JOC Article

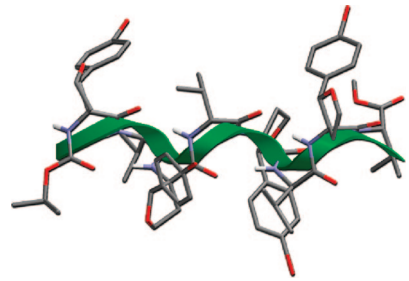
Stable Right- and Left-Handed Peptide Helices containing C^{α}-Tetrasubstituted α-Amino Acids

Andreas A. Grauer,[†] Chiara Cabrele,[‡] Manfred Zabel,[§] and Burkhard König*[,†]

Institute for Organic Chemistry, University of Regensburg, D-93040 Regensburg, Germany, X-ray Crystallography, University of Regensburg, D-93040 Regensburg, Germany, and Faculty of Chemistry and Biochemistry, Ruhr-University Bochum, D-44780 Bochum, Germany

burkhard.koenig@chemie.uni-regensburg.de

Received February 3, 2009



Short peptidomimetics with stable secondary structures in solution are of interest for applications in chemistry, biology, and medicine. One way to rigidify the backbone of a peptide is the use of cyclic C^{α}-tetrasubstituted α-amino acids (TAAs) like compound **14**. The structures resulting from the incorporation of this unnatural amino acid into peptides were investigated. In total, 13 different peptides with a length of up to eight residues and alternating sequences of TAA **14** and (*S*)- or (*R*)-valine were synthesized. Their structures were characterized by X-ray diffraction analysis and NMR and CD measurements showing that the *all-S*-backbone-configured peptides **5** and **6** $(SS)_{2-3}$ form right-handed 3_{10}-helices, while the *all-R*-configured peptides **11**−**13** $(RR)_{2-4}$ form left-handed 3_{10}-helices in the solid state and solution.

Introduction

The de novo design of peptides and peptidomimetics with a defined and predictable three-dimensional structure[1,2] has received considerable interest from chemists and biologists in recent years. Short peptide sequences consisting only of natural α-amino acids typically show flexible structures. In contrast, stable structures in solution can be accomplished by replacing natural amino acids by nonproteinogenic analogues which may induce a defined secondary structure even in short peptides.[3] Such amino acid mimetics attracted much attention in the last years because of their potential use as peptide models, biological probes, drug candidates, or catalysts.[4] Their often more rigid structure leads to conformational constraints that might lock the peptide in its bioactive or catalytically active conformation.[5] An additional advantage can be an increase of the peptide's metabolic stability after incorporation of amino acid mimetics.[6] One very successful way among others[7] to increase peptide backbone rigidity is the use of C^{α}-tetrasubstituted α-amino acids

[†] Institute for Organic Chemistry, University of Regensburg.
[‡] Faculty of Chemistry and Biochemistry, Ruhr-University Bochum.
[§] X-ray Crystallography, University of Regensburg.

(1) (a) Ellis, T. K.; Martin, C. H.; Tsai, G. M.; Ueki, H.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 6208–6214. (b) Komarov, I. V.; Grigorenko, A. O.; Turov, A. V.; Khilya, V. P. *Russ. Chem. Rev.* **2004**, *73*, 785–810. (c) Vass, E.; Hollosi, M.; Besson, F.; Buchet, R. *Chem. Rev.* **2003**, *103*, 1917–1954.

(2) Special issue: Wu, Y.-D.; Gellman, S. *Acc. Chem. Res.* **2008**, *41*, 1231–1232.

(3) (a) Balducci, D.; Bottoni, A.; Calvaresi, M.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **2006**, *17*, 3273–3281. (b) Paradisi, M. P.; Torrini, I.; Zecchini, G. P.; Lucente, G. *Tetrahedron* **1995**, *51*, 2379–2386. (c) Jimenez, A. I.; Ballano, G.; Cativiela, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 396–399.

(4) (a) Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C.; Broxterman, Q.; Kaptein, B. *J. Inclusion Phenom.* **2005**, *51*, 121–136. (b) Hruby, V. J.; Agnes, R. S. *Biopolymers* **1999**, *51*, 391–410. (c) Tanaka, M. *Chem. Pharm. Bull.* **2007**, *55*, 349–358. (d) Etienne, M. A.; Aucoin, J. P.; Fu, Y.; McCarley, R. L.; Hammer, R. P. *J. Am. Chem. Soc.* **2006**, *128*, 3522–3523. (e) Rossi, P.; Felluga, F.; Tecilla, P.; Formaggio, F.; Crisma, M.; Toniolo, C.; Scrimin, P. *J. Am. Chem. Soc.* **1999**, *121*, 6948–6949. (f) Sissi, C.; Rossi, P.; Felluga, F.; Formaggio, F.; Palumbo, M.; Tecilla, P.; Toniolo, C.; Scrimin, P. *J. Am. Chem. Soc.* **2001**, *123*, 3169–3170.

(5) March, D. R.; Abbenante, G.; Bergman, D. A.; Brinkworth, R. I.; Wickramasinghe, W.; Begun, J.; Martin, J. L.; Fairlie, D. P. *J. Am. Chem. Soc.* **1996**, *118*, 3375–3379.

(6) Balducci, D.; Emer, E.; Piccinelli, F.; Porzi, G.; Recanatini, M.; Sandri, S. *Tetrahedron: Asymmetry* **2005**, *16*, 3785–3794.

10.1021/jo900222g CCC: $40.75
Published on Web 04/08/2009

(TAA).[8] α-Aminoisobutyric acid (Aib), which also occurs in natural peptide sequences of peptaibiomics or peptaibols,[9] is the most extensively investigated compound of this kind. The helical tendencies of Aib containing peptides are well characterized, showing that short strands form a stable 3_{10}-helix while longer helices emerge into mixed 3_{10}/α-helices or pure α-helices.[10] Cycloaliphatic C^{α}-tetrasubstituted α-amino acids Ac_nc ($n = 3-9$)[11] with varying ring sizes are also well studied.[12] However, the lack of a C^{α}-stereocenter and of a side-chain functional group for further derivatization is a drawback of these compounds. Therefore, the synthesis of cyclic C^{α}-tetrasubstituted α-amino acids which show at least one stereocenter[13] and have an additional functional group in their side chain was investigated in recent years,[14] but only very few examples of successful incorporation into peptide chains have been reported.[15] We have recently introduced the C^{α}-tetrasubstituted tetrahydrofuran amino acid **rac-14** that has two stereocenters at the quaternary C^{α}- and at C^{β}-atom. The brominated arene substituent allows further functionalization by standard Pd(II) or Cu(I) catalysis.[16] When inserted into small tripeptides, the molecule induces stable secondary structures in solution by the formation of β-turns.[17]

We now extend this concept by incorporating the unnatural amino acid into longer peptide chains to form stable helices as structurally predictable and tunable scaffolds for peptide mimetics. The high steric hindrance of the C^{α}-tetrasubstituted α-amino acids hampers the peptide synthesis.[18] Therefore, alternating structures of tetrahydrofuran amino acid **rac-14** and *S*- or *R*-valine were envisaged. The use of the two different valine enantiomers allows the synthesis of helical peptides with different backbone screw sense. We report here the synthesis of isomeric di-, tetra-, and hexapeptides and of one octapeptide shown in Figure 1. Their structures were analyzed in solid state and in solution.

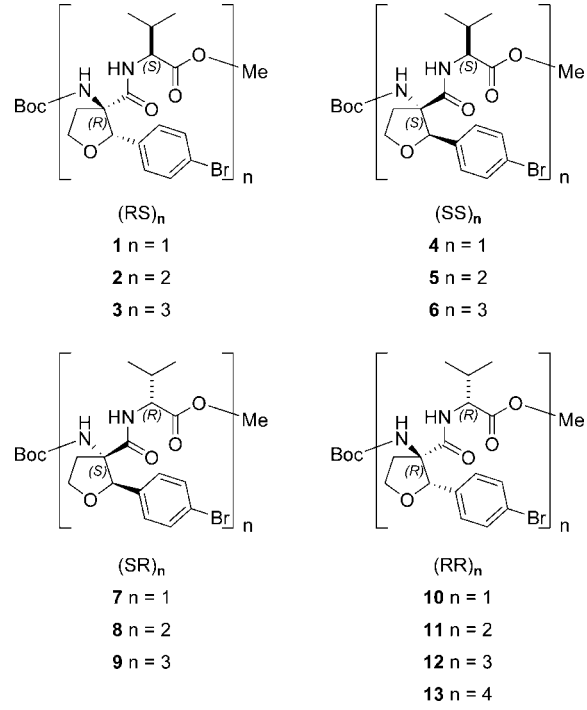


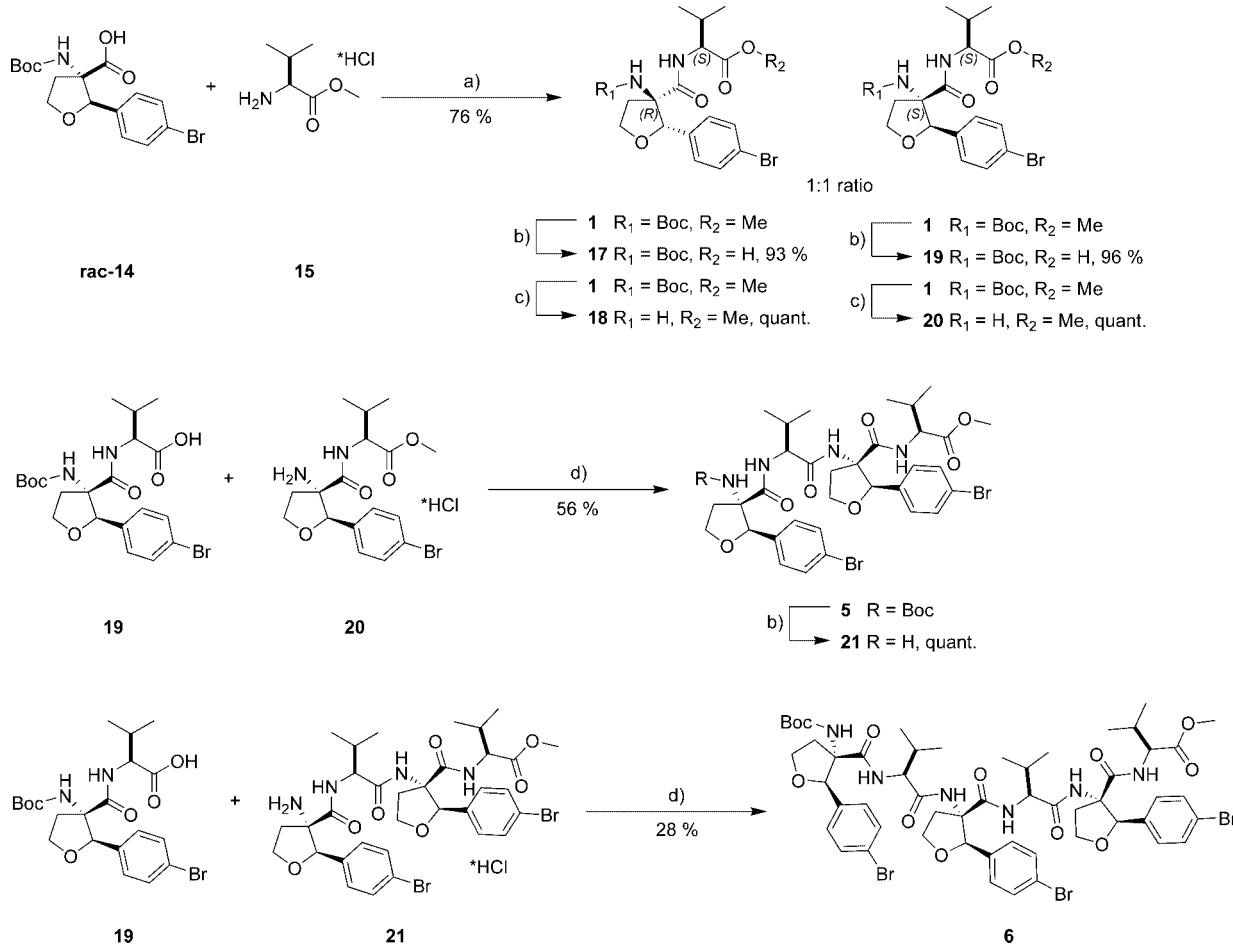
FIGURE 1. TAA-containing isomeric di-, tetra-, hexa-, and octapeptides prepared and investigated in this study.

Results and Discussion

Synthesis. The target peptides were prepared by a combination of protecting and deprotecting steps together with standard solution-phase peptide coupling chemistry. The synthesis is shown exemplary for hexapeptide **6** $(SS)_3$ in Scheme 1 and starts from the N-terminally Boc-protected racemic tetrahydrofuran amino acid Boc-TAA-OH **rac-14**.[17] The compound was coupled with either H-*S*-Val-OMe·HCl **15** or H-*R*-Val-OMe·HCl **16** using EDC/HOBt to give the dipeptides **1**, **4** or **7**, **10**, respectively. Two diastereomers emerged from the coupling reaction, which were separated by column chromatography. The isolated dipeptides **1**, **4**, **7**, and **10** were then used separately in the next steps to yield enantiomerically pure tetrapeptides. To achieve this, two equimolar amounts of compound **4** were deprotected either C-terminal with 1 M aqueous LiOH to give the free acid **19** or N-terminal with HCl saturated diethyl ether cleaving the Boc protecting group. Carboxylic acid **19** and amine **20** were coupled using HATU/HOAt to give tetrapeptide **5** in 56% yield. Tetrapeptides **2**, **8**, and **11** were obtained analogously in comparable yields. Compound **5** was Boc deprotected and subsequently coupled with dipeptide acid **19** to give hexapeptide **6**. The same procedure was used to synthesize hexapeptides **3**, **9**, and **12**. Octapeptide **13** was obtained by coupling the Boc-

(7) Hruby, V. J.; Li, G.; Haskell-Luevano, C.; Shenderovich, M. *Biopolymers* **1997**, *43*, 219–266.
(8) Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. *Biopolymers* **2001**, *60*, 396–419.
(9) (a) Degenkolb, T.; Brückner, H. *Chem. Biodiversity* **2008**, *5*, 1817–1843. (b) Degenkolb, T.; Kirschbaum, J.; Brückner, H. *Chem. Biodiversity* **2007**, *4*, 1052–1067. (c) Duclohoer, H. *Chem. Biodiversity* **2007**, *4*, 1023–1026.
(10) (a) Toniolo, C.; Benedetti, E. *Macromolecules* **1991**, *24*, 4004–4009. (b) Crisma, M.; Saviano, M.; Moretto, V.; Broxterman, Q. B.; Kaptein, B.; Toniolo, C. *J. Am. Chem. Soc.* **2007**, *129*, 15471–15473. (c) Alemán, C. *J. Phys. Chem. B* **1997**, *101*, 5046–5050. (d) Di Blasio, B.; Pavone, V.; Saviano, M.; Lombardi, A.; Nastri, F.; Pedone, C.; Benedetti, E.; Crisma, M.; Anzolin, M.; Toniolo, C. *J. Am. Chem. Soc.* **1992**, *114*, 6273–6278. (e) Smythe, M. L.; Nakaie, C. R.; Marshall, G. R. *J. Am. Chem. Soc.* **1995**, *117*, 10555–10562. (f) Smythe, M. L.; Huston, S. E.; Marshall, G. R. *J. Am. Chem. Soc.* **1993**, *115*, 11594–11595.
(11) Ac_3c (1-aminocyclopropanecarboxylic acid)−Ac_9c (1-aminocyclononanecarboxylic acid).
(12) (a) Willisch, H.; Hiller, W.; Hemmasi, B.; Bayer, E. *Tetrahedron* **1991**, *47*, 3047–3958. (b) Toniolo, C. *Biopolymers* **1989**, *28*, 247–257. (c) Crisma, M.; Bonora, G. M.; Toniolo, C.; Barone, V.; Benedetti, E.; Di Blasio, B.; Pavone, V.; Pedone, C.; Santini, A.; Fraternali, F.; Bavoso, A.; Lelj, F. *Int. J. Biol. Macromol.* **1989**, *11*, 345–352. (d) Perczel, A.; Hollosi, M.; Foxman, B. M.; Fasman, G. D. *J. Am. Chem. Soc.* **1991**, *113*, 9772–9784.
(13) (a) Burgess, K.; Li, W. *Tetrahedron Lett.* **1995**, *36*, 2725–2728. (b) Moye-Sherman, D.; Jin, S.; Ham, I.; Lim, D.; Scholtz, J. M.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9435–9443. (c) Williams, R. M.; Fegley, G. J. *J. Org. Chem.* **1993**, *58*, 6933–6935. (d) Ma, D.; Ding, K.; Tian, H.; Wang, B.; Cheng, D. *Tetrahedron* **2002**, *13*, 961–969.
(14) (a) Maity, P.; Konig, B. *Biopolymers* **2008**, *90*, 8–27. (b) Pirrung, M. C.; Dunlap, S. E.; Trink, S. E. *Helv. Chim. Acta* **1989**, *72*, 1301–1310. (c) Burgess, K.; Ho, K. K. *Tetrahedron Lett.* **1992**, *33*, 5677–5680. (d) Curry, K.; Peet, M. J.; Magnuson, D. S. K.; McLennan, H. *J. Med. Chem.* **1988**, *31*, 864–867. (e) Mancuse, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482. (f) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599. (g) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732.
(15) (a) Yokum, T. S.; Gauthier, T. J.; Hammer, R. P.; McLaughlin, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1167–1168. (b) Obrecht, D.; Altorfer, M.; Bohdal, U.; Daly, J.; Huber, W.; Labhardt, A.; Lehmann, C.; Mueller, K.; Ruffieux, R.; Schoenholzer, P. *Biopolymers* **1997**, *42*, 575–626. (c) Gershonov, E.; Granoth, R.; Tzehoval, E.; Gaoni, Y.; Fridkin, M. *J. Med. Chem.* **1996**, *39*, 4833–4843. (d) Burgess, K.; Ho, K. K. *J. Am. Chem. Soc.* **1994**, *116*, 799–800.
(16) (a) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164–5173. (b) Kuwabe, S. I.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202–12206. (c) Vorogushin, A. V.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146–8149.
(17) Maity, P.; Zabel, M.; König, B. *J. Org. Chem.* **2007**, *72*, 8046–8053.
(18) Toniolo, C.; Formaggio, F.; Kaptein, B.; Broxterman, Q. *Synlett* **2006**, *9*, 1295–1310.

SCHEME 1. Synthesis of Hexapeptide 6[a]



[a] Key: (a) DIPEA, EDC, HOBt, dry DMF, 24 h, rt; (b) LiOH, water/THF, 24 h, rt; (c) HCl satd diethyl ether, DCM, 24 h, rt; (d) DIPEA, HATU, HOAt, dry DMF, 24 h, rt.

deprotected hexapeptide **29** with dipeptide acid **25**.[19] All synthetic procedures and characterization data are provided in the Supporting Information.

Structure Analysis. The structure of the peptides was determined in the solid state by X-ray crystallography and in solution by 2D-NMR, temperature-dependent ^{1}H NMR, and CD measurements.

Solid-State Structure Analysis. From all four dipeptides crystal structures were obtained (Figure 2) showing that the pairs **1**, **7** and **4**, **10** are enantiomeric in configuration and structure. The structures indicate that molecules **4** (*SS*) and **10** (*RR*) with either two *S*-configured amino acids or two *R*-configured amino acids in their amide backbone show a turn-like structure, whereas the other two compounds **1** (*RS*) and **7** (*SR*) do not have this structural feature. This correlation becomes even more pronounced in the structures of tetrapeptides **5** $(SS)_2$ and **11** $(RR)_2$, which were again determined by X-ray crystal structure analysis (Figure 3): The homochiral tetrapeptides form a characteristic 3_{10}-helix in the solid state.[20] The helix is right-handed for the *all-S*-configured peptide **5** and left-handed for the *all-R*-configured enantiomer **11**.

For both peptides **5** $(SS)_2$ and **11** $(RR)_2$ the average backbone torsion angles φ and ψ of all four amino acids were determined (Table 1). The φ-angles are between the values of an ideal 3_{10}- and an α-helix. The ψ-angles are in good agreement with those of an ideal 3_{10}-helix.[21] One ψ-angle in compound **5** is slightly smaller than expected, while another in compound **11** is larger. This indicates the still high flexibility of the tetrapeptides that form just one turn of a 3_{10}-helix. The average $i \leftarrow i+3$ C═O···N intramolecular hydrogen bond angles were found to be 133.9° (molecule **5**) and 131.9° (molecule **11**): both values are slightly higher than those reported for other 3_{10}-helices but still significantly smaller than those of an α-helix. The pitch (axial translation) for the two peptides being 6.61 Å (**5**) for the right-handed and 6.42 Å (**11**) for the left-handed helix is larger than expected for a 3_{10}-helix. A slightly smaller number of residues per turn (3.16 and −3.20) leads to a higher axial translation per residue for the new tetrapeptides than for an ideal 3_{10}-helix. The extension from tetra- to hexa- and octapeptides results in smaller torsion angles φ and ψ of compounds **6** $(SS)_3$ (−60.2°, −26.7°) and **13** $(RR)_4$ (59.8°, 26.3°) and less variation in comparison to their smaller homologues **5** and **11**, respectively. This indicates a more stable structure which can be ascribed to the increased number of intramolecular hydrogen bonds. The average $i \leftarrow i+3$ C═O···N intramolecular hydrogen bond angles,

(19) During the synthesis of compound **13**, racemization of the C^{α}-carbon of the last amino acid (valine) in the sequence occurred. This was observed when analyzing the crystal structure of **13**. However, this has no influence on the helical structure of the molecule in solid state or in solution. For detailed information about all reactions performed, see the Supporting Information.

(20) Similar properties have been reported for N_{α}-blocked tripeptides: Toniolo, C.; Benedetti, E. *ISI Atlas Sci. Biochem.* **1988**, *1*, 225–230.

(21) (a) Crisma, M.; Formaggio, F.; Moretto, A.; Toniolo, C. *Biopolymers* **2006**, *84*, 3–12. (b) Donohue, J. *Proc. Natl. Acad. Sci. U.S.A.* **1953**, *39*, 470–478.

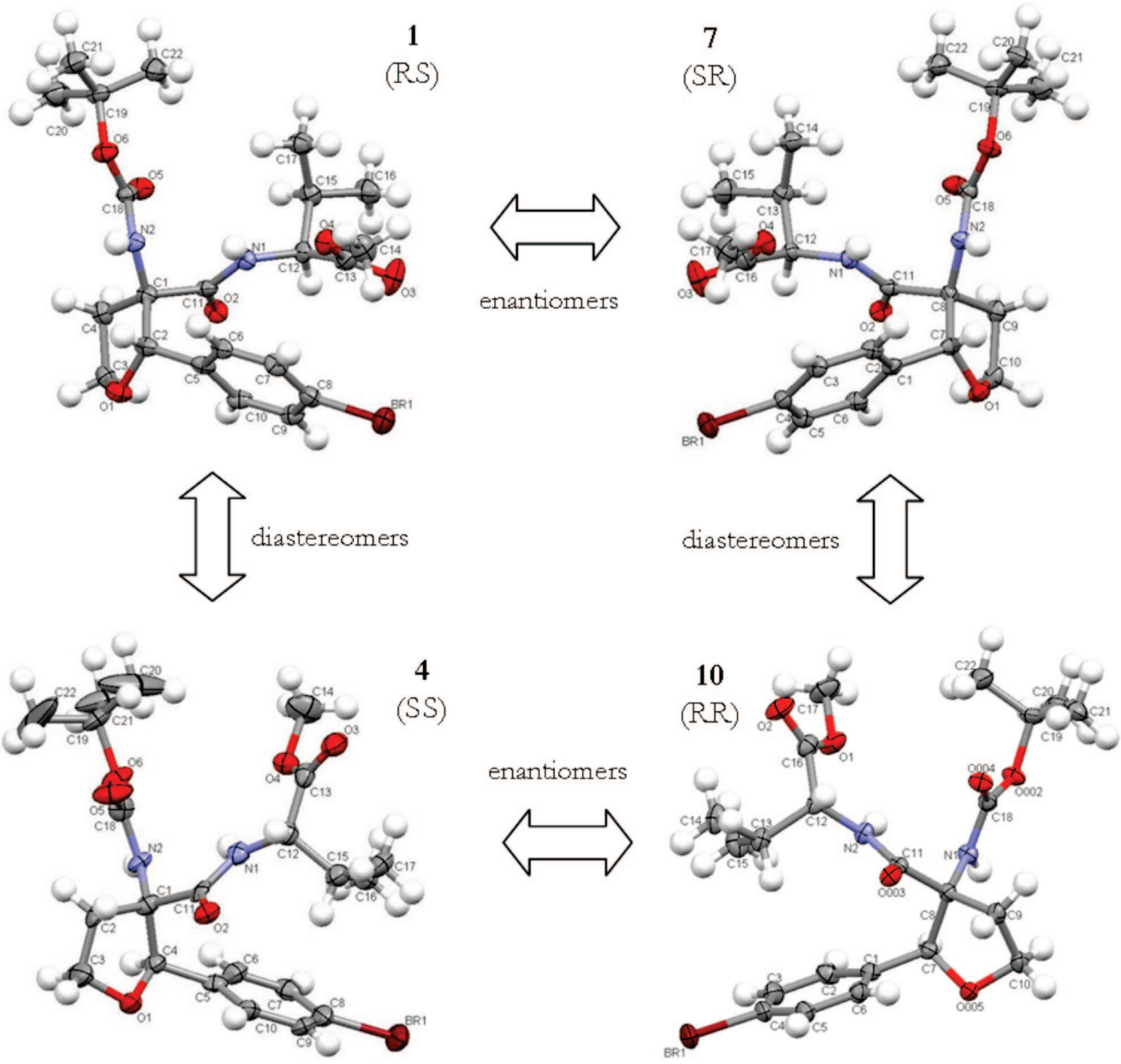


FIGURE 2. Crystal structures of dipeptides **1** (*RS*), **7** (*SR*), **4** (*SS*), and **10** (*RR*).

133.8° for compound **6** and 132.9° for compound **13**, are in the same range as those determined for the tetrapeptides.

All *i*←*i*+3 C═O···H−N intramolecular H-bonds are of typical length with N···O═C distances between 2.81 and 3.04 Å. This corresponds well to values of type 2 (amide−amide) hydrogen bonds, which are of an expected N···O═C distance between 2.8 and 3.0 Å.[22]

The determined parameters and their comparison to examples from the literature assign a 3_{10}-helical geometry to all four crystal structures. However, the higher C═O···N intramolecular hydrogen bond angles, the reduced number of residues per turn, and the higher pitch result in helices that are a little more stretched than the ideal 3_{10}-helix.

NMR Measurements. One compound of each length (tetra-, hexa-, and octamer) was investigated by NMR spectroscopy to gain information about its structure in solution. With peptides **5** $(SS)_2$, **6** $(SS)_3$, and **13** $(RR)_4$, temperature-dependent ^{1}H NMR studies were performed in DMSO-d_6 solution (temperature range 300−373 K). Tetrapeptide **5** showed a high temperature dependency for two NH-proton resonances (N1H and N2H; −5.40 and −5.72 ppb/K, respectively), indicating that these two protons are not involved in intramolecular hydrogen bonds. In contrast, the N3H and N4H protons are part of intramolecular hydrogen bonds, as supported by their much smaller temperature coefficients (−1.12 ppb/K for N3H and −1.72 ppb/K for N4H). These results correlate to the X-ray diffraction structure of **5**, in which protons N1H and N2H are not involved in intramolecular hydrogen bonds, while the other two (N3H and N4H) form *i*←*i*+3 C═O···H−N intramolecular hydrogen bonds. Similar results were found for the variable-temperature NMR of peptide **6**, where again two proton resonances for N1H and N2H were strongly temperature dependent (−4.63 and −8.25 ppb/K), while the other four NH-protons involved in hydrogen bonds showed only slight resonance shifts (N3H −2.21 ppb/K, N4H −1.31 ppb/K, N5H −0.97 ppb/K, N6H −1.36 ppb/K). Also for octapeptide **13**, N1H and N2H exhibit large temperature coefficients (−4.56 and −7.92 ppb/K, respectively), whereas

(22) Görbitz, C. H. *Acta Crystallogr. B* **1989**, *45*, 390–395.

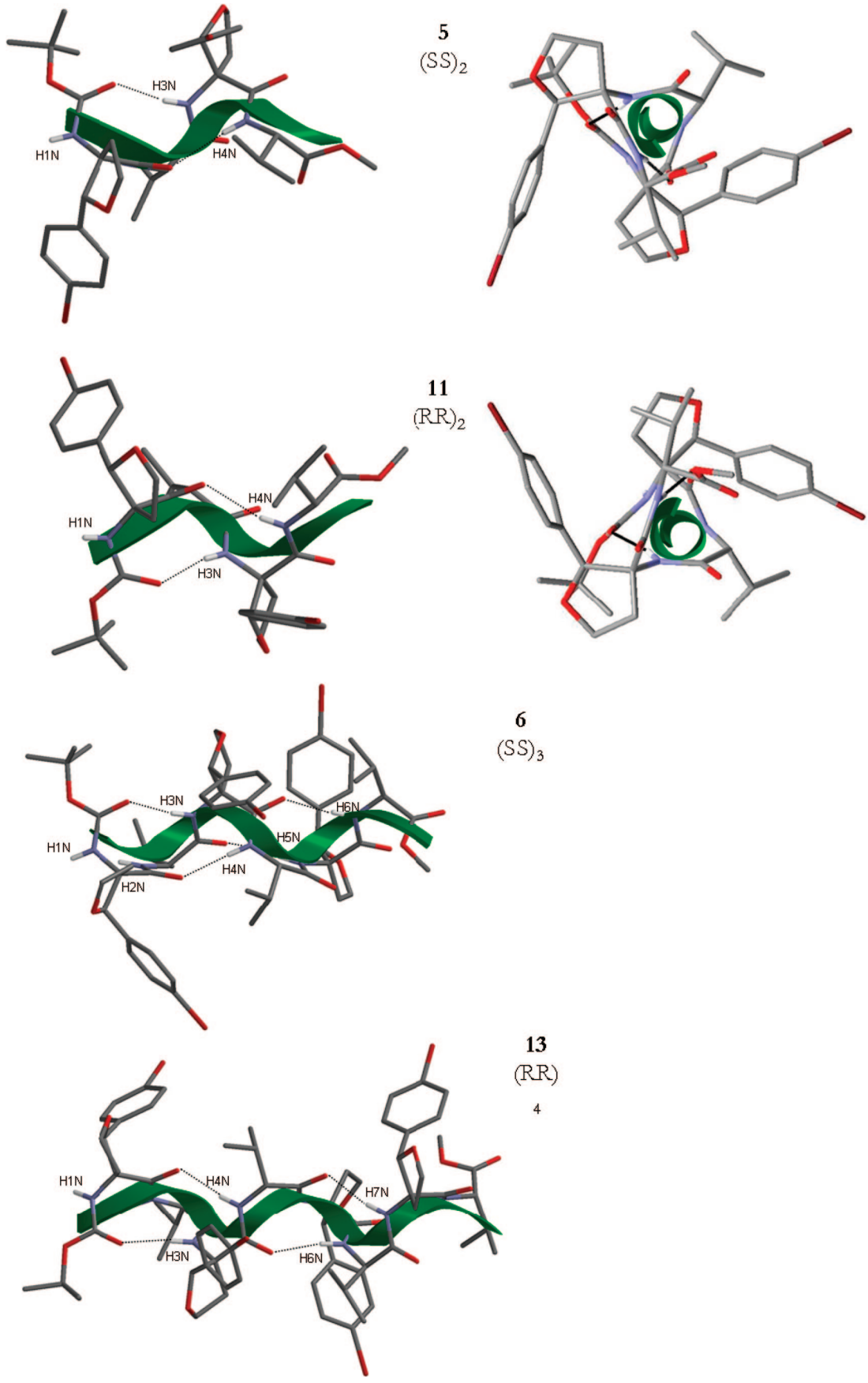


FIGURE 3. Crystal structures of the helical peptides **5**, **6**, **11**, and **13**. Top: the right-handed and left-handed helices **5** and **11** (view from the side on the left; view perpendicular to the helical axis on the right). Middle: the structure of the right-handed hexapeptide **6**. Bottom: the left-handed helix forming octapeptide **13**. Hydrogen atoms except NH-protons were omitted for clarity.

TABLE 1. Structural Parameters Derived from the Crystal Structures of Compounds 5, 6, 11, and 13[a]

parameter	**5** $(SS)_2$	**11** $(RR)_2$	**6** $(SS)_3$	**13** $(RR)_4$	3_{10}-helix	α-helix
φ (deg)	−61.6	61.7	−60.2	59.8	−57	−63
ψ (deg)	−28.4	30.9	−26.7	26.3	−30	−42
N···O=C hydrogen bond angle (deg)	133.9	131.9	133.8	132.9	128	156
N···O=C hydrogen bond distance (Å)	3.00	2.99	2.99	3.04	2.81	2.86
rotation (per residue) (deg)	111.5	111.1	111.6	111.6	111	99
residues per turn	3.16	−3.20	3.12	3.10	3.24	3.63
axial translation (per residue) (Å)	2.09	2.01	2.10	2.10	1.94	1.56
axial translation (per helical turn) (Å)	6.61	6.42	6.55	6.51	6.29	5.67

[a] The literature data for an ideal right-handed 3_{10}- and an α-helix[9a,21] are reported for comparison.

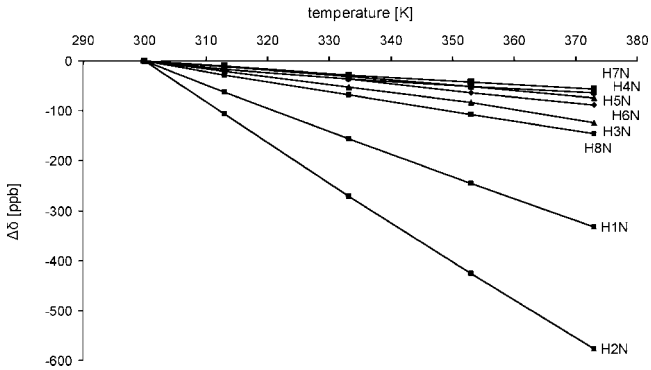


FIGURE 4. Temperature-dependent NMR of the octapeptide helix **13** in deuterated DMSO as solvent recorded in a temperature range of 300−373 K.

all other proton resonances have a much smaller temperature dependency (N3H −1.68 ppb/K, N4H −0.82 ppb/K, N5H −1.00 ppb/K, N6H −1.20 ppb/K, N7H −0.77, N8H −1.99) (Figure 4). These results clearly show that all peptides adopt a stable C-terminal helical structure in solution.

It is known that short peptides containing C^{α}-tetrasubstituted α-amino acids can undergo an α/3_{10}-helix transition in solution.[23] To determine the predominant helix type in DMSO, ROESY spectra of **5**, **6**, and **13** were recorded in DMSO-d_6. For all three peptides, strong sequential d_{NN} NOE cross-peaks were observed. These cross-peaks evoke from the interaction of the NH proton of amino acid *i* with the NH proton of amino acid *i*+1 and are characteristic for helical structures in solution and with that provide another proof for the C-terminal helical structure adopted by the investigated peptides in solution. To discriminate between the α- and 3_{10}-helix, the ROE spectra were searched for the $d_{\alpha N}$ (*i*, *i*+2) contacts characteristic for 3_{10}-helices and the $d_{\alpha N}$ (*i*, *i*+4) contacts normally observed for α-helices. These cross signals originate from the interaction between the C^{α}-proton of amino acid *i* and the NH proton of amino acid *i*+2 or *i*+4. In contrast to peptides consisting only of C^{α}-tetrasubstituted α-amino acids, in our case it was possible to observe this kind of interaction due to the presence of valine in the peptide chain. For the tetrapeptide **5** only the $d_{\alpha N}$ (*i*, *i*+2) (*i* = 2) was found, indicating the presence of a C-terminal 3_{10}-helix. For the hexapeptide **6**, two $d_{\alpha N}$ (*i*, *i*+2) (*i* = 2 and 4) cross-peaks were found, but no $d_{\alpha N}$ (*i*, *i*+4) (*i* = 2) NOE contact was detected. Accordingly, these findings clearly indicate a preference for the formation of a 3_{10}-helix over an α-helix. For compound **13**, no structural insights could be obtained by its ROESY spectrum, due to strong overlap of the C^{α}-proton resonances.[24]

The NMR measurements strongly indicate that the investigated peptides based on alternating natural and C^{α}-tetrasubstituted unnatural α-amino acids form stable helices in solution, as they do in the solid state. The hexamers prefer a 3_{10}-helix structure in deuterated DMSO.

CD Measurements. The conformation of all synthesized peptides was further investigated in methanol by CD spectroscopy.

Figure 5 shows the effect of the peptide chain length elongation on the dichroic properties of the oligopeptides. Peptides **1** (*RS*), **2** $(RS)_2$, and **3** $(RS)_3$, which have no helix character based on the NMR investigation, show two opposite CD bands near 210 nm (positive) and 222 nm (negative), with a crossover close to 215 nm. The intensity of the CD spectra decreases by increasing the peptide-chain length. Similarly, peptides **8** $(SR)_2$ and **9** $(SR)_3$ (no helix character based on NMR) are characterized by much less intense CD curves than dipeptide **7** (*SR*): they still show a broad minimum near 210 nm, whereas the positive shoulder of **7** at 230 nm disappears until it becomes a weak negative shoulder for hexapeptide **9**. Upon elongation of dipeptide **4** (*SS*) to tetrapeptide **5** $(SS)_2$ and hexapeptide **6** $(SS)_3$ (right-handed 3_{10}-helix in the crystal), the minimum near 205 nm is slightly red-shifted and increases in intensity, whereas the positive CD contribution above 215 nm is substituted by a negative maximum near 222 nm, followed by a minimum near 234 nm.

The CD spectra of peptides **11**−**13** $(RR)_{2-4}$ (left-handed 3_{10}-helix in the crystal) are reminiscent of the one of dipeptide **10** (*RR*) but shifted toward positive ellipticity values, which leads to the appearance of a maximum near 210 nm and a positive valley near 222 nm. Moreover, a new positive band is detected near 233 nm, whose intensity increases when going from tetrapeptide **11** up to octapeptide **13**. The corresponding enantiomers **5** $(SS)_2$ and **6** $(SS)_3$ also show this band, obviously opposite in sign, whereas the tetra- and hexapeptides from the (*RS*) and (*SR*) series do not (Figure 6): as only the peptides from the (*RR*) and (*SS*) series adopt a 3_{10}-helical structure in the crystal and show NOEs characteristic of helical structures, this band near 233 nm, together with the increased CD intensity in the range of 210−230 nm, should reflect the presence of an ordered structure that becomes better defined in the larger oligopeptides (CD intensity over 210−230 nm: **6** > **5**, and **13** > **12** > **11**).

We assume that the dipeptides contain the highest amount of disordered and irregular conformations. Therefore, the increase in the ordered peptide fraction of the larger peptides can be visualized by subtracting the CD spectrum of the dipeptides from the CD spectra of the larger peptides. This eliminates the CD contribution of the disordered fraction and possible CD contributions from the aromatic group of the TAA. The difference CD spectra for the four peptide series (*SS*, *RR*, *SR*, *RS*) are shown in Figure 7. The difference CD spectra obtained for the peptides $(SS)_{2-3}$ and $(RR)_{2-4}$ that adopt a right-handed and left-handed 3_{10}-helix, respectively, in the crystal are characterized by a red-shifted helix-like band pattern (panel

(23) Moretto, A.; Formaggio, F.; Kaptein, B.; Broxterman, Q. B.; Wu, L.; Keiderling, T. A.; Toniolo, C. *Biopolymers* **2008**, *90*, 567–574.

(24) (a) Wüthrich, K. H. *NMR of proteins and nucleic acids*; J. Wiley & Sons: New York, 1986. (b) Clore, G. M.; Gronenborn, A. M. *Crit. Rev. Biochem. Mol. Biol.* **1989**, *24*, 479–564. (c) Clore, G. M.; Gronenborn, A. M. *Protein Eng.* **1987**, *1*, 275–288.

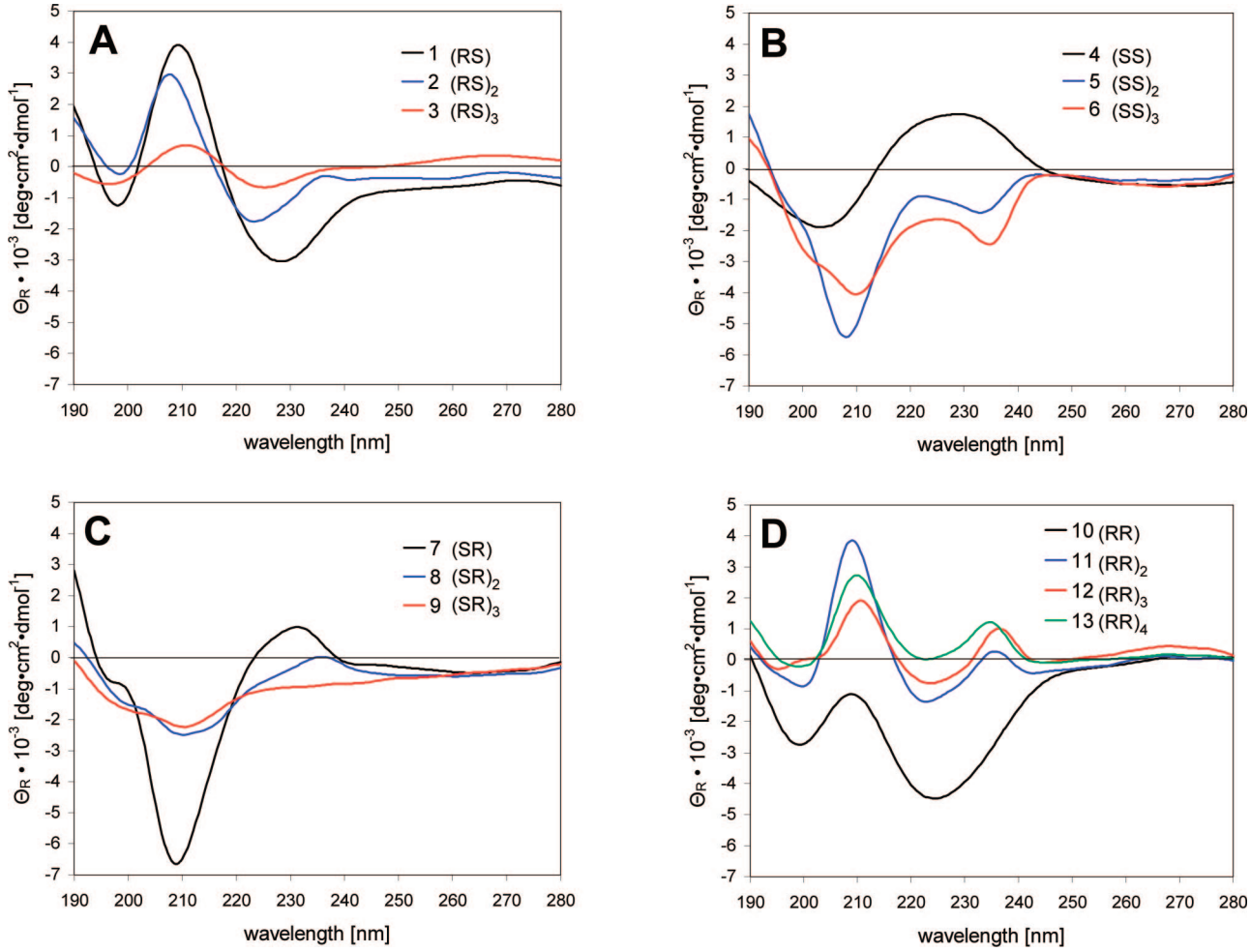


FIGURE 5. CD spectra of compounds **1**−**3** $(RS)_{1-3}$ (panel **A**), **4**−**6** $(SS)_{1-3}$ (panel **B**), **7**−**9** $(SR)_{1-3}$ (panel **C**), and **10**−**13** $(RR)_{1-4}$ (panel **D**), recorded in methanol at a peptide concentration of 1 mM.

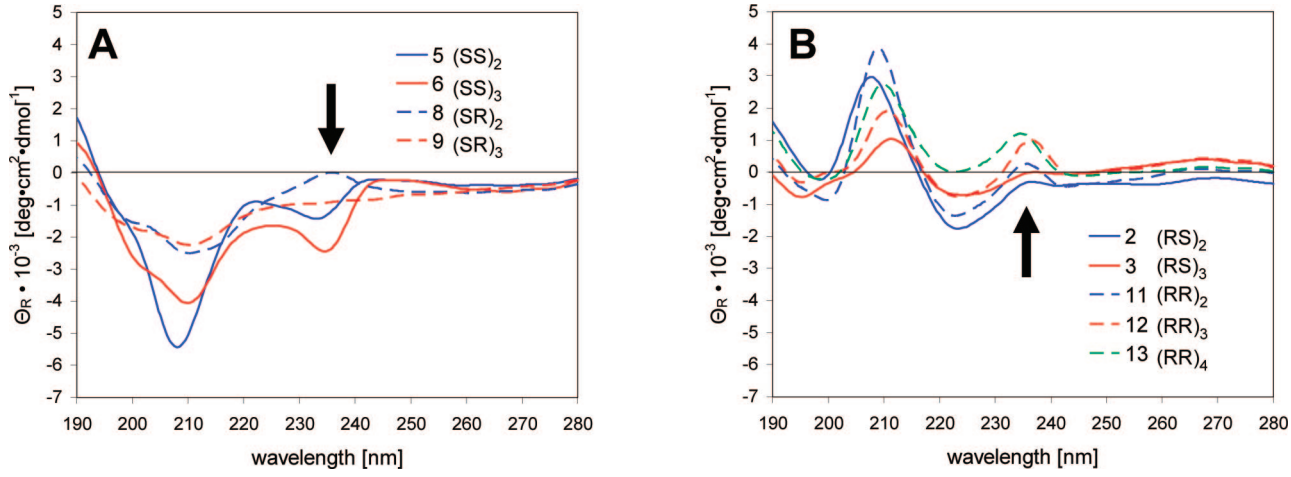


FIGURE 6. Comparison of the CD spectra of the helical peptides **5**, **6** (panel A), and **11**−**13** (panel B) with the nonhelical oligomers **8**, **9** and **2**, **3**, respectively.

A of Figure 7), with two minima for (**5**−**4**) and (**6**−**4**) or two maxima for (**11**−**10**), (**12**−**10**), and (**13**−**10**) near 210 and 230 nm.

The remarkable red shift of the longer wavelength band can be due to the highly hydrophobic character of the peptides.[25] The intensity of the spectra increases with the peptide length, suggesting an increase in ordered structure; moreover, for the tetrapeptides of both series the ratio between the ellipticity values at 230 and 210 nm is <1, whereas for the larger peptides this ratio becomes >1. This suggests that the tetrapeptides are likely to form both a 3_{10}- and an α-helical turn in methanol, whereas the larger peptides are able to build a stable short α-helix. The tendency of peptide chains with eight or more amino acids in length to form an preferred α-helical structure was previously discribed.[9a] The difference CD spectra obtained for the peptides $(SR)_{2-3}$ and $(RS)_{2-3}$ are completely different from those ones

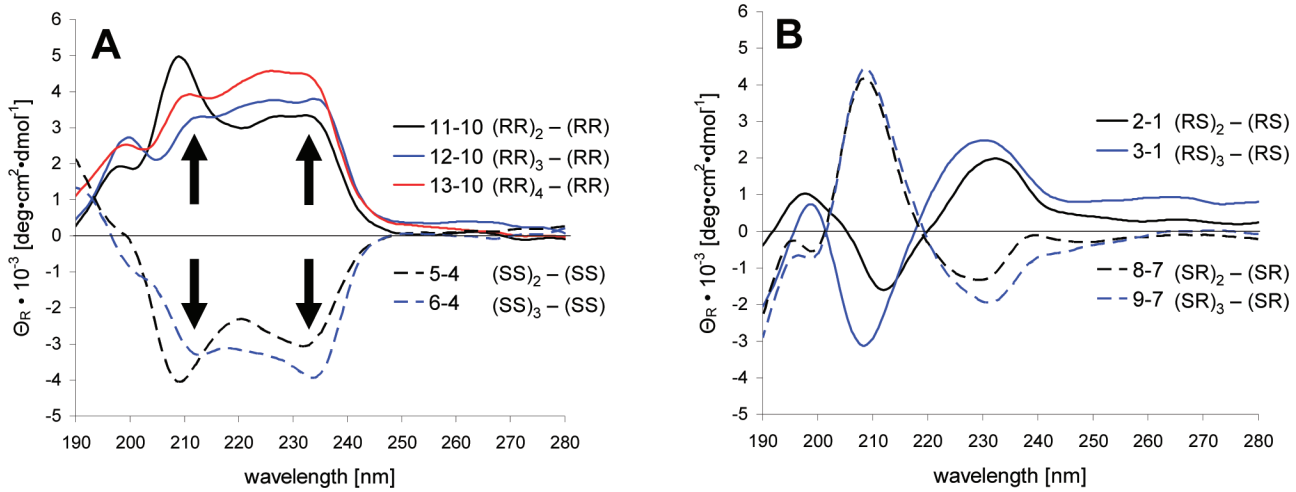


FIGURE 7. (A) Difference CD spectra of oligopeptides $(RR)_{2-4}$ *minus* dipeptide (*RR*) and of oligopeptides $(SS)_{2-3}$ *minus* dipeptide (*SS*). (B) Difference CD spectra of oligopeptides $(RS)_{2-3}$ *minus* dipeptide (*RS*) and of oligopeptides $(RS)_{2-3}$ *minus* dipeptide (*RS*).

of the peptides $(SS)_{2-3}$ and $(RR)_{2-4}$, which excludes a helical conformation.

Conclusion

In summary, we have prepared 13 new peptides based on an alternated sequence of the *S*- or *R*-configured α-amino acid valine and the unnatural C^{α}-tetrasubstituted tetrahydrofuran α-amino acid **rac-14**. Homo- and heterochiral stereoisomers with up to eight residues in length were systematically synthesized in good yields and high purity by solution-phase chemistry. X-ray crystallography, NMR, and CD measurements showed that all homochiral peptides, even the tetrapeptides, form helical structures in the solid state and in solution. The handedness of the helix is determined by the use of *S*-amino acids for right-handed or *R*-amino acids for left-handed peptide helices.

The stable and predictable secondary structure of the new peptides makes them suitable for applications as scaffolds and peptidomimetics. Additional moieties, e.g., dyes, can be introduced by metal-catalyzed functionalization of the brominated arene substituent.[17] Comparison of the crystallographic data of octamer **13** $(RR)_4$ with an idealized α-helix geometry reveals that the residues *i*, *i*+3, and *i*+6 of the octamer correspond to residues *i*, *i*+3, and *i*+7 of the natural α-helix. These positions are of importance for numerous protein−protein interactions, as the side chains of these residues are located on the same face of an amphipathic α-helical protein or peptide segment.[26]

Experimental Section

For further details regarding the ^1H and ^{13}C NMR assignments of compounds **1**, **2**, **4**, **17**, and **18**, see the Supporting Information.[27]

(2*S*)-Methyl 2-(2-(4-Bromophenyl)-3-(*tert*-butoxycarbonylamino)tetrahydrofuran-3-carboxamido)-3-methylbutanoate (1/4). Under an atmosphere of nitrogen, compound **rac-14** (1.50 g, 3.88 mmol, 1 equiv) was dissolved in 3.9 mL of DMF (1 mL/mmol) and cooled to 0 °C in an ice bath. To the solution were added DIPEA (1.99 mL, 11.7 mmol, 3 equiv), HOBt (793 mg, 5.83 mmol, 1.5 equiv), and EDC (1.03 mL, 5.83 mmol, 1.5 equiv) in order. H-Val-OMe·HCl **15** (911 mg, 5.44 mmol, 1.4 equiv) was slowly added in portions. The mixture was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched with 6 mL of water and 4 mL of 1 M aqueous $KHSO_4$ and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed twice with brine. Afterward, the solution was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was then purified by column chromatography on flash silica gel (PE/diethyl ether 80:20) to give the product as two diasteriomers as colorless solids with an overall yield of 76% (1.47 g, 2.94 mmol).

1. R_f (PE/diethyl ether 70:30) = 0.24. Mp: 147 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.48 (d, $^3J_{H,H}$ = 6.9, 3 H, 18), 0.61 (d, $^3J_{H,H}$ = 6.9, 3 H, 18), 1.47 (s, 9 H, 1), 1.86 (septet, $^3J_{H,H}$ = 4.6, $^3J_{H,H}$ = 6.8, 1 H, 17), 2.52−2.71 (m, 1 H, 7), 2.73−2.92 (m, 1 H, 7), 3.70 (s, 3 H, 16), 4.21 (dd, $^3J_{H,H}$ = 4.4, $^3J_{H,H}$ = 8.5, 1 H, 13), 4.27−4.45 (m, 2 H, 8), 5.42 (bs, 1 H, 10), 6.16 (bs, 1 H, NH), 6.48 (d, $^3J_{H,H}$ = 8.0, 1 H, NH), 7.24 (d, $^3J_{H,H}$ = 8.2, 2 H, 20), 7.41 (d, $^3J_{H,H}$ = 8.5, 2 H, 21). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.3 (+, 1 C, 18), 18.3 (+, 1 C, 18), 28.4 (+, 3 C, 1), 31.0 (+, 1 C, 17), 36.1 (−, 1 C, 7), 52.2 (+, 1 C, 16), 57.3 (+, 1 C, 13), 66.6 (−, 1 C, 8), 67.5 (C_{quat}, 1 C, 6), 80.2 (C_{quat}, 1 C, 2), 80.4 (+, 1 C, 10), 121.6 (C_{quat}, 1 C, 22), 127.0 (+, 2 C, 20), 131.3 (+, 2 C, 21), 136.4 (C_{quat}, 1 C, 19), 154.2 (C_{quat}, 1 C, 4), 171.2 (C_{quat}, 1 C, 11), 172.1 (C_{quat}, 1 C, 14). IR (neat) (cm^{-1}): $\tilde{\nu}$ = 3384, 3271, 2959, 2518, 2361, 1725, 1673, 1527, 1491, 1437, 1373, 1211, 1147, 1072, 1009, 830, 802. MS (CI, NH_3): *m*/*z* = 500.9 (100) [MH^+], 518.0 (17) [MNH_4^+]. Anal. Calcd for $C_{22}H_{31}BrN_2O_6$ (499.4): C, 52.95; H, 6.28; N, 5.59. Found: C, 53.02; H, 6.33; N, 5.50. MF: $C_{22}H_{31}BrN_2O_6$. MW: 499.4.

4. R_f (PE/diethyl ether = 70:30) = 0.20. Mp: 135 °C. ^1H NMR (300 MHz, benzene-d_6): δ = 0.68 (d, $^3J_{H,H}$ = 6.9, 6 H, 18), 1.44 (s, 9 H, 1), 1.70−1.91 (m, 1 H, 17), 2.22−2.42 (m, 1 H, 7), 2.59−2.81 (m, 1 H, 7), 3.15 (s, 3 H, 16), 3.75−3.94 (m, 1 H, 13), 3.92 (dd, $^3J_{H,H}$ = 7.1, $^3J_{H,H}$ = 16.2, 8), 4.27 (dd, $^2J_{H,H}$ = 4.9, $^3J_{H,H}$ = 7.9, 1 H, 8), 5.51 (bs, 1 H, 10), 6.40 (s, 1 H, NH), 6.75 (d, $^3J_{H,H}$ = 5.8, 1 H, NH), 7.20 (d, $^3J_{H,H}$ = 8.5, 2 H, 20), 7.30 (d, $^3J_{H,H}$ = 8.2, 2 H, 21). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9 (+, 1 C, 18), 18.7 (+, 1 C, 18), 28.4 (+, 3 C, 1), 31.8 (+, 1 C, 17), 36.1 (−, 1 C, 7), 52.1 (+, 1 C, 16), 57.2 (+, 1 C, 13), 66.5 (−, 1 C, 8), 67.6 (C_{quat}, 1 C, 6), 80.2 (C_{quat}, 1 C, 2), 80.7 (+, 1 C, 10), 121.6 (C_{quat}, 1 C, 22), 127.3 (+, 2 C, 20), 131.0 (+, 2 C, 21), 135.5 (C_{quat}, 1 C, 19), 154.3 (C_{quat}, 1 C, 4), 171.3 (C_{quat}, 1 C, 11 + 14). IR (neat) (cm^{-1}): $\tilde{\nu}$ = 3440, 3271, 2957, 2874, 2357, 1742, 1719, 1652, 1507, 1367, 1244, 1162, 1088, 1014, 987, 798. MS (CI, NH_3): *m*/*z* = 500.9 (100) [MH^+], 518.0 (33) [MNH_4^+]. Anal. Calcd for

(25) Ohmae, E.; Fukumizu, Y.; Iwakura, M.; Gekko, K. *J. Biochem.* **2005**, *137*, 643–652.
(26) Davis, J. M.; Tsou, L. K.; Hamilton, A. D. *Chem. Soc. Rev.* **2007**, *36*, 326–334.
(27) CCDC 726669–726676 contain the supplementary crystallographic data for the compounds **4**, **1**, **5**, **11**, **13**, **6**, **7**, and **10** in this order. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

$C_{22}H_{31}BrN_2O_6$ (499.4): C, 52.91; H, 6.26; N, 5.61. Found: C, 53.02; H, 6.33; N, 5.50. MF: $C_{22}H_{31}BrN_2O_6$. MW: 499.4.

(*S*)-2-((2*S*,3*R*)-2-(4-Bromophenyl)-3-(*tert*-butoxycarbonylamino)tetrahydrofuran-3-carboxamido)-3-methylbutanoic Acid (17). Compound **1** (440 mg, 0.88 mmol) was dissolved in 22 mL of a MeCN/water mixture (4:1, 25 mL/mmol). To the solution was added 1 M aqueous LiOH (970 μL, 0.97 mmol) drop by drop. The mixture was stirred overnight at room temperature. After acidification with 1 M aqueous $KHSO_4$ solution, the mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the product as colorless solid 93% yield (400 mg, 0.82 mmol). Mp: 133−135 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.44 (d, $^3J_{H,H}$ = 5.2, 3 H, 16), 0.62 (d, $^3J_{H,H}$ = 5.8, 3 H, 16), 1.42 (m, 9 H, 1), 1.78−1.95 (m, 1 H, 15), 2.41−2.65 (m, 1 H, 7), 2.67−2.86 (m, 1 H, 7), 4.13−4.39 (m, 3 H, 8 + 13), 5.39 (bs, 1 H, 10), 6.17 (bs, 1 H, NH), 6.47 (d, $^3J_{H,H}$ = 7.7, 1 H, NH), 7.20 (d, $^3J_{H,H}$ = 8.2, 2 H, 18), 7.35 (d, $^3J_{H,H}$ = 8.8, 2 H, 19). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.2 (+, 1 C, 16), 18.4 (+, 1 C, 16), 28.4 (+, 3 C, 1), 30.7 (−, 1 C, 15), 36.0 (−, 1 C, 7), 57.2 (+, 1 C, 13), 66.5 (−, 1 C, 8), 67.5 (C_{quat}, 1 C, 6), 80.2 (+, 1 C, 10), 80.3 (C_{quat}, 1 C, 2), 121.6 (C_{quat}, 1 C, 20), 127.0 (+, 2 C, 18), 131.4 (+, 2 C, 19), 136.4 (C_{quat}, 1 C, 17), 154.3 (C_{quat}, 1 C, 4), 171.4 (C_{quat}, 1 C, 11), 176.3 (C_{quat}, 1 C, 14). IR (neat) (cm^{-1}): $\tilde{\nu}$ = 3397, 3334, 2967, 2891, 1734, 1710, 1667, 1492, 1256, 1164, 1067, 1044, 1010, 827, 793. MS (ES, DCM/MeOH + 10 mM NH_4OAc): *m*/*z* = 485.1 (100) [MH^+], 502.2 (57) [MNH_4^+], 523.1 (26) [MK^+], 1007.3 (22) [2 M + K^+]; 409.0 (35) [M − ^{t}BuOH − H^+], 483.1 (100) [M − H^+]. MF: $C_{21}H_{29}BrN_2O_6$. MW: 485.37.

(*S*)-Methyl 2-((2*S*,3*R*)-3-Amino-2-(4-bromophenyl)tetrahydrofuran-3-carboxamido)-3-methylbutanoate (18). Compound **1** (290 mg, 0.58 mmol) was dissolved under ice bath cooling at 0 °C in diethyl ether. To this solution was added 4.1 mL of ice-cold HCl saturated ether (7 mL/mmol Boc), and the mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure to give the HCl salt of the product as a white hygroscopic solid in quantitative yield (250 mg, 0.57 mmol). No further purification was necessary. Mp > 180 °C. ^{1}H NMR (300 MHz, MeOH-d_4): δ = 0.62 (d, $^3J_{H,H}$ = 8.2, 3 H, 14), 0.64 (d, $^3J_{H,H}$ = 8.0, 3 H, 14), 1.78 (sextet, $^3J_{H,H}$ = 6.7, 1 H, 13), 2.36 (ddd, $^3J_{H,H}$ = 2.5, $^3J_{H,H}$ = 7.3, $^2J_{H,H}$ = 14.4, 1 H, 3), 3.00 (dt, $^3J_{H,H}$ = 14.4, $^3J_{H,H}$ = 9.3, 1 H, 1 H, 3), 3.67 (s, 3 H, 12), 3.84 (d, $^3J_{H,H}$ = 6.6, 1 H, 9), 4.18 (dt, $^3J_{H,H}$ = 7.2, $^3J_{H,H}$ = 9.3, 1 H, 4), 4.54 (dt, $^3J_{H,H}$ = 2.5, $^3J_{H,H}$ = 9.1, 1 H, 4), 4.99 (s, 1 H, 6), 7.32 (d, $^3J_{H,H}$ = 8.2, 2 H, 16), 7.53 (d, $^3J_{H,H}$ = 8.8, 2 H, 17). ^{13}C NMR (75 MHz, MeOH-d_4): δ = 19.1 (+, 1 C, 14), 19.4 (+, 1 C, 14), 31.1 (+, 1 C, 13), 36.0 (−, 1 C, 3), 52.6 (+, 1 C, 12), 60.6 (+, 1 C, 9), 67.8 (−, 1 C, 4), 70.0 (C_{quat}, 1 C, 2), 86.8 (+, 1 C, 10), 123.8 (C_{quat}, 1 C, 18), 129.2 (+, 2 C, 16), 132.8 (+, 2 C, 17), 136.2 (C_{quat}, 1 C, 15), 169.2 (C_{quat}, 1 C, 7), 173.3 (C_{quat}, 1 C, 10). IR (neat) (cm^{-1}): $\tilde{\nu}$ = 3288, 2965, 2874, 2362, 2341, 1749, 1684, 1646, 1519, 1488, 1157, 1074, 1010, 841. MS (ES, DCM/MeOH + 10 mM NH_4OAc): *m*/*z* = 399.1 (100) [MH^+]. MF: $C_{17}H_{23}BrN_2O_4 \cdot HCl$. MW: 435.74.

(*S*)-Methyl 2-((2*S*,3*R*)-2-(4-Bromophenyl)-3-((*S*)-2-((2*S*,3*R*)-2-(4-bromophenyl)-3-(*tert*-butoxycarbonylamino)tetrahydrofuran-3-carboxamido)-3-methylbutanamido)tetrahydrofuran-3-carboxamido)-3-methylbutanoate (2). Under an atmosphere of nitrogen, compound **17** (150 mg, 0.31 mmol, 1 equiv) was dissolved in 2.5 mL of DMF (8 mL/mmol) and cooled to 0 °C in an ice bath. To the solution were added DIPEA (159 μL, 0.93 mmol, 3 equiv), HOAt (64 mg, 0.46 mmol, 1.5 equiv), and HATU (176 mg, 0.46 mmol, 1.5 equiv) in sequence. The amine **18** (148 mg, 0.34 mmol, 1.1 equiv) was then slowly added in portions. The mixture was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched with 2 mL of water and 1 mL of 1 M aqueous $KHSO_4$ and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed twice with brine. Afterward, the solution was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was then purified by column chromatography on flash silica gel (PE/diethyl ether 60:40, R_f = 0.14) to give the product as colorless solids with an overall yield of 67% (180 mg, 0.21 mmol). Mp: 159−161 °C. ^{1}H NMR (600 MHz, COSY, $CDCl_3$): δ = 0.65 (d, $^3J_{H,H}$ = 6.8, 3 H, 38), 0.67 (d, $^3J_{H,H}$ = 7.2, 3 H, 28), 0.74 (d, $^3J_{H,H}$ = 6.6, 3 H, 38), 0.81 (d, $^3J_{H,H}$ = 6.8, 3 H, 28), 1.48 (s, 9 H, 1), 1.91−1.99 (m, 1 H, 37), 2.00−2.06 (m, 1 H, 27), 2.46−2.61 (m, 2 H, 19 + 29), 2.82−2.91 (m, 1 H, 29), 3.15 (bs, 1 H, 19), 3.59−70 (m, 4 H, 9 + 18), 3.98−4.08 (m, 1 H, 30), 4.16 (dd, $^3J_{H,H}$ = 5.5, $^3J_{H,H}$ = 8.8, 1 H, 15), 4.23 (dd, $^3J_{H,H}$ = 8.7, $^3J_{H,H}$ = 15.7, 1 H, 20), 4.33 (dt, $^3J_{H,H}$ = 2.8, $^3J_{H,H}$ = 8.5, 1 H, 30), 4.43 (dt, $^3J_{H,H}$ = 5.3, $^3J_{H,H}$ = 8.6, 1 H, 20), 5.00 (s, 1 H, 22), 5.21 (s, 1 H, 32), 5.84 (s, 1H 5), 6.32 (s, 1H, 8), 6.87 (d, $^3J_{H,H}$ = 7.7, 1 H,14), 7.14 (d, $^3J_{H,H}$ = 8.4, 2 H, 24), 7.17 (d, $^3J_{H,H}$ = 8.6, 2 H, 34), 7.28 (d, $^3J_{H,H}$ = 7.9, 2 H, 25), 7.35 (d, $^3J_{H,H}$ = 8.4, 2 H, 35), 7.48 (s, 1 H, 11). ^{13}C NMR (150 MHz, HSQC, HMBC, $CDCl_3$): δ = 17.4 (+, 1 C, 28), 17.7 (+, 1 C, 38), 18.7 (+, 1 C, 38), 19.0 (+, 1 C, 28), 28.4 (+, 3 C, 1), 30.0 (+, 1 C, 27), 31.2 (+, 1 C, 37), 35.5 (−, 1 C, 29), 35.6 (−, 1 C, 19), 51.8 (+, 1 C, 18), 57.5 (+, 1 C, 15), 59.7 (+, 1 C, 9), 67.4 (−, 1 C, 30), 67.6 (−, 1 C, 20), 69.0 (C_{quat}, 1 C, 6), 69.6 (C_{quat}, 1 C, 12), 81.7 (C_{quat}, 1 C, 2), 83.8 (+, 1 C, 32), 84.3 (+, 1 C, 22), 121.7 (C_{quat}, 1 C, 36), 122.6 (C_{quat}, 1 C, 26), 127.7 (+, 2 C, 24), 127.9 (+, 2 C, 34), 131.0 (+, 2 C, 35), 131.4 (+, 2 C, 25), 135.1 (C_{quat}, 1 C, 23), 136.6 (C_{quat}, 1 C, 33), 155.5 (C_{quat}, 1 C, 4), 189.7 (C_{quat}, 1 C, 13), 169.9 (C_{quat}, 1 C, 10), 171.0 (C_{quat}, 1 C, 7), 171.8 (C_{quat}, 1 C, 16). IR (neat) (cm^{-1}): $\tilde{\nu}$ = 3252, 3312, 3241, 2964, 2941, 2884, 2361, 2341, 1736, 1668, 1595, 1519, 1463, 1259, 1118, 1010, 994, 829. MS (ES, DCM/MeOH + 10 mM NH_4OAc): *m*/*z* = 867.3 (100) [MH^+], 884.3 (74) [MNH_4^+]; 865.3 (100) [M − H^+], 925.3 (55) [M + OAc^-]. HR-MS (PI-LSIMS, MeOH/DCM/NBA): [MH^+] calcd for $C_{38}H_{50}Br_2N_4O_9$ 865.2023, found 865.2022. MF: $C_{38}H_{50}Br_2N_4O_9$. MW: 866.63.

Acknowledgment. We thank the Fonds der Chemischen Industrie, the University of Regensburg, and the DFG graduate college 760 for support.

Supporting Information Available: Experimental procedures, characterization data for all new compounds, and X-ray (CIF), NMR, and CD data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900222G