmol) in THF (8 mL) and HMPT (4 mL), with LDA (4.3 mmol), and **12c** (1.40 g, 4.53 mmol) in THF (7 mL). Yield: 1.06 g (61%) of an oily 10:1 mixture of **13c** and **14c**. Data of this mixture: IR ( $\text{CHCl}_3$ ): 3060*w*, 3030*w*, 3000*w*, 2990*w*, 2930*s*, 2860*m*, 2100*s*, 1815*s*, 1655*s*, 1600*w*, 1580*w*, 1500*w*, 1470*w*, 1450*m*, 1440*w*, 1320*m*, 1290*m*, 1250*m*, 1045*m*, 1025*m*, 980*m*, 895*w*, 700*s*. CI-MS ( $\text{NH}_3$ ): 433 (100,  $[\text{M}+1]^+$ ), 405 (7), 250 (15). Anal. Calcd for  $\text{C}_{26}\text{H}_{32}\text{N}_4\text{O}$ : C, 72.19; H, 7.46; N, 12.95. Found: C, 72.38; H, 7.32; N, 12.95. Data of **13c** (from the mixture):  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 7.90–7.80 (*m*, 2 arom. H); 7.55–7.45 (*m*, 1 arom. H); 7.45–7.30 (*m*, 2 arom. H); 7.15–7.10 (*m*, 5 arom. H); 3.24 (*t*,  $J = 6.9$ ,  $\text{CH}_2\text{N}_3$ ); 3.21, 3.14 (*AB*,  $J = 13.5$ ,  $\text{PhCH}_2$ ); 2.05–1.90 (*m*,  $\text{CH}_2$ ); 1.60–1.50 (*m*,  $\text{CH}_2$ ); 1.25–1.20 (*m*, 7  $\text{CH}_2$ ).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 179.5 (*s*, CO); 159.6 (*s*, CN); 134.3 (*s*, 1 arom. C); 132.2 (*d*, 1 arom. CH); 129.9, 128.5, 127.9, 127.5 (4*d*, 2 arom. CH each); 126.9 (*d*, 1 arom. CH); 125.6 (*s*, 1 arom. C); 74.6 (*s*, C(4)); 51.2 (*t*,  $\text{CH}_2\text{N}_3$ ); 43.6 (*t*,  $\text{PhCH}_2$ ); 37.2 (*t*,  $\text{CH}_2$ ); 29.2 (*t*,  $\text{CH}_2$ ); 29.1 (*t*, 2  $\text{CH}_2$ ), 29.0, 28.8, 28.6, 26.5, 23.8 (5*t*, 5  $\text{CH}_2$ ).

Data of **14c** (from the mixture):  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 7.95–7.90 (*m*, 2 arom. H); 7.45–7.35 (*m*, 3 arom. H); 7.35–7.30 (*m*, 3 arom. H); 7.30–7.05 (*m*, 2 arom. H); 4.11 (*t*,  $J = 6.6$ ,  $\text{CH}_2\text{O}$ ); 3.84 (*s*,  $\text{PhCH}_2$ ); 2.45–2.35 (*m*,  $\text{CH}_2$ ); 1.75–1.60 (*m*, 1 H); 1.60–1.45 (*m*,  $\text{CH}_2$ ); 1.45–1.05 (*m*, 11 H).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 128.2, 128.1, 127.7, 125.2 (4*d*, 2 arom. CH each); 74.5 (*t*,  $\text{CH}_2$ ).

*Synthesis of N-[ω-azido-1-benzyl-1-(N,N-dimethylcarbamoyl)alkyl]benzamides (15). General procedure.*

To a solution of the mixture of **13** and **14** in acetonitrile was added dropwise condensed dimethylamine and the mixture stirred at rt for 2–5 h. The product was purified by FCC ( $\text{Et}_2\text{O}$ /hexane 3:2).

*N-[13-Azido-1-benzyl-1-(N,N-dimethylcarbamoyl)tridecyl]benzamide (15a)*. From **13a/14a** (0.50 g, 1.1 mmol) in acetonitrile (5 mL). FCC gave 0.45 g (96%) of **15a** as a colorless thick oil. IR ( $\text{CHCl}_3$ ): 3360*w*, 3060*w*, 3030*w*, 3000*m*, 2930*s*, 2860*m*, 2100*s*, 1655*s*, 1625*s*, 1605*m*, 1580*w*, 1505*s*, 1480*s*, 1460*m*, 1455*m*, 1400*m*, 1350*w*, 1255*m*, 1150*w*, 1105*w*, 1080*w*, 1055*w*, 1030*w*, 880*w*, 700*m*.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 8.00 (br. *s*, NH); 7.75–7.65 (*m*, 2 arom. H); 7.50–7.45 (*m*, 1 arom. H); 7.45–7.35 (*m*, 2 arom. H); 7.20–7.15 (*m*, 3 arom. H); 7.05–6.95 (*m*, 2 arom. H); 4.13, 3.22 (*AB*,  $J = 14.1$ ,  $\text{PhCH}_2$ ); 3.50–2.90 (br. *s*,  $\text{Me}_2\text{N}$ ); 3.25 (*t*,  $J = 7.0$ ,  $\text{CH}_2\text{N}_3$ ); 3.15–2.90 (*m*, 1 H); 2.25–1.90 (*m*, 1 H); 1.65–1.50 (*m*, 2  $\text{CH}_2$ ); 1.45–1.20 (*m*, 8  $\text{CH}_2$ ).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 171.1, 165.7 (2*s*, 2 CO); 136.5, 135.7 (2*s*, 2 arom. C); 131.0 (*d*, 1 arom. CH); 129.4, 129.0, 128.3, 126.7 (4*d*, 2 arom. CH each); 126.6 (*d*, 1 arom. CH); 66.2 (*s*,  $\text{C}_q$ ); 51.3 (*t*,  $\text{CH}_2\text{N}_3$ ); 38.8 (*t*,  $\text{PhCH}_2$ ); 38.5 (*q*,  $\text{Me}_2\text{N}$ ); 33.7 (*t*,  $\text{CH}_2$ ); 29.4 (*t*, 6  $\text{CH}_2$ ); 29.0, 28.7, 26.6, 24.3 (4*t*, 4  $\text{CH}_2$ ). CI-MS ( $\text{NH}_3$ ):

506 (100,  $[M+1]^+$ ), 478 (85,  $[M+1-N_2]^+$ ), 461 (70). Anal. Calcd for  $C_{30}H_{43}N_5O_2$ : C, 71.25; H, 8.57; N, 13.85. Found: C, 71.08; H, 8.31; N, 13.68.

*N*-[12-Azido-1-benzyl-1-(*N,N*-dimethylcarbamoyl)dodecyl]benzamide (**15b**). From **13b/14b** (0.20 g, 0.44 mmol) in acetonitrile (2 mL). FCC gave 0.19 g (94%) of **15b** as a colorless thick oil. IR ( $CHCl_3$ ): 3660 *w*, 3240 *w*, 3100 *w*, 3080 *w*, 3060 *w*, 3020 *w*, 3000 *w*, 2930 *s*, 2860 *s*, 2100 *s*, 1655 *m*, 1625 *s*, 1605 *w*, 1580 *w*, 1505 *s*, 1480 *s*, 1470 *m*, 1455 *m*, 1395 *m*, 1350 *w*, 1300 *w*, 1255 *m*, 1210 *w*, 1150 *w*, 1110 *w*, 1080 *w*, 1055 *w*, 1030 *w*, 1000 *w*, 880 *w*, 700 *m*.  $^1H$ -NMR ( $CDCl_3$ ): 8.01 (br. *s*, NH); 7.75–7.70 (*m*, 2 arom. H); 7.50–7.45 (*m*, 1 arom. H); 7.45–7.35 (*m*, 2 arom. H); 7.20–7.15 (*m*, 3 arom. H); 7.05–7.00 (*m*, 2 arom. H); 4.14, 3.23 (*AB*,  $J = 14.2$ ,  $PhCH_2$ ); 3.60–2.80 (br. *s*,  $Me_2N$ ); 3.25 (*t*,  $J = 6.9$ ,  $CH_2N_3$ ); 3.10–2.95 (*m*, 1 H); 2.05–1.90 (*m*, 1 H); 1.50–1.20 (*m*, 9  $CH_2$ ).  $^{13}C$ -NMR ( $CDCl_3$ ): 171.1, 165.6 (2*s*, 2 CO); 136.5, 135.7 (2*s*, 2 arom. C); 130.9 (*d*, 1 arom. CH); 129.4, 128.3, 127.9, 126.7 (4*d*, 2 arom. CH each); 126.6 (*d*, 1 arom. CH); 66.1 (*s*,  $C_q$ ); 51.3 (*t*,  $CH_2N_3$ ); 38.7 (*t*,  $PhCH_2$ ); 38.4 (*q*,  $Me_2N$ ); 33.6, 29.3 (2*t*, 2  $CH_2$ ); 29.2 (*t*, 4  $CH_2$ ); 28.9, 28.6, 26.5, 24.2 (4*t*, 4  $CH_2$ ). CI-MS ( $NH_3$ ): 492 (8,  $[M+1]^+$ ), 464 (8,  $[M+1-N_2]^+$ ), 447 (100), 419 (5). Anal. Calcd for  $C_{29}H_{41}N_5O_2$ : C, 70.84; H, 8.41; N, 14.24. Found: C, 71.01; H, 8.20; N, 14.43.

*N*-[11-Azido-1-benzyl-1-(*N,N*-dimethylcarbamoyl)undecyl]benzamide (**15c**). From **13c/14c** (0.84 g, 1.94 mmol) in acetonitrile (10 mL). FCC gave 0.76 g (91%) of **15c** as a colorless thick oil. IR ( $CHCl_3$ ): 3660 *w*, 3355 *m*, 3060 *w*, 3030 *w*, 3000 *m*, 2930 *s*, 2860 *m*, 2100 *s*, 1655 *s*, 1625 *s*, 1605 *m*, 1580 *m*, 1505 *s*, 1480 *s*, 1455 *m*, 1400 *s*, 1350 *w*, 1300 *w*, 1255 *m*, 1180 *w*, 1115 *m*, 1080 *w*, 1055 *w*, 1030 *w*, 1000 *w*, 880 *w*, 700 *m*.  $^1H$ -NMR ( $CDCl_3$ ): 8.00 (br. *s*, NH); 7.75–7.70 (*m*, 2 arom. H); 7.50–7.40 (*m*, 1 arom. H); 7.40–7.30 (*m*, 2 arom. H); 7.20–7.10 (*m*, 3 arom. H); 7.00–6.90 (*m*, 2 arom. H); 4.12, 3.22 (*AB*,  $J = 14.0$ ,  $PhCH_2$ ); 3.50–2.85 (br. *s*,  $Me_2N$ ); 3.24 (*t*,  $J = 7.0$ ,  $CH_2N_3$ ); 3.10–2.90 (*m*, 1 H); 2.00–1.85 (*m*, 1 H); 1.60–1.50 (*m*,  $CH_2$ ); 1.50–1.20 (*m*, 7  $CH_2$ ).  $^{13}C$ -NMR ( $CDCl_3$ ): 170.9, 165.6 (2*s*, 2 CO); 136.4, 135.5 (2*s*, 2 arom. C); 130.9 (*d*, 1 arom. CH); 129.4, 128.2, 127.8, 126.6 (4*d*, 2 arom. CH each); 126.4 (*d*, 1 arom. CH); 65.8 (*s*,  $C_q$ ); 51.1 (*t*,  $CH_2N_3$ ); 38.5 (*t*,  $PhCH_2$ ); 38.3 (*q*,  $Me_2N$ ); 33.4, 29.2 (2*t*, 2  $CH_2$ ); 29.1 (*t*, 3  $CH_2$ ); 28.8, 28.5, 26.4, 24.1 (4*t*, 4  $CH_2$ ). CI-MS ( $NH_3$ ): 450 (8,  $[M+1-N_2]^+$ ), 433 (100), 405 (5). Anal. Calcd for  $C_{28}H_{39}N_5O_2$ : C, 70.41; H, 8.23; N, 14.66. Found: C, 70.63; H, 8.20; N, 14.44.

*Synthesis of N-[ω-amino-1-benzyl-1-(N,N-dimethylcarbamoyl)alkyl]benzamides (16). General procedure.* To a solution of **15** (1 equiv.) in THF under  $N_2$  atmosphere at rt was added  $Et_3P$  (1.4 equiv.) and the mixture stirred at rt for 2.5 h. The spontaneous elimination of  $N_2$  ceased after *ca.* 20 min. After addition of water (2.8 equiv.) and stirring for 2 h, the mixture was poured into  $CHCl_3/MeOH/NH_3$  (85:14:1), filtered through  $SiO_2$ , and evaporated. The product contained traces of  $Et_3PO$ , which could not be removed.

*N*-[13-Amino-1-benzyl-1-(*N,N*-dimethylcarbamoyl)tridecyl]benzamide (**16a**). From **15a** (0.35 g, 0.69 mmol), Et<sub>3</sub>P (0.14 mL, 0.97 mmol), and H<sub>2</sub>O (0.035 g, 1.94 mmol). Yield: 0.33 g (95%) of **16a** as a colorless thick oil. IR (CHCl<sub>3</sub>): 3620w (br), 3360w (br), 3060w, 3030w, 3000m, 2930s, 2860m, 1660m, 1625s, 1605m, 1580w, 1505s, 1480s, 1455m, 1400m, 1250w, 1220w, 1180w, 1150w, 1110m, 1080w, 1050w, 1030w, 880w, 700m. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.99 (br. s, NH); 7.75–7.65 (m, 2 arom. H); 7.50–7.45 (m, 1 arom. H); 7.45–7.35 (m, 2 arom. H); 7.20–7.15 (m, 3 arom. H); 7.05–6.95 (m, 2 arom. H); 4.12, 3.22 (AB, *J* = 14.2, PhCH<sub>2</sub>); 3.60–2.80 (br. s, Me<sub>2</sub>N); 3.05–2.95 (m, 1 H); 2.67 (t, *J* = 7.0, CH<sub>2</sub>N); 2.00–1.90 (m, 1 H); 1.35–1.15 (m, 10 CH<sub>2</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 170.8, 165.6 (2s, 2 CO); 136.3, 135.2 (2s, 2 arom. C); 130.8 (d, 1 arom. CH); 129.4, 128.1, 127.7, 126.5 (4d, 2 arom. CH each); 126.3 (d, 1 arom. CH); 65.4 (s, C<sub>q</sub>); 41.1 (t, CH<sub>2</sub>N); 38.2 (t, PhCH<sub>2</sub>); 38.1 (q, Me<sub>2</sub>N); 33.2 (t, CH<sub>2</sub>); 29.1 (t, 5 CH<sub>2</sub>); 29.0 (t, 2 CH<sub>2</sub>); 26.4, 23.9, 18.6 (3t, 3 CH<sub>2</sub>). ESI-MS (MeOH): 480 (100, [*M*+1]<sup>+</sup>).

*N*-[12-Amino-1-benzyl-1-(*N,N*-dimethylcarbamoyl)dodecyl]benzamide (**16b**). From **15b** (0.24 g, 0.49 mmol), Et<sub>3</sub>P (0.11 mL, 0.75 mmol), and H<sub>2</sub>O (0.025 g, 1.40 mmol). Yield: 0.23 g (quant.) of **16b** as a colorless thick oil. IR (CHCl<sub>3</sub>): 3360m (br), 3070w, 3030w, 3000m, 2930s, 2860m, 1660s, 1625s, 1605m, 1580m, 1505s, 1480s, 1455m, 1400m, 1255w, 1180w, 1150w, 1110w, 1080w, 1050w, 1030w, 880w, 705m. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.99 (br. s, NH); 7.75–7.70 (m, 2 arom. H); 7.50–7.35 (m, 2 arom. H); 7.20–7.15 (m, 3 arom. H); 7.05–6.95 (m, 3 arom. H); 4.12, 3.22 (AB, *J* = 14.1, PhCH<sub>2</sub>); 3.19 (br. s, Me<sub>2</sub>N); 3.05–2.90 (m, 1 H); 2.70 (t, *J* = 6.4, CH<sub>2</sub>N); 2.05–1.80 (m, 1 H); 1.95 (br. s, NH<sub>2</sub>); 1.50–1.40 (m, CH<sub>2</sub>); 1.40–1.00 (m, 8 CH<sub>2</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 171.1, 165.7 (2s, 2 CO); 136.5, 135.6 (2s, 2 arom. C); 131.0 (d, 1 arom. CH); 129.5, 128.3, 128.0, 126.7 (4d, 2 arom. CH each); 126.6 (d, 1 arom. CH); 66.1 (s, C<sub>q</sub>); 41.7 (t, CH<sub>2</sub>N); 38.7 (t, PhCH<sub>2</sub>); 38.5 (q, Me<sub>2</sub>N); 33.7, 32.7 (2t, 2 CH<sub>2</sub>); 29.4 (t, 2 CH<sub>2</sub>); 29.34 (t, 2 CH<sub>2</sub>); 29.30 (t, 2 CH<sub>2</sub>); 26.7, 24.2 (2t, 2 CH<sub>2</sub>). CI-MS (i-butane): 466 (100, [*M*+1]<sup>+</sup>).

*N*-[11-Amino-1-benzyl-1-(*N,N*-dimethylcarbamoyl)undecyl]benzamide (**16c**). From **15c** (0.57 g, 1.19 mmol), Et<sub>3</sub>P (0.27 mL, 1.83 mmol), and H<sub>2</sub>O (0.13 g, 7.22 mmol). Yield: 0.52 g (97%) of **16c** as a colorless thick oil. IR (CHCl<sub>3</sub>): 3360m, 3060w, 3000m, 2930s, 2860m, 1660s, 1625s, 1610m, 1580m, 1510s, 1480s, 1460m, 1400m, 1255w, 1215w, 1150m, 1110m, 1080w, 1055w, 1030w, 880w, 700m. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.99 (br. s, NH); 7.70–7.65 (m, 2 arom. H); 7.50–7.45 (m, 1 arom. H); 7.45–7.35 (m, 2 arom. H); 7.20–7.15 (m, 3 arom. H); 7.05–6.95 (m, 2 arom. H); 4.12, 3.22 (AB, *J* = 14.2, PhCH<sub>2</sub>); 3.19 (br. s, Me<sub>2</sub>N); 3.10–2.95 (m, 1 H); 2.65 (t, *J* = 6.9, CH<sub>2</sub>N); 2.05–1.90 (m, 1 H); 1.60–1.10 (m, 8 CH<sub>2</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 171.0, 165.6 (2s, 2 CO); 136.5, 135.6 (2s, 2 arom. C); 130.9 (d, 1 arom. CH); 129.4, 128.3, 127.9, 126.6 (4d, 2 arom. CH each); 126.5 (d, 1 arom. CH); 66.1 (s, C<sub>q</sub>); 42.0 (t, CH<sub>2</sub>N); 38.7 (t, PhCH<sub>2</sub>); 38.4 (q, Me<sub>2</sub>N); 33.6 (t, CH<sub>2</sub>); 29.3 (t, 3 CH<sub>2</sub>); 29.2 (t, 3 CH<sub>2</sub>); 26.7, 24.2 (2t, 2 CH<sub>2</sub>). CI-MS (NH<sub>3</sub>): 452 (100, [*M*+1]<sup>+</sup>).

*HCl catalyzed cyclization reactions with 16. General procedure.* Through a 1.9 mM solution of **16** in boiling toluene, dry HCl gas was bubbled for 1.5–2 h, and the boiling mixture stirred for 15 h. Evaporation of the solvent and FCC (Et<sub>2</sub>O/hexane 1:1) gave the lactam (**18**).

*N*-(3-Benzyl-2-oxo-1-azacyclopentadec-3-yl)benzamide (**18a**). From **16a** (0.20 g, 0.42 mmol) in toluene (373 mL). Yield: 0.048 g (27%) of **18a**. Colorless solid, mp 257.7–265.8 °C (decomp.). Crystals suitable for an X-ray crystal-structure determination were obtained from Et<sub>2</sub>O/hexane/CH<sub>2</sub>Cl<sub>2</sub>. IR (CHCl<sub>3</sub>): 3620<sub>w</sub> (br), 3450<sub>w</sub>, 3380<sub>w</sub>, 3100<sub>w</sub>, 3060<sub>w</sub>, 3030<sub>w</sub>, 3010<sub>w</sub>, 2940<sub>s</sub>, 2880<sub>w</sub>, 2860<sub>m</sub>, 1675<sub>m</sub>, 1650<sub>s</sub>, 1605<sub>w</sub>, 1580<sub>w</sub>, 1510<sub>w</sub>, 1485<sub>s</sub>, 1465<sub>m</sub>, 1455<sub>m</sub>, 1265<sub>m</sub>, 1230<sub>w</sub>, 1215<sub>w</sub>, 1205<sub>w</sub>, 1125<sub>m</sub> (br), 1050<sub>w</sub>, 1030<sub>w</sub>, 880<sub>w</sub>, 715<sub>m</sub>, 705<sub>m</sub>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.75–7.70 (*m*, 2 arom. H); 7.63 (*s*, NH); 7.50–7.45 (*m*, 1 arom. H); 7.45–7.35 (*m*, 2 arom. H); 7.20–7.15 (*m*, 3 arom. H); 7.10–7.00 (*m*, 2 arom. H); 5.80–5.30 (*m*, CH<sub>2</sub>NH); 3.85, 3.10 (*AB*, *J* = 13.8, PhCH<sub>2</sub>); 3.85–3.70 (*m*, 1 H of CH<sub>2</sub>N); 3.20–2.95 (*m*, 1 H of CH<sub>2</sub>N + 1 H); 1.80–1.00 (*m*, 21 H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 172.5, 166.5 (2<sub>s</sub>, 2 CO); 136.1, 135.4 (2<sub>s</sub>, 2 arom. C); 131.3 (*d*, 1 arom. CH); 129.8, 128.5, 128.2 (3<sub>d</sub>, 2 arom. CH each); 126.9 (*d*, 3 arom. CH); 67.4 (*s*, C<sub>q</sub>); 65.3 (*t*, CH<sub>2</sub>N); 41.9 (*t*, PhCH<sub>2</sub>); 39.7, 36.4, 29.7, 27.2, 27.0, 26.7, 26.4, 26.2, 25.8, 24.9, 23.2 (11<sub>t</sub>, 11 CH<sub>2</sub>). ESI-MS (MeOH): 480 (100, [*M*+2 Na]<sup>+</sup>), 466 (5, [*M*+MeOH]<sup>+</sup>), 435 (8, [*M*+1]<sup>+</sup>).

*N*-(3-Benzyl-2-oxo-1-azacyclotetradec-3-yl)benzamide (**18b**). From **16b** (0.07 g, 0.15 mmol) in toluene (100 mL). Yield: 0.019 g (30%) of pure **18b** (and 0.025 g of a mixture of **18b** and Me<sub>2</sub>NH<sub>2</sub>Cl). Colorless solid, mp 267.0–268.0 °C (decomp.). Crystals suitable for an X-ray crystal-structure determination were obtained from hexane/CH<sub>2</sub>Cl<sub>2</sub>. IR (CHCl<sub>3</sub>): 3450<sub>w</sub>, 3370<sub>w</sub>, 3000<sub>w</sub>, 2995<sub>w</sub>, 2935<sub>s</sub>, 2860<sub>m</sub>, 1670<sub>m</sub>, 1650<sub>s</sub>, 1605<sub>w</sub>, 1580<sub>w</sub>, 1510<sub>s</sub>, 1485<sub>s</sub>, 1460<sub>m</sub>, 1445<sub>w</sub>, 1365<sub>w</sub>, 1355<sub>w</sub>, 1130<sub>w</sub>, 1030<sub>w</sub>, 910<sub>w</sub>, 880<sub>w</sub>, 700<sub>m</sub>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.75–7.70 (*m*, 2 arom. H); 7.64 (br. *s*, NH); 7.50–7.35 (*m*, 3 arom. H); 7.25–7.15 (*m*, 3 arom. H); 7.10–7.05 (*m*, 2 arom. H); 5.91 (br *t*, CH<sub>2</sub>NH); 3.90, 3.09 (*AB*, *J* = 13.8, PhCH<sub>2</sub>); 3.75–3.65 (*m*, 1 H of CH<sub>2</sub>N); 3.15–2.95 (*m*, 1 H of CH<sub>2</sub>N + 1 H); 1.80–1.05 (*m*, 19 H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 172.4, 166.3 (2<sub>s</sub>, 2 CO); 136.0, 135.4 (2<sub>s</sub>, 2 arom. C); 131.2 (*d*, 1 arom. CH); 129.7, 128.4, 128.0 (3<sub>d</sub>, 2 arom. CH each); 126.8 (*d*, 3 arom. CH); 65.2 (*s*, C<sub>q</sub>); 61.8 (*t*, CH<sub>2</sub>N); 39.3 (*t*, PhCH<sub>2</sub>); 36.2, 27.8, 26.0, 25.9, 25.7, 25.0, 23.2, 23.0, 22.9, 21.2 (10<sub>t</sub>, 10 CH<sub>2</sub>). CI-MS (i-butane): 421 (100, [*M*+1]<sup>+</sup>).

*N*-(3-Benzyl-2-oxo-1-azacyclotridec-3-yl)benzamide (**18c**). From **16c** (0.33 g, 0.80 mmol) in toluene (300 mL). Yield: 0.034 g (11%) of **18c**. Colorless solid, mp 250.0–251.0 °C (decomp.). IR (CHCl<sub>3</sub>): 3440<sub>w</sub>, 3360<sub>w</sub>, 3050<sub>w</sub>, 2995<sub>w</sub>, 2920<sub>s</sub>, 2850<sub>m</sub>, 1670<sub>m</sub>, 1645<sub>s</sub>, 1600<sub>w</sub>, 1575<sub>w</sub>, 1510<sub>s</sub>, 1480<sub>s</sub>, 1460<sub>m</sub>, 1440<sub>m</sub>, 1340<sub>w</sub>, 1320<sub>w</sub>, 1290<sub>w</sub>, 1260<sub>w</sub>, 1140<sub>w</sub>, 1115<sub>m</sub>, 880<sub>w</sub>, 700<sub>m</sub>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.75–7.70 (*m*, 2 arom. H); 7.61 (br. *s*, NH); 7.50–7.45 (*m*, 1 arom. H); 7.45–7.35 (*m*, 2 arom. H); 7.20–7.10 (*m*, 3 arom. H); 7.10–7.05 (*m*, 2 arom. H); 5.79 (br *d*, CH<sub>2</sub>NH); 3.90, 3.10 (*AB*, *J* = 13.9, PhCH<sub>2</sub>); 3.80–3.70 (*m*, 1 H of

CH<sub>2</sub>N); 3.20–2.95 (*m*, 1 H of CH<sub>2</sub>N + 1 H); 1.85–1.70 (*m*, 1H); 1.70–1.15 (*m*, 16 H). CI-MS (i-butane): 407 (100, [*M*+1]<sup>+</sup>).

*12-Amino-2-benzamido-2-benzyl-dodecanoic acid (19c)*. An analogous experiment with **16c** in non-dried toluene gave 51% of **19c**. Colorless solid, mp 144.0–145.0 °C (decomp.). IR (KBr): 3680–2340s (br), 3420*m*, 3350*m*, 3050*m*, 2920*s*, 2850*s*, 1660*s*, 1640*s*, 1630*s*, 1600*s*, 1570*s*, 1510*s*, 1475*s*, 1455*s*, 1440*s*, 1385*s*, 1325*m*, 1310*m*, 1180*w*, 1115*w*, 1070*w*, 1030*w*, 1000*w*, 875*w*, 700*s*. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.74 (*s*, NH); 7.65–7.55 (*m*, 2 arom. H); 7.45–7.30 (*m*, 3 arom. H); 7.15–7.05 (*m*, 5 arom. H); 3.71, 3.10 (*AB*, *J* = 13.1, PhCH<sub>2</sub>); 3.60–3.00 (*m*, NH<sub>2</sub>); 2.76 (*t*-like, *J* ≈ 7.6, CH<sub>2</sub>N); 2.65–2.60 (*m*, 1 H); 1.95–1.80 (*m*, 1H); 1.75–1.05 (*m*, 8 CH<sub>2</sub>). <sup>13</sup>C-NMR (CD<sub>3</sub>OD): 178.5, 168.5 (2*s*, 2 CO); 139.5, 137.1 (2*s*, 2 arom. C); 132.3 (*d*, 1 arom. CH); 130.9, 129.6, 128.7, 127.5 (4*d*, 2 arom. CH each); 127.1 (*d*, 1 arom. CH); 68.5 (*s*, C<sub>q</sub>); 42.1 (*t*, CH<sub>2</sub>N); 40.6 (*t*, PhCH<sub>2</sub>); 36.9, 30.5, 30.3 (3*t*, 3 CH<sub>2</sub>); 30.1 (*t*, 2 CH<sub>2</sub>); 30.0, 28.4, 27.3, 25.6 (4*t*, 4 CH<sub>2</sub>). ESI-MS (MeOH): 463 (18, [*M*+K]<sup>+</sup>), 447 (100, [*M*+Na]<sup>+</sup>), 425 (35, [*M*+1]<sup>+</sup>).

*BF<sub>3</sub> catalyzed reactions with 16a*. To a solution of **16a** (0.15 g, 0.31 mmol) in toluene (60 mL) at 100 °C, BF<sub>3</sub>·Et<sub>2</sub>O (0.47 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added and the mixture stirred for 19 h. Evaporation of the solvent and FCC (Et<sub>2</sub>O/hexane 1:1 and then CHCl<sub>3</sub>/MeOH/NH<sub>3</sub> 85:14:1) gave lactam (**18a**) (0.009 g, 7%), an unstable product (**20a**) (0.013 g, 10%), azlactone (**17a**) (0.040 g, 30%), and the acid (**21a**) (0.049 g, 35%). The unstable **20a** converted into **17a**.

*4-(12-Aminododecyl-4-benzyl-1,3-oxazol-5(4H)-one (17a)*. Colorless oil. IR (CHCl<sub>3</sub>): 3650*w*, 3580*w*, 3360*w*, 3260*w*, 3020*m*, 2920*s*, 2850*m*, 1810*m*, 1655*s*, 1600*w*, 1580*w*, 1510*m*, 1490*m*, 1480*m*, 1450*m*, 1320*m*, 1290*m*, 1240*w*, 1130*m* (br), 1065*s*, 1040*s*, 1020*s*, 970*m*, 930*m*, 910*m*, 700*s*. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.85–7.80 (*m*, 2 arom. H); 7.60–7.50 (*m*, 1 arom. H); 7.50–7.35 (*m*, 2 arom. H); 7.15–7.05 (*m*, 5 arom. H); 3.90–3.80 (*m*, NH<sub>2</sub>); 3.21, 3.14 (*AB*, *J* = 13.4, PhCH<sub>2</sub>); 3.00–2.85 (*m*, 2 H); 2.05–1.95 (*m*, 2 H); 1.75–1.55 (*m*, 5 H); 1.40–1.10 (*m*, 15 H). CI-MS (NH<sub>3</sub>): 435 (100, [*M*+1]<sup>+</sup>).

*2-Amino-14-benzamido-2-benzyl-tetradecanoic acid (21a)*. Colorless solid, mp 121.7–122.2 °C. IR (CHCl<sub>3</sub>): 3700–3210*m*, 3210–2200*s*, 3110*m*, 3050*m*, 3020*m*, 2920*s*, 2840*s*, 1650*m*, 1640*s*, 1630*s*, 1575*s*, 1510*s*, 1480*s*, 1465*s*, 1450*m*, 1440*m*, 1385*s*, 1325*w*, 1310*w*, 1180*w*, 1115*w*, 1075*w*, 1025*w*, 1000*w*, 875*w*, 700*m*. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.66 (*s*, NH); 7.55–7.50 (*m*, 2 arom. H); 7.40–7.35 (*m*, 1 arom. H); 7.35–7.25 (*m*, 2 arom. H); 7.10–7.00 (*m*, 5 arom. H); 3.70, 3.09 (*AB*, *J* = 13.1, PhCH<sub>2</sub>); 3.30–3.25 (*m*, 1 H); 2.80–2.75 (*m*, 2 H); 2.55–2.50 (*m*, 1 H); 1.90–1.50 (*m*, 2H); 1.40–1.00 (*m*, 18 H). CI-MS (NH<sub>3</sub>): 453 (100, [*M*+1]<sup>+</sup>), 435 (11, [*M*-H<sub>2</sub>O]<sup>+</sup>), 409 (100, [*M*-CO<sub>2</sub>]<sup>+</sup>).

*Methyl 2-amino-14-benzamido-2-benzyl-tetradecanoate (22a)*. In an analogous experiment, a solution of **16a** (0.15 g, 0.31 mmol) in toluene (62 mL) and BF<sub>3</sub>·Et<sub>2</sub>O (0.47 mmol) in CH<sub>2</sub>Cl<sub>2</sub> at 90 °C was stirred for 2 h. Then, MeOH (0.06 g, 1.88 mmol) was added and the mixture heated to reflux for 21 h. Evaporation



of the solvent and FCC (CHCl<sub>3</sub>/MeOH/NH<sub>3</sub> 85:14:1) gave 0.116 g (80%) of **22a**. Colorless thick oil. IR (CHCl<sub>3</sub>): 3400*m*(br), 3050*w*, 2980*m*, 2920*s*, 2850*s*, 1730*m*, 1660*s*, 1600*w*, 1580*w*, 1515*s*, 1485*s*, 1450*m*, 1370*w*, 1350*m*, 1240*m*, 1180*m*, 1170–1090*s*, 1070*s*, 1025*s*, 880*w*, 700*m*. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.70–7.65 (*m*, 2 arom. H); 7.55–7.45 (*m*, 1 arom. H); 7.45–7.35 (*m*, 2 arom. H); 7.20–7.15 (*m*, 3 arom. H); 7.05–6.95 (*m*, 2 arom. H); 6.96 (*s*, NH); 4.10–3.70 (*m*, NH<sub>2</sub>); 3.91, 3.16 (*AB*, *J* = 13.5, PhCH<sub>2</sub>); 3.82 (*s*, MeO); 2.92 (*t*, *J* = 7.7, CH<sub>2</sub>N); 2.85–2.70 (*m*, 1 H); 2.00–1.85 (*m*, 1 H); 1.65–1.55 (*m*, CH<sub>2</sub>); 1.40–1.10 (*m*, 9 CH<sub>2</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>): 173.9, 166.7 (2*s*, 2 CO); 136.3, 135.1 (2*s*, 2 arom. C); 131.4 (*d*, 1 arom. CH); 129.5, 128.5, 128.1, 126.6 (4*d*, 2 arom. CH each); 126.7 (*d*, 1 arom. CH); 66.4 (*s*, C<sub>q</sub>); 52.6 (*q*, MeO); 40.64, 40.60, 40.4, 35.1 (4*t*, 4 CH<sub>2</sub>); 29.4 (*t*, 3 CH<sub>2</sub>); 29.2 (*t*, 2 CH<sub>2</sub>); 29.0, 28.9, 26.3, 24.2 (4*t*, 4 CH<sub>2</sub>). CI-MS (NH<sub>3</sub>): 481 (5, [M+NH<sub>4</sub>]<sup>+</sup>), 467 (100, [M+1]<sup>+</sup>).

*BF<sub>3</sub> catalyzed reaction with 16c*. To a solution of **16c** (0.137 g, 0.30 mmol) in toluene (150 mL) at 100 °C, BF<sub>3</sub>.Et<sub>2</sub>O (0.30 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added and the mixture stirred for 13 h. Then, additional BF<sub>3</sub>.Et<sub>2</sub>O (0.30 mmol) was added, the mixture stirred at 100 °C for 7.5 h, diisopropyl(ethyl)amine (2 x 30 mmol) added, and the boiling mixture stirred for 13 h. Evaporation of the solvent and FCC (Et<sub>2</sub>O/hexane 1:1 and then CHCl<sub>3</sub>/MeOH/NH<sub>3</sub> 85:14:1) gave the lactam (**18c**) (0.010 g, 8%) and a less stable product (**20c**) (0.028 g, 23%).

*13-Benzyl-1-phenyl-15-oxa-2,16-diazabicyclo[12.2.1]octadecan-14-one (20c)*. Colorless oil, which slowly decomposed at rt. IR (CHCl<sub>3</sub>): 3660*w*, 3580*w*, 3350*w*, 3300*w*(br), 3010*w*, 2920*s*, 2850*m*, 1810*s*, 1650*s*, 1575*w*, 1490*w*, 1460*w*, 1450*m*, 1390*w*, 1320*m*, 1290*m*, 1225*w*, 1205*w*, 1130*s*(br), 1040*m*, 970*s*(br), 890*w*, 695*s*. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.85–7.80 (*m*, 2 arom. H); 7.60–7.45 (*m*, 1 arom. H); 7.45–7.35 (*m*, 2 arom. H); 7.20–7.10 (*m*, 5 arom. H); 7.10–6.60 (*m*, NH); 4.15–4.10 (*m*, NH); 3.20, 3.12 (*AB*, *J* = 13.3, PhCH<sub>2</sub>); 3.00–2.85 (*m*, CH<sub>2</sub>); 2.05–1.95 (*m*, CH<sub>2</sub>); 1.70–1.55 (*m*, CH<sub>2</sub>); 1.30–1.10 (*m*, 7 CH<sub>2</sub>). <sup>13</sup>C-NMR (CD<sub>3</sub>OD): 179.9 (*s*, CO); 134.4 (*s*, 1 arom. C); 132.5 (*d*, 1 arom. CH); 130.1, 128.7, 128.1, 127.7 (4*d*, 2 arom. CH each); 127.1 (*d*, 1 arom. CH); 125.7 (*s*, 1 arom. C); 94.2 (*s*, NCN); 74.9 (*s*, NC<sub>q</sub>); 43.8 (*t*, CH<sub>2</sub>N); 41.5 (*t*, PhCH<sub>2</sub>); 40.3, 37.4 (2*t*, 2 CH<sub>2</sub>); 29.3 (*t*, 3 CH<sub>2</sub>); 27.4, 26.3, 24.0, 19.0 (4*t*, 4 CH<sub>2</sub>). CI-MS (NH<sub>3</sub>): 407 (100, [M+1]<sup>+</sup>).

*X-Ray Crystal-Structure Determination of 18a and 18b (Figure 1).*<sup>63</sup> All measurements were made on a Rigaku AFC5R diffractometer using graphite-monochromated MoK<sub>α</sub> radiation ( $\lambda$  = 0.71073 Å) and a 12kW rotating anode generator. The intensities were corrected for Lorentz and polarization effects, but not for absorption. Equivalent reflections were merged. Data collection and refinement parameters are given below, and views of the molecules are shown in Figure 1. The structures of **18a** and **18b** were solved by direct methods using SHELXS86,<sup>64</sup> respectively, which revealed the positions of all non-hydrogen atoms.

In both cases, the macrocyclic ring is disordered and two sets of positions were defined for five and seven consecutive CH<sub>2</sub> groups, respectively. The site occupation factor of the major conformation of these groups refined to 0.662(4) and 0.667(5), respectively. Similarity restraints were applied to the chemically equivalent bond lengths and angles involving all disordered C-atoms, while neighboring atoms within and between each disordered conformation were restrained to have similar atomic displacement parameters. The non-hydrogen atoms were refined anisotropically. The amide H-atoms were placed in the positions indicated by difference electron density maps and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 $U_{eq}$  of its parent C-atom. The refinement of each structure was carried out on  $F^2$  by using full-matrix least-squares procedures, which minimized the function  $\sum w(F_o^2 - F_c^2)^2$ . Corrections for secondary extinction were not applied. Neutral atom scattering factors for non-H-atoms were taken from ref.<sup>65</sup>, and the scattering factors for H-atoms were taken from ref.<sup>66</sup>. Anomalous dispersion effects were included in  $F_c$ ; the values for  $f'$  and  $f''$  were those of ref.<sup>68</sup>. The values of the mass attenuation coefficients are those of ref.<sup>69</sup>. All calculations were performed using the SHELXL97 program.<sup>70</sup> Crystal data for **18a**: Crystallized from Et<sub>2</sub>O/hexane/CH<sub>2</sub>Cl<sub>2</sub>, C<sub>28</sub>H<sub>38</sub>N<sub>2</sub>O<sub>2</sub>,  $M = 434.60$ , colorless, prism, crystal dimensions 0.18 × 0.23 × 0.40 mm, monoclinic, space group  $C2/c$ ,  $Z = 8$ , reflections for cell determination 23,  $2\theta$  range for cell determination 21–37°,  $a = 26.026(5)$  Å,  $b = 10.833(3)$  Å,  $c = 21.330(4)$  Å,  $\beta = 119.83(1)^\circ$ ,  $V = 5217(2)$  Å<sup>3</sup>,  $D_X = 1.107$  g·cm<sup>-3</sup>,  $\mu(\text{MoK}\alpha) = 0.069$  mm<sup>-1</sup>,  $T = 295$  K,  $\omega$  scans,  $2\theta_{\text{max}} = 55^\circ$ , total reflections measured 6444, symmetry independent reflections 5989, reflections with  $I > 2\sigma(I)$  2327, reflections used in refinement 5989, parameters refined 370, restraints 223, final  $R$  (on  $F$ ;  $I > 2\sigma(I)$  reflections) = 0.0751,  $wR = 0.2682$  ( $w = [\sigma^2(F_o^2) + (0.1293P)^2]^{-1}$  where  $P = (F_o^2 + 2F_c^2)/3$ , goodness of fit 1.006, final  $\Delta_{\text{max}}/\sigma = 0.002$ ,  $\Delta\rho$  (max; min) = 0.33; -0.33 e Å<sup>-3</sup>.

Crystal data for **18b**: Crystallized from CH<sub>2</sub>Cl<sub>2</sub>/hexane, C<sub>27</sub>H<sub>36</sub>N<sub>2</sub>O<sub>2</sub>,  $M = 420.58$ , colorless, plate, crystal dimensions 0.10 × 0.35 × 0.47 mm, monoclinic, space group  $C2/c$ ,  $Z = 8$ , reflections for cell determination 23,  $2\theta$  range for cell determination 24–45°,  $a = 24.951(3)$  Å,  $b = 10.683(4)$  Å,  $c = 20.996(2)$  Å,  $\beta = 118.377(7)^\circ$ ,  $V = 4924(2)$  Å<sup>3</sup>,  $D_X = 1.135$  g·cm<sup>-3</sup>,  $\mu(\text{MoK}\alpha) = 0.071$  mm<sup>-1</sup>,  $T = 173(1)$  K,  $\omega/2\theta$  scans,  $2\theta_{\text{max}} = 55^\circ$ , total reflections measured 6134, symmetry independent reflections 5692, reflections with  $I > 2\sigma(I)$  3655, reflections used in refinement 5692, parameters refined 335, restraints 117, final  $R$  (on  $F$ ;  $I > 2\sigma(I)$  reflections) = 0.0485,  $wR = 0.1419$  ( $w = [\sigma^2(F_o^2) + (0.0637P)^2 + 1.4002P]^{-1}$  where  $P = (F_o^2 + 2F_c^2)/3$ , goodness of fit 1.021, final  $\Delta_{\text{max}}/\sigma = 0.001$ ,  $\Delta\rho$  (max; min) = 0.35; -0.21 e Å<sup>-3</sup>.

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Bu<sub>3</sub>P a slow evolution of gas was observed.

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