An Unexpected Formation of a 14-Membered Cyclodepsipeptide

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The treatment of diluted solutions of the hydroxy diamides **6a** and **6b** in toluene with HCl gas at 100° gave the dimeric, 14-membered cyclodepsipeptide **10** in up to 72% yield (*Scheme 3*). The same product was formed from the linear dimer of **6b**, the depsipeptide **11**, under the same conditions (*cf. Scheme 4*). All attempts to prepare the cyclic seven-membered monomer **9**, starting with different precursors and using different lactonization methods failed, and **10** was the only product which was isolated (*cf. Scheme 6*). For example, the reaction of the ester **20** with NaH in toluene at 80° led exclusively to the cyclodimer **10**. On the other hand, the base-catalyzed cyclization of the hydroxy diester **22**, which is the 'O-analogue' of **20**, yielded neither the seven-membered dilactone, nor the 14-membered tetralactone, but only the known trimer **23** and tetramer **24** of 2,2-dimethylpropano-3-lactone (*cf. Scheme 7*).

1. Introduction. – The continuous and current interest in cyclic depsipeptides is a result of their well-known biological activity. A large number of them have been isolated from natural sources, mainly from marine or surface cultures of the corresponding microorganisms (*cf.* [1–8]). Typical examples are the antibiotics valinomycin [9–11] and the enniatins [12], which act as ionophores [13]. The most demanding step in the synthesis of such compounds is the cyclization. As they contain amide groups and at least one ester group in the core, the cyclic depsipeptides could be prepared by the formation of either the amide or ester bonds as the ring-closure step.

The cyclization *via* amide-bond formation (lactamization; *e.g.*, [14–16]) is usually carried out by following protocols for the synthesis of cyclopeptides with coupling reagents. On the other hand, successful cyclizations *via* ester-bond formation (lactonization; *e.g.*, [17–19]) have also been described. In the last few years, the number of reports on the use of macrolactonizations in the preparation of cyclodepsipeptides has increased remarkably [6–8][20][21]. A useful method for the ring closure of depsipeptides, which contain α,α-disubstituted α-amino acids, is the so-called 'direct amide cyclization' method, developed in our laboratory [22–28]. The basic concept is that an amide of type **1** in a toluene solution or suspension is treated with dry HCl gas. Cyclization by elimination of the corresponding ammonium chloride leads to the intermediate 1,3-oxazol-5(4*H*)-one of type **2**. In the absence of other nucleophiles, the oxazolone undergoes a ring enlargement *via* intramolecular nucleophilic attack of the OH group at the C=O C-atom of the neighboring lactone group, leading to the depsipeptide **3** (*Scheme 1*).

As reported earlier, this method has been used efficiently for the synthesis of morpholine-2,5-diones (*i.e.*, six-membered cyclic depsipeptides) [23][29] as well as for

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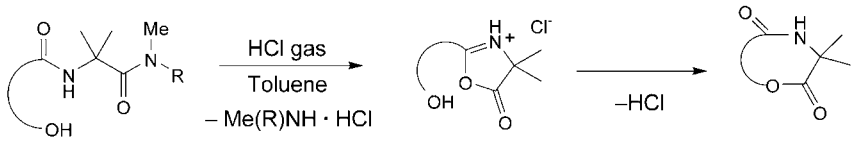
[1]) Part of the planned Ph.D. thesis of *B. I.*, Universität Zürich.

Scheme 1



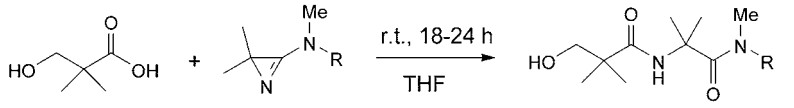
1 R = Me, Ph **2** **3**

some 9-, 12-, 15- [23], 16- [27], and 19-membered rings [30]. For the preparation of the 6-, 9-, 12-, and 15-membered rings of type **3**, the linear precursors **1** have been prepared by coupling α-hydroxy acids with 2*H*-azirin-3-amines, whereas β-hydroxy acids and 2*H*-azirin-3-amines led to the precursors of the 16- and 19-membered cyclodepsipeptides. The azirines themselves have been a target of our studies for some years [31–36], mainly because they proved to be useful synthons for α,α-disubstituted α-amino acids in peptide synthesis [31][33][34][37–40].

Because the reaction of α-hydroxy acids with 2*H*-azirin-3-amines, followed by the 'direct amide cyclization', proved to be a convenient access to morpholine-2,5-diones, we intended to generalize this reaction sequence. Therefore, we carried out the reaction under similar conditions with some β-hydroxy acids in order to obtain seven-membered cyclic depsipeptides. In the present paper, we report the results of the reaction of 2*H*-azirin-3-amines with 3-hydroxy-2,2-dimethylpropanoic acid (**4**).

2. Results and Discussion. – 2.1. *Direct Amid Cyclization.* As a model β-hydroxy acid, we chose 3-hydroxy-2,2-dimethylpropanoic acid (**4**), mainly due to its commercial availability and its previous use in this type of reaction [26][27]. The linear dipeptides **6** were prepared by the standard procedure [26] of coupling **4** with the corresponding 2*H*-azirin-3-amine (**5a** or **5b**; *cf.* [31] and refs. cit. therein), to yield **6a** and **6b**, respectively, in excellent yields and without side products (*Scheme 2*).

Scheme 2



4 **5a** R = Me **6a** R = Me 73%
b R = Ph **b** R = Ph 97%

Although the general protocol proposed MeCN as a solvent [26], THF turned out to be a better solvent in this particular case. In addition to the spectroscopic characterization of **6a** and **6b** (*cf.* [27]), their structures were established by X-ray crystallography (*Fig. 1*).

The conformations of the backbones of **6a** and **6b** are very similar, with the exception of the orientation of the OH group. In **6a**, the NH group forms an

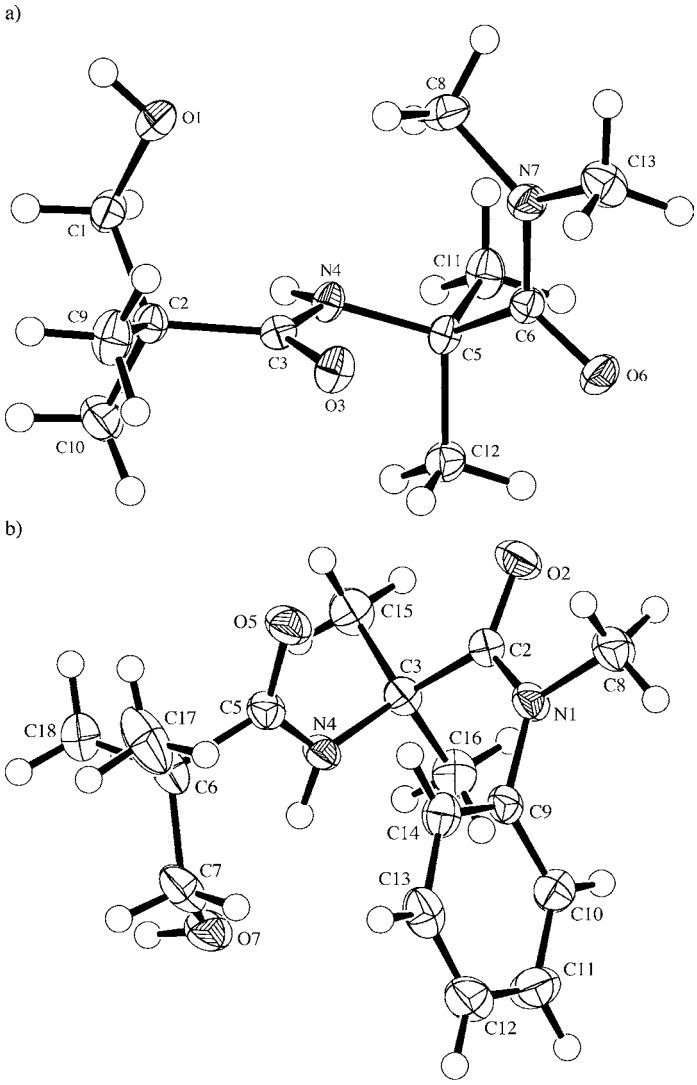


Fig. 1. *ORTEP Plots* [41] *of the molecular structures of* a) **6a** *and* b) *one of the two symmetry-independent molecules of* **6b** (arbitrary numbering of the atoms; 50% probability ellipsoids)

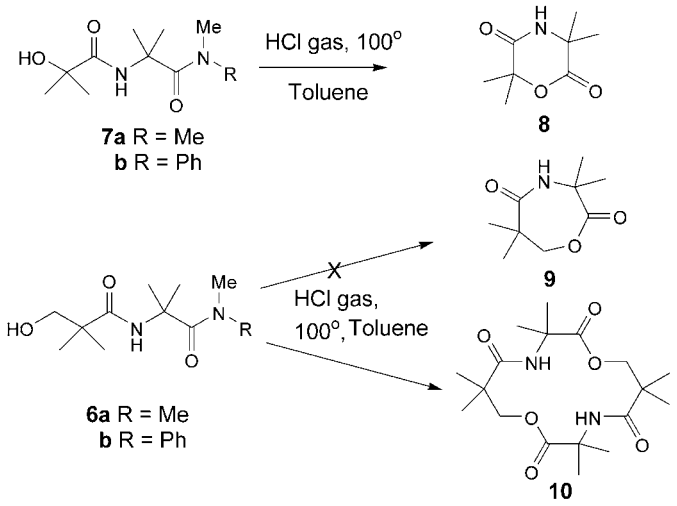
intermolecular H-bond with its adjacent amide O-atom from a neighboring molecule (N(4) ··· O(6″) 2.885(1) Å; N(4)–H ··· O(6″) 161(1)°). This interaction links the molecules into extended chains, which run parallel to the *y*-axis and have a graph set motif [42] of C(5). The OH group forms an intermolecular H-bond with its adjacent amide O-atom from a different neighboring molecule (O(1) ··· O(3′) 2.770(2) Å; O(1)–H ··· O(3′) 169(2)°) and thereby also links the molecules into infinite chains, which run parallel to the *y*-axis and have a graph set motif of C(6). The combination of

the intermolecular interactions links the molecules into a two-dimensional network, which lies parallel to the *xy*-plane.

In the case of **6b**, there are two symmetry-independent molecules in the asymmetric unit and they have almost identical conformations. The NH group in each molecule forms an intramolecular H-bond with the OH group (*e.g.*, N(4) ··· O(7) 2.728(2) Å; N(4)–H ··· O(7) 142(1)° in molecule A) to yield a six-membered loop with a graph set motif of S(6). The OH group of molecule A forms an intermolecular H-bond with the primary amide O-atom of molecule B (O(7) ··· O(25′) 2.684(1) Å; O(7)–H ··· O(25′) 173(2)°), while the OH group of molecule B has a similar interaction with a different molecule A (O(27) ··· O(5″) 2.692(1) Å; O(27)–H ··· O(5″) 174(2)°). These interactions link the molecules into infinite chains in which both symmetry-independent molecules are incorporated in an alternating ···A···B···A···B ··· sequence. These chains run parallel to the *y*-axis and have a binary graph set motif of $C_2^2(12)$.

The dipeptide **6b** was subjected to the reaction conditions of the 'direct amide cyclization', *i.e.*, dry HCl gas was bubbled through a toluene suspension of **6b** at 100°. It was expected that **6b** would react in an analogous manner to the amide **7**, which gave 3,3,6,6-tetramethylmorpholine-2,5-dione (**8**) in up to 60% yield [43] (*Scheme 3*). Surprisingly, only the dimer of the expected seven-membered ring **9**, namely the 14-membered 3,3,6,6,10,10,13,13-octamethyl-1,8-dioxa-4,11-diazacyclotetradecane-2,5,9,12-tetraone (**10**), was formed in 72% yield (*Scheme 3*).

Scheme 3



The ^{1}H-NMR spectrum of **10** showed no signal for OH groups and confirmed the presence of NH groups. Two *singlets* for Me groups and a *singlet* for CH_2 were also clearly distinguished. The ^{13}C-NMR spectra showed the presence of two C=O groups (174.3 and 178.2 ppm in (D_6)DMSO), which was further confirmed by the IR spectrum (KBr; 1723 and 1673 cm^{-1}). Furthermore, the ^{13}C-NMR spectrum indicated two

different types of Me_2C groups, in addition to a CH_2O group. With this set of data, the distinction between the monomeric lactone **9** and the dimer **10** was not possible. However, the mass spectra (CI and ESI mode) indicated a molecular weight of 370, which corresponds to the 14-membered depsipeptide **10**. Finally, its structure was confirmed by X-ray crystallography (*Fig. 2*).

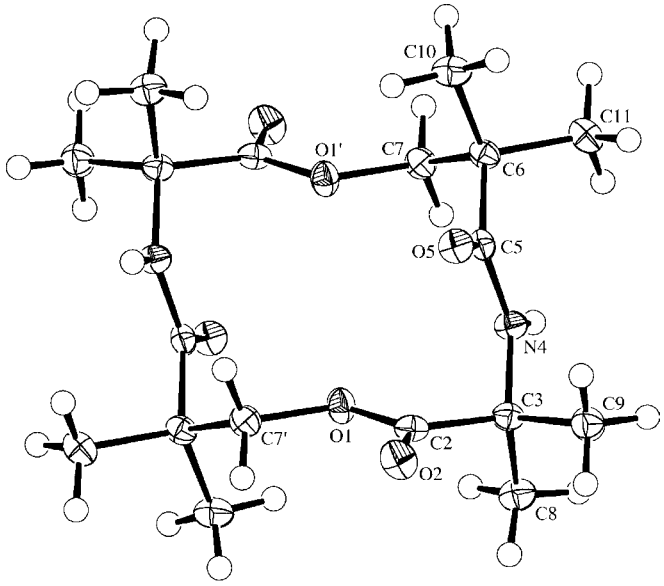


Fig. 2. *ORTEP Plot* [41] *of the molecular structure of* **10** (arbitrary numbering of the atoms; 50% probability ellipsoids)

The molecule is oriented across a crystallographic center of inversion. The symmetry-unique NH group forms a very weak intermolecular H-bond with the amide O-atom from the same amide group of an adjacent molecule (N(4) ··· O(5′) 3.483(2) Å; N(4)–H ··· O(5′) 170°). This interaction links the molecules into extended chains, which run parallel to the *z*-axis and have a graph set motif of C(4). The other amide group in the molecule participates in an identical intermolecular interaction of necessity because of the centrosymmetric nature of the molecule. The chains thereby formed also run parallel to the *z*-axis, but in the opposite direction. The molecules themselves bridge adjacent chains, so that the combination of both interactions links the molecules into two-dimensional networks which lie parallel to the (100) plane. The cross-linking of the chains also builds H-bonded loops involving four molecules and yields the graph set motif of $R_4^4(26)$.

To obtain the seven-membered, monomeric cyclodepsipeptide **9** (*Scheme 3*), we repeated the reaction with varying concentrations of the starting material **6b** and different reaction times. However, under all conditions **10** was formed as the sole product, although in variable yields. Thus, the maximum yield of 72% was obtained at a

concentration of 20 mM, whereas with a concentration of 2 mM the yield dropped to 35%, and at a concentration of 40 mM the yield was only 61%.

The rate-determining step of the 'direct amide cyclization' is assumed to be the formation of the oxazolone ring (see *Scheme 1*), a process favored by the precipitation of the corresponding ammonium salt. Thus, the formation of the lactone is a function of the salt's solubility in toluene[2]). As a result, *N*,*N*-dimethyl amides of type **6a** should react more easily than *N*-methyl-*N*-phenyl amides like **6b** under the conditions of the 'direct amide cyclization', because the initially formed $Me_2NH \cdot HCl$ is less soluble in toluene than $Ph(Me)NH \cdot HCl$.

Therefore, we also used **6a** as a starting material. The cyclization with HCl gas in toluene at 100° gave again the product **10**. The lower yield (32%) is mainly caused by purification difficulties (see *Exper. Part*).

To prepare **10** by a specific synthesis, we synthesized the open-chain precursor, the linear depsipeptide **11**, according to standard procedures, starting from the commercially available methyl ester **12**. After protection of the OH group by benzylation to give **13** and deprotection of the COOMe group, the intermediate **14** was coupled with **5b** to yield the diamide **15**. The product of its acid-catalyzed hydrolysis **16** was coupled with **6b** to give **17**, which, after deprotection, gave **11** in a total yield of 24% (*Scheme 4*). Crystallization from a mixture of CH_2Cl_2, i-PrOH, and hexane gave crystals, which were suitable for an X-ray crystal-structure determination (*Fig. 3*).

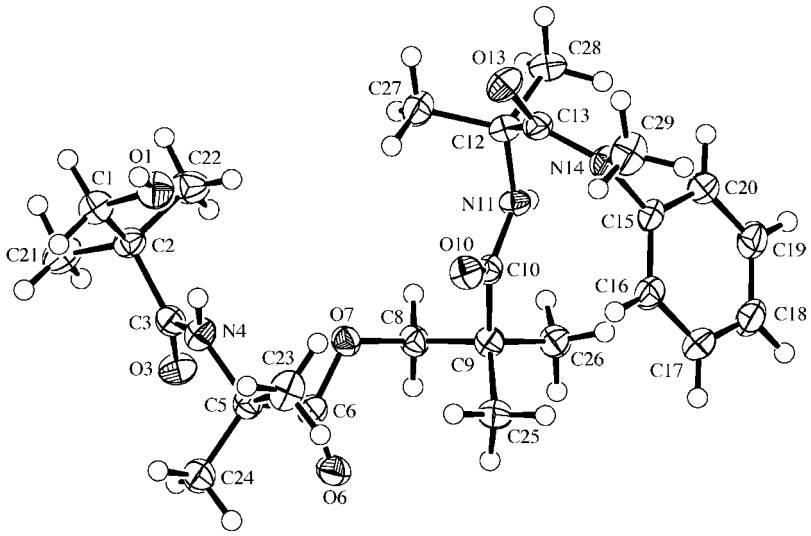


Fig. 3. *ORTEP Plot* [41] *of the molecular structure of* **11** (arbitrary numbering of the atoms; 50% probability ellipsoids)

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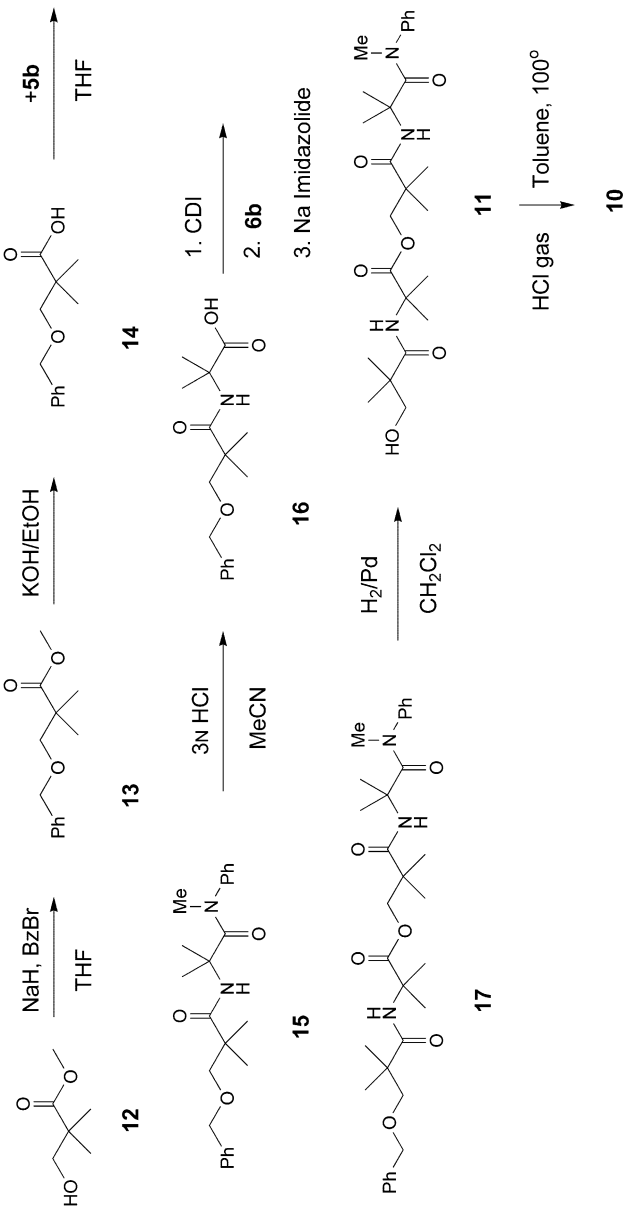
[2]) It has been shown previously that the formation of a 16-membered cyclic depsipeptide, which was obtained in toluene (heterogeneous conditions) in 60% yield, does not occur in homogeneous solution in DMF [26].

Scheme 4


NaH, BzBr
THF
KOH/EtOH
+5b
THF
1. CDI
2. 6b
3. Na Imidazolide
3N HCl
MeCN
H2/Pd
CH2Cl2
HCl gas
Toluene, 100°
12
13
14
15
16
17
11
10

Although the molecule is achiral, the crystal structure is chiral. The absolute structure has not been determined and was defined arbitrarily. The amide NH group closest to the OH group forms an intramolecular H-bond with the OH O-atom (N(4) ··· O(1) 2.709(3) Å; N(4)–H ··· O(1) 135(3)°). This gives rise to a six-membered loop with a graph set motif of S(6), analogous to compound **6b** (*Fig. 1*). The other amide group forms an intermolecular H-bond with the adjacent amide O-atom from a neighboring molecule (N(11) ··· O(13″) 2.932(3) Å; N(11)–H ··· O(13″) 155(3)°). This interaction links the molecules into infinite chains, which run parallel to the *y*-axis and have a graph set motif of C(5). The OH group forms an intermolecular H-bond with its adjacent amide O-atom from a different neighboring molecule (O(1) ··· O(3′) 2.655(3) Å; O(1)–H ··· O(3′) 158(4)°) and thereby also links the molecules into infinite chains, which run parallel to the *y*-axis and have a graph set motif of C(6). The combination of intermolecular interactions links the molecules into a two-dimensional network, which lies parallel to the *yz*-plane.

Compound **11** was subjected to cyclization under the standard conditions of the 'direct amide cyclization'. Once more, the 14-membered cyclodepsipeptide **10** was the only product that could be isolated, with the moderate yield of 42%.

2.2. *Other Lactonization Methods.* After all attempts to obtain the seven-membered ring **9** by the 'direct amide cyclization' failed, even after a ten-fold dilution of the reaction mixture, we were faced with a number of classical lactonization options, starting mainly with the corresponding hydroxy acid **18**, which was obtained easily from either of the amides **6** by hydrolysis in an acidic medium. The crystal structure of **18** is shown in *Fig. 4*.

The NH group forms an intermolecular H-bond with the O-atom of the OH group of a neighboring molecule (N(4) ··· O(7‴) 3.086(2) Å; N(4)–H ··· O(7‴) 165(2)°). This interaction links the molecules into extended chains, which run parallel to the *y*-axis and have a graph set motif of C(6). The OH group forms an intermolecular H-bond with C=O of the COOH group from a different neighboring molecule (O(7) ··· O(2″) 2.746(2) Å; O(7)–H ··· O(2″) 170(2)°). This interaction also links the molecules into infinite chains, which run parallel to the *y*-axis and have a graph set motif of C(9). The OH group of COOH forms an intermolecular H-bond with the amide O-atom of a third neighboring molecule (O(1) ··· O(5′) 2.606(2) Å; O(1)–H ··· O(5′) 172(2)°). Again, this interaction links the molecules into infinite chains, which run parallel to the *y*-axis and have a graph set motif of C(7). The combination of all H-bonding interactions links the molecules into a two-dimensional network, which lies parallel to the *xy*-plane.

The variety of lactonization methods is enormous, and we could try only a few of them. As starting point, we used the review by *Nicolaou* [44] where the classical methods of *Yamaguchi* and co-workers [45], *Corey* and *Nicolaou* [46], and *Mukaiyama et al.* [47] are mentioned. Unfortunately, none of the above reactions yielded the desired product, and the only products obtained were the activated acid derivates, namely the *Yamaguchi* mixed anhydride and the *Corey* active ester. Some modern variations of these methods [48] were also tried, but they also failed to give the desired product. The most common cyclization methods, with DCC or its water-soluble derivatives and analogues, gave as the only product 2-(2-hydroxy-1,1-dimethylethyl)-4,4-dimethyl-1,3-oxazol-5(4*H*)-one (**19**) in 36% yield (*Scheme 5*). This is the postulated intermediate of the prospected 'direct amide cyclization' **6** → **9**. Even after addition of

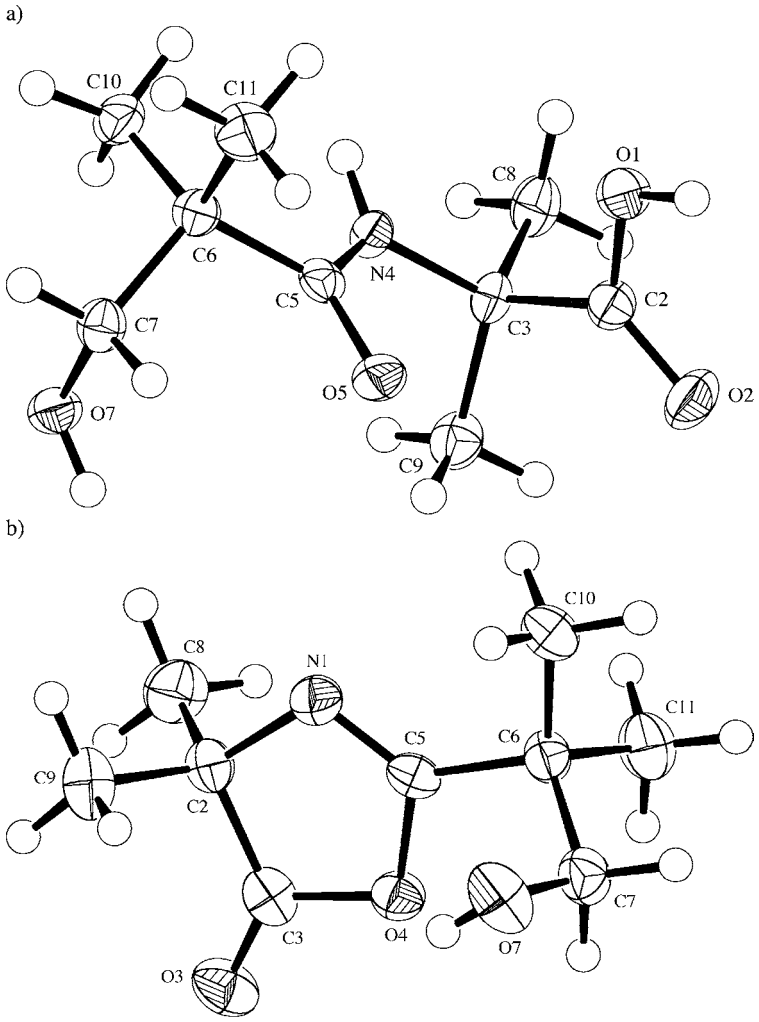
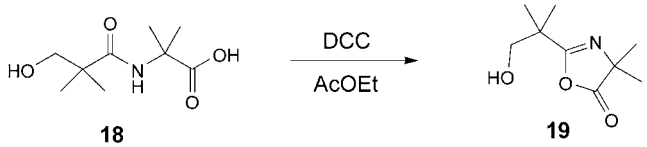


Fig. 4. *ORTEP Plots* [41] *of the molecular structures of* a) **18** *and* b) *one of the two symmetry-independent molecules of* **19** (arbitrary numbering of the atoms; 50% probability ellipsoids)

Scheme 5



18 **19**

4-(dimethylamino)pyridine (DMAP) to a mixture of **18** and *N*,*N*′-dicyclohexylcarbodiimide (DCC), a procedure suitable for the synthesis of medium sized lactones [49],

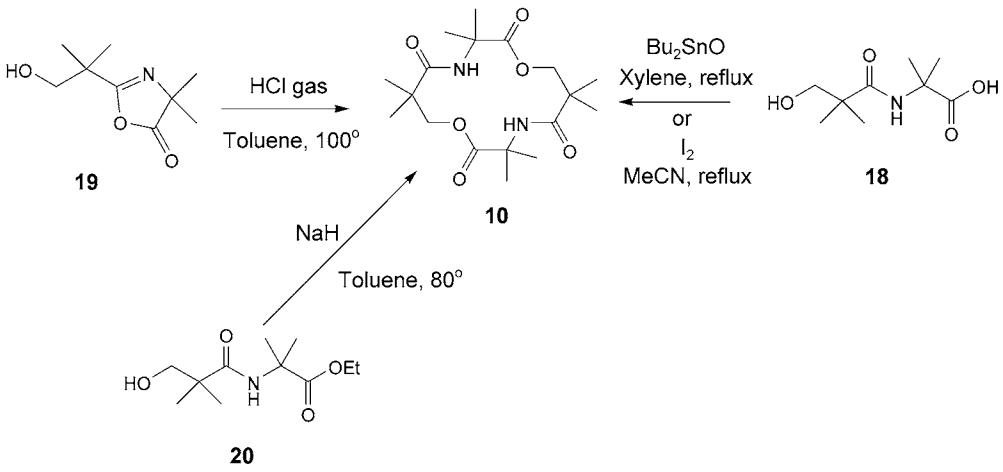
the reaction path did not change, and **19** was isolated as the only product, although in moderate yield.

In general, 1,3-oxazol-5(4*H*)-ones are reactive species; in the case of **19**, the geminal dimethyl group seems to stabilize it, so that it could be isolated in crystalline form. In the IR spectrum (KBr), **19** showed a characteristic strong C=O absorption at 1836 cm^{-1}, and in the ^{13}C-NMR spectrum, the *singlets* for C=O and C=N appeared at 182.8 and 166.6 ppm, respectively. The structure of **19** was established by X-ray crystallography (*Fig. 4*).

The asymmetric unit contains two symmetry-independent molecules, the conformations of which differ only in the orientation of the OH group. The OH group of molecule A forms an intermolecular H-bond with the N-atom of molecule B (O(7)···N(21′) 2.891(2) Å; O(7)–H···N(21′) 159(3)°). In turn, molecule B has an identical interaction with another molecule A. These interactions link the molecules into extended ···A···B···A···B··· chains, which run parallel to the *y*-axis and have a graph set motif [42] of $C_2^2(12)$.

As **19** is expected to be the intermediate in the 'direct amide cyclization' **6** → **9**, we attempted to transform **19** to the depsipeptide **9** in polar, aprotic solvents (AcOEt, MeCN), but all attempts failed. After two days of heating **19** under reflux, only the starting material was isolated. Another way of converting **19** to the depsipeptide **9** was the 'direct amide cyclization'. This reaction yielded again only product **10** in excellent yield (86%; *Scheme 6*).

Scheme 6



The next step on the way to the synthesis of the seven-membered **9** was to try out some reactions involving salts of metals, such as Sb [50], Sn [51], Ag [52], Sc [53], and Ru [54], which are known to catalyze the formation of small- and medium-sized lactones. Most of these attempts failed in the case of **18**, and only few led to a definite product, namely once more the dimeric cyclodepsipeptide **10** (*Scheme 6*). Surprisingly, the reaction with I_2 in boiling MeCN, which was initially used to cyclize terpene-like hydroxy acids [55], gave again the 14-membered ring **10** in moderate yield (*Scheme 6*).

Recently, *Richard et al.* have reported the synthesis of seven-membered lactones, containing an amino group in their basic structure, by treatment of the corresponding hydroxy esters with NaH in a toluene suspension [56]. Therefore, we treated the ester **20** under the same conditions. To our disappointment, this reaction yielded again the dimeric compound **10** as the sole product.

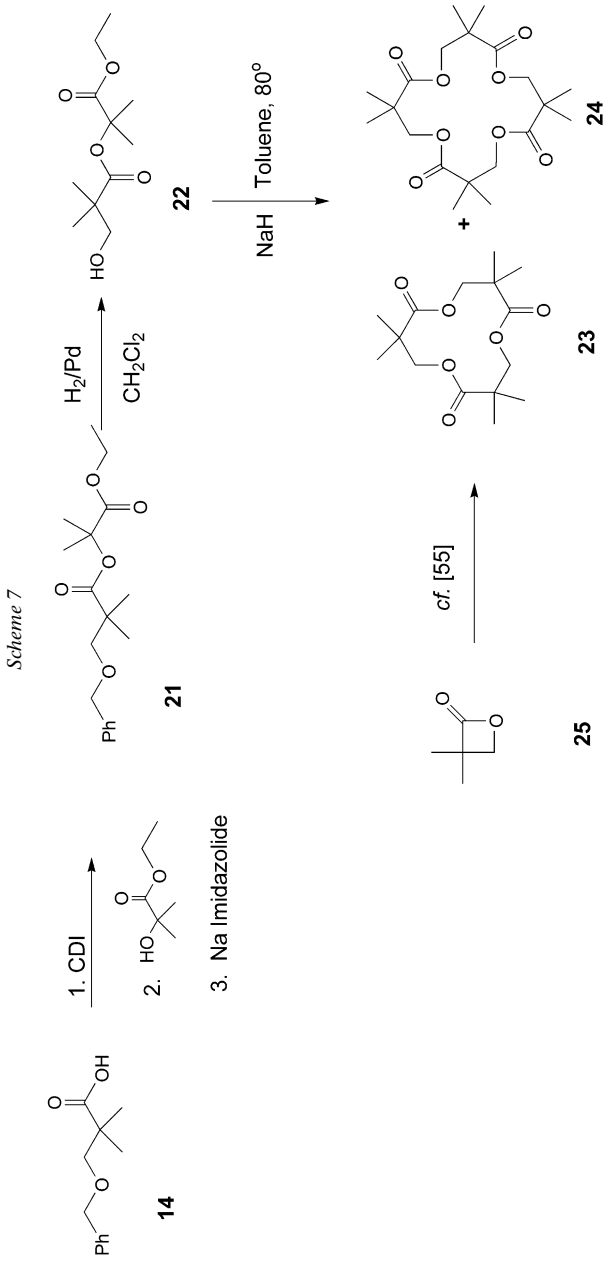
The discrepancy between the reactions of 6-hydroxy-4-azahexanoates [56] and **6** is very surprising. One of the possible reasons for the failure of this method in the case of **6** could lie in the presence of the amide bond and its rigidity. With the aim of verifying this hypothesis, the ester analogue of the amide **6**, *i.e.*, the diester **22**, was synthesized in the same way as compound **11** (*Scheme 7*).

Subjecting compound **22** to the reaction conditions described in [56] led to a mixture of products, among which the tri- and tetralactones **23** and **24**, respectively, were isolated as the main products. None of the expected seven-membered dilactone could be detected. As an additional product, 2-hydroxyisobutanoic acid was also obtained. The structures of **23** and **24**, *i.e.*, the cyclic tri- and tetramers, respectively, of 3-hydroxy-2,2-dimethylpropanoic acid (**4**) were confirmed by X-ray crystal-structure analyses (*Fig. 5*). It turned out that these compounds are already known, and the crystal-structure of **24** has been published previously [57]. They have been prepared by oligomerization of β-lactone **25**. Therefore, we propose that, in the reaction of **22** with NaH, **25** is formed by the intramolecular nucleophilic attack of the OH group at the central ester group and cleavage of this ester. Then, **25** undergoes the oligomerization. Apparently, the alternative nucleophilic attack at the terminal ester group of **22**, which would lead to the seven-membered dilactone, cannot compete with the formation of the β-lactone.

3. Conclusions. – In conclusion, our attempts to prepare the seven-membered cyclic depsipeptide 2,3,4,5,6,7-hexahydro-3,3,6,6-tetramethyl-1,4-oxazepine-2,5-dione (**9**) by the 'direct amide cyclization' starting with 3-hydroxy-2,2-dimethyl-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]propanamide (**6b**) failed. The only product obtained was the dimeric 14-membered cyclodepsipeptide **10**, which was formed in a very good yield. Furthermore, the attempts to prepare the monomeric lactone **9** by various classical lactonization procedures also failed, and in almost all cases **10** was obtained as the main product in yields of 28–72%. Six different methods for the synthesis of **10** were developed. Despite all the variations in reaction conditions and the knowledge of the crystal structures of the starting materials and some of the intermediates, there is no convincing explanation for this unexpected result, and additional experiments are required.

We thank the analytical units of our institute for spectra and analysis, and the *Swiss National Science Foundation* and *F. Hoffmann-La Roche AG*, Basel, for financial support.

Scheme 7


1. CDI
2.
3. Na Imidazolide
14
21
H_2/Pd
CH_2Cl_2
22
NaH
Toluene, 80°
24
+
23
cf. [55]
25

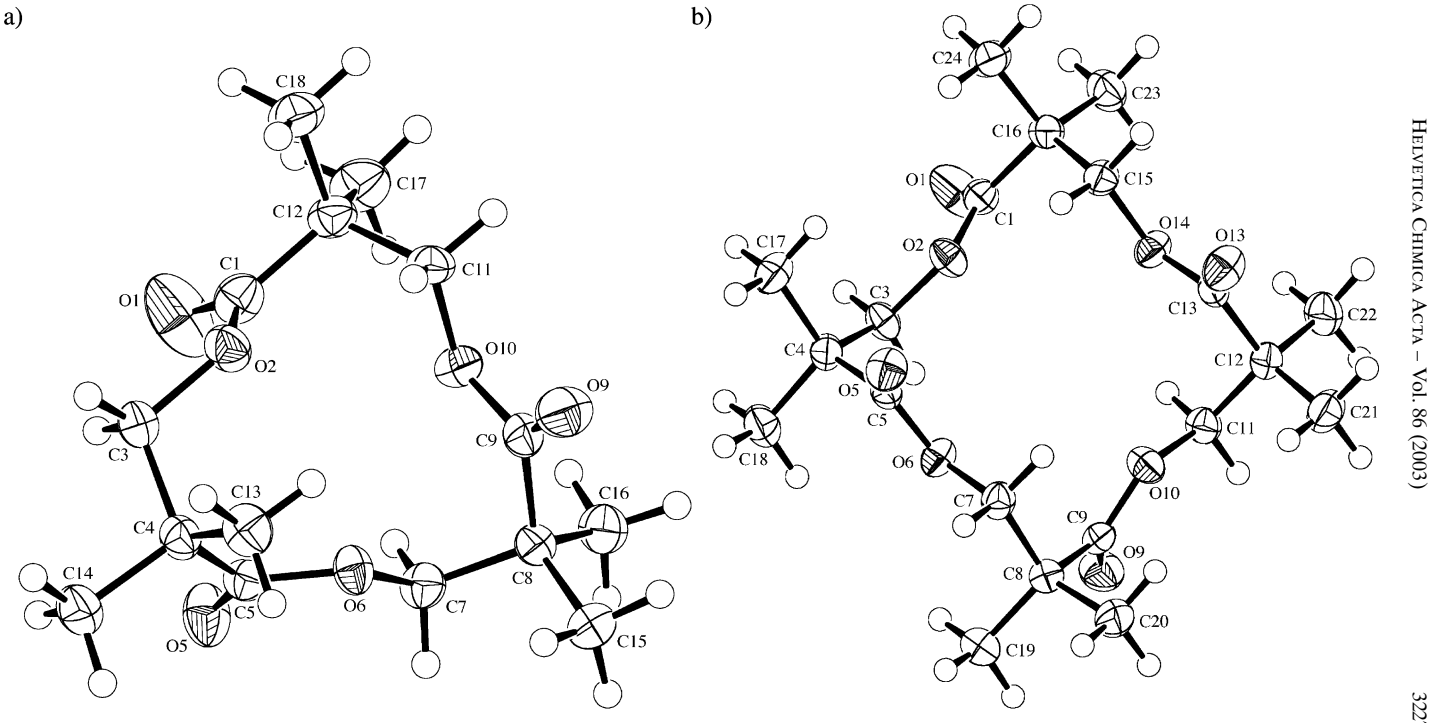


Fig. 5. *ORTEP Plots* [41] *of the molecular structures of* a) *one of the two symmetry-independent molecules of* **23** *and* b) **24** (arbitrary numbering of the atoms; 50% probability ellipsoids)

Experimental Part

1. *General.* The starting materials *2,2,*N,N-*tetramethyl*-N-*phenyl-2*H-*azirin-3-amine* (**5a**) and *2,2,*N-*trimethyl*-N-*phenyl-2*H-*azirin-3-amine* (**5b**) were prepared according to standard procedures (*cf.* [31] and refs. cit. therein). All other products used were commercially available. TLC: *Merck* TLC aluminium sheets, silica gel *60* F_{254}. Prep. TLC: *Merck* PLC plates (glass), silica gel *60* F_{254}, 2 mm and 40–63 μm. Flash column chromatography (CC): *Uetikon-Chemie* '*Chromatographiegel*' *C-560*. M.p.: *Büchi 540* apparatus, uncorrected. IR Spectra: *Perkin-Elmer Spectrum one* spectrometer; in KBr, unless otherwise stated, absorption bands in cm^{-1}. ^{1}H- (300 MHz) and ^{13}C-NMR (75.5 MHz) spectra: *Bruker ARX-300* instrument; in $CDCl_3$ at 300 K; TMS as internal standard, unless otherwise stated; δ in ppm, coupling constants J in Hz. HSQC and HMBC spectra: *Bruker DRX-600* instrument; ^{1}H- (600 MHz) and ^{13}C-NMR (150 MHz). MS: *Finnigan MAT-90* for electron-impact ionization (EI), *Finnigan SSQ-700* for chemical ionization (CI, with NH_3) and electrospray ionization (ESI, in MeOH + NaI), unless otherwise stated.

2. *Coupling with 2*H-*Azirin-3-amines.* N-*[1-(*N,N-*Dimethylcarbamoyl)-1-methylethyl]-3-hydroxy-2,2-dimethylpropanamide* (**6a**). To a soln. of *3-hydroxy-2,2-dimethylpropanoic acid* (**4**; 806 mg, 6.84 mmol) in dry THF (5 ml), **5a** (1.231 g, 7.52 mmol) was added dropwise. The mixture was stirred at r.t. for 36 h, the solvent was evaporated, and the remaining solid was purified by CC (SiO_2, MeOH/CH_2Cl_2 1:10) and dried in h.v. Yield: 1.200 g (76%) of **6a**. Pale yellow crystals. M.p. 126.2–127.4°. ^{1}H-NMR: 1.10, 1.33 (2*s*, 2 Me_2C); 3.22 (*s*, Me_2N); 3.46 (*s*, CH_2O); 3.90 (br. *s*, OH); 6.79 (br. *s*, NH). ^{13}C-NMR: 22.1, 26.3 (2*q*, 2 Me_2C); 41.6 (*s*, Me_2C); 42.4 (*q*, Me_2N); 58.7 (*s*, Me_2C); 70.4 (*t*, CH_2O); 174.1, 177.2 (2*s*, 2 CO). CI-MS: 231 (68, $[M+1]^+$), 186 (100).

3-Hydroxy-2,2-dimethyl-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]propanamide* (**6b**). To a soln. of **4** (806 mg, 6.84 mmol) in dry THF (5 ml), **5b** (1.309 g, 7.52 mmol) was added dropwise. The mixture was stirred at r.t. for 24 h, the solvent was evaporated, and the remaining solid was purified by CC (SiO_2, MeOH/CH_2Cl_2 1:20) and dried in h.v. Yield: 1.86 g (93%) of **6b**. White solid. M.p. 102.8–103.3° ([27]: 103.4–104°). ^{1}H-NMR: 1.11, 1.38 (2*s*, 2 Me_2C); 3.28 (*s*, MeN); 3.44 (*s*, CH_2O); 3.90 (br. *s*, OH); 6.77 (br. *s*, NH); 7.25–7.45 (*m*, 5 arom. H). ^{13}C-NMR: 22.2, 26.3 (2*q*, 2 Me_2C); 41.6 (*s*, Me_2C); 43.6 (*q*, MeN); 58.7 (*s*, Me_2C); 70.4 (*t*, CH_2O); 128.2 (*d*, 1 arom. CH); 128.4, 129.5 (2*d*, 4 arom. CH); 144.4 (*s*, 1 arom. C); 174.1, 177.2 (2*s*, 2 CO).

3. *Cyclizations to 3,3,6,6,10,10,13,13-Octamethyl-1,8-dioxa-4,11-diazacyclotetradecane-2,5,9,12-tetraone* (**10**). 3.1. *Direct Amide Cyclizations. Procedure A.* A suspension of **6b** (584 mg, 2 mmol) in dry toluene (100 ml) was heated to 100°, and HCl gas was bubbled through the suspension for 7 min. Then, the mixture was allowed to cool to r.t. while bubbling N_2 through it (*ca.* 20 min). The solvent was evaporated, and the white residue was washed with 3 × 15 ml of CH_2Cl_2 and dried in h.v. Yield: 267 mg (72%) of **10**. White powder. M.p. 299.2–300.4°. IR: 3393v*s* (NH), 2990*s*, 2977*s*, 2935*m*, 1723v*s* (C=O), 1673v*s* (C=O), 1523v*s*, 1171v*s* (C–O). ^{1}H-NMR ((D_7)DMF): 1.12, 1.40 (2*s*, 2 Me_2C each); 4.00 (*s*, 2 CH_2O); 7.64 (*s*, 2 NH). ^{13}C-NMR ((D_7)DMF): 22.1, 24.6 (2*q*, 2 Me_2C each); 41.6, 55.4 (2*s*, 2 Me_2C); 71.3 (*t*, CH_2O); 174.3 (*s*, C=O). ^{13}C-NMR ((D_6)DMSO): 20.9, 23.2 (2*q*, 2 Me_2C each); 40.4, 54.4 (2*s*, 2 Me_2C); 70.1 (*t*, CH_2O); 173.0, 174.3 (*s*, C=O). CI-MS: 388 (34, $[M+NH_4]^+$), 371 (100, $[M+1]^+$). ESI-MS: 393 (100, $[M+Na]^+$). Anal. calc. for $C_{18}H_{30}N_2O_6$ (370.45): C 58.36, H 8.16, N 7.56; found C 57.94, H 8.18, N 7.47.

Procedure B. A suspension of **6a** (230 mg, 1 mmol) in dry toluene (50 ml) was heated to 100°, and HCl gas was bubbled through the suspension for 3 min. Then, the mixture was allowed to cool to r.t. while bubbling N_2 through it (*ca.* 20 min). The solvent was evaporated, the white residue was washed with 3 × 10 ml of CH_2Cl_2, and the remaining solid was recrystallized from MeCN to yield 60 mg (32%) of **10**.

Procedure C. A suspension of **11** (see *Sect. 4*; 477 mg, 1 mmol) in dry toluene (50 ml) was heated to 100°, and HCl gas was bubbled through the suspension for 3 min. Workup as described in *Procedure A* gave 92 mg (49%) of **10**.

3.2. *Other Lactonization Methods. 2-[(3-Hydroxy-2,2-dimethylpropanoyl)amino]-2-methylpropanoic Acid* (**18**). To a soln. of **6b** (2.00 g, 7.35 mmol) in THF (10 ml), 3N HCl (10 ml) was added dropwise at 0° under constant stirring. After 8 h at r.t., THF was removed *i.v.*, and the H_2O phase was extracted with AcOEt (5 × 20 ml). The combined org. fractions were dried ($MgSO_4$), and the solvent was evaporated. The remaining brownish crystals were washed twice with Et_2O/PrOH 100:1. Yield: 1.312 g (92%) of **18**. White crystals. M.p. 142.3–143.4° ([27]: 142.8–144.0°). ^{1}H-NMR ((D_6)DMSO): 1.00, 1.35 (2*s*, 2 Me_2C); 3.36 (*s*, CH_2O); 5.00 (br. *s*, OH); 7.52 (br. *s*, NH); 12.12 (br. *s*, COOH).

Procedure D. A soln. of **18** (205 mg, 1 mmol) and I_2 (15 mg, 0.06 mmol) in dry MeCN (15 ml) was heated to reflux for 3 d. After evaporation of the solvent, the residue was washed with 5% $Na_2S_2O_3$ soln. and extracted with AcOEt, and the combined org. fractions were dried ($MgSO_4$). Purification by CC yielded 89 mg (49%) of **10** as a white powder.

Procedure E. A soln. of **18** (103 mg, 0.5 mmol) and Bu_2SnO (25 mg, 0.1 mmol) in dry xylene (25 ml) was heated under reflux for 2 d in a *Dean–Stark* apparatus (N_2 atmosphere). Then, the solvent was evaporated *i.v.*, the solid residue was washed with Et_2O (2×10 ml) and then with warm acetone (5×10 ml). The acetone fraction was concentrated to 5 ml, cooled, and filtered to yield 36 mg (38%) of **10**.

Ethyl 2-[(3-Hydroxy-2,2-dimethylpropanoyl)amino]-2-methylpropanoate (**20**). A soln. of **6b** (584 mg, 2 mmol) in a 10% EtOH soln. in toluene (110 ml) was heated to 100°, and HCl gas was bubbled through the suspension for 7 min. Then, the mixture was allowed to cool to r.t. while bubbling N_2 through it (*ca.* 20 min). The solvent was evaporated, and purification by CC (CH_2Cl_2/acetone 100:1) yielded 397 mg (86%) of **20**. Colorless oil. ^{1}H-NMR: 1.14 (*s*, Me_2C); 1.28 (*t*, *Me*CH_2O); 1.43 (*s*, Me_2C); 3.53 (*d*, CH_2OH); 4.05 (*q*, MeCH_2O); 6.79 (*s*, NH). ^{13}C-NMR: 15.6 (*q*, Me); 22.1, 26.3 (2*q*, 2 Me_2C); 41.6 (*s*, Me_2C); 61.4 (*t*, CH_2O); 69.1 (*t*, CH_2O); 76.8 (*s*, Me_2C); 174.3, 178.6 (2*s*, 2 CO). ESI-MS: 254 (100, $[M+Na]^+$).

Procedure F. To a soln. of **20** (232 mg, 1 mmol) in dry toluene (5 ml), NaH (40 mg of a 60% suspension in mineral oil, 1 mmol) was added slowly at 0° and under constant stirring (N_2 atmosphere). After 4.5 h at 80°, the mixture was acidified with 0.1N HCl (*ca.* 6 ml) to pH 5, and extracted with CH_2Cl_2 and AcOEt. The combined org. fractions were dried ($MgSO_4$) and evaporated *i.v.* The crystalline residue was washed with CH_2Cl_2 to yield 52 mg (28%) of **10**.

4. *Synthesis of 2-Methyl-2-[*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]carbamoyl]propyl 2-[(3-Hydroxy-2,2-dimethylpropanoyl)amino]-2-methylpropanoate* (**11**).

Methyl 3-Benzyloxy-2,2-dimethylpropanoate (**13**). To a suspension of NaH (440 mg of a 60% suspension in mineral oil, 11 mmol) in dry THF (15 ml) methyl 3-hydroxy-2,2-dimethylpropanoate (1.322 g, 10 mmol) was added dropwise at 0° under constant stirring. The mixture was stirred at r.t. for 1 h, then BzBr (1.710 g, 10 mmol) was added. After heating under reflux for 3 h, the mixture was cooled, washed with brine (2×25 ml), the brine fractions were extracted with AcOEt, and the combined org. fractions were dried ($MgSO_4$). Purification by CC (SiO_2, hexane/Et_2O 10:1) yielded 1.05 g (47%) of **13**. Colorless oil. IR (film): 2976*m*, 2863*m*, 1736v*s* (C=O), 1475*s*, 1454*s*, 1363*m*, 1308*s*, 1226*s*, 1192*s*, 1152*s* (C–O), 1100*s* (C–O), 1029*m*, 738*m*, 698*m*. ^{1}H-NMR: 1.37 (*s*, Me_2C); 3.62 (*s*, CH_2O); 3.84 (*s*, MeO); 4.68 (*s*, PhCH_2); 7.40–7.52 (*m*, 5 arom. H). ^{13}C-NMR: 22.4 (*q*, Me_2C); 43.6 (*t*, CH_2); 51.7 (*s*, Me_2C); 73.1 (*q*, MeO); 76.9 (*t*, Ph*C*H_2); 127.3, 127.6, 128.2 (3*d*, 5 arom. CH); 138.4 (*s*, 1 arom. C); 176.8 (*s*, C=O). EI-MS: 222 (28, $M^{+\bullet}$), 116 (26), 107 (20), 101 (20), 91 (100), 65 (8).

3-Benzyloxy-2,2-dimethylpropanoic Acid (**14**). To a soln. of **13** (1.00 g, 4.5 mmol) in EtOH (20 ml), 8 ml of 2N KOH were added at 0°. After 1 h stirring at r.t., the org. solvent was evaporated *i.v.*, and the remaining soln. was acidified with 1N HCl to pH 1 and extracted with Et_2O. The org. fractions were dried ($MgSO_4$) and evaporated *i.v.* The residue was recrystallized from hexane. Yield: 830 mg (88%) of **14**. White crystals. M.p. 62.1–63.8°. IR: 2975*m*, 2861*m*, 1707v*s* (C=O), 1454*s*, 1364*m*, 1163*w*, 1100*s* (C–O), 738*m*, 698*m*. ^{1}H-NMR ((D_6)DMSO): 1.07 (*s*, Me_2C); 3.42 (*s*, CH_2O); 4.49 (*s*, PhCH_2); 7.25–7.42 (*m*, 5 arom. H); 12.21 (*s*, COOH). ^{13}C-NMR ((D_6)DMSO): 22.2 (*q*, Me_2C); 40.6 (*s*, Me_2C); 72.3 (*t*, CH_2O); 76.7 (PhCH_2); 127.2, 127.3, 128.1 (3*d*, 5 arom. CH); 138.4 (*s*, 1 arom. C); 177.3 (*s*, COOH). EI-MS: 208 (7, $M^{+\bullet}$), 107 (49), 91 (100), 79 (9), 65 (9).

3-Benzyloxy-2,2-dimethyl-N-*[1-methyl-1-(*N*-methyl*-N*-phenylcarbamoyl)ethyl]propanamide* (**15**). To a soln. of **14** (800 mg, 3.85 mmol) in THF (10 ml), a soln. of **5b** (670 mg, 3.85 mmol) in THF (2 ml) was added dropwise. After 24 h, the solvent was removed *i.v.*, and the residue was purified by CC (CH_2Cl_2/MeOH 40:1). Yield: 1.230 g (84%) of **15**. White solid. M.p. 105.6–106.8°. IR: 3339v*s* (NH), 2992*m*, 2956*m*, 2838*m*, 1644v*s* (C=O), 1593*m*, 1253*s*, 1103*s* (C–O), 976*w*, 753*m*, 713*m*, 618*w*. ^{1}H-NMR: 0.98, 1.31 (2*s*, 2 Me_2C); 3.08 (*s*, CH_2O); 3.14 (*s*, MeN); 4.31 (*s*, PhCH_2); 6.96 (*s*, NH), 7.12–7.27 (*m*, 10 arom. H). ^{13}C-NMR: 22.8, 26.4 (2*q*, 2 Me_2C); 41.2 (*q*, MeN); 42.5, 57.4 (2*s*, 2 Me_2C); 73.3 (*t*, CH_2O); 76.4 (*t*, PhCH_2); 127.4, 127.5, 127.7, 127.9, 128.3, 129.1 (6*d*, 10 arom. CH); 137.6, 145.1 (2*s*, 2 arom. C); 173.2, 175.2 (2*s*, 2 C=O). ESI-MS: 405 (100, $[M+Na]^+$).

2-[(3-Benzyloxy-2,2-dimethylpropanoyl)amino]-2-methylpropanoic Acid (**16**). To a soln. of **15** (1.200 g, 3.14 mmol) in THF (5 ml), 3N HCl (5 ml) was added dropwise at 0°. The mixture was left overnight at r.t., the org. solvent was evaporated *i.v.*, and the residue was extracted with AcOEt. The combined org. fractions were washed with brine and dried ($MgSO_4$). After evaporation, the crystals were washed with Et_2O/hexane 2:1. Yield: 818 mg (89%). White crystals. M.p. 109.4–110.2°. IR: 3355v*s* (OH), 2989–2863*s* (br.), 1717v*s* (C=O), 1620v*s* (C=O), 1533v*s*, 1468*s*, 1397*s*, 1257*s*, 1162*s*, 1162*s*, 1092v*s*, 1012*m*, 930*m*, 829*s*, 753*s*, 704*m*, 693*m*. ^{1}H-NMR: 1.17, 1.46 (2*s*, 2 Me_2C); 3.44 (*s*, CH_2O); 4.56 (*s*, PhCH_2); 7.31–7.39 (*m*, 5 arom. H, NH). ^{13}C-NMR: 22.8, 24.8 (2*q*, 2 Me_2C); 42.5, 56.6 (2*s*, 2 Me_2C); 73.6 (*t*, CH_2O); 76.4 (*t*, Ph*C*H_2); 127.6, 127.9, 128.4 (3*d*, 5 arom. CH); 137.2 (*s*, 1 arom. C); 177.2, 178.0 (2*s*, 2 C=O). CI-MS: 295 (18), 294 (100, $[M+1]^+$).

*2-Methyl-2-{*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]carbamoyl}propyl 2-[(3-Benzyloxy-2,2-dimethylpropanoyl)amino]-2-methylpropanoate* (**17**). To a soln. of **16** (1.00 g, 3.41 mmol) in dry THF (15 ml), 1,1′-carbonyldiimidazole (CDI; 552 mg, 3.41 mmol) was added. After 2 h stirring at r.t., **6b** (934 mg, 3.41 mmol) was added, followed by the dropwise addition of a Na-imidazolide suspension (73 mg imidazole, 45 mg of a 60% NaH suspension in mineral oil and 3 ml of THF). After stirring overnight, the org. solvent was removed *i.v.*, and the residue was purified by CC (CH_2Cl_2/acetone 60:1). Yield: 1.276 g (66%) of **17**. White solid. M.p. 114.2–115.8°. IR: 3353*s* (NH), 2980*m*, 2934*m*, 2873*m*, 1739v*s* (C=O), 1702*m*, 1664v*s* (br., C=O), 1594*s*, 1520*s*, 1494*m*, 1454*m*, 1385*m*, 1382*m*, 1150v*s* (C–O), 1091*m*, 1023*m*, 923*m*, 904*m*, 738*m*, 705*m*. ^{1}H-NMR: 1.13, 1.14 (2*s*, 2 Me_2C); 1.44 (*s*, 2 Me_2C); 3.27 (*s*, MeN); 3.42 (*s*, CH_2OH); 4.03 (*s*, CH_2O); 4.57 (*s*, PhCH_2); 7.04 (*s*, NH); 7.21–7.41 (*m*, 10 arom. H, NH). ^{13}C-NMR: 22.3, 22.9, 24.7, 25.2 (4*q*, 4 Me_2C); 41.4 (*q*, MeN); 42.5, 42.7, 55.8, 58.3 (4*s*, 4 Me_2C); 70.9 (*t*, CH_2O); 73.5 (*t*, CH_2O); 76.6 (PhCH_2); 127.5, 127.7, 128.0, 128.3, 128.3, 129.3 (6*d*, 10 arom. H); 137.6, 144.3 (2*s*, 2 arom. C); 173.6, 173.7, 174.0, 175.8 (4*s*, 4 C=O). CI-MS: 590 (100, $[M+Na]^+$).

Compound **11**. To a soln. of **17** (1.200 g, 2.11 mmol) in dry CH_2Cl_2 (15 ml), 150 mg of Pd/C were added, and the mixture was stirred under an H_2 atmosphere at r.t. overnight. The suspension was filtered over *Celite*, and evaporated *i.v.* The product was used without further purification. Yield: 901 mg (89%) of **11**. White crystals. M.p. 139.2–140.3°. IR: 3358v*s* (OH), 3281*m*, 2981*m*, 2886*m*, 1746v*s* (C=O), 1664v*s*, 1623v*s*, 1592*s*, 1533v*s*, 1382*s*, 1264*s*, 1224*m*, 1144v*s*, 1140*m*, 1062*m*, 1024*w*, 781*m*, 708*s*. ^{1}H-NMR ((D$_6$)DMSO): 0.99, 1.04, 1.31, 1.38 (4*s*, 4 Me_2C); 3.20 (*s*, MeN); 3.34 (*d*, $^3J=6$, CH_2O); 3.91 (*s*, CH_2O); 4.97 (*t*, $^3J=6$, OH); 7.16–7.28 (*m*, 2 arom. H, NH); 7.30–7.40 (*m*, 3 arom. H); 7.58 (*s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 21.9, 22.1, 24.6, 25.9 (4*q*, 4 Me_2C); 41.6, 42.6, 54.8, 56.4 (4*s*, 4 Me_2C); 67.5, 69.9 (2*t*, 2 CH_2O); 126.3, 127.0, 128.7 (3*d*, 5 arom. CH); 137.8 (*s*, 1 arom. C); 172.3, 173.6, 173.7, 175.6 (4*s*, 4 C=O). ESI-MS: 500 (100, $[M+Na]^+$).

5. *Formation of 2-(2-Hydroxy-1,1-dimethylethyl)-4,4-dimethyl-1,3-oxazol-5(4*H*)-one* (**19**).

Procedure F. A soln. of **18** (103 mg, 0.5 mmol) and *N,N′*-dicyclohexylcarbodiimide (DCC; 104 mg, 0.5 mmol) in AcOEt (10 ml) was stirred overnight at r.t., then filtered, washed with AcOEt, and the solvent was evaporated *i.v.* Recrystallisation of the residue from MeCN yielded 33 mg (36%) of **19** as white crystals. M.p. 128.1–128.8°. IR: 3327v*s* (OH), 2928v*s*, 2850v*s*, 1836v*s*, 1626v*s*, 1574v*s*, 1536v*s*, 1436*m*, 1311*s*, 1271*m*, 1243*s*, 1088*s*, 1045*m*, 892*m*, 641*s*. ^{1}H-NMR ((D$_6$)DMSO): 1.13, 1.30 (2*s*, 2 Me_2C); 3.41 (*d*, $^3J=6$, CH_2OH); 4.91 (*t*, $^3J=6$, OH). ^{13}C-NMR ((D$_6$)DMSO): 21.3, 24.2 (2*q*, 2 Me_2C); 64.9, 67.4 (2*s*, 2 Me_2C); 166.6 (*s*, C=N); 181.8 (*s*, C=O). CI-MS: 204 (100, $[M+NH_4]^+$), 186 (30, $[M+1]^+$), 174 (10), 158 (6).

Procedure G. A soln. of **18** (103 mg, 0.5 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (86 mg, 0.5 mmol) in AcOEt (10 ml) was stirred overnight at r.t., then washed with brine, and extracted with AcOEt. The combined org. fractions were dried ($MgSO_4$), the solvent was evaporated *i.v.*, and the residue was purified by CC (CH_2Cl_2/acetone 150:1). Yield: 26 mg (28%) of **19**.

Procedure H. A soln. of **18** (103 mg, 0.5 mmol) and 4-(dimethylamino)pyridine (DMAP; 66 mg, 0.5 mmol) in CH_2Cl_2 (10 ml) was stirred for 15 min at r.t. Then, DCC (103 mg, 0.5 mmol) was added. The mixture was left overnight, then filtered, washed with AcOEt, and the solvent was evaporated *i.v.* Purification by CC (CH_2Cl_2/acetone 150:1) yielded 42 mg (45%) of **19**.

A suspension of **19** (185 mg, 1 mmol) in dry toluene (50 ml) was heated to 100°, and HCl gas was bubbled through the suspension for 3 min. Workup as described in *Procedure A* gave 159 mg (86%) of **10**.

6. *Synthesis and Cyclization of 1-(Ethoxycarbonyl)-1-methylethyl 3-Hydroxy-2,2-dimethylpropanoate* (**22**) *1-(Ethoxycarbonyl)-1-methylethyl 3-Benzyloxy-2,2-dimethylpropanoate* (**21**). To a soln. of **14** (1.00 g, 3.41 mmol) in dry THF (15 ml), CDI (552 mg, 3.41 mmol) was added, and the mixture was stirred at r.t. for 2 h. Then, methyl 2-hydroxy-2,2-dimethylethanoate (450 mg, 3.41 mmol) was added, followed by the dropwise addition of 3 ml of a Na-imidazolide suspension (73 mg of imidazole, 45 mg of a 60% NaH suspension in mineral oil, and 3 ml of THF). After stirring overnight, the org. solvent was removed *i.v.*, and the residue was purified by CC (CH_2Cl_2/acetone 100:1). Yield: 780 mg (48%) of **21**. Colorless oil. IR (film): 2983*m*, 1743v*s* (C=O), 1471*w*, 1383*w*, 1293*m*, 1179*s* (C–O), 1130*s* (C–O), 1028*m*, 738*w*, 698*w*. ^{1}H-NMR: 1.21 (*s*+*t*, Me_2C, *Me*CH_2O); 1.52 (*s*, Me_2C); 3.47 (*s*, CH_2O); 3.76 (*q*, MeCH_2O); 4.52 (*s*, PhCH_2); 7.25–7.32 (*m*, 5 arom. H). ^{13}C-NMR: 13.9 (*q*, Me); 22.2, 24.3 (2*q*, 2 Me_2C); 43.4 (*s*, Me_2C); 60.9 (*t*, Me*C*H$_2$O); 73.2 (*t*, CH_2O); 76.7 (*t*, PhCH_2); 77.9 (*s*, Me_2C); 127.2, 127.3, 128.1 (3*d*, 5 arom. CH); 138.5 (*s*, 1 arom. CH); 172.5, 175.1 (2*s*, 2 C=O). ESI-MS: 345 (100, $[M+Na]^+$).

Compound **22**. To a soln. of **21** (900 mg, 2.79 mmol) in dry CH_2Cl_2 (15 ml), 120 mg of Pd/C were added, and the mixture was stirred under H_2 atmosphere at r.t. overnight. The suspension was filtered over *Celite*, and evaporated *i.v.* The product was used without further purification. Yield: 589 mg (91%) of **22**. Colorless oil. IR (film): 3528*w* (br.), 2885*m*, 2939*m*, 1743v*s* (C=O), 1474*m*, 1296*s*, 1180*m* (C–O), 1128*s* (C–O), 1053*m*, 882*w*,

Table. *Crystallographic Data of Compounds* **6a**, **6b**, **10**, **11**, **18**, **19**, *and* **23**

	6a	**6b**	**10**	**11**	**18**	**19**	**23**
Crystallized from	$CDCl_3$/AcOEt/acetone	toluene/CH_2Cl_2/AcOEt	$CDCl_3$/MeOH	CH_2Cl_2/i-PrOH/hexane	toluene/acetone/i-PrOH	MeCN/acetone/CH_2Cl_2	CH_2Cl_2/acetone
Empirical formula	$C_{11}H_{22}N_2O_3$	$C_{16}H_{24}N_2O_3$	$C_{18}H_{30}N_2O_6$	$C_{25}H_{39}N_3O_6$	$C_9H_{17}NO_4$	$C_9H_{15}NO_3$	$C_{15}H_{24}O_6$
Formula weight [g mol^{-1}]	230.31	292.38	370.44	477.60	203.24	185.22	300.35
Crystal color, habit	yellow, prism	colorless, prism	colorless, prism	colorless, prism	yellow, plate	colorless, prism	colorless, plate
Crystal dimensions [mm]	$0.12 \times 0.20 \times 0.25$	$0.18 \times 0.20 \times 0.25$	$0.10 \times 0.12 \times 0.20$	$0.10 \times 0.12 \times 0.20$	$0.02 \times 0.15 \times 0.17$	$0.15 \times 0.15 \times 0.25$	$0.02 \times 0.18 \times 0.23$
Temp. [K]	160(1)	160(1)	160(1)	160(1)	160(1)	160(1)	160(1)
Crystal system	monoclinic	triclinic	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P\bar{1}$	$P2_1/c$	$P2_1$	$P2_1/n$	$P2_1/c$	$P2_1/c$
Z	4	4	2	2	4	8	8
Reflections for cell determination	3944	9546	2273	3173	2004	3721	5976
2θ Range for cell determination [°]	4 – 60	2 – 60	4 – 55	4 – 55	4 – 50	4 – 50	4 – 50
Unit cell parameters a [Å]	8.6612(1)	8.9268(1)	9.1635(2)	9.3227(2)	8.2708(2)	11.7684(5)	9.8304(1)
b [Å]	10.4339(2)	11.9930(1)	9.6501(2)	11.1213(2)	8.2429(2)	10.5276(4)	11.9228(2)
c [Å]	14.4276(2)	16.4091(2)	10.8786(3)	12.8333(3)	15.7690(4)	16.1536(8)	27.7139(5)
α [°]	90	99.0727(5)	90	90	90	90	90
β [°]	100.5340(6)	92.8174(5)	103.3648(8)	99.6690(9)	98.9548(9)	90.464(2)	97.1582(6)
γ [°]	90	108.5531(6)	90	90	90	90	90
V [Å^3]	1281.85(3)	1635.33(3)	935.93(4)	1311.66(5)	1061.95(5)	2001.3(2)	3222.92(9)
D_x [g cm^{-3}]	1.193	1.187	1.314	1.209	1.271	1.229	1.238
$\mu(\mathrm{Mo}K_\alpha)$ [mm^{-1}]	0.0863	0.0820	0.0981	0.0861	0.0992	0.0918	0.0948
Scan type	ϕ and ω	ϕ and ω	ϕ and ω	ϕ and ω	ω	ϕ and ω	ϕ and ω
$2\theta_{(\max)}$ [°]	60	60	55	55	50	50	50
Total reflections measured	36257	68555	21539	32002	14054	30962	51446
Symmetry independent reflections	3749	9576	2140	3177	1859	3521	5680
Reflections with $I > 2\sigma(I)$	3038	6579	1713	2118	1330	2425	3981
Reflections used in refinement	3749	6579	1713	3176	1330	3521	5677
Parameters refined	160	396	119	329	139	252	392
R [on$F$; $I > 2\sigma(I)$ reflections]	0.0432	0.0500	0.0412	0.0410	0.0411	0.0570	0.0436
wR [on$F$; $I > 2\sigma(I)$ reflections]	–	0.0496	0.0447	–	0.0379	–	–
wR [onF^2; all indept. reflections]	0.1204	–	–	0.0965	–	0.1556	0.1120
Weighting parameter [p][a])	–	0.005	0.005	–	0.005	–	–
Weighting parameters [a; b][b])	0.0527; 0.3914	–	–	0.0436; 0	–	0.0585; 0.9613	0.0552; 0.1627
Goodness-of-fit	1.046	2.870	2.901	0.995	1.865	1.090	1.037
Secondary extinction coefficient	0.029(5)	$2.7(3) \times 10^{-6}$	$3.9(8) \times 10^{-6}$	0.025(3)		0.011(2)	0.0036(6)
Final $\Delta_{\max}/\sigma$	0.001	0.0004	0.0004	0.001	0.0002	0.001	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.34; −0.36	0.28; −0.22	0.25; −0.20	0.18; −0.19	0.18; −0.21	0.22; −0.22	0.20; −0.21

[a]) $w^{-1} = \sigma^2(F_o) + (pF_o)^2$. [b]) $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$ where $P = (F_o^2 + 2F_c^2)/3$.

758*w*, 670*w*. ^{1}H-NMR: 1.11 (*s*, *Me*$_2$C); 1.22 (*t*, *Me*CH$_2$O); 1.53 (2*s*, 2 *Me*$_2$C); 3.53 (*d*, CH$_2$OH); 4.13 (*q*, MeC*H*$_2$O). ^{13}C-NMR: 13.8 (*q*, Me); 21.5, 24.4 (2*q*, 2 *Me*$_2$C); 44.3 (*s*, Me$_2$*C*); 61.3 (*t*, Me*C*H$_2$O); 70.0 (*t*, CH$_2$O); 78.5 (*s*, Me$_2$*C*); 172.6, 176.1 (2*s*, 2 C=O). ESI-MS: 255 (100, [*M* + Na]$^+$).

3,3,7,7,11,11-Hexamethyl-1,5,9-trioxacyclododecane-2,6,10-trione (**23**) *and 3,3,7,7,11,11,15,15-Octamethyl-1,5,9,13-tetraoxacyclohexadecane-2,6,10,14-tetraone* (**24**). To a soln. of **22** (232 mg, 1 mmol) in dry toluene (5 ml), NaH (40 mg of a 60% suspension in mineral oil, 1 mmol) was added slowly at 0° and under constant stirring (N$_2$ atmosphere). After 5 h at 80°, the mixture was acidified with 0.1N HCl (*ca.* 6 ml) to pH 5 and extracted with CH_2Cl_2 . The combined org. fractions were dried ($MgSO_4$) and evaporated *i.v.* The crystalline residue was purified by CC (CH_2Cl_2/acetone 200:1) to yield 24 mg (8%) of **23**. (M.p. 132.1–134.2°) [57] and 38 mg (9.5%) of **24**. M.p. 1446.–146.0°) [57].

7. *X-Ray Crystal-Structure Determination of* **6a**, **6b**, **10**, **11**, **18**, **19**, *and* **23** (*Table* and *Figs.* 1–5)[3]). All measurements were made on a *Nonius KappaCCD* diffractometer [58] with graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. The data collection and refinement parameters are given in the *Table* and views of the molecules are shown in *Figs. 1–5*. Data reductions were performed with *HKL Denzo* and *Scalepack* [59]. The intensities were corrected for *Lorenz* and polarization effects, but not for absorption. The structures were solved by direct methods using SIR92 [60], which revealed the positions of all non-H-atoms. There were two symmetry-independent molecules in the asymmetric units of **6b**, **19**, and **23**. In each case, the atomic coordinates of the two molecules were tested carefully for a relationship from a higher symmetry space group with the program PLATON [61], but none could be found. The non-H-atoms were refined anisotropically. Except for **10**, the amide and OH H-atoms in the structures 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 in all structures were placed in geometrically calculated positions, and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent atom (1.5U_{eq} for the Me groups of **6a**, **11**, **19**, and **23**). For **6b**, **10**, and **18**, each structure was refined on F using full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o| - |F_c|)^2$. Refinement of the remaining structures was carried out on F^2 by minimizing the corresponding function based on F^2. Corrections for secondary extinction were applied with the exception of **18**. In **6b**, **10**, **11**, **18**, and **23**, six, two, one, three, and three reflections, respectively, were omitted from the final refinement of each structure because their observed intensities were much lower than the calculated values as a result of being partially obscured by the beam stop. Neutral-atom scattering factors for non-H-atoms were taken from [62a] and the scattering factors for H-atoms were taken from [63]. Anomalous dispersion effects were included in F_c [64]; the values for f' and f'' were those of [62b]. The values of the mass attenuation coefficients are those of [62c]. All calculations were performed using the teXsan crystallographic software package [65] for **6b**, **10**, and **18**, and the SHELXL97 program [66] for **6a**, **11**, **19**, and **23**.

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[3]) CCDC-210670-210676 contain supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB12 1EZ, UK (fax : +44-(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk))

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Received May 22, 2003