Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 1079–1094

14-Membered cyclodepsipeptides with alternating β-hydroxy and α-amino acids by cyclodimerization

Boyan Iliev, Anthony Linden, Roland Kunz and Heinz Heimgartner*

Institute of Organic Chemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland

Received 6 October 2005; revised 28 October 2005; accepted 2 November 2005

Available online 28 November 2005

Abstract—The cyclodimerization (twinning) of β-hydroxy acid amides of type **1** under 'direct amide cyclization' (DAC) conditions is described. Although other coupling methods also gave moderate results, best yields were obtained via DAC, reaching 88% for the cyclodimer **10**. In all cases, when starting with racemic material, only the trans-substituted cyclodepsipeptides were isolated. Simple molecular modeling revealed that the formation of the cyclodimer is thermodynamically slightly more favorable than that of the cyclomonomer. The proposal that cyclodimer formation is preferred because of the presence of intramolecular H-bonds could not be confirmed by X-ray crystallography. The influence of substituents, both in the amino acid and in the hydroxy acid moieties, was also studied. It is shown, that cyclodimerization was successful only when the hydroxy acid moiety is α,α-disubstituted.

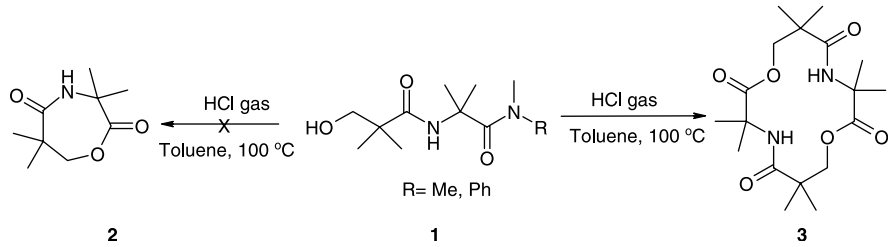
1. Introduction

In a recent paper,[1] we reported that amides **1**, when subjected to the conditions of the 'direct amide cyclization' reaction,[2–9] yielded only the dimerized product **3**. The 14-membered cyclodepsipeptide **3** was isolated as the sole product and none of the expected seven-membered monomer **2** could be detected (Scheme 1).

In order to explain this unexpected result, we investigated some other lactonization methods with derivatives of **1**, including that described by Richard et al.,[10] which, in the case of ethyl 6-hydroxyhexanoates, had resulted in the formation of seven-membered lactones. Again, in all experiments with derivatives of **1**, where a defined product could be isolated, we obtained only the dimeric product **3**.

Cyclic 14-membered depsipeptides with the same ring skeleton as **3** have been known since the 1960s, and the dimerization process is not as surprising as it seems at first. Since the discovery, isolation, and identification of serratamolide (**4**: R=H, R′=$(CH_2)_6CH_3$, Scheme 2) from *Serratia marcescens* in 1961,[11] the proof of its antibiotic activity,[12] and its first total synthesis by Shemyakin et al.,[13] the interest in depsipeptides containing β-hydroxy acids has increased significantly, mainly because of their antibiotic properties. The other important biological role of the same compound is its use as a surface-active agent under the name of serrawettin W1,[14] and it has been patented for use as a pesticide as well.[15]

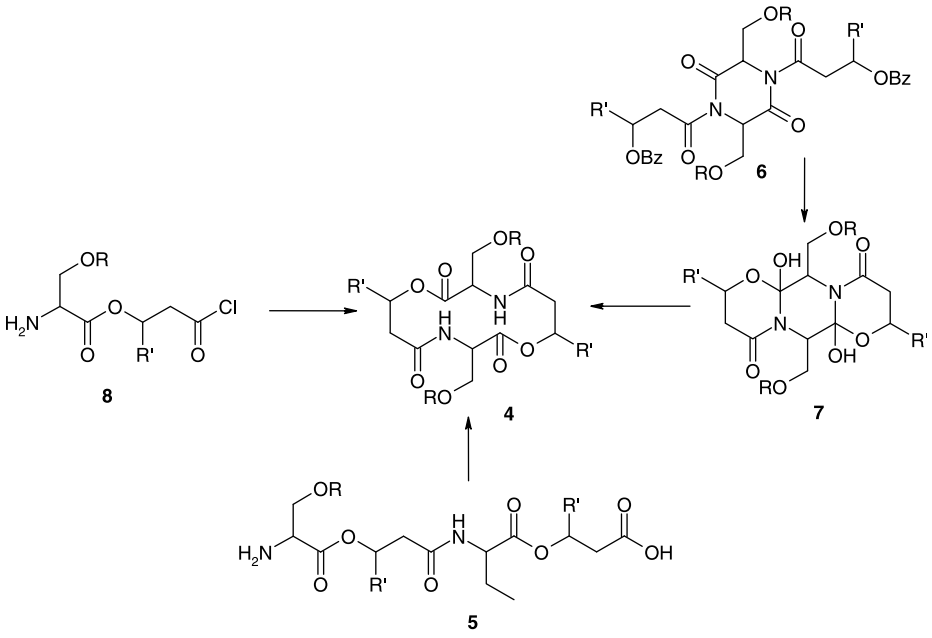
The synthetic pathways to serratamolide (**4**) and its derivatives are numerous, but the approaches can be divided



Scheme 1.

Keywords: Cyclodepsipeptides; Cyclodimerization; Twinning; 2*H*-Azirin-3-amines; 1,3-Oxazole-5(4*H*)-ones.
* Corresponding author. Tel.: +41 44 6354282; fax: +41 44 6356836; e-mail: heimgart@oci.unizh.ch

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.002



Scheme 2.

into three main groups: classical ring closure of linear precursors, usually by lactam bond formation (**5**→**4**), ring enlargement (**6**→**7**→**4**), and cyclization by twinning (**8**→**4**) (Scheme 2).

The main feature of the last-mentioned method is that the cyclization is performed with the monomeric linear precursor, and the twinning, or cyclodimerization, takes place during the course of the reaction. Some basic theories have been offered as an explanation of this dimerization. One of the most popular proposals states that it is mainly due to intermolecular hydrogen bonding between carbonyl and amine groups that are formed during the reaction.[16,17] In the case of **4**, the two planar *trans*-amide groups form a trans-annular hydrogen bond (intramolecular) and thus favor the formation of a 14-membered ring. That no monomeric product was formed in the reaction can probably be explained by the fact that such an intramolecular interaction would not be possible within a seven-membered ring. However, the contribution of hydrogen bonding tends to be overestimated as some dimerizations also take place in polar solvents, which could interfere with such an intramolecular interaction.[17] Another theory proposed by Ovchinnikov et al.[18] is that the cyclization is preceded by a linear polycondensation, which results in linear dimers and oligomers, which, under the conditions of high dilution, may undergo cyclization. The extent of the ring closure is determined principally by the most stable conformation of a given linear peptide, being close to that of the cyclic product. On the other hand, the formation of trimers seems to be statistically unfavorable.

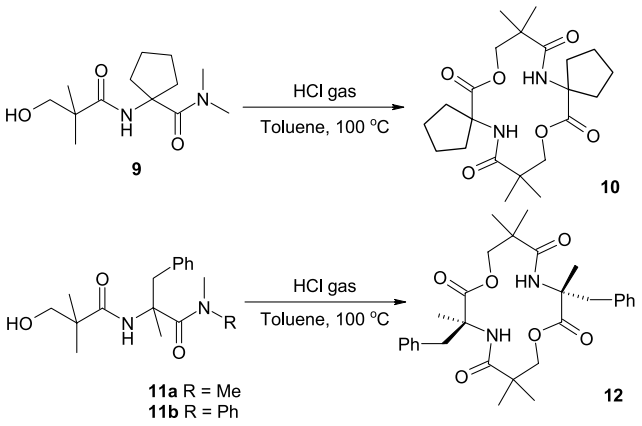
The reason for the preferred dimerization in the case of **1** is most probably a defined conformation of the linear precursor and the stability of the transition state. Another reason could be the rigidity of the amide bond in **1**, although the reactions with an ester analogue of compound **1** showed that again oligomerization occurred to give tri- and tetrameric structures of the β-hydroxy acid.[1] Therefore, most probably the dimerization is not a result of the amide bond rigidity.

In order to further investigate the cyclodimerization of dipeptide analogues of type **1** under the conditions of the 'direct amide cyclization' we synthesized some other amide precursors, which differ in the substitution in the α-amino acid as well as in the β-hydroxy acid moiety, including chiral compounds. Furthermore, we tried to get some information from computer modeling of key compounds.

2. Results and discussion

It is known from previous experiments[5–7,19,20] that dipeptides of type **1**, in which the two methyl groups in the amino acid residue are replaced by a cyclopentane ring (i.e., the compounds contain 1-aminocyclopentane carboxylic acid instead of 1-aminoisobutyric acid (Aib)), react in a very similar way to **1**. Therefore, our first target was amide **9**, which was conveniently prepared by the coupling of 3-hydroxy-2,2-dimethylpropanoic acid with *N*,*N*-dimethyl-1-azaspiro[2.4]hept-1-en-2-amine in analogy to Ref. 1 ('azirine/oxazolone method'; see also Ref. 21). After bubbling HCl gas through a solution of **9** in toluene (20 mM) at 100 °C for 4 min, 88% of the corresponding 14-membered cyclodepsipeptide **10** was obtained (Scheme 3). Similarly, the linear racemic dipeptides **11a**,**b**[22] carrying two different substituents on the C(α) atom, were also synthesized by the 'azirine/oxazolone method'. 'Direct amide cyclization' of **11b** yielded, upon cyclization, 68% of the dimeric *meso*-compound **12** as the sole product.

This was clearly indicated by the ^{1}H and ^{13}C NM spectra, which show only one set of signals. The structures of **10** and **12** were established by X-ray crystallography (Fig. 1).



Scheme 3.

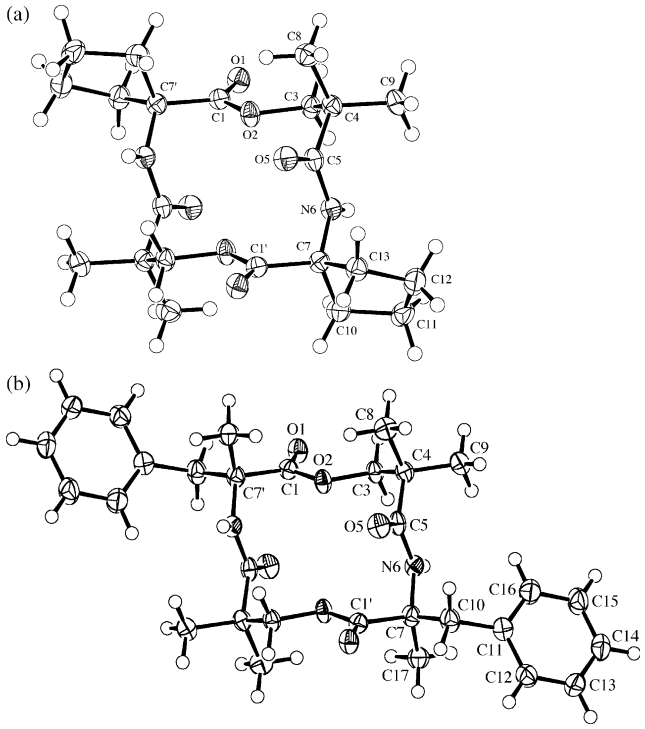
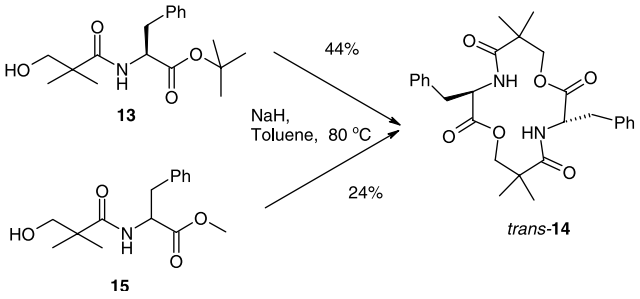


Figure 1. ORTEP plots[23] of the molecular structures of (a) **10** and (b) **12** (50% probability ellipsoids, arbitrary numbering of atoms).

The backbones of the two structures are very similar and also resemble the structures of the previously reported tetramethyl analogue **3**.[1] In the case of **10**, the molecule sits about a crystallographic centre of inversion. The cyclopentane ring has an envelope conformation with the spiro C-atom as the envelope flap. Each amide NH group forms an intermolecular hydrogen bond with a lactone carbonyl O-atom of an adjacent molecule. The molecular symmetry results in there being two parallel hydrogen bonds running in opposite directions between each molecule. These interactions link the molecules into extended double-bridged chains, which run parallel to the [1 0 0] direction. Taken individually, the repeat unit in the chain generated by one of the interactions has a graph set motif[24] of C(5). The pair of hydrogen bonds linking two adjacent molecules forms a loop with a graph set motif of $R_2^2(16)$. In the case of **12**, the space group is centrosymmetric and the molecule again sits about a crystallographic centre of inversion. Therefore, **12** has the (7*RS*,7′*SR*)-configuration, that is, **12** is the trans-isomer. The hydrogen bonding pattern in the crystals of **12** is the same as for **10**.

The nature of the cyclodimerization in the case of **11** is remarkable. Starting with a racemic precursor **11**, one would expect that a mixture of cis- and trans-substituted cyclodimers would be obtained, but only the trans-isomer **12** has been formed in 68% yield.

As mentioned before, factors that might influence the cyclization are not only the type, but also the number of substituents in the amino acid moiety. Therefore, a cyclization experiment was carried out with an analogue of **11**, which contains a monosubstituted amino acid. Direct amide cyclization was not an option in this case, since the intermediate oxazolone does not form smoothly in the case of monosubstituted substrates.[25] Therefore, we used the base catalyzed lactonization described in Ref. 10. When a solution of the enantiomerically pure **13** was heated in toluene (200 mM) in the presence of 1 equiv of NaH, the 14-membered cyclic depsipeptide *trans*-**14** was obtained as the only isolable product in 44% yield. In order to compare the configurations of the two stereogenic centers, the analogous cyclization was performed with a racemic starting material, that is, methyl ester **15** (Scheme 4). Surprisingly, a single cyclodepsipeptide was again obtained in 24% yield and was identical with *trans*-**14** in all respects.



Scheme 4.

The ^{1}H NMR spectrum of the cyclized product obtained from **13** using a shift reagent (Pirkle reagent) and HPLC on a chiral adsorbent (Chiracel OD-H, Merck Whelk-O 1) showed the presence of only one compound, which was identical with the product obtained from the cyclization of **15**. X-ray crystallography of both products confirmed their identical structure and proved that the benzyl groups are trans-oriented (Fig. 2). The space group of *trans*-**14** is centrosymmetric and the molecule sits about a crystallographic centre of inversion, so the two stereogenic centres have inverted configurations, that is, (7*RS*,7′*SR*). The hydrogen bonding pattern is again analogous to that of **12** and **10**.

As the precursor **13** was optically active ($[\alpha]_D^{25}$ +44.6 (*c* 1, $CHCl_3$)), an inversion of the configuration at one of the stereogenic centers has taken place during the cyclization step. With the aim of avoiding this inversion, another cyclization was attempted with the corresponding free hydroxy acid **16**, which was obtained from the basic

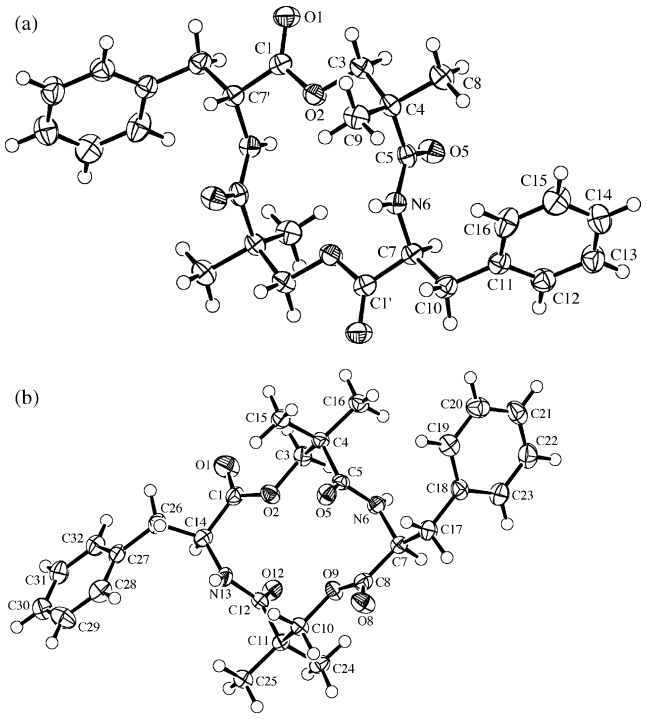


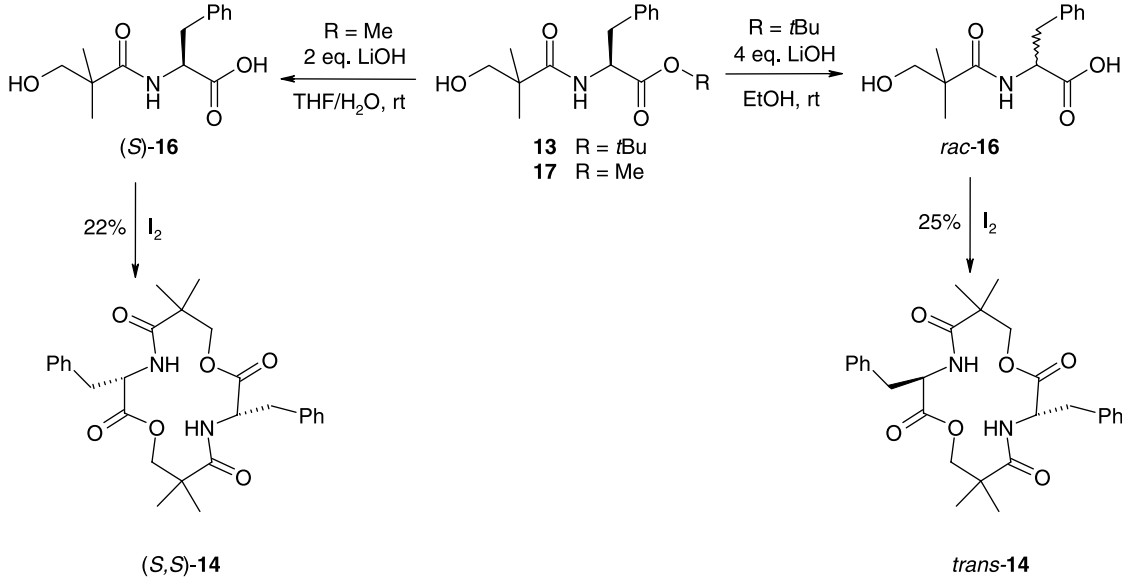
Figure 2. ORTEP plots[23] of the molecular structures of (a) *trans*-**14** and (b) molecule A of (*S*,*S*)-**14** (50% probability ellipsoids, arbitrary numbering of atoms).

hydrolysis of **13**. Cyclization of both *rac*-**16** and (*S*)-**16** was achieved under neutral conditions using I_2 as a catalyst,[26] which has previously proven to be efficient for the synthesis of depsipeptide **3**.[1] The product obtained from *rac*-**16** was again the *meso*-compound *trans*-**14a**, while the enantiomerically pure acid (*S*)-**16**, obtained by a milder hydrolysis of its methyl ester **17**, yielded also only one cyclodepsipeptide, namely (*S*,*S*)-**14** (Scheme 5).

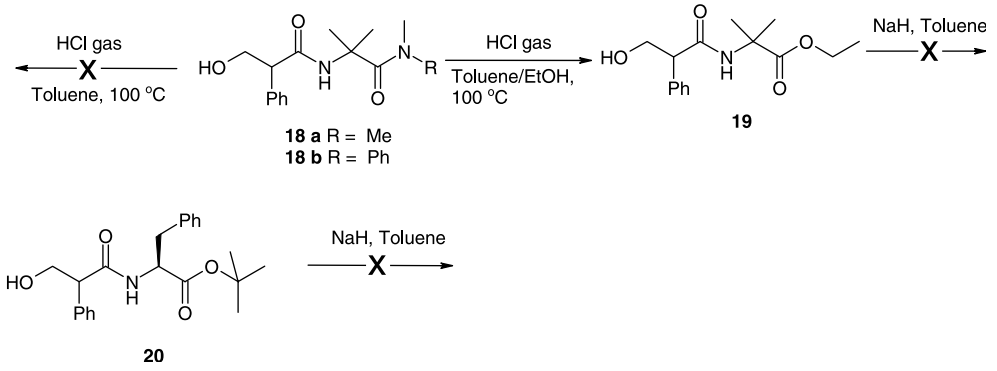
Analytical HPLC of both of these compounds on a chiral column (Whelk-O 1 column, hexane/EtOH 10:1) clearly shows two different peaks with retention times of 10.8 and 10.9 min, respectively. The HPLC diagram of a mixture of the two compounds under the same conditions also showed two peaks, proving once more their different structure. Furthermore, it was shown, that (*S*,*S*)-**14** is optically active. For this reason, we expected that it is the cis-isomer with the (*S*,*S*)-configuration, which was subsequently proven by X-ray crystallography (Fig. 2).

In the crystal structure of (*S*,*S*)-**14**, there are two symmetry-independent molecules A and B in the asymmetric unit, but the conformations of the two molecules are almost identical. The space group permits the compound in the crystal to be enantiomerically pure, but the absolute configuration of the molecule has not been determined. The enantiomer used in the refinement was based on the expected (*S*)-configuration of each chiral centre in the molecule. The crystal is merohedrally twinned, with twin operator [1 0 0/0 −1 0/0 0 −1] and the major twin domain has a volume fraction of 0.640(1). Each amide group in molecule A forms an intermolecular hydrogen bond with an amide O-atom of an adjacent molecule A. This results in there being two parallel hydrogen bonds running in opposite directions between each molecule. The interactions link the molecules into extended double-bridged ···A···A···A··· chains, which run parallel to the [1 0 0] direction. Taken individually, the repeat unit in the chain generated by one of the interactions has a graph set motif[24] of C(4). The pair of hydrogen bonds linking two adjacent molecules forms a loop with a graph set motif of $R_2^2(18)$. The molecules of type B are similarly linked into extended double-bridged ···B···B···B··· chains, which also run parallel to the [1 0 0] direction.

From these results it could be concluded that monosubstituted amino acids in amides of type **1** do not prevent the cyclodimerization. Next, the influence of the disubstitution of C(α) of the β-hydroxy acid should be investigated and, therefore, analogous dipeptides containing a α-monosubstituted β-hydroxy acid were synthesized and subjected to cyclization procedures. Tropic acid (3-hydroxy-2-phenylpropanoic acid) turned out to be an interesting starting material



Scheme 5.



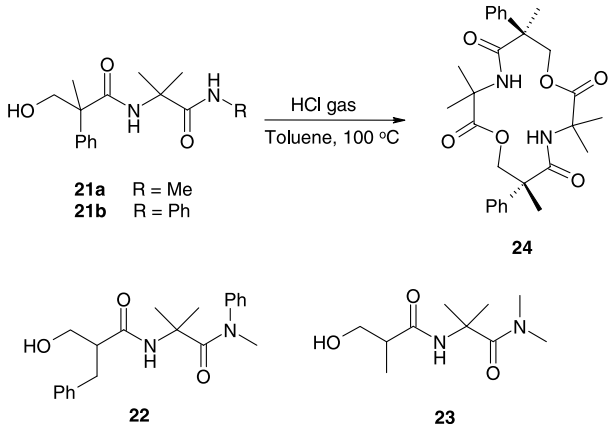
Scheme 6.

for this study. Thus, amides **18a** and **18b** were prepared by coupling tropic acid with 2,2,*N*,*N*-tetramethyl-2*H*-azirin-3-amine and 2,2, *N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine, respectively, and subjected to the conditions of the 'direct amide cyclization'. Surprisingly, the cyclization failed and only traces of the corresponding 1,3-oxazol-5(4*H*)-one were identified in the crude reaction mixture by IR and NMR spectroscopy. Column chromatography led to no identifiable products. Furthermore, the corresponding ethyl ester **19**, derived from either of the amides **18** by treatment with HCl gas in the presence of EtOH, did not yield cyclic products upon treatment with NaH. Other lactonization procedures, proven to be successful in the case of amide derivatives,[1] also failed to give the desired cyclic depsipeptide in this case (Scheme 6).

When tropic acid was coupled with L-phenylalanine *t*-butylester.HCl, amide **20** was obtained as a mixture of two diastereoisomers. They were separated on a Whelk-O 1 preparative HPLC column, and we attempted to cyclize each of them, in order to determine the stereospecificity of the NaH cyclization. Unfortunately both the racemic and the enantiomerically pure substrates failed to give cyclic depsipeptides (Scheme 6).

The reason for the failure of cyclization of **18**–**20** could be a steric hindrance of the phenyl group in the α-position or its electronic effect. To examine this possibility, 3-hydroxy-2-methyl-2-phenylpropanoic acid was prepared[27] and coupled with the corresponding 2*H*-azirin-3-amines to give **21a**,**b**. The third explanation could be that the cyclization is thermodynamically unfavorable when the substrate is monosubstituted in the α-position of the β-hydroxy acid moiety. Therefore, α-benzyl-β-hydroxypropanoic acid and β-hydroxyisobutyric acid were synthesized according to known procedures[28] and coupled with 2,2,*N*,*N*-tetramethyl-2*H*-azirin-3-amine to give amides **22** and **23**, respectively, as substrates for the cyclization (Scheme 7).

As expected, amide **21b** cyclized under DAC conditions to yield the 14-membered cyclodepsipeptide **24** in moderate yield. This result suggests that amides of type **18/21** bearing a phenyl group at C(α) of the hydroxy acids do cyclize when α,α-disubstituted, that is, the phenyl group in **18** was not the reason for its failure to give cyclic products. Compound **24** was isolated as a colorless solid, which showed only one set of signals in the NMR spectra. Therefore it could be suggested that only one stereoisomer, as a *meso*-compound, has been obtained. Careful crystallization from a mixture of toluene/acetonitrile/acetone gave crystals suitable for X-ray crystallography. The molecular structure of **24** is depicted in Figure 3, showing that again the trans-isomer has been obtained.



Scheme 7.

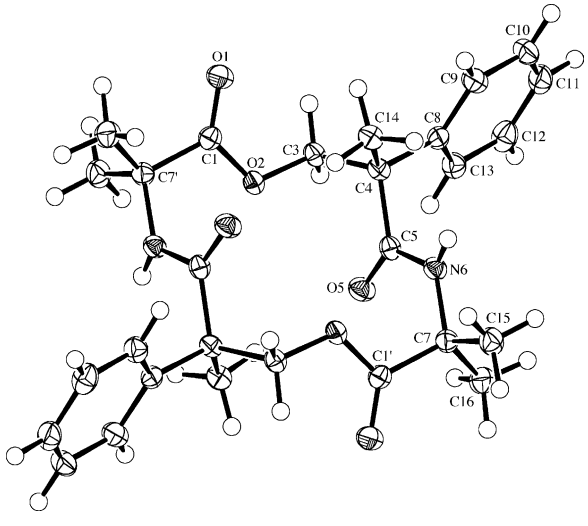


Figure 3. ORTEP plot[23] of the molecular structure of **24** (50% probability ellipsoids, arbitrary numbering of atoms).

Since the space group is centrosymmetric, **24** is a *meso*-compound. The molecule sits about a crystallographic centre of inversion, so therefore has the (4*RS*,4′*SR*)-configuration. Remarkably, the amide groups are not involved in any

hydrogen bonds. Although amide O-atoms in adjacent molecules appear to be positioned correctly to accept a hydrogen bond from the amide H-atom, the H···O distance of 2.98 Å is much too long for it to be considered a hydrogen bond. This is probably the result of molecular bulk preventing the molecules packing close enough together for intermolecular hydrogen bonds to form.

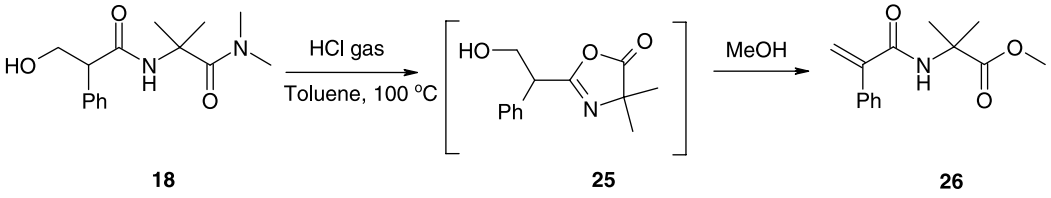
Amides **22** and **23** failed to cyclize under the DAC reaction conditions, as was the case with **18**. Upon monitoring the reaction of **18** by IR spectroscopy, the formation of the corresponding 1,3-oxazol-5(4*H*)-one **25**, which is the expected intermediate in the cyclization reaction, was observed (strong absorption at 1820–1830 cm^{-1}),[29] and after addition of methanol to the reaction mixture, methyl ester **26** was isolated in 58% yield (Scheme 8).

The formation of a methyl ester and the IR spectra strongly suggest the presence of a 1,3-oxazol-5(4*H*)-one as an intermediate. It seems that the oxazolone formation and dehydration in the case of **18** are competitive reactions. In order to get an indication of which reaction takes place first, a similar set of experiments was carried out with benzyl derivative **22**. Upon bubbling HCl gas through a solution of **22** in toluene/methanol (20%), the only product obtained was the corresponding hydroxy ester **27** (Scheme 9). When the reaction was carried out under the conditions described for **18**, that is, oxazolone formation with HCl gas in toluene (monitoring by IR, increasing absorption at 1826 cm^{-1}) and addition of methanol after saturation, the dehydrated ester **28** and the dehydrated amide **29** were obtained in addition to **27** (Scheme 9).

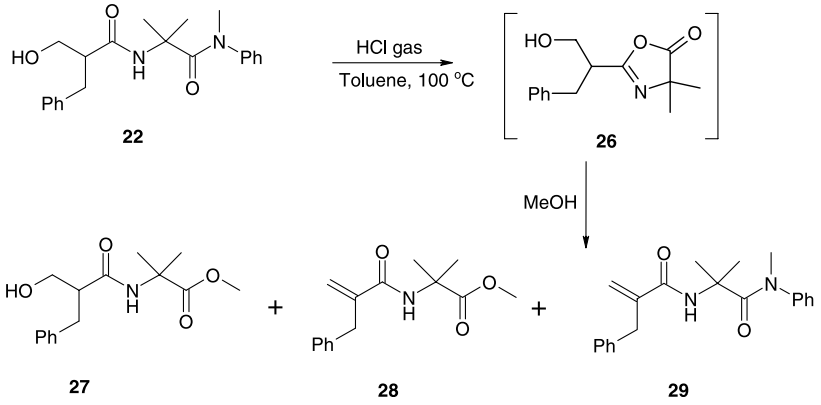
This result suggests that when the reaction is carried out in the presence of a nucleophile, such as methanol, oxazolone **26** is formed first and is immediately transformed into the corresponding hydroxy ester **27**. On the other hand, in the absence of a nucleophile, the intermediate oxazolone **26** eliminates water, leading to 2-vinyl oxazolones and thus preventing further cyclization. The formation of **28** and **29** can be explained by the competitive ring opening of **26** by the nucleophiles methanol and *N*-methylaniline, respectively. This result is an additional indication that the cyclodimerization process occurs via an oxazolone intermediate.

Another variation of the starting materials for the direct amide cyclization (DAC) is the insertion of aromatic β-hydroxy acids or β-hydroxycycloalkane carboxylic acids. The first of these derivatives, salicylamide **30**, was obtained from salicylic acid by coupling with the corresponding 2*H*-azirin-3-amine (Scheme 10).[5,19]

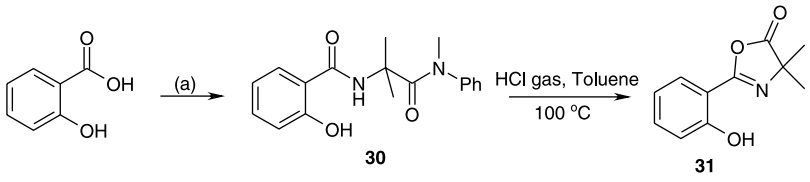
Compound **30** was subjected to the DAC conditions. The starting material disappeared quickly (TLC), but even after



Scheme 8.

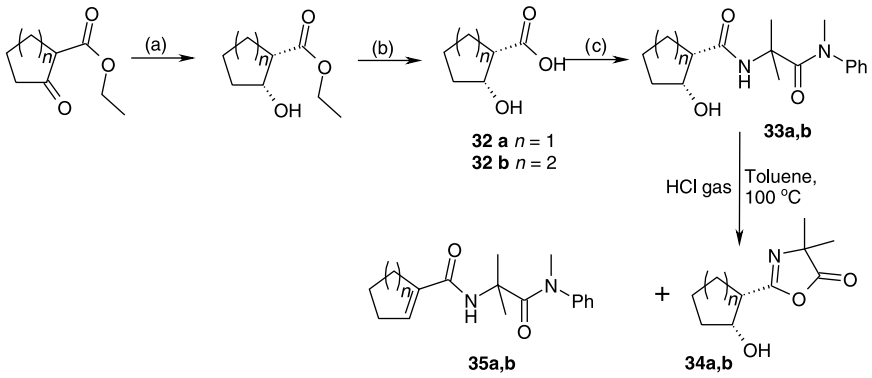


Scheme 9.



(a) 2,2,*N*-Trimethyl-*N*-phenyl-2*H*-azirin-3-amine,THF

Scheme 10.



(a) Yeast, H_2O; Ref. 32; (b) LiOH, THF/H_2O; (c) 2,2,*N*-Trimethyl-*N*-phenyl-2*H*-azirin-3-amine,THF.

Scheme 11.

35 min the only product formed was the corresponding oxazolone **31**. After its isolation, further exposure to the same reaction conditions did not propagate the reaction further, and the oxazolone **31** was recovered. The stability of the oxazolone is in this case extremely high, and apparently a ring enlargement reaction is sterically disfavored.

Crystals of **31** suitable for X-ray crystal structure determination were grown from a mixture of deuterochloroform and dichloromethane by slow evaporation of the solvent. The five-membered heterocycle is planar and the phenyl residue is almost coplanar with the ring. The hydroxy group forms an intramolecular hydrogen bond with the imine N-atom. The interaction can be described by the graph set motif[24] of S(6) (for crystallographic details see Section 4).

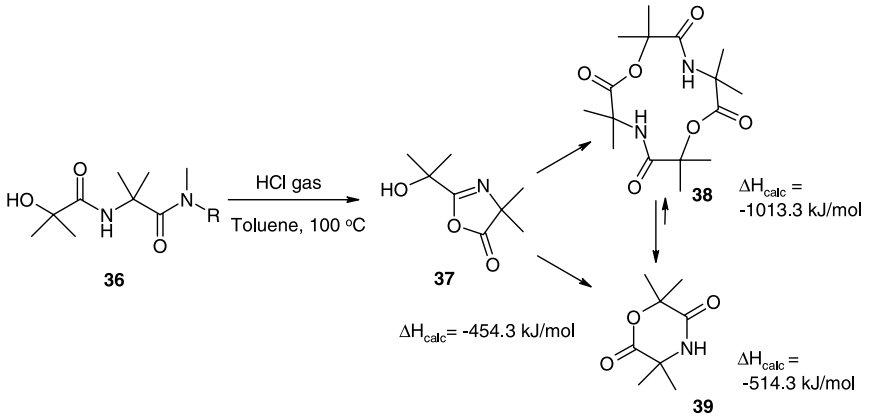
Next, the aromatic ring in **30** was replaced by a cycloaliphatic one. The preparation of the precursors **33a**,**b** was achieved in three steps according to Scheme 11. The cyclization under the standard conditions led to a mixture of two products, the oxazolone **34** and the dehydrated amide **35**, but no cyclodepsipeptide could be detected.

2.1. Computer modeling

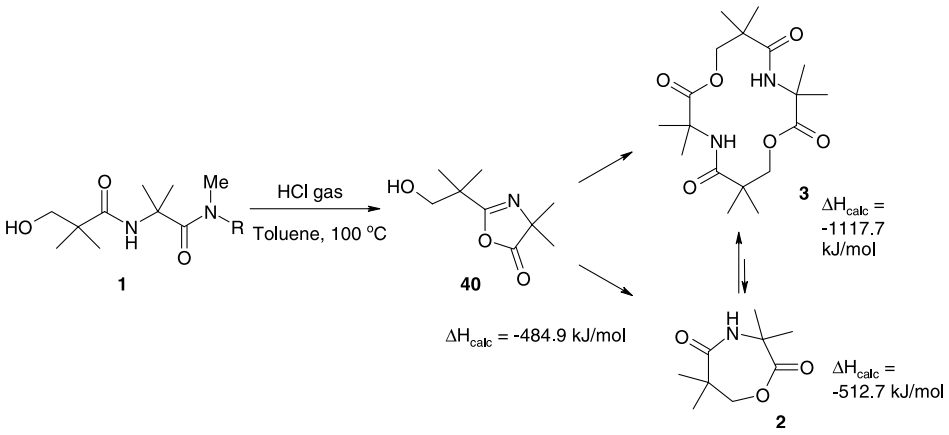
As we were searching for an explanation for the preferred cyclodimerization process of diamides of type **1**, we carried out some simple quantum mechanical calculations. Especially surprising was the discrepancy with the lower homologue **36**, which under the DAC conditions gave the cyclic monomer **39** exclusively. Assuming that the reaction proceeds indeed via the oxazolone intermediates (**37** and **40**, respectively), we compared the energies of the corresponding monomeric and dimeric ring structures, both in the cases of α-hydroxy acids and β-hydroxy acids (Schemes 12 and 13).

AM1 calculations[30] with Ampac v.6.5.5[31] revealed that the transition state required to achieve a nucleophilic attack of the oxazolone hydroxy group on the carbonyl C-atom is more favorable in the case of **40** than in **37**, which is to be expected, having in mind the length of the alkyl chain to which the OH group is bound. Nevertheless, under the DAC conditions, **36** gives **39**, whereas **1** undergoes the twinning process.

Direct comparison of the heats of formation (ΔH) of **38** and **39**, as well as those of **3** and **2**, reveals that in the first case (Scheme 12) the formation of the dimer **38** is energetically more unfavorable than the formation of the monomer **39** ($2E_{39} < E_{38}$). In the second case (Scheme 12), formation of the dimer **3** is energetically more favorable than the formation of the monomer ($2E_2 > E_3$), which suggests that the cause for the different products formed is thermodynamic. This crude modeling helps to understand why the dimers of type **3** could be the main products of the direct



Scheme 12.



Scheme 13.

amide cyclization of **1**, but it does not explain why they are the only products formed. An equilibrium between the monomeric and dimeric forms under the strongly acidic conditions of the DAC is to be expected in both cases (between **2** and **3** on the one hand and between **39** and **38** on the other). This equilibrium might be shifted almost completely in one direction in the case of **3** and in the other in the case of **39**.

3. Conclusions

Upon investigating the reasons for the cyclodimerization of β-hydroxy acid amides of type **1** under various conditions, we were able to isolate five different 14-membered cyclodimers of type **3**. Although other coupling methods also gave moderate results, the best yields were obtained via the 'direct amide cyclization' (DAC), reaching 88% for the cyclodimer **10**. It is worth mentioning that in all cases, when starting with racemic material, only the trans-substituted cyclodepsipeptides were isolated.

The cyclodimerization is most probably a result of the greater thermodynamic stability of the 14-membered ring compared with the seven-membered one. Another factor, which might contribute to the cyclodimerization, as suggested in the literature, is H-bond formation, which would be more pronounced in the 14-membered ring, although the structures of all cyclodepsipeptides, which were characterized by X-ray crystallography, showed no evidence of intramolecular H-bonding.

Molecular modeling using simple AM1 calculations shows in the case of **1** that the formation of the dimeric depsipeptide is indeed thermodynamically favored over the formation of the monomer, but it does not explain why the 14-membered ring is the only product formed. A mixture of the monomeric and dimeric forms is to be expected. Thus, the reason for the exclusive cyclodimerization of compounds of type **1** remains unclear and further investigation in this area is needed.

Variation in the substitution pattern of the starting compounds showed that mono-substitution in the amino acid moiety does not prevent twinning (**13**, **15**, and **16** yielded *trans*-**14**, although not via DAC). Using I_2 mediated lactonization allowed for the selective synthesis of both (*S*,*S*)-**14** (starting with (*S*)-**16**) and *trans*-**14** (starting with *rac*-**16**). If, on the other hand, the hydroxy acid moiety is monosubstituted (as in **18**, **19**, **27**), although the formation of the intermediate 1,3-oxazol-5(*4H*)-one has been monitored by IR, dehydration occurs and no cyclic products are formed. Therefore, the synthesis of β-hydroxy acid containing cyclic depsipeptides via DAC is useful only if the starting amides contain α,α-disubstituted acids.

4. Experimental

4.1. General

Thin-layer chromatography (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 chromatography (CC): Uetikon-Chemie 'Chromatographiegel' C-560. Mp: Büchi 540 apparatus, uncorrected. IR Spectra: Perkin-Elmer Spectrum one spectrometer; in KBr, unless otherwise stated, absorption bands in cm^{-1}. ^1H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra: Bruker ARX-300 or Bruker DRX-600 instrument; ^1H NMR (600 MHz) and ^{13}C NMR (150 MHz); in $CDCl_3$ at 300 K; TMS as internal standard, unless otherwise stated; δ in ppm, coupling constants J in Hz. Mass spectrometry (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.

2,2,*N*,*N*-Tetramethyl-2*H*-azirin-3-amine, 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine, 2-benzyl-2,*N*-dimethyl-*N*-phenyl-2*H*-azirin-3-amine and *N*,*N*-dimethyl-1-azaspiro[2.4]hept-1-en-2-amine were prepared according to standard procedures (Refs. 5 and 7 and references cited therein). 3-Hydroxy-2-benzylpropanoic acid was prepared by the method of Monteil et al.[28] and methyltropic acid from hydroptropic aldehyde by hydroxymethylation, followed by oxidation, according to Geffken.[27] Hydroxy acids **32** were synthesized by the method of Seebach et al.[32] All other products used were commercially available.

General procedure 1 (GP1). To a solution of a hydroxy acid (2–6 mmol) in dry THF (5–20 mL), 1.05 equiv of the corresponding 2*H*-azirin-3-amine were added dropwise. The mixture was stirred at rt for 12–36 h, the solvent evaporated and the remaining solid purified by column chromatography (CC) over silica gel and dried in h.v.

General procedure 2 (GP2). According to GP1, the reaction was stirred overnight, the solvent evaporated, the solid residue washed with Et_2O and recrystallized from AcOEt.

General procedure 3 (GP3). To a solution of a hydroxy acid (3 mmol) in dry THF (10 mL) was added the corresponding phenylalanine ester hydrochloride (3.0 mmol) and 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT, 916 mg, 98%, 3.0 mmol). To the cooled mixture were added dropwise 12 mmol (1.21 g) of Et_3N. The mixture was stirred at rt overnight, the solvent was partially evaporated, AcOEt was added and the solution was washed with 5% aq $KHSO_4$ and with saturated aq $NaHCO_3$ solutions. The combined organic fractions were dried over $MgSO_4$, evaporated, purified by CC, and dried in h.v.

General procedure 4 (GP4). To a solution of an ester (2.0 mmol) in 10 mL EtOH was added $LiOH \cdot H_2O$ (336 mg, 8 mmol). The reaction was stirred overnight at rt, acidified with 6 N HCl, the organic solvent was evaporated in vacuo and the residue extracted with AcOEt. The crude acids were used in the next reaction step without further purification.

General procedure 5 (GP5). A suspension of an amide (1 mmol) in dry toluene (50 mL) was heated to 100 °C, and dry HCl gas was bubbled through the suspension for 5–15 min. Then, the mixture was allowed to cool to rt while bubbling N_2 through it (ca. 20 min). The solvent was evaporated, the white residue was washed with 3×15 mL of CH_2Cl_2 and dried in h.v.

General procedure 6 (GP6). According to GP5, after bubbling N_2 through the reaction mixture (ca. 20 min) the solvent was evaporated, and the residue purified by CC.

General procedure 7 (GP7). To a solution of **13** or **15** (1 mmol) in dry toluene (5 mL), NaH (40 mg of a 60% suspension in mineral oil, 1 mmol) was added slowly at 0 °C and under constant stirring (N_2-atmosphere). After 6 h at 80 °C, the mixture was acidified with 0.1 N HCl ($\sim$5 mL) to pH 5 and extracted with CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$) and evaporated i.v. The crystalline residue was purified by CC (CH_2Cl_2/acetone 200:1) and dried in h.v.

General procedure 8 (GP8). To a solution of a hydroxy acid (1 mmol) in acetonitrile (5 mL), I_2 (25 mg, 0.1 mmol) was added. After 2 days under reflux, the mixture was cooled and the solvent evaporated. After addition of 20 mL of AcOEt and washing with aq $Na_2S_2O_3$, the combined organic fractions were dried ($MgSO_4$) and evaporated i.v. The crystalline residue was purified by CC.

General procedure 9 (GP9). A suspension of an amide (1 mmol) in a toluene/20% ethanol solution (60 mL) was heated to 100 °C, and dry HCl gas was bubbled through the suspension for 10 min. Then, the mixture was allowed to cool to rt while bubbling N_2 through it (ca. 20 min). The solvent was evaporated and the oily residue was purified by CC.

General procedure 10 (GP10). A suspension of an amide (0.5 mmol) in dry toluene (25 mL) was heated to 100 °C, and dry HCl gas was bubbled through the suspension for 10 min. Then, the mixture was allowed to cool to rt while bubbling N_2 through it (ca. 20 min). The solvent was removed i.v. and MeOH (15 mL) was added to the residue and stirred at rt for 1 h in the presence of 500 mg SiO_2. The silica gel was filtered, the solvent was evaporated and the oily residue was purified by CC.

4.2. Preparation of 3-hydroxy-2-methylpropanoic acid

To a solution of methyl (*R*)-3-hydroxy-2-methylpropanoate (1.0 g, 8.38 mmol) in THF/water 75:10 (10 mL) LiOH (1.55 g, 33.5 mmol) was added at 0 °C. The mixture was stirred overnight, the organic solvent evaporated, the residue acidified with 6 N HCl to pH 1 and extracted with AcOEt. The colorless oil was used in the next reaction without further purification. Yield: 768 mg (88%). Spectroscopic data in accordance with previously published data.[33] The optical purity has not been determined. ^{1}H NMR((d_6)-DMSO): 1.04 (d, $J=5.9$ Hz, CH_3); 2.31–2.38 (m, CH); 3.38–3.44, 3.52–3.61 (2m, CH_2); 4.62 (br s, OH); 11.95 (br s, COOH).

4.3. Coupling of β-hydroxy acids with 2*H*-azirin-3-amines

4.3.1. 3-Hydroxy-2,2-dimethyl-*N*-[1-(*N*,*N*-dimethylcarbamoyl)cyclopentyl]propanamide (9). According to GP1, 3-hydroxy-2,2-dimethylpropanoic acid (806 mg, 6.84 mmol) in dry THF (10 mL), *N*,*N*-dimethyl-1-azaspiro[2.4]hept-1-en-2-amine (1.037 g, 7.52 mmol), 18 h, CC (SiO_2, acetone/CH_2Cl_2 1:20). Yield: 1.330 g (76%) of **9**. White solid. Mp 180.6–181.9 °C (AcOEt). IR: 3397vs, 3279s, 2960s, 2873m, 1644vs, 1542vs, 1469m, 1393s, 1309m, 1257m, 1212w, 1164m, 1119w, 1061s, 1011w, 983w, 911w, 817w, 669m. ^{1}H NMR ((d_6)-DMSO): 1.14 (s, Me_2C); 1.71 (m, $2CH_2$); 1.81–2.00, 2.28–2.48 (2m, $2CH_2$); 2.99 (s, Me_2N); 3.56 (br s, OH); 4.46 (s, CH_2O); 7.42 (br s, NH). ^{13}C NMR ((d_6)-DMSO): 22.8 (q, Me_2C); 24.2 (t, CH_2); 37.2 (t, CH_2); 37.7 (q, Me_2N); 42.8, 66.2 (2s, 2C); 69.1 (t, CH_2O); 172.7, 176.9 (2s, 2CO). CI-MS: 257 (21, $[M+H]^+$), 212.3 (100, $[M-NMe_2]^+$). Anal. Calcd for $C_{13}H_{24}N_2O_3$ (256.35): C 60.91, H 9.44, N 10.93; found: C 60.24, H 9.50, N 10.76.

4.3.2. 3-Hydroxy-2,2-dimethyl-*N*-[1-methyl-1-(*N*,*N*-dimethylcarbamoyl)-2-phenylethyl]propanamide (11a). According to GP1, 3-hydroxy-2,2-dimethylpropanoic acid (436 mg, 2.00 mmol) in dry THF (5 mL), 2-benzyl-2,*N*,*N*-trimethyl-2*H*-azirin-3-amine (395 mg, 2.1 mmol), 24 h, CC (SiO_2, acetone/CH_2Cl_2 1:20). Yield: 538 mg (88%) of **11a**. White powder. Mp 92.6–94.9 °C. ^{1}H NMR ((d_6)DMSO): 1.05 (s, Me_2C); 1.29 (s, Me); 3.09 (s, Me_2N); 3.13–3.38 (m, PhCH_2); 3.54 (s, CH_2O); 4.77 (br s, OH); 6.92 (br s, NH); 7.06–7.36 (m, Ph). ^{13}C NMR ((d_6)DMSO): 22.4 (q, Me_2C); 24.8 (q, Me); 37.3 (q, MeN); 41.0 (s, Me_2C); 43.8 (t, PhCH_2);

70.1 (t, CH_2O); 128.3, 128.8, 129.4 (3d, 5 arom. CH); 136.1 (s, arom. C); 173.1, 175.2 (2s, 2CO). CI-MS: 307 (100, $[M+H]^+$), 262 (25, $[M-NMe_2]^+$).

Recrystallization from DMSO/diethyl ether yielded crystals of **11a**, suitable for an X-ray crystal structure determination.

4.3.3. 3-Hydroxy-2,2-dimethyl-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)-2-phenylethyl]propanamide (11b). According to GP1, 3-hydroxy-2,2-dimethylpropanoic acid (436 mg, 2.00 mmol) in dry THF (5 mL), 2-benzyl-2,*N*-dimethyl-*N*-phenyl-2*H*-azirin-3-amine (525 mg, 2.1 mmol), 28 h, CC (SiO_2, acetone/CH_2Cl_2 1:30). Yield: 618 mg (84%) of **11b**. White powder. Mp 62.0–64.2 °C. IR: 3385vs, 3291vs, 3060m, 2941vs, 1701vs, 1634vs, 1591s, 1454s, 1386s, 1312s, 1238s, 1193m, 1165m, 1111m, 1053s, 886m, 908w, 834w, 772s, 705s. ^{1}H NMR: 0.98, 1.08 (2s, Me_2C); 1.33 (s, Me); 3.29 (s, MeN); 3.41 (m, PhCH_2); 3.54 (s, CH_2O); 3.77 (br s, OH); 6.89 (br s, NH); 7.12–4.10 (m, 2Ph). ^{13}C NMR: 22.1 (q, *Me*$_2$C); 24.1 (q, Me); 41.8 (q, MeN); 43.4 (s, Me$_2$*C*); 43.7 (t, Ph*C*H$_2$); 70.4 (t, CH_2O); 127.1, 128.3, 128.8, 129.5, 130.1 (5d, 10 arom. CH); 136.1, 144.2 (2s, 2 arom. C); 173.0, 177.1 (2s, 2CO). CI-MS: 369 (30, $[M+H]^+$), 262 (100, $[M-N(Me)Ph]^+$), 234.2 (20), 160.1 (18), 134.1 (36), 107.1 (26). Anal. Calcd for $C_{22}H_{28}N_2O_3$ (368.48): C 71.71, H 7.66, N 7.60; found: C 71.79, H 7.82, N 7.07.

4.3.4. 3-Hydroxy-2-phenyl-*N*-[1-methyl-1-(*N*,*N*-dimethylcarbamoyl)ethyl]propanamide (18a). According to GP2, 3-hydroxy-2-phenylpropanoic acid (tropic acid, 332 mg, 2.00 mmol) in dry THF (5 mL), 2,2,*N*,*N*-tetramethyl-2*H*-azirin-3-amine (249 mg, 2.1 mmol), 8 h. Yield: 440 mg (79%) of **18a**. White powder. Mp 160.8–161.3 °C (AcOEt). IR: 3421m, 3296s, 3060m, 2936m, 1651vs, 1619vs, 1540s, 1491m, 1454w, 1396s, 1271m, 1219m, 1123s, 1068m, 1051m, 913w, 750m, 702m. ^{1}H NMR: 1.88, 1.94 (2s, Me_2C); 3.28 (s, Me_2N); 3.87–4.12 (m, CH_2); 4.42 (br t, J= 6.8 Hz, CH); 6.98 (s, NH); 7.50–7.62 (m, Ph). ^{13}C NMR: 24.3, 24.5 (2q, *Me*$_2$C); 38.0 (q, Me$_2$N); 56.9 (s, Me$_2$*C*); 54.7 (d, CH); 64.9 (t, CH_2O); 127.7, 128.2, 129.0 (3d, 5 arom. CH); 136.7 (s, arom. C); 171.9, 172.6 (2s, 2CO). ^{1}H NMR ((*d*$_6$)DMSO): 1.38, 1.32 (2s, Me_2C); 2.71 (s, Me_2N); 3.42–3.58, 3.60–3.69, 3.87–3.94 (3m, CH, CH_2); 4.78 (t, OH); 7.22–7.36 (m, Ph); 8.31 (s, NH). ^{13}C NMR ((*d*$_6$)DMSO): 25.5, 25.8 (2q, *Me*$_2$C); 37.0 (q, Me$_2$N); 53.9 (s, Me$_2$C); 55.4 (d, CH); 63.2 (t, CH_2O); 126.6, 127.7, 128.0 (3d, 5 arom. CH); 138.1 (s, arom. C); 170.2, 171.7 (2s, 2CO). CI-MS: 279 (80, $[M+H]^+$), 234 (100, $[M-NMe_2]^+$), 206 (22), 157 (18), 104 (8).

4.3.5. 3-Hydroxy-2-phenyl-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]propanamide (18b). According to GP2, 3-hydroxy-2-phenylpropanoic acid (tropic acid, 332 mg, 2.00 mmol) in dry THF (5 mL), 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (365 mg, 2.1 mmol), 9 h. Yield: 578 mg (85%) of **18b**. White powder. Mp 128.6–129.9 °C (AcOEt). IR: 3298s, 3274s, 3055m, 2940m, 1673vs, 16,124vs, 1545s, 1488m, 1462w, 1394s, 1270m, 1124s, 1099s, 1060m, 913m, 745m. ^{1}H NMR: 1.76, 1.89 (2s, Me_2C); 3.31 (s, MeN); 3.91–4.19 (m, CH_2); 4.36–4.42 (m, CH); 7.05 (s, NH); 7.41–7.55, 7.60–7.87 (2m, 2Ph). ^{13}C NMR: 24.6, 24.8 (2q, *Me*$_2$C); 41.1 (*q*, MeN); 57.4 (s, Me$_2$*C*); 55.0 (d, CH); 67.3 (t, CH_2O); 127.6, 127.7, 128.2, 128.5, 128.8, 129.1 (6d, 10 arom. CH); 136.7, 143.8 (2s, 2 arom. C); 173.1, 173.9 (2s, 2CO). ESI-MS: 363 (100, $[M+Na]^+$).

4.3.6. 3-Hydroxy-2-methyl-2-phenyl-*N*-[1-methyl-(*N*,*N*-dimethylcarbamoyl)ethyl]propanamide (21a). According to GP1, 3-hydroxy-2-methyl-2-phenylpropanoic acid (360 mg, 2.00 mmol) in dry THF (5 mL), 2,2,*N*,*N*-tetramethyl-2*H*-azirin-3-amine (249 mg, 2.1 mmol), 36 h, CC (SiO_2, acetone/CH_2Cl_2 1:10). Yield: 455 mg (78%) of **21a**. Colorless crystals. Mp 147.6–148.4 °C (toluene). IR: 3533s, 3280vs, 3054s, 2928vs, 1708vs, 1622vs, 1526vs, 1394s, 1264s, 1208s, 1118s, 1050m, 976m, 900w, 770m, 751m, 802m. ^{1}H NMR: 1.50 (s, Me_2C); 1.61 (s, Me), 3.00 (*s*, Me_2N); 3.55–3.70, 4.05–4.19 (2m, CH_2O); 4.45 (br s, OH); 7.18–7.41 (m, Ph, NH). ^{13}C NMR: 21.4 (q, *Me*$_2$C); 25.0 (q, Me); 37.7 (q, Me$_2$N); 51.5, 56.4 (2s, 2Me$_2$*C*); 68.7 (t, CH_2O); 126.5, 126.9, 128.3 (3d, 5 arom. CH); 141.5 (s, arom. C); 172.6, 175.3 (2s, 2CO). CI-MS: 293 (88, $[M+H]^+$), 248 (100, $[M-NMe_2]^+$), 113 (28). Anal. Calcd for $C_{16}H_{24}N_2O_3$ (292.38): C 65.73, H 8.27, N 9.58; found: C 65.69, H 8.40, N 9.59.

4.3.7. 3-Hydroxy-2-methyl-2-phenyl-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]propanamide (21b). According to GP1, 3-hydroxy-2-methyl-2-phenylpropanoic acid (360 mg, 2.00 mmol) in dry THF (5 mL) 2-benzyl-2,*N*-dimethyl-*N*-phenyl-2*H*-azirin-3-amine (365 mg, 2.1 mmol), 28 h, CC (SiO_2, acetone/CH_2Cl_2 1:20). Yield: 608 mg (86%) of **21b**. White solid. Mp 132.1–133.0 °C. IR: 3451s, 3282vs, 3057m, 2992s, 1709s, 1635vs, 1592s, 1445s, 1395s, 1262m, 1157m, 1123m, 1092s, 1026s, 921m. ^{1}H NMR: 1.30, 1.38 (2s, Me_2C); 1.48 (s, Me), 3.22 (s, MeN); 3.55–3.61, 4.00–4.10 (2m, CH_2O); 4.63 (br s, OH); 6.61 (br s, NH); 7.18–7.41 (m, 2Ph). ^{13}C NMR: 21.8 (q, *Me*$_2$C); 25.7 (q, Me); 41.5 (q, MeN); 52.3, 58.8 (2s, 2Me$_2$*C*); 69.2 (t, CH_2O); 126.3, 126.6, 126.9, 127.1, 127.2, 128.1, 128.3, 128.4, 128.6, 129.4 (10d, 10 arom. CH); 141.6, 144.2 (2s, 2 arom. C); 173.7, 176.0 (2s, 2CO). ESI-MS: 731 (48, $[2M+Na]^+$), 377 (100, $[M+Na]^+$), 248 (16).

4.3.8. 3-Hydroxy-2-benzyl-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]propanamide (22). According to GP2, 3-hydroxy-2-benzylpropanoic acid (360 mg, 2.00 mmol) in dry THF (5 mL), 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (365 mg, 2.1 mmol), 8 h. Yield: 560 mg (79%) of **22**. White powder. Mp 162.4–163.9 °C. IR: 3409m, 3277s, 3060w, 2932m, 1630vs, 1592s, 1544s, 1493s, 1395s, 1254m, 1188w, 1092s, 1070m, 769m, 743m, 703s, 617m. ^{1}H NMR: 1.27, 1.33 (2s, Me_2C); 2.38–2.42, 2.61–2.73, 2.88–3.01 (3m, CH_2, CH); 3.27 (s, MeN); 3.66–3.73 (m, OH); 6.18 (br s, NH); 7.11–7.41 (m, 2Ph). ^{13}C NMR: 26.2, 27.0 (2q, *Me*$_2$C); 34.3 (t, CH_2); 41.5 (q, MeN); 50.8 (d, CH); 59.0 (*s*, Me$_2$*C*); 63.6 (t, CH_2O); 126.3, 128.2, 128.3, 128.5, 129.0, 129.4 (6d, 10 arom. CH); 139.3, 144.4 (2s, 2 arom. C); 173.8, 174.0 (2s, 2CO). ESI-MS: 377 (100, $[M+Na]^+$). Anal. Calcd for $C_{16}H_{24}N_2O_3$ (354.45): C 65.73, H 8.27, N 9.58; found: C 60.24, H 9.50, N 10.76.

4.3.9. 3-Hydroxy-2-methyl-*N*-[1-methyl-1-(*N*,*N*-dimethylcarbamoyl)ethyl]propanamide (23). According to GP1, 3-hydroxy-2-methylpropanoic acid (416 mg, 4.00 mmol)

in dry THF (5 mL), 2,2,*N*,*N*-tetramethyl-2*H*-azirin-3-amine (498 mg, 4.2 mmol), 38 h, CC (SiO_2, acetone/CH_2Cl_2 1:20). Yield: 790 mg (83%) of **23**. Colorless crystals. Mp 118.7–120.0 °C. IR: 3418s, 1619vs, 1540s, 1397s, 1279m, 1226s, 1124s, 1077m, 1036m. ^{1}H NMR: 1.09 (d, $J=6.1$ Hz, Me); 1.58 (s, Me_2C); 2.59 (m, CH); 3.06 (s, Me_2N); 3.63 (d, CH_2); 4.21 (br s, OH); 7.70 (s, NH). ^{13}C NMR: 13.7 (q, Me); 25.5, 25.6 (2q, Me_2C); 37.9 (q, MeN); 56.3 (*s*, Me_2C); 42.3 (d, CH); 64.8 (t, CH_2O); 173.0, 174.9 (2s, 2CO). ESI-MS: 455 (20, $[2M+Na]^+$), 239 (100, $[M+Na]^+$). Anal. Calcd for $C_{10}H_{20}N_2O_3$ (216.28): C 55.53, H 9.32, N 12.95; found: C 55.74, H 9.71, N 13.12.

4.3.10. 2-Hydroxy-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]benzamide (30). According to GP1, salicylic acid (276 mg, 2.00 mmol) in dry THF (5 mL), 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (365 mg, 2.1 mmol), CC (SiO_2, acetone/CH_2Cl_2 1:20). Yield: 565 mg (92%) of **30**. Colorless crystals. Mp 146.1–147.8 °C. IR: 3533s, 3280vs, 3054s, 2928vs, 1708vs, 1622vs, 1526vs, 1394s, 1264s, 1208s, 1118s, 1050m, 976m, 900w, 770m, 751m, 802m. ^{1}H NMR: 1.43 (s, Me_2C); 3.22 (s, MeN); 6.68–6.74 (m, 1 arom. H); 6.76 (br s, NH); 6.92–7.0 (m, 2H arom);7.11–7.28 (m, 4 arom. H); 7.31–7.42 (m, 2 arom. H); 12.1 (s, OH). ^{13}C NMR: 26.4 (q, Me_2C); 41.4 (q, MeN); 58.4 (s, Me_2C); 119.9 (s, arom. C); 126.6, 126.8, 127.3, 127.9, 128.2, 128.9, 129.3 (7d, 9 arom. CH); 134.1, 142.2 (2s, 2 arom. C); 172.9, 177.5 (2s, 2CO). ESI-MS: 335 (100, $[M+Na]^+$).

4.3.11. (1*R*,2*S*)-2-Hydroxy-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]cyclopentanecarboxamide (33a). According to GP1, (1*R*,2*S*)-2-hydroxycyclopentanoic acid (**32a**, 260 mg, 2.00 mmol) in dry THF (5 mL), 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (365 mg, 2.1 mmol), CC (SiO_2, acetone/CH_2Cl_2 1:10). Yield: 530 mg (86%) of **33a**. White powder. Mp 153.4–155.0 °C. IR: 3289s, 2943s, 1708vs, 1636vs, 1593s, 1494s, 1390s, 1240s, 1092s, 1028m, 919m, 732s. ^{1}H NMR: 1.42 (s, Me_2C); 1.57–1.68, 1.70–1.77, 1.79–1.96 (3m, $3CH_2$, CH); 3.27 (s, MeN); 4.35 (m, CHO); 6.38 (br s, NH); 7.24–7.41 (m, Ph, NH). ^{13}C NMR: 21.9 (t, CH_2); 26.1, 26.4 (2q, Me_2C); 26.8, 33.9 (2t, $2CH_2$); 41.4 (q, MeN); 50.2 (d, CH); 58.6 (s, Me_2C); 74.2 (d, CHO); 128.1, 128.3, 129.4 (3d, 5 arom. CH); 144.2 (s, arom. C); 173.4, 176.1 (2s, 2CO). ESI-MS: 327 (100, $[M+Na]^+$).

4.3.12. (1*R*,2*S*)-2-Hydroxy-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]cyclohexanecarboxamide (33b). According to GP1, (1*R*,2*S*)-2-hydroxycyclohexanoic acid (**32b**, 288 mg, 2.00 mmol) in dry THF (5 mL), 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (365 mg, 2.1 mmol), 12 h, CC (SiO_2, acetone/CH_2Cl_2 1:10). Yield: 566 mg (89%) of **33b**.White powder. Mp 171.2–172.9 °C. IR: 3290s, 3020m, 2948s, 1711vs, 1635vs, 1599s, 1491s, 1421m, 1391s, 1239s, 1091s, 1022m, 919m, 731s. ^{1}H NMR: 1.37, 1.42 (2s, Me_2C); 1.43–1.52, 1.62–1.74, 1.77–1.83, 1.86–1.95 (4m, $4CH_2$, CH); 3.21 (s, MeN); 3.97 (m, CHO); 6.41 (br s, NH); 7.22–7.41 (m, Ph, NH). ^{13}C NMR: 19.2, 24.4, 24.9 (3t, $3CH_2$); 25.9, 26.1 (2q, Me_2C); 31.7 (t, CH_2); 41.4 (q, MeN); 47.9 (d, CH); 59.4 (s, Me_2C); 66.7 (d, CHO); 127.9, 128.2, 129.3 (3d, 5 arom. CH); 142.2 (s, arom. C); 172.1, 177.4 (2s, 2CO). ESI-MS: 341 (100, $[M+Na]^+$).

4.4. Preparation of dipeptide esters

4.4.1. *tert*-Butyl (*S*)-2-(3-hydroxy-2,2-dimethylpropanoylamino)-3-phenylpropanoate (13). According to GP3, 3-hydroxy-2,2-dimethylpropanoic acid (654 mg, 3 mmol), L-phenylalanine *tert*-butyl ester hydrochloride (774 mg, 3.0 mmol), CC (SiO_2, acetone/CH_2Cl_2 1:30). Yield: 857 g (89%) of **13**. Colorless solid. Mp 82.7–84.1 °C. $[\alpha]_D^{25}$ +44.6 (*c* 1, $CHCl_3$). IR: 3265vs, 3006s, 2982vs, 2867s, 1721vs, 1635vs, 1543vs, 1455s, 1392s, 1315s, 1165vs, 1102m, 963s, 850m. ^{1}H NMR: 1.09 (s, Me_2C); 1.45 (s, Me_3C), 3.00–3.17 (m, $PhCH_2$); 3.42–3.51 (m, CH_2O); 3.72 (br s, OH); 4.63–4.78 (m, CH); 6.94 (br s, NH); 7.13–7.36 (m, Ph). ^{13}C NMR: 22.3 (q, Me_2C); 27.8 (q, Me_3C); 37.6 (t, CH_2); 43.1 (s, Me_2C); 53. (d, CH); 69.9 (t, CH_2); 82.3 (s, Me_3C); 126.9, 128.3, 129.3 (3d, 5 arom. CH); 136.1 (s, arom. C); 170.8, 177.1 (2s, 2CO). CI-MS: 322 (88, $[M+H]^+$), 266 (100, $[M-{}^t\mathrm{Bu}]^+$). Anal. calcd for $C_{18}H_{27}NO_4$ (321.42): C 67.26, H 8.47, N 4.36; found: C 67.04, H 8.66, N 4.20.

4.4.2. Methyl (*RS*)-2-(3-hydroxy-2,2-dimethylpropanoylamino)-3-phenylpropanoate (15). According to GP3, 3-hydroxy-2,2-dimethylpropanoic acid (654 mg, 3 mmol), DL-phenylalanine methyl ester hydrochloride (639 mg, 3.0 mmol), CC (SiO_2, acetone/CH_2Cl_2 1:30). Yield: 673 g (80%) of **15**. Pale yellow oil. ^{1}H NMR: 1.03 (s, Me_2C); 2.98–3.12 (m, $PhCH_2$); 3.36–3.49 (m, CH_2O); 3.67 (s, MeO); 4.68–74 (m, CH); 6.50 (br s, NH); 7.13–7.38 (m, Ph). ^{13}C NMR: 22.2 (q, Me_2C); 37.6 (t, CH_2); 43.0 (s, Me_2C); 52.2 (d, CH); 52.9 (q, MeO); 69.5 (t, CH_2); 127.0, 128.4, 129.1 (3d, 5 arom. CH); 135.8 (s, arom. C); 172.2, 177.3 (2s, 2CO). CI-MS: 280 (100, $[M+H]^+$), 162 (18). Anal. Calcd for $C_{15}H_{13}NO_4$ (279.34): C 64.50, H 7.58, N 5.01; found: C 64.15, H 7.73, N 4.89.

4.4.3. Methyl (*S*)-2-(3-hydroxy-2,2-dimethylpropanoylamino)-3-phenylpropanoate (17). According to GP3, 3-hydroxy-2,2-dimethylpropanoic acid (654 mg, 3 mmol), L-phenylalanine methyl ester hydrochloride (639 mg, 3.0 mmol), CC (SiO_2, acetone/CH_2Cl_2 1:30). Yield: 720 g (86%) of **17**. Pale yellow oil. ^{1}H NMR: 1.05 (s, Me_2C); 3.00–3.09 (m, $PhCH_2$); 3.38–3.48 (m, CH_2O); 3.69 (s, MeO); 4.71 (t, $J=6.0$ Hz, CH); 6.52 (s, NH); 7.14–7.36 (m, Ph). ^{13}C NMR: 22.3 (q, Me_2C); 37.7 (t, CH_2); 43.0 (s, Me_2C); 52.1 (d, CH); 53.0 (q, MeO); 69.6 (t, CH_2); 127.0, 128.4, 129.1 (3d, 5 arom. CH); 135.9 (s, arom. C); 172.3, 177.5 (2s, 2CO). CI-MS: 280 (100, $[M+H]^+$), 162 (18).

4.4.4. *tert*-Butyl (*R*,*S*)-2-(3-hydroxy-2-phenylpropanoylamino)-3-phenylpropanoate (20). According to GP3, tropic acid (498 mg, 3 mmol), L-phenylalanine *tert*-butyl ester hydrochloride (774 mg, 3.0 mmol), CC (SiO_2, acetone/CH_2Cl_2 1:30). Yield: 974 mg (88%) of **20**. Pale yellow crystals. Mp 117.4–119.1 °C. IR: 3426s, 3290s, 3059m, 1738vs, 1658vs, 1635s, 1551m, 1454m, 1368s, 1223s, 1154vs, 1059m, 1023m, 845m, 740m, 701s. ^{1}H NMR ((*d*$_6$)DMSO): 1.28, 1.31 (2s, Me_3C); 2.91–3.10 (m, $PhCH_2$); 3.50–3.62, 3.69–3.80 (2m, CH_2O); 4.00–4.16, 4.60–4.78 (2m, 2CH); 5.81–6.00 (m, OH); 6.73 (d, $J=$ 3.7 Hz, NH); 6.93–7.27 (m, 2Ph). ^{13}C NMR: 27.8, 27.9 (2q, Me_3C); 37.7 (t, CH_2); 53.1, 53.5, 54.3, 54.4 (4d, 2CH); 64.7, 64.8 (t, CH_2O); 81.8 (s, Me_3C); 127.7, 128.2, 128.3, 128.4, 129.0, 129.3 (6d, 10 arom. CH); 136.1, 136.8 (2*s*, 2

arom. C); 171.0, 173.2 (2s, 2CO). CI-MS: 370 (85, $[M+H]^+$), 313 (100, $[M-{}^t\mathrm{Bu}]^+$).

4.5. Saponification of dipeptide amides

4.5.1. (*RS*)-2-(3-Hydroxy-2,2-dimethylpropanoylamino)-3-phenylpropanoic acid (*rac*-16). According to GP4, from **13** (642 mg, 2.0 mmol). Yield 454 mg (79%) of **13**. White solid. Mp 91.3–94.9 °C. ^{1}H NMR: 0.99, 1.02 (2s, Me_2C); 2.96–3.02, 3.08–3.14 (2m, PhCH_2); 3.21–3.41 (m, CH_2O); 4.66–4.78 (m, CH); 6.95 (br s, NH); 6.98–7.18 (m, Ph). ^{13}C NMR: 22.0 (q, Me_2C); 37.0 (t, CH_2); 43.3 (s, Me_2C); 53.1 (d, CH); 69.3 (t, CH_2); 127.0, 128.4, 129.3 (3d, 5 arom. CH); 135.8 (s, arom. C); 174.0, 178.1 (2s, 2CO). ESI-MS: 288 (100, $[M+H]^+$).

4.5.2. (*S*)-2-(3-Hydroxy-2,2-dimethylpropanoylamino)-3-phenylpropanoic acid ((*S*)-16). According to GP4, from **17** (558 mg, 2.0 mmol). Yield: 442 mg (79%) of (*S*)-**16**. Colorless oil, $[\alpha]_D^{25}$ +44.1 (*c* 1, $CHCl_3$). IR: 3369vs, 3192s, 2963s, 1723vs, 1643vs, 1529vs, 1455s, 1394m, 1287m, 1254s, 1179m, 1111w, 1049s, 913w, 699s. ^{1}H NMR: 0.99, 1.01 (2s, Me_2C); 2.88–2.94, 3.02–3.14 (2m, PhCH_2); 3.38 (m, CH_2O); 4.71–4.83 (m, CH); 6.71 (br s, NH); 6.98–7.18 (m, Ph). ^{13}C NMR: 21.1 (q, Me_2C); 36.1 (t, CH_2); 42.4 (s, Me_2C); 52.2 (d, CH); 68.5 (t, CH_2); 126.1, 127.6, 128.4 (3d, 5 arom. CH); 134.9 (s, arom. C); 173.2, 177.2 (2s, 2CO). ESI-MS: 288 (100, $[M+Na]^+$).

4.6. Solvolysis of dipeptide amides under DAC conditions

4.6.1. Ethyl 2-(3-hydroxy-2-phenylpropanoylamino)-2-methylpropanoate (19). According to GP9, **18** (278 mg, 1 mmol) in toluene/EtOH 80:20 (60 mL), CC (AcOEt/hexane 1:10). Yield: 209 mg (76%) of **19**. Colorless oil. IR: 3237vs, 3068s, 2980s, 1734vs, 1642vs, 1557s, 1475s, 1383m, 1288s, 1164s, 1070m, 1037s, 872w, 751m, 699s. ^{1}H NMR: 1.10 (t, J=6.1 Hz, Me); 1.42 (s, Me_2C); 3.50–3.60, 3.63–3.72 (2m, CH_2); 3.91–4.13 (m, CH, CH_2); 6.02 (s, OH); 7.11–7.29 (m, Ph, NH). ^{13}C NMR: 13.9 (q, Me); 24.5 (q, Me_2C); 54.4 (d, CH); 56.6 (s, Me_2C); 61.5 (t, CH_2); 65.1 (t, CH_2O); 127.7, 128.3, 129.0 (3d, 5 arom. CH); 136.5 (s, arom. C); 172.8, 174.2 (2s, 2CO). ESI-MS: 280 (100, $[M+H]^+$).

4.6.2. Methyl 2-methyl-2-(2-phenylacryloylamino)-propanoate (26). According to GP10, **18** (139 mg, 0.5 mmol) in toluene (30 mL), CC (AcOEt/hexane 1:10). Yield: 72 mg (58%) of **26**. White crystals. Mp 116.8–117.4 °C. IR: 3328m, 3068m, 2960vs, 2861s, 1727vs, 1657s, 1533s, 1460s, 1382m, 1276vs, 1139s, 1073s, 944w, 731m. ^{1}H NMR: 1.56 (s, Me_2C); 3.77 (s, MeO); 5.60, 6.10 (2*s*, H_2C=); 6.28 (br s, NH); 7.30–7.42 (m, Ph). ^{13}C NMR: 24.6 (q, Me_2C); 52.6 (s, MeO); 56.7 (s, Me_2C); 121.7 (t, H_2C=); 127.9, 128.6, 128.9 (3d, 5 arom. CH); 136.8 (s, C=CH_2); 144.7 (s, arom. C); 166.6, 174.7 (2s, 2CO). CI-MS: 265 (6, $[M+NH_4]^+$), 249 (14), 248 (100, $[M+H]^+$).

4.6.3. Methyl 2-(2-benzyl-3-hydroxypropanoylamino)-2-methylpropanoate (27). According to GP9, **22** (188 mg, 0.5 mmol) in toluene/MeOH 80:20 (30 mL), CC (AcOEt/hexane 1:10). Yield: 81 mg (58%) of **22**. Colorless oil. ^{1}H NMR: 1.41, 1.44 (2s, Me_2C); 2.59 (m, CH); 2.82 (m, CH_2); 3.51, (br s, OH); 3.71 (m, MeO, CH_2); 6.50 (s, NH); 7.11–7.31 (m, Ph). ^{13}C NMR: 26.3 (q, Me_2C); 35.2 (t, CH_2); 48.4 (s, MeO); 51.1 (d, CH); 55.1 (s, Me_2C); 66.0 (t, CH_2); 126.6, 128.4, 128.9 (3d, 5 arom. CH); 138.0 (s, arom. C); 170.9, 172.9 (2s, 2CO). CI-MS: 281 (16), 280 (100, $[M+H]^+$).

4.7. Attempted cyclization reactions

4.7.1. Direct amide cyclization.

4.7.1.1. 8,8,19,19-Tetramethyl-10,21-dioxa-6,17-diazadispiro[4.6.4.6]docosane-7,11,18,22-tetraone (10). According to GP5, **9** (256 mg, 1 mmol) in dry toluene (50 mL) for 15 min. Yield: 186 mg (88%) of **10**. White powder. Mp 344.8–346.4 °C (decomp.). IR: 3386vs, 3029w, 2989s, 2936s, 1715vs, 1668vs, 1519vs, 1470m, 1268vs, 1190m, 1126vs, 1012m, 804w, 699s. ^{1}H NMR ((*d*$_7$)DMF): 1.00 (s, 2Me_2C); 1.46–1.54 (m, 4CH_2); 1.75–1.82, 1.88–1.94 (2m, 4CH_2); 3.94 (s, 2CH_2O); 7.69 (s, 2NH). ^{13}C NMR ((*d*$_7$)DMF): 22.8 (q, 2Me_2C); 24.7, 36.1 (2t, 8CH_2); 41.3, 65.2 (2s, Me_2C, 2C); 70.8 (t, 2CH_2O); 173.9, 174.5 (2s, 4CO). CI-MS: 441 (21), 440 (90, $[M+Na]^+$), 423 (100, $[M+H]^+$). Anal. Calcd for $C_{22}H_{34}N_2O_6$ (422.53): C 62.54, H 8.11, N 6.63; found: C 61.89, H 8.07, N 6.56.

Recrystallization from DMF/toluene/ethyl acetate yielded crystals of **10**, suitable for an X-ray crystal structure determination.

4.7.1.2. 3,10-Dibenzyl-3,6,6,10,13,13-hexamethyl-1,8-dioxa-4,11-diazacyclotetradecane-2,5,9,12-tetraone (12). According to GP 5, **11** (368 mg, 1 mmol) in dry toluene (50 mL), for 15 min. Yield: 177 mg (34%) of **12**. White solid. Mp 288.1–290.5 °C (decomp.). IR: 3520m, 3460vs, 3057w, 2970s, 1744vs, 1660vs, 1527vs, 1483s, 1364s, 1260s, 1236m, 1121vs, 1020w, 719m, 701s. ^{1}H NMR: 1.11, 1.25, 1.46 (3s, 6Me); 3.28–3.38 (m, 2PhCH_2); 4.09 (s, 2CH_2O); 7.07 (s, 2NH); 7.21–7.31 (m, 10 arom. H). ^{13}C NMR: 21.3, 21.8 (2q, 2Me_2C); 28.7 (q, 2Me); 39.7 (s, 2Me_2C); 41.3 (t, 2CH_2); 58.4 (s, 2C); 70.2 (t, 2CH_2O); 126.1, 127.3, 129.6 (3d, 10 arom. CH); 135.0 (s, 2 arom. C); 171.7, 173.2 (2s, 4CO). ESI-MS: 545 (100, $[M+Na]^+$).

Recrystallization from DMF/benzene/CH_2Cl_2/hexane/*i*-PrOH yielded crystals of **12**, suitable for an X-ray crystal structure determination.

4.7.1.3. 3,6,6,10,13,13-Hexamethyl-3,10-diphenyl-1,8-dioxa-4,11-diazacyclotetradecane-2,5,9,12-tetraone (24). According to GP6, **21a** (292 mg, 1 mmol) in dry toluene (50 mL), 15 min, (SiO_2, acetone/CH_2Cl_2 1:60). Yield: 75 mg (30%) of **24**. White solid. Mp 251.6–253.1 °C (decomp.). IR: 3526m, 3435vs, 3023w, 2987s, 1736vs, 1665vs, 1519vs, 1384s, 1276s, 1142vs, 1081w, 998s, 770m, 699s. ^{1}H NMR: 1.30, 1.51, 1.60 (3s, 6Me); 4.41–4.61 (m, 2CH_2O); 7.07 (s, 2NH); 7.28–7.42 (m, 10 arom. H). ^{13}C NMR: 22.6, 24.5 (2q, 2Me_2C); 25.7 (q, 2Me); 50.6 (s, 2Me_2C); 56.1 (s, 2C); 70.0 (t, 2CH_2O); 126.4, 127.7, 128.9 (3d, 10 arom. CH); 141.0 (s, 2 arom. C); 172.9,173.5 (2s, 4CO). CI-MS: 513 (32), 512 (100, $[M+NH_4]^+$), 495 (28, $[M+H]^+$).

Recrystallization from toluene/MeCN/acetone yielded crystals of **24**, suitable for an X-ray crystal structure determination.

4.7.1.4. Reaction of 22 under DAC conditions. A suspension of **22** (188 mg, 0.5 mmol) in toluene (30 mL) was heated to 100 °C, and dry HCl gas was bubbled through the suspension for 20 min (IR monitoring). Then, the mixture was allowed to cool to rt while bubbling N_2 through it (ca. 20 min), MeOH was added to the solution and stirred at rt for 1 h. The solvent was evaporated, the oily residue was purified by CC (AcOEt/hexane 1:10) yielding **27** (13 mg, 9%), **28** (28 mg, 21%) and **29** (36 mg, 30%).

4.7.1.4.1. Methyl 2-(2-benzylacryloylamino)-2-methylpropanoate (28). Colorless oil. IR: 3332m, 3069m, 2954vs, 2861s, 1727vs, 1661s, 1537s, 1454s, 1364m, 1282vs, 1241s, 1144s, 1073s, 1026m, 931w, 731m, 701m. ^{1}H NMR: 1.46, 1.49 (2s, Me_2C); 3.61 (s, CH_2); 3.71 (s, MeO); 5.22, 5.79 (2s, H_2C=); 6.32 (br s, NH); 7.14–7.32 (m, Ph). ^{13}C NMR: 24.5 (q, Me_2C); 38.5 (t, CH_2); 52.4 (s, MeO); 56.4 (s, Me_2C); 119.6 (t, H_2C=); 126.4, 128.4, 128.8 (3d, 5 arom. CH); 138.2 (s, arom. C); 144.4 (s, C=CH_2); 167.3, 174.8 (2s, 2CO). CI-MS: 263 (18), 262 (100, $[M+H]^+$).

4.7.1.4.2. 2-Benzyl-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]acrylamide (29). White solid. Mp 119.1–121.6 °C. IR: 3282s, 3060w, 2932m, 1634vs, 1598s, 1541s, 1481s, 1421m, 1390s, 1254m, 1172w, 1090s, 1079m, 769m, 703s. ^{1}H NMR: 1.41 (s, Me_2C); 3.20 (s, MeN); 3.46 (s, CH_2); 5.10, 5.53 (2s, H_2C=); 6.18 (br s, NH); 7.09–7.39 (m, 2Ph). ^{13}C NMR: 26.1 (q, Me_2C); 38.4 (t, CH_2); 41.3 (q, MeN); 58.1 (s, Me_2C); 120.0 (t, H_2C=); 126.5, 127.8, 128.1, 128.6, 129.0, 129.4 (6d, 10 arom. CH); 138.4, 143.4 (2s, 2 arom. C); 144.4 (s, C=CH_2); 166.5, 173.1 (2s, 2CO). CI-MS: 237 (52, $[M+H]^+$), 230 (100, $[M-N(Me)Ph]^+$), 108 (18).

4.7.1.5. 2-(2-Hydroxyphenyl)-4,4-dimethyl-1,3-oxazol-5(4*H*)-one (31). According to GP6, **30** (156 mg, 0.5 mmol) in dry toluene (50 mL), 5 min (SiO_2, acetone/CH_2Cl_2 1:40). Yield: 73 mg (74%) of **31**. Colorless crystals. Mp 68.2–69.0 °C. IR: 3079m, 2977s, 1823vs, 1643vs, 1615vs, 1579s, 1478s, 1320vs, 1251s, 1206s, 1090s, 1016s, 915s, 735s. ^{1}H NMR: 1.55 (s, Me_2C); 6.84–7.08, 7.41–7.49, 7.68–7.73 (3m, 4 arom. H). ^{13}C NMR: 24.8 (q, Me_2C); 64.5 (s, Me_2C); 108.8 (s, arom. C); 117.2, 119.3, 128.2, 134.5 (d, 4 arom. CH); 160.0 (s, C=N); 161.8 (s, arom. C); 178.6 (s, CO). CI-MS: 206 (100, $[M+NH_4]^+$).

Recrystallization from $CDCl_3/CH_2Cl_2$ yielded crystals of **31**, suitable for an X-ray crystal structure determination.

4.7.1.6. Reaction of 33a under DAC conditions. According to GP6, **33a** (152 mg, 0.5 mmol) in dry toluene (50 mL), 6 min, CC (SiO_2, acetone/CH_2Cl_2 1:10). Yield: 51 mg (34%) of **35a** and 30 mg (28%) of **34a**.

4.7.1.6.1. *N*-[1-Methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]cyclopent-1-enecarboxamide (35a). White solid. Mp 109.6–111.1 °C. ^{1}H NMR: 1.53 (s, Me_2C); 1.84–1.95, 2.22–2.26, 2.37–2.44 (3m, $3CH_2$); 3.26 (s, Me_2N); 5.81 (m, CH=); 6.43 (br s, NH); 7.20–7.23, 7.29–7.34 (m, Ph). ^{13}C NMR: 23.4 (t, CH_2); 26.6 (q, Me_2C); 31.0, 31.1, 32.8 (3t, $3CH_2$); 41.3 (q, MeN); 57.7 (s, Me_2C); 117.9 (s, C=); 127.6, 127.8, 129.1 (d, 5 arom. CH); 139.4 (d, CH=); 144.5 (s, arom. C); 169.0, 173.1 (2s, 2CO). ESI-MS: 202 (100, $[M+Na]^+$).

4.7.1.6.2. 2-(2-Hydroxycyclopentyl)-4,4-dimethyl-1,3-oxazol-5(4*H*)-one (34a). White solid. Mp 98.0–102.1 °C (decomp.). IR: 3080w, 2980m, 1822vs, 1642s, 1597s, 1472m, 1382w, 1216m, 1095s, 1018m, 916s. ^{1}H NMR: 1.56 (s, Me_2C); 1.54–1.75, 1.79–1.98 (2m, $3CH_2$, CH); 4.41 (m, CHO). ^{13}C NMR: 22.4 (t, CH_2); 25.4, 25.8 (2q, Me_2C); 27.8, 31.1 (3t, $3CH_2$); 54.4 (d, CH); 62.3 (s, Me_2C); 76.1 (d, CHO); 162.5 (s, C=N); 173.1 (s, CO). CI-MS: 229 (100, $[M+NH_4]^+$).

4.7.1.7. Reaction of 33b under DAC conditions. According to GP6, **33b** (158 mg, 0.5 mmol) in dry toluene (50 mL), 6 min, CC (SiO_2, acetone/CH_2Cl_2 1:10). Yield: 51 mg (34%) of **35b** and 31 mg (31%) of **34b**.

4.7.1.7.1. *N*-[1-Methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]cyclohex-1-enecarboxamide (35b). White crystals. Mp 112.1–113.8 °C. ^{1}H NMR: 1.46 (s, Me_2C); 1.52–1.62, 1.84–1.96, 2.01–2.14 (3m, $4CH_2$); 3.26 (s, MeN); 5.85 (m, CH=); 6.53 (br s, NH); 7.18–7.20, 7.30–7.36 (m, Ph). ^{13}C NMR: 21.4, 21.9, 23.8, 25.2 (4t, $4CH_2$); 26.6 (q, Me_2C); 41.3 (q, MeN); 57.6 (s, Me_2C); 117.1 (s, CH=); 127.7, 129.1, 129.3 (3d, 5 arom. CH); 133.9 (d, CH=); 144.5 (s, arom. C); 169.6, 173.2 (2s, 2CO). ESI-MS: 323 (100, $[M+Na]^+$).

4.7.1.7.2. 2-(2-Hydroxycyclohexyl)-4,4-dimethyl-1,3-oxazol-5(4*H*)-one (34b). White solid. Mp 101.1–105.2 °C (decomp.). IR: 3288w, 3017m, 29,619m, 1824vs, 1638s, 1595s, 1490m, 1421m, 1380m, 1092s, 917s. ^{1}H NMR: 1.39, 1.43 (2s, Me_2C); 1.44–1.56, 1.64–1.89, 1.90–1.98 (3m, $4CH_2$); 4.01 (m, CHO). ^{13}C NMR: 19.8, 24.9, 26.6 (3t, $3CH_2$); 26.0, 26.1 (q, Me_2C); 31.9 (t, CH_2); 49.0 (d, CH); 64.0 (s, Me_2C); 66.9 (d, CHO); 163.1 (s, C=N); 176.8 (s, CO). CI-MS: 215 (100, $[M+NH_4]^+$).

4.7.2. Other cyclizations.

4.7.2.1. *trans*-3,10-Dibenzyl-6,6,13,13-tetramethyl-1,8-dioxa-4,11-diazacyclotetradecane-2,5,9,12-tetraone (*trans*-14). According to GP7, **15** (321 mg, 1 mmol) or **13** (279 mg, 1 mmol). Yield of *trans*-**14**: 108 mg (44%) (from **13**) and 60 mg (24%) (from **15**), respectively. Colorless crystals. Mp 232.9–234.6 °C (decomp.). $[\alpha]_D^{25}$ 0 (*c* 1, $CHCl_3$). IR: 3374vs, 3024w, 2966m, 1732vs, 1645vs, 1531s, 1366m, 1282s, 1179s, 1108w, 1001m, 751m, 700m. ^{1}H NMR: 0.90, 0.98 (2s, Me_2C); 3.06 (d, J= 5.8 Hz, CH_2); 3.91–3.96 (m, CH_2); 4.80–4.84 (m, CH); 5.89 (d, J=3.9 Hz, NH); 6.97–6.99 (m, 6 arom. H); 7.10–7.25 (m, 4 arom. H). ^{13}C NMR: 21.6, 22.7 (2q, Me_2C); 37.6 (t, $2CH_2$); 42.2 (s, 2C); 52.5 (d, 2CH); 70.9 (t, $2CH_2O$); 127.2, 128.6, 129.3 (3d, 10 arom. CH); 135.7 (s, 2 arom. C); 170.0, 174.0 (2s, 4CO). ESI-MS: 517 (100, $[M+Na]^+$), 444 (11). CI-MS: 513 (30), 512 (100, $[M+NH_4]^+$), 496 (12), 495 (30, $[M+H]^+$). Anal. Calcd for $C_{28}H_{34}N_2O_6$ (494.59): C 68.00, H 6.93, N 5.66; found: C 67.69, H 7.08, N 5.48.

Recrystallization from *i*-PrOH/CH_2Cl_2/hexane yielded crystals of *trans*-**14**, suitable for an X-ray crystal structure determination.

According to GP8, *rac*-**16** (287 mg, 1 mmol), CC (CH_2Cl_2/acetone 200:1) yielded *trans*-**14** as white crystals in 25% yield (62 mg). $[\alpha]_D^{25}$ 0 (*c* 1, $CHCl_3$).

4.7.2.2. *cis*-(*S*,*S*)-3,10-Dibenzyl-6,6,13,13-tetramethyl-1,8-dioxa-4,11-diazacyclotetradecane-2,5,9,12-tetraone ((*S*,*S*)-14). According to GP8, (*S*)-**16** (1 mmol, 287 mg), CC (CH_2Cl_2/acetone 200:1). Yield: 54 mg (22%) of (*S*,*S*)-**14b**. Mp 212.1–214.4 °C (decomp.). $[\alpha]_D^{25}$ −26.3 (*c* 1, $CHCl_3$). ^{1}H NMR: 0.88, 1.08 (2s, $2Me_2C$); 3.13 (s, $2CH_2O$); 3.91–4.04, 4.11–4.22 (2m, $2CH_2$); 4.83–5.00 (m, 2CH); 5.83 (br s, 2NH); 7.03–7.14, 7.28–7.42 (2m, 2Ph). ^{13}C NMR: 21.5, 22.7 (2q, $2Me_2C$); 37.6 (t, $2CH_2$); 42.1 (s, 2C); 53.3 (d, 2CH); 71.0 (t, $2CH_2$); 127.3, 128.7, 129.4 (3d, 10 arom. CH); 136.1 (s, 2 arom. C); 169.7, 174.3 (2s, 4CO). ESI-MS: 517 (100, $[M+Na]^+$), 444 (11).

Recrystallization from CH_2Cl_2/*sec*-BuOH yielded crystals of (*S*,*S*)-**14**, suitable for an X-ray crystal structure determination.

4.8. X-ray crystal structure determination of 10, 11a, 12, *trans*-14, (*S*,*S*)-14, 24, and 31

All measurements were made on a Nonius KappaCCD area-detector diffractometer[34] using graphite-monochromated Mo K_α radiation (λ 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. The data collection and refinement parameters are given below[35] and views of the molecules are shown in Figures 1–3. Data reduction was performed with HKL Denzo and Scalepack.[36] The intensities were corrected for Lorentz and polarization effects, but not for absorption. Equivalent reflections were merged. Each structure was solved by direct methods using SIR92,[37] which revealed the positions of all non-hydrogen atoms.

In the case of **10**, **12**, *trans*-**14** and **24**, the molecule sits about a crystallographic centre of inversion.

In the case of (*S*,*S*)-**14**, there are two symmetry-independent molecules in the asymmetric unit. The atomic coordinates of the two molecules were tested carefully for a relationship from a higher symmetry space group using the program PLATON,[38] but none could be found. The crystal is merohedrally twinned. Successful refinement of the structure was achieved using the twin operator [1 0 0/ 0 −1 0/0 0 −1] and the major twin domain has a volume fraction of 0.640(1).

The non-hydrogen atoms were refined anisotropically. Any amide or hydroxy H-atoms in the structures were placed in the positions indicated by a difference electron density map 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 using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the methyl groups). Except for **11a**, the refinement of each structure was carried out on F^2 by using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2-F_c^2)^2$. The refinement of the structure of **11a** was carried out on *F* by minimizing the corresponding function based of *F*. Corrections for secondary extinction were applied.

Neutral atom scattering factors for non-hydrogen atoms were taken from Ref. 39, and the scattering factors for H-atoms were taken from Ref. 40. Anomalous dispersion effects were included in F_c;[41] the values for f' and f'' were those of Ref. 42. The values of the mass attenuation coefficients are those of Ref. 43. All calculations were performed using the SHELXL97 program[44] with the exception of **11a**, where the teXsan crystallographic software package[45] was used.

Crystal data for **10**. $C_{22}H_{34}N_2O_6$, M=422.52, colorless, plate, crystal dimensions 0.05×0.12×0.30 mm, triclinic, space group *P*bar, Z=1, reflections for cell determination 2354, 2θ range for cell determination 4–55°, a=6.0630(5) Å, b=9.5495(6) Å, c=10.7064(9) Å, α=66.451(3)°, β=83.228(4)°, γ=71.733(5)°, V=539.61(7) Å^3, T=160 K, D_x=1.300 g cm^{-3}, μ(Mo K_α)=0.0941 mm^{-1}, $2\theta_{(max)}$=55°, total reflections measured =11,110, symmetry independent reflections =2457, reflections with $I>2\sigma(I)$=1919, reflections used in refinement =2455, parameters refined =143, $R(F)$ [$I>2\sigma(I)$ reflections] =0.0473, $wR(F^2)$ [all data] =0.1277 ($w=[\sigma^2(F_o^2)+(0.0624P)^2+0.093P]^{-1}$ where $P=(F_o^2+2F_c^2)/3$), goodness of fit =1.059, secondary extinction coefficient 0.09(2), final Δ_{max}/σ=0.001, $\Delta\rho$ (max; min) =0.30; −0.28 *e* Å^{-3}.

Crystal data for **11a**. $C_{17}H_{26}N_2O_3$, M=306.40, colorless, prism, crystal dimensions 0.15×0.15×0.25 mm, monoclinic, space group $P2_1/n$, Z=4, reflections for cell determination 4110, 2θ range for cell determination 4–55°, a=8.1009(1) Å, b=17.1770(3) Å, c=12.6459(2) Å, β=101.112(1)°, V=1726.67(5) Å^3, T=160 K, D_x=1.179 g cm^{-3}, μ(Mo K_α)=0.0806 mm^{-1}, $2\theta_{(max)}$=55°, total reflections measured =37,684, symmetry independent reflections =3973, reflections used in refinement [$I>2\sigma(I)$]=2947, parameters refined =208, $R(F)$ =0.0469, $wR(F)$=0.0479 $w=[\sigma^2(F_o)+(0.005F_o)^2]^{-1}$, goodness of fit =2.962, secondary extinction coefficient =3.3(5)×10^{-6}, final Δ_{max}/σ=0.0005, $\Delta\rho$ (max; min)=0.39; −0.27 *e* Å^{-3}.

Crystal data for **12**. $C_{30}H_{38}N_2O_6$, M=522.64, colorless, tablet, crystal dimensions 0.05×0.10×0.20 mm, monoclinic, space group $P2_1/n$, Z=2, reflections for cell determination 2439, 2θ range for cell determination 4–50°, a=6.0109(2) Å, b=17.3238(5) Å, c=12.9060(5) Å, β=91.855(2)°, V=1343.22(8) Å^3, T=160 K, D_x=1.292 g cm^{-3}, μ(Mo K_α)=0.0896 mm^{-1}, $2\theta_{(max)}$=50°, total reflections measured =17,323, symmetry independent reflections =2359, reflections with $I>2\sigma(I)$ =1731, reflections used in refinement =2358, parameters refined =180, $R(F)$ [$I>2\sigma(I)$ reflections]=0.0540, $wR(F^2)$ [all data] =0.1283 ($w=[\sigma^2(F_o^2)+(0.0395P)^2+0.6836P]^{-1}$ where $P=(F_o^2+2F_c^2)/3$), goodness of fit=1.129, secondary extinction coefficient=0.013(2), final Δ_{max}/σ=0.001, $\Delta\rho$ (max; min)=0.35; −0.18 *e* Å^{-3}.

Crystal data for trans-**14**. $C_{28}H_{34}N_2O_6$, M=494.58, colorless, needle, crystal dimensions 0.05×0.05×0.25 mm, monoclinic, space group $C2/c$, Z=4, reflections for cell determination 2421, 2θ range for cell determination 4–50°,

$a=18.6829(6)$ Å, $b=14.5471(5)$ Å, $c=10.0381(3)$ Å, $\beta=104.943(2)°$, $V=2635.9(2)$ Å^3, $T=160$ K, $D_x=1.246$ g cm^{-3}, μ(Mo K$_\alpha$)$=0.0875$ mm^{-1}, $2\theta_{(max)}=50°$, total reflections measured$=18{,}709$, symmetry independent reflections$=2333$, reflections with $I>2\sigma(I)=1579$, reflections used in refinement$=2333$, parameters refined$=170$, $R(F)$ [$I>2\sigma(I)$ reflections]$=0.0456$, $wR(F^2)$ [all data]$=0.1156$ ($w=[\sigma^2(F_o^2)+(0.041P)^2+1.0127P]^{-1}$ where $P=(F_o^2+2F_c^2)/3$), goodness of fit$=1.040$, secondary extinction coefficient$=0.0040(7)$, final $\Delta_{max}/\sigma=0.001$, $\Delta\rho$ (max; min)$=0.18$; -0.17 e Å^{-3}.

Crystal data for (S,S)-**14**. $C_{28}H_{34}N_2O_6$, $M=494.58$, colorless, prism, crystal dimensions $0.13\times0.13\times0.30$ mm, monoclinic, space group $P2_1$, $Z=4$, reflections for cell determination 7591, 2θ range for cell determination 4–60°, $a=5.4181(2)$ Å, $b=35.569(1)$ Å, $c=13.3108(4)$ Å, $\beta=90.090(1)°$, $V=2565.2(2)$ Å^3, $T=160$ K, $D_x=1.281$ g cm^{-3}, μ(Mo K$_\alpha$)$=0.0899$ mm^{-1}, $2\theta_{(max)}=60°$, total reflections measured$=52{,}489$, symmetry independent reflections$=7611$, reflections with $I>2\sigma(I)=5073$, reflections used in refinement$=7606$, parameters refined$=675$, $R(F)$ [$I>2\sigma(I)$ reflections]$=0.0446$, $wR(F^2)$ [all data]$=0.0899$ ($w=[\sigma^2(F_o^2)+(0.036P)^2]^{-1}$ where $P=(F_o^2+2F_c^2)/3$), goodness of fit$=1.025$, secondary extinction coefficient$=0.012(1)$, final $\Delta_{max}/\sigma=0.001$, $\Delta\rho$ (max; min)$=0.23$; -0.21 e Å^{-3}.

Crystal data for **24**. $C_{28}H_{34}N_2O_6$, $M=494.58$, colorless, prism, crystal dimensions $0.22\times0.25\times0.32$ mm, triclinic, space group $P\bar{1}$, $Z=1$, reflections for cell determination 2078, 2θ range for cell determination 4–50°, $a=5.9467(3)$ Å, $b=10.1233(5)$ Å, $c=10.9664(5)$ Å, $\alpha=73.363(3)°$, $\beta=83.818(3)°$, $\gamma=76.704(3)°$, $V=614.97(5)$ Å^3, $T=160$ K, $D_x=1.335$ g cm^{-3}, μ(Mo K$_\alpha$)$=0.0938$ mm^{-1}, $2\theta_{(max)}=50°$, total reflections measured$=8138$, symmetry independent reflections$=2137$, reflections with $I>2\sigma(I)=1796$, reflections used in refinement$=2136$, parameters refined$=171$, $R(F)$ [$I>2\sigma(I)$ reflections]$=0.0390$, $wR(F^2)$ [all data]$=0.1010$ ($w=[\sigma^2(F_o^2)+(0.043P)^2+0.2587P]^1$ where $P=(F_o^2+2F_c^2)/3$), goodness of fit$=1.067$, secondary extinction coefficient$=0.052(9)$, final $\Delta_{max}/\sigma=0.001$, $\Delta\rho$ (max; min)$=0.18$; -0.25 e Å^{-3}.

Crystal data for **31**. $C_{11}H_{11}NO_3$, $M=205.21$, colorless, prism, crystal dimensions $0.10\times0.17\times0.30$ mm, monoclinic, space group $P2_1/n$, $Z=4$, reflections for cell determination 2470, 2θ range for cell determination 4–55°, $a=5.6230(2)$ Å, $b=8.9884(4)$ Å, $c=20.2034(8)$ Å, $\beta=93.985(3)°$, $V=1018.65(7)$ Å^3, $T=160$ K, $D_x=1.338$ g cm^{-3}, μ(Mo K$_\alpha$)$=0.0982$ mm^{-1}, $2\theta_{(max)}=55°$, total reflections measured$=21{,}205$, symmetry independent reflections$=2333$, reflections with $I>2\sigma(I)=1834$, reflections used in refinement$=2331$, parameters refined$=143$, $R(F)$ [$I>2\sigma(I)$ reflections]$=0.0517$, $wR(F^2)$ [all data]$=0.1359$ ($w=[\sigma^2(F_o^2)+(0.0581P)^2+0.2986P]^{-1}$ where $P=(F_o^2+2F_c^2)/3$), goodness of fit$=1.107$, secondary extinction coefficient$=0.032(6)$, final $\Delta_{max}/\sigma=0.001$, $\Delta\rho$ (max; min)$=0.21$; -0.22 e Å^{-3}.

Acknowledgements

We thank the analytical sections of our institute for the spectra and analyses. Financial support of the Swiss National Science Foundation and F. Hoffmann-La Roche AG, Basel, is gratefully acknowledged.

References and notes

1. Iliev, B.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2003**, *86*, 3215–3234.
2. Obrecht, D.; Heimgartner, H. *Helv. Chim. Acta* **1984**, *67*, 526–533.
3. Obrecht, D.; Heimgartner, H. *Helv. Chim. Acta* **1987**, *70*, 329–338.
4. Obrecht, D.; Heimgartner, H. *Helv. Chim. Acta* **1990**, *73*, 221–228.
5. Villalgordo, J. M.; Heimgartner, H. *Helv. Chim. Acta* **1997**, *80*, 748–766.
6. Koch, K. N.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2000**, *83*, 233–257.
7. Koch, K. N.; Linden, A.; Heimgartner, H. *Tetrahedron* **2001**, *57*, 2311–2326.
8. Heimgartner, H.; Arnhold, F. S.; Fritschi, S.; Koch, K. N.; Linden, A.; Magirius, J. E. F. *J. Heterocycl. Chem.* **1999**, *36*, 1539–1547.
9. Linden, A.; Ghorbani-Salman Pour, F.; Breitenmoser, R. A.; Heimgartner, H. *Acta Crystallogr., Sect. C* **2001**, *57*, 634–637.
10. Richard, S.; Prie, G.; Guignard, A.; Thibonet, J.; Luc Parrain, J.; Duchene, A.; Abarbri, M. *Helv. Chim. Acta* **2003**, *86*, 726–732.
11. Wasserman, H.; Keggi, J.; McKeon, J. *J. Am. Chem. Soc.* **1961**, *83*, 4107–4108.
12. Wasserman, H.; Keggi, J.; McKeon, J. *J. Am. Chem. Soc.* **1962**, *84*, 2978–2982.
13. Shemyakin, M. M.; Antonov, V. K.; Shkrob, A. M.; Schelokov, V. I.; Agadzhanyan, Z. E. *Tetrahedron* **1965**, *21*, 3537–3572.
14. Matsuyama, T.; Bhasin, A.; Harshey, R. *J. Bacteriol.* **1995**, *177*, 987–991.
15. Strobel, G., Morrison, S., Cassella, M. U.S. Pat. Appl. US2001-858871, Publ. 2003.
16. Hassall, C.; Martin, T.; Schofield, J. *Tetrahedron Lett.* **1964**, *5*, 3741–3743.
17. Hassall, C.; Martin, T.; Schofield, J. *J. Chem. Soc., Sect. C* **1967**, *32*, 997–1003.
18. Ovchinnikov, Y.; Ivanov, V.; Kiryushkin, A.; Shemyakin, M. *Dokl. Akad. Nauk SSSR* **1963**, *153*, 122–125.
19. Philipova, I.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2005**, *88*, 1711–1733.
20. Stoykova, S. A. Ph.D. Thesis, University of Zurich, 2004.
21. Heimgartner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238–265.
22. The crystal structure of **11a** was established by X-ray crystallography (see Section 4). Since the space group is centrosymmetric, the crystals are racemic. The *trans*-amide group is planar. The amide NH group forms an intramolecular hydrogen bond with the hydroxy O-atom, while the hydroxy group forms an intermolecular hydrogen bond with the O-atom of the amide group in the centre of the molecule of a neighboring molecule, thereby linking the molecules into extended chains.
23. Johnson, C. K., *ORTEPII*, Report ORNL-5138; Oak Ridge National Laboratory: Oak Ridge, Tennessee, 1976.

24. Bernstein, J.; Davis, R. E.; Shimoni, L.; Chang, N.-L. *Angew. Chem.* **1995**, *107*, 1689–1708. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1555–1573.
25. Wipf, P.; Heimgartner, H. *Helv. Chim. Acta* **1987**, *70*, 354–368.
26. Fujita, T.; Hanyu, N.; Mino, T.; Sakamoto, M. *Synthesis* **2001**, *12*, 1846–1851.
27. Geffken, D. *Arch. Pharm.* **1979**, *312*, 360–361.
28. Monteil, T.; Danvy, D.; Plaquevent, J.; Duhamel, L.; Duhamel, P.; Gros, C.; Schwartz, J.; Lecomte, J. *Synth. Commun.* **2001**, *31*, 211–218.
29. Obrecht, D.; Heimgartner, H. *Chimia* **1982**, *36*, 78–81.
30. Dewar, M. J.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.
31. *AMPAC* 6.5.5, Semichem Inc., 7128 Summit, Shawnee, KS66216.
32. Herradon, D.; Seebach, D. *Helv. Chim. Acta* **1989**, *72*, 690–714.
33. Seebach, D.; Zimmermann, J. *Helv. Chim. Acta* **1986**, *69*, 1147–1152.
34. Hooft, R. *KappaCCD Collect Software*, Nonius BV: Delft, The Netherlands, 1999.
35. CCDC 284106-284112 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.
36. Otwinowski, Z.; Minor, W. In *Methods in Enzymology*; Carter, C. W., Jr., Sweet, R. M., Eds.; Macromolecular Crystallography; Academic: New York, 1997; Vol. 276, pp 307–326; Part A.
37. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435.
38. Spek, A. L. *PLATON*, Program for the Analysis of Molecular Geometry, University of Utrecht: The Netherlands, 2003.
39. Maslen, E. N.; Fox, A. G.; O'Keefe, M. A. In Wilson, A. J. C., Ed.; International Tables for Crystallography; Kluwer Academic: Dordrecht, 1992; Vol. C, pp 477–486; Table 6.1.1.1.
40. Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175–3187.
41. Ibers, J. A.; Hamilton, W. C. *Acta Crystallogr.* **1964**, *17*, 781–782.
42. Creagh, D. C.; McAuley, W. J. In Wilson, W. J. C., Ed.; International Tables for Crystallography; Kluwer Academic: Dordrecht, 1992; Vol. C, pp 219–222; Table 4.2.6.8.
43. Creagh, D. C.; Hubbell, J. H. In Wilson, A. J. C., Ed.; International Tables for Crystallography; Kluwer Academic: Dordrecht, 1992; Vol. C, pp 200–206; Table 4.2.4.3.
44. Sheldrick, G. M. *SHELXL97*, Program for the Refinement of Crystal Structures, University of Göttingen: Germany, 1997.
45. teXsan: *Single Crystal Structure Analysis Software*, Version 1.10, Molecular Structure Corporation: The Woodlands, Texas, 1999.