ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

# Cyclic α,β-Tetrapeptoids: Sequence-Dependent Cyclization and Conformational Preference

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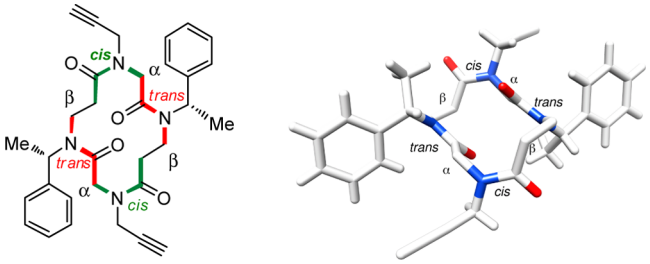
**Received May 27, 2013**

## ABSTRACT




**The presence of at least one *N*-Cα branched side chain is crucial for successful cyclization of α,β-tetrapeptoids. The *ctct* amide sequence revealed in the crystal structure of the 14-membered cyclotetrapeptoid 8 is also the most populated conformation in solution and is reminiscent of the predominant amide arrangement of the 12-membered cyclic tetrapeptides (CTPs).**

Cyclic peptides represent an intriguing class of natural and nonnatural products regarding their conformations and broad ranging biological activities.[1] In particular, naturally occurring CTPs act as histone deacetylase and tyrosinase inhibitors with anticancer and antimicrobial activities.[2] Small cyclic peptides including tetramers represent ideal scaffolds to constrain a peptide in its bioactive conformation, typically a β-turn.[3] However, the formation of constrained cyclic peptides is often challenging since the transoid form of the main-chain amides results in extended conformations which are detrimental to peptide ring closure.[4] Head-to-tail cyclization of short-chain peptides can be promoted by incorporation of turn-inducing residues such as D-amino acids, *gem*-disubstituted amino acids, proline residues, or *N*-alkylated amino acids.[5] However, these backbone modifications considerably limit the diversity of the final cyclotetrapeptides. To overcome this problem, specific synthetic strategies are in constant development.[6] Another approach is to use more likely accessible cyclic pseudopeptides. Among them, cyclopeptoids (i.e., cyclic

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(1) (a) Degenkolb, T.; Gams, W.; Brückner, H. *Chem. Biodiversity* **2008**, *5*, 693. (b) Matsoukas, J.; Apostolopoulos, V.; Lazoura, E.; Deraos, G.; Matsoukas, M.-T.; Katsara, M.; Tselios, T.; Deraos, S. *Curr. Med. Chem.* **2006**, *13*, 2221. (c) Tan, N. H.; Zhou, J. *Chem. Rev.* **2006**, *106*, 840.

(2) (a) Darkin-Rattray, S. J.; Gurnett, A. M.; Myers, R. W.; Dulski, P. M.; Crumley, T. M.; Allocco, J. J.; Cannova, C.; Meinke, P. T.; Colletti, S. L.; Bednarek, M. A.; Singh, S. B.; Goetz, M. A.; Dombrowski, A. W.; Polishook, J. D.; Schmatz, D. M. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 13143. (b) Kijima, M.; Yoshida, M.; Sugita, K.; Horinouchi, S.; Beppu, T. *J. Biol. Chem.* **1993**, *268*, 22429. (c) Kawagishi, H.; Somoto, A.; Kuranari, J.; Kimura, A.; Chiba, S. *Tetrahedron Lett.* **1993**, *34*, 3439.

(3) (a) Hruby, V. J.; Balse, P. M. *Curr. Med. Chem.* **2000**, *7*, 945. (b) Tyndall, J. D. A.; Pfeiffer, B.; Abbenante, G.; Fairlie, D. P. *Chem. Rev.* **2005**, *105*, 793. (c) Arbor, S.; Marshall, G. R. *J. Comput. Aided Mol. Des.* **2009**, *23*, 87.

(4) (a) Besser, D.; Olender, R.; Rosenfeld, R.; Arad, O.; Reissmann, S. *J. Peptide Res.* **2000**, *56*, 337. (b) Schmidt, U.; Langner, J. *J. Peptide Res.* **1997**, *49*, 67.

(5) Davies, J. S. *J. Peptide Sci.* **2003**, *9*, 471. (b) Cavelier-Frontin, F.; Pépe, G.; Verducci, J.; Siri, D.; Jacquier, R. *J. Am. Chem. Soc.* **1992**, *114*, 8885.

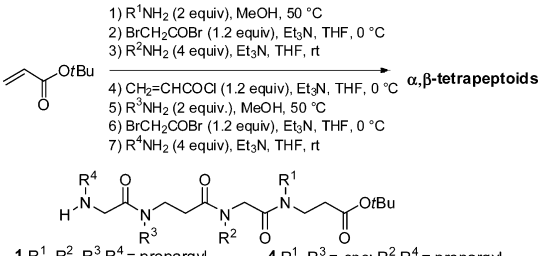
(6) (a) White, C. J.; Yudin, A. K. *Nat. Chem.* **2011**, *3*, 306. (b) Lambert, J. N.; Mitchell, J. P.; Roberts, K. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 471.

10.1021/ol401478j 

*N*-substituted glycine oligomers) represent promising cyclopeptide surrogates since their sequence is highly tunable by the so-called submonomer synthesis[7] and their macrocyclization has been shown to proceed more easily compared to peptides, even for constrained rings.[8] The cyclization efficiency is mainly due to the easy *cis*−*trans* isomerization of the backbone *N*,*N*-disubstituted amides. An initial study on the cyclization of α-peptoids was reported by the Kirshenbaum group in 2007.[9] Cyclization of oligomers from pentamer to 20-mer lengths occurred efficiently using PyBOP, but ring closure of the tetramer proceeded with only a 12% yield. A constrained 12-membered cyclopeptoid was however efficiently obtained using PyBOP (65% yield) by De Riccardis et al., allowing the first X-ray analysis of a cyclotetrapeptoid. The crystal structure unveiled a *cis-trans-cis-trans* (*ctct*) tetralactam core geometry.[10] Cyclization of β-peptoids (*N*-substituted β-alanine oligomers) has been investigated by our group.[11] The efficient cyclization of a tetramer bearing propargyl side chains gave rise to a 16-membered ring that adopted an all-*cis* arrangement in the crystal structure. Recently, we have introduced a novel peptoid backbone composed of α- and β-peptoid monomers in alternation.[12] Employing HATU-optimized conditions, we successfully prepared a cyclic α,β-tetrapeptoid carrying benzyloxyethyl side chains on the α-residues and (*S*)-1-phenylethyl side chains (*spe*) on the β-residues in 82% yield for the macrocyclization.[12a] However, during our ongoing project aimed at developing cyclic templates for multivalent ligand display,[13] we encountered difficulties in cyclizing α,β-tetramers, meant to yield rare 14-membered cyclopseudopeptides.[14] Herein, we present a study relating to the cyclization of α,β-tetrapeptoids with different sequence patterns and the conformational behavior of these 14-membered rings in solid state and solution.

The synthesis of α,β-alternating peptoids combines the solution-phase submonomer syntheses of α- and β-peptoids (Scheme 1). Linear α,β-tetrapeptoid precursors with pendant allyl, propargyl, and isopropyl groups were prepared following a solution-phase submonomer method previously optimized for gram-scale preparation of pure peptoids using volatile amines.[15] Accordingly, *N*-allyl, *N*-propargyl, and mixed *N*-isopropyl, *N*-allyl tetrapeptoids **1**, **2**, and **3** were prepared in seven steps with a single final purification by flash chromatography in 45%, 42%, and 36% yield, respectively. Intermediate purification was, however, required when installing *spe* side chains, and with this modification linear compounds **4** to **7** were obtained with overall yields ranging from 32% to 49% (see Supporting Information (SI) for details).

**Scheme 1.** Synthesis of Linear α,β-Tetrapeptoids




**1** R$^1$, R$^2$, R$^3$,R$^4$ = propargyl
**2** R$^1$, R$^2$, R$^3$,R$^4$ = allyl
**3** R$^1$, R$^3$ = isopropyl; R$^2$,R$^4$ = allyl
**4** R$^1$, R$^3$ = *spe*; R$^2$,R$^4$ = propargyl
**5** R$^1$, R$^3$ = *spe*; R$^2$,R$^4$ = allyl
**6** R$^1$, R$^3$ = propargyl; R$^2$,R$^4$ = *spe*
**7** R$^1$, R$^3$, R$^4$ = propargyl; R$^2$ = *spe*

Our initial aim was to synthesize cyclic α,β-tetrapeptoids bearing four propargyl or allyl side chains ready for the ligation of carbohydrate ligands. However, the first attempt at cyclizing **1** using an HATU-mediated procedure[11] after TFA deprotection of the *t*Bu ester was unsuccessful. Only a small amount of the expected cyclotetrapeptoid was formed. Other conditions that have proved efficient in peptoid ring closure such as DPPA, PyBOP, and EDCI/HOBt were likewise tested on **1** and **2**, but no or little macrocyclization occurred and we instead isolated the derived activated species. We then attempted to cyclize **1** using HATU at 50 °C, using conventional heating or microwave activation (MW).[16] With these conditions, macrocyclization occurred but mass spectrometry analysis revealed the presence of a mixture of the expected cyclotetrapeptoid ( < 10%) and the dimeric form, i.e. the α,β-cyclooctapeptoid (21% and 27% yield for oil bath and MW heating, respectively). Higher dilution of the reaction mixture did not improve the yield of monomeric form.

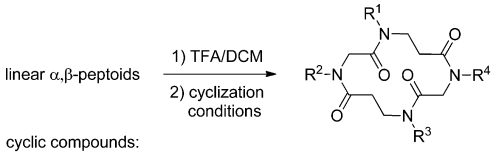
Keeping in mind that the formation of cyclic α,β-tetrapeptoids can be highly efficient,[12a] we decided to examine the sequence requirements for efficient cyclization, in particular by introducing the chiral α-branched *spe* side chain. The latter is known to slightly promote the *cis*

(7) (a) Zuckermann, R. N.; Kerr, J. M.; Kent, S. B. H.; Moos, W. H. *J. Am. Chem. Soc.* **1992**, *114*, 10646. (b) Culf, A. S.; Ouellette, R. J. *Molecules* **2010**, *15*, 5282. (c) Zuckermann, R. N. *Biopolymers* **2011**, *96*, 545.
(8) Yoo, B.; Shin, S. B. Y.; Huang, M. L.; Kirshenbaum, K. *Chem.—Eur. J.* **2010**, *16*, 5528.
(9) Shin, S. B.; Yoo, B.; Todaro, L. J.; Kirshenbaum, K. *J. Am. Chem. Soc.* **2007**, *129*, 3218.
(10) Maulucci, N.; Izzo, I.; Bifulco, G.; Aliberti, A.; De Cola, C.; Comegna, D.; Gaeta, C.; Napolitano, A.; Pizza, C.; Tedesco, C.; Flot, D.; De Riccardis, F. *Chem. Commun.* **2008**, 3927.
(11) Roy, O.; Faure, S.; Thery, V.; Didierjean, C.; Taillefumier, C. *Org. Lett.* **2008**, *10*, 921.
(12) (a) Hjelmgaard, T.; Faure, S.; Caumes, C.; De Santis, E.; Edwards, A. A.; Taillefumier, C. *Org. Lett.* **2009**, *11*, 4100. (b) De Santis, E.; Hjelmgaard, T.; Caumes, C.; Faure, S.; Alexander, B. D.; Holder, S. J.; Siligardi, G.; Taillefumier, C.; Edwards, A. A. *Org. Biomol. Chem.* **2012**, *10*, 1108.
(13) Cecioni, S.; Faure, S.; Darbost, U.; Bonnamour, I.; Parrot-Lopez, H.; Roy, O.; Taillefumier, C.; Wimmerová, M.; Praly, J.-P.; Imberty, A.; Vidal, S. *Chem.—Eur. J.* **2011**, *17*, 2146.
(14) (a) Karle, I. L.; Handa, B. K.; Hassall, C. H. *Acta Crystallogr.* **1975**, *B31*, 555. (b) Di Blasio, B.; Lombardi, A.; D'Auria, G.; Saviano, M.; Isernia, C.; Maglio, O.; Paolillo, L.; Pedone, C.; Pavone, V. *Biopolymers* **1993**, *33*, 621. (c) Haas, K.; Ponikwar, W.; Nöth, H.; Beck, W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1086. (d) Casiraghi, G.; Rassu, G.; Auzzas, L.; Burreddu, P.; Gaetani, E.; Battistini, L.; Zanardi, F.; Curti, C.; Nicastro, G.; Belvisi, L.; Motto, I.; Castorina, M.; Giannini, G.; Pisano, C. *J. Med. Chem.* **2005**, *48*, 7675. (e) Beierle, J. M.; Horne, W. S.; van Maarseveen, J. H.; Waser, B.; Reubi, J. C.; Ghadiri, M. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 4725. (f) Montero, A.; Beierle, J. M.; Olsen, C. A.; Ghadiri, M. R. *J. Am. Chem. Soc.* **2009**, *131*, 3033. (g) Xu, Z.; Wheeler, K. A.; Baures, P. W. *Molecules* **2012**, *17*, 5346.
(15) Caumes, C.; Hjelmgaard, T.; Remuson, R.; Faure, S.; Taillefumier, C. *Synthesis* **2011**, 257.
(16) Cini, E.; Botta, C. B.; Rodriquez, M.; Taddei, M. *Tetrahedron Lett.* **2009**, *50*, 7159.

conformation of peptoid amides and hence to favor helical structures.[17] We thus speculated that the *spe* side chain may also promote cyclization of short peptoids. Compounds **4** and **5** carrying two *spe* side chains on the $\beta$-peptoid residues and either a propargyl or an allyl group on the α-peptoid residues were submitted to several cyclization conditions after acid C-terminus deprotection (Table 1). The DPPA conditions successfully used to access cyclic $\beta$-tetrapeptoids[11] proved inefficient (entry 1). Uronium-based coupling reagents (HATU, TBTU) and the pentafluorophenol derivative FDPP provided the cyclic α,$\beta$-tetrapeptoids **8** and **9** in yields of ~30% (entries 2−4 and 6). The best results were, however, obtained using the coupling system EDCI/HOBt described for example for aza-$\beta^3$-cyclotetrapeptide formation.[18] Thus, the cyclic α,$\beta$-tetrapeptoids **8** and **9** were isolated in 64% and 51% yields, respectively (entries 5, 8), and the presence of the cyclic dimer was not detected by mass spectrometry. We were then able to demonstrate that the *spe* side chain could be interchanged with the less bulky and nonaromatic isopropyl side chain without loss of cyclization efficiency (macrocycle **10**, entries 9 and 11 vs macrocycle **9**, entries 6 and 8). To increase yields when using HATU, MW activation was tested but unfortunately without success (entry 10). Next, to explore the importance of the *spe* location on the backbone, cyclizations of **4** and **6** were compared. The efficiency was slightly higher for the oligomer **6** when using EDCI/HOBt (67% vs 64%, entries 13 and 5) and was significantly increased in the case of HATU as the coupling reagent (57% vs 32%, entries 12 and 2). These results indicate that cyclization is promoted by the presence of an *spe* side chain on the α-residues. We further demonstrated that only one *spe* side chain, located in the middle of the backbone, can ensure the formation of cyclic tetrapeptoids as exemplified by the cyclization of **7** in 73% yield (entry 14). This study shows that at least one *N*-Cα branched side chain such as *spe* or isopropyl is needed to allow cyclization of α,$\beta$-tetrapeptoids. The impact is greater when the bulky side chain is located on α-residues, possibly because the $\beta$-peptoid residues are more flexible than α-peptoid residues and their amide conformation is more difficult to control.[19]

We were pleased to obtain crystals suitable for X-ray analysis by slow evaporation of compound **8** in dry methanol. The 14-membered cyclotetrapeptoid **8** adopts a *βcis-αtrans-βcis-αtrans* (*ctct*, in the *N*-to-*C* direction) conformation in a zigzag arrangement which, exclusive of the *spe* lateral chains, is centrosymmetric (Figure 1). The few crystal structures of α,$\beta$-CTPs described in the literature display a *tttt* conformation.[14a−c] It is interesting to note that the *ctct* arrangement is known to be predominant

**Table 1.** Cyclization of α,$\beta$-Tetrapeptoids




cyclic compounds:
**8** $R^1$, $R^3$ = *spe*; $R^2$,$R^4$ = propargyl
**9** $R^1$, $R^3$ = *spe*; $R^2$,$R^4$ = allyl
**10** $R^1$, $R^3$ = isopropyl; $R^2$,$R^4$ = allyl
**11** $R^1$, $R^3$ = propargyl; $R^2$,$R^4$ = *spe*
**12** $R^1$, $R^3$, $R^4$ = propargyl; $R^2$ = *spe*

| entry | linear precursor | cyclization conditions[a] | cyclic compd | yield (%)[b] |
|---|---|---|---|---|
| 1 | **4** | DPPA/DIEA | **8** | – |
| 2 | **4** | HATU/DIEA | **8** | 32 |
| 3 | **4** | FDPP/DIEA | **8** | 35 |
| 4 | **4** | TBTU/$Et_3N$/HOBt | **8** | 27 |
| 5 | **4** | EDCI/$Et_3N$/HOBt | **8** | **64** |
| 6 | **5** | HATU/DIEA | **9** | 33 |
| 7 | **5** | PyBOP/DIEA | **9** | 47 |
| 8 | **5** | EDCI/$Et_3N$/HOBt | **9** | **51** |
| 9 | **3** | HATU/DIEA | **10** | 28 |
| 10 | **3** | HATU/DIEA/μwaves | **10** | 19 |
| 11 | **3** | EDCI/$Et_3N$/HOBt | **10** | **50** |
| 12 | **6** | HATU/DIEA | **11** | 57 |
| 13 | **6** | EDCI/$Et_3N$/HOBt | **11** | **67** |
| 14 | **7** | EDCI/$Et_3N$/HOBt | **12** | **73** |

[a] Conditions for HATU: HATU (1.2 equiv), DIEA (5 equiv), $CH_2Cl_2$/DMF 4:1 (5 mM), rt, 72 h; conditions for EDCI: EDCI (6 equiv), $Et_3N$ (6 equiv), HOBt (6 equiv), $CH_2Cl_2$ (5 mM), rt, 72 h; see SI for the other cyclization conditions. [b] Isolated yields.

in 12-membered α-CTPs.[20] Indeed, analysis of the α-CTP structures deposited in the Cambridge Structural Database (version 5.34) revealed that 16 over 21 rings crystallized with the *ctct* conformation. The sole crystal structure of α-tetracyclopeptoid also features a *ctct* conformation.[10] In brief, the analysis of compound **8** in the solid state suggests that the 14-membered cyclic α,$\beta$-tetrapeptoids may adopt the *ctct* amide arrangement that predominates for the 12-membered α-CTP and peptoids.

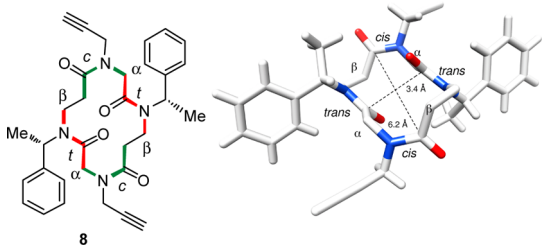



**Figure 1.** X-ray crystal structure of cyclic α,$\beta$-tetrapeptoid **8**. (Left) Structure of **8** showing the *βcis-αtrans-βcis-αtrans* conformation (*cis* amides in green; *trans* amides in red). (right) Side view of the crystal structure (H-atoms of the backbone are omitted for clarity).

(17) (a) Armand, P.; Kirshenbaum, K.; Goldsmith, R. A.; Farr-Jones, S.; Barron, A. E.; Truong, K. T. V.; Dill, K. A.; Mierke, D. F.; Cohen, F. E.; Zuckermann, R. N.; Bradley, E. K. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 4309. (b) Sui, Q.; Borchardt, D.; Rabenstein, D. L. *J. Am. Chem. Soc.* **2007**, *129*, 12042.

(18) Salaün, A.; Mocquet, C.; Perochon, R.; Lecorgne, A.; Le Grel, B.; Potel, M.; Le Grel, P. *J. Org. Chem.* **2008**, *73*, 8579.

(19) (a) Caumes, C.; Roy, O.; Faure, S.; Taillefumier, C. *J. Am. Chem. Soc.* **2012**, *134*, 9553. (b) Laursen, J. S.; Engel-Andreasen, J.; Fristrup, P.; Harris, P.; Olsen, C. A. *J. Am. Chem. Soc.* **2013**, *135*, 2835.

(20) (a) Seebach, D.; Bezençon, O.; Jaun, B.; Thomas Pietzonka, T.; Matthews, J. L.; Kühnle, F. N. M.; Schweizer, W. B. *Helv. Chim. Acta* **1996**, *79*, 588. (b) Che, Y.; Marshall, G. R. *J. Med. Chem.* **2006**, *49*, 111.

Using proton NMR experiments, the relative ratio of *cis* and *trans* amides bearing an *spe* side chain can be easily measured by integration of the benzylic signals.[17b] It was thus anticipated that 1D NMR studies of heterooligomers bearing *spe* side chains on either the α or *β* residues would give crucial information on the geometry of the different amides constituting the tetracyclic core of the molecules. As mentioned above, the *spe* side chain is well-known to slightly promote the *cis* geometry of peptoid amides as observed for the linear precursor **6** or **7** exhibiting a *cis*/*trans* ratio of ~55:45 (Table 2). Consistent with the literature,[19b] slight excesses of *trans* amides were observed for linear peptoids **4** and **5** where the *spe* side chains are located on the *β*-residues. The *cis*/*trans* ratio for the cyclopeptoid **8** was measured in different solvents. A *cis*/*trans* ratio of 16:84 was determined in $CDCl_3$ (Table 2), and an average of 30:70, in other solvents ($CD_3OD$, $CD_3CN$, and acetone-$d^6$). The *cis*/*trans* ratios for cyclopeptoid **9** exhibited the same tendency. This high proportion of *trans* conformation at *β*-residues is in accordance with the solid-state conformation (Figure 1). When the *spe* side chains were placed on α-peptoid residues (**11** and **12**), the *cis*/*trans* ratios revealed a large proportion of *cis* conformer (Table 2) again in accordance with the backbone conformation in the X-ray crystal structure. Overall, this NMR study seems to indicate that the *βcis*-α*trans*-*βcis*-α*trans* conformation observed in the crystal structure is also the predominant conformation in solution, independently of the side chain sequences.

**Table 2.** *Cis*/*trans* Ratios for Amides Bearing an *spe* Side Chain

| linear peptoids | *cis*/*trans* ratio[a] | cyclic peptoids | *cis*/*trans* ratio[a] |
|---|---|---|---|
| **4** | 43:57 | **8** | 16:84 |
| **5** | 47:53[b] | **9** | 36:64[b] |
| **6** | 55:45 | **11** | 74:26 |
| **7** | 53:47 | **12** | 79:21[b] |

[a] Determined by $^1$H NMR in $CDCl_3$. [b] Determined by HSQC in $CDCl_3$.

Conformational analysis of macrocycle **8** through a simulated annealing approach provided candidate structures for the 10 possible *cis*/*trans* states: *cccc*, *ctcc*, *cctc*, *cctt*, *ctct*, *tctc*, *cttc*, *tttc*, *cttt*, *tttt*. These different conformations were classified into 20 subgroups, and the geometry of the lowest energy conformation of each subgroup was optimized at the DFT (B3LYP/6-31G(d,p)) level (see SI for details). The structure of the lowest energy was found to be a *βcis*-α*trans*-*βcis*-α*trans* arrangement whose conformation matches perfectly with the conformation of **8** in the solid state (superposition shown in the SI). Unlike previous findings on *β*-tetracyclopeptoids,[11] the solution and solid-state conformations of **8** are identical.

The comparison of the crystal structures of tetramer **8** and cyclic α,*β*-octamer **13** recently published by us[21] reveals striking similarities. Indeed, both structures have the presence of two α*trans*-*βcis* segments in a turn-like conformation in common (Figure 2). The fact that this specific conformation is also present in an unconstrained cyclic octamer, having a different side chain sequence than tetramer **8**, suggests that the observed turn may represent a privileged conformation of the α,*β*-peptoid family. This observation might pave the way toward novel peptoid secondary structures based on the α,*β*-peptoid backbone and alternating *cis* and *trans* main-chain amides.[22]

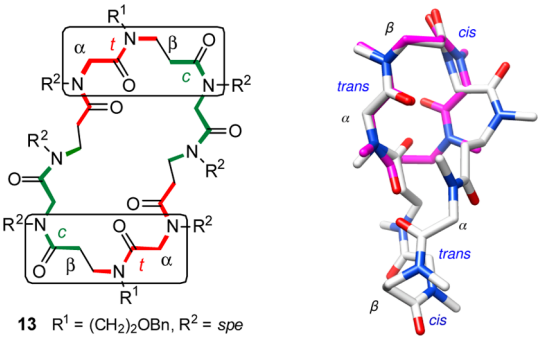



**Figure 2.** Superimposition of the X-ray structures of the cyclic α,*β*-tetrapeptoid **8** (in magenta) and the cyclic α,*β*-octapeptoid **13** (for clarity, H-atoms and side chains are omitted).

**Acknowledgment.** This work was supported by funding from the French Ministry of Higher Education and Research (MESR). We gratefully thank A. Job and B. Légeret (Clermont-Université) for HPLC and mass spectrometry analysis. The authors thanks also the University of Lorraine for XRD facilities.

**Supporting Information Available.** Full experimental procedures; characterization of new compounds; HPLC data for **8**–**12**; $^1$H and $^{13}$C NMR spectra for all compounds; molecular modeling on cyclopeptoid **8**; crystallographic data for **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) De Santis, E.; Hjelmgaard, T.; Faure, S.; Roy, O.; Didierjean, C.; Alexander, B. D.; Siligardi, G.; Hussain, R.; Jávorfi, T.; Edwards, A. A.; Taillefumier, C. *Amino Acids* **2011**, *41*, 663.

(22) (a) Crapster, J. A.; Guzei, I. A.; Blackwell, H. E. *Angew. Chem., Int. Ed.* **2013**, *52*, 5079. (b) Roy, O.; Caumes, C.; Esvan, Y.; Didierjean, C.; Faure, S.; Taillefumier, C. *Org. Lett.* **2013**, *15*, 2246.

The authors declare no competing financial interest.