β-Peptides

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Alternating Asymmetric Self-Induction in Functionalized Pyrrolidine Oligomers**

Konstantin V. Kudryavtsev, Polina M. Ivantcova, Andrei V. Churakov, Steffen Wiedmann, Burkhard Luy, Claudia Muhle-Goll, Nikolay S. Zefirov, and Stefan Bräse**

Artificial structurally well-defined polymers have excited interest as functional mimetics of natural biomacromolecules, exhibiting additional properties not occurring in the living world.[1] Specific conformational organization of natural and synthetic polymeric objects leading to unique folding accounts for the molecular recognition, which is one of the driving principles in important natural processes. Some non-natural oligomeric species adopt specific and well-defined conformations dictated by the structure of monomeric units and intramolecular interactions and are defined as foldamers.[2] One of the most studied unnatural foldamer types are β-peptides that adopt stable folded helical, sheet, and turn-like conformations.[3] β-Peptides are stable towards natural enzymes, and appropriate design leads to discovery of β-peptide ligands for complicated pharmaceutical targets, such as protein–protein interactions.[4] The application of pyrrolidine-3-carboxylic acid (Pca) for the construction of β-polypeptide chain rigidifies the molecular backbone and provides additional stabilization of the secondary structure of the oligomer in solution.[5]

The typical synthesis of a β-peptide backbone is based on the arsenal of peptide chemistry methods, including routine sequences of amino group protection–deprotection steps and multiple activations of carboxylic functionality for amide bond construction. Herein we disclose a fundamentally novel synthetic method towards well-defined highly functionalized short β-peptides that avoids protection, deprotection, and activation procedures and allows to generate efficiently stereoregular oligomeric pyrrolidine-based molecules. The developed method, called cycloadditive oligomerization, has been used for the synthesis of a set of racemic and enantiopure oligomers containing a Pca backbone. The realized approach determines highly diverse structural characteristics of β-peptide oligomers, which are characterized by various physicochemical methods, including X-ray analysis.

The oligomerization utilized azomethine ylide 1,3-dipolar cycloaddition[6] as a chain-growth approach (Scheme 1). 5-Arylpyrrolidine-2,4-dicarboxylate units serve both as linked elements and as auxiliaries to determine stereo- and enantioselectivities of the cycloaddition process. The starting 5-arylpyrrolidine-2,4-dicarboxylic acid diesters **3a** (X = H, Br) for oligomer synthesis were obtained from iminoesters **1** and *tert*-butyl acrylate in racemic[7] and enantiopure[8] forms by 1,3-dipolar cycloaddition using Lewis acids for the azomethine ylide generation step (Scheme 1, Table 1). Asymmetric synthesis of the monomer (−)-**3a**-H was effectively conducted with the enantiopure ligand **4**[8] on a gram scale, and single recrystallization provided the target compound with more than 99% *ee*. Subsequent N-acryloylation of monomers **3a** with acryloyl chloride transformed them into dipolarophiles **2b** with a sterically hindered amide residue connected to the ethylene fragment. We supposed that these unique dipolarophiles would induce good diastereo- and enantioselectivities under iterative cycloaddition steps with iminoesters **1** (Scheme 1).

Indeed, dimers **3b** were effectively synthesized by cycloaddition of acrylamides **2b** with Schiff bases **1** (X = H, Br) in presence of AgOAc as a Lewis acid agent for azomethine ylide generation (Table 1, entries 4–6). Comparison of ^{1}H NMR spectra of the cycloaddition reaction mixtures and

[*] Prof. Dr. K. V. Kudryavtsev, Dipl.-Chem. P. M. Ivantcova, Prof. Dr. N. S. Zefirov
Department of Chemistry
M.V. Lomonosov Moscow State University
Leninskie Gory 1/3, 119991 Moscow (Russian Federation)
E-mail: kudr@org.chem.msu.ru
Prof. Dr. K. V. Kudryavtsev, Prof. Dr. N. S. Zefirov
Institute of Physiologically Active Compounds
Russian Academy of Sciences
142432 Chernogolovka, Moscow region (Russian Federation)
Dr. A. V. Churakov
Institute of General and Inorganic Chemistry
Russian Academy of Sciences
Leninskii prosp. 31, 119991 Moscow (Russian Federation)
S. Wiedmann, Prof. Dr. B. Luy, Dr. C. Muhle-Goll, Prof. Dr. S. Bräse
Institute of Organic Chemistry (IOC)
Karlsruhe Institute of Technology (KIT)
Fritz-Haber-Weg 6, 76131 Karlsruhe (Germany)
E-mail: stefan.braese@kit.edu
Prof. Dr. B. Luy
Institute for Biological Interfaces II
Karlsruhe Institute of Technology (KIT)
POB 3640, 76021 Karlsruhe (Germany)
Prof. Dr. S. Bräse
Institute of Toxicology and Genetics (ITG)
Karlsruhe Institute of Technology (KIT)
76344 Eggenstein-Leopoldshafen (Germany)

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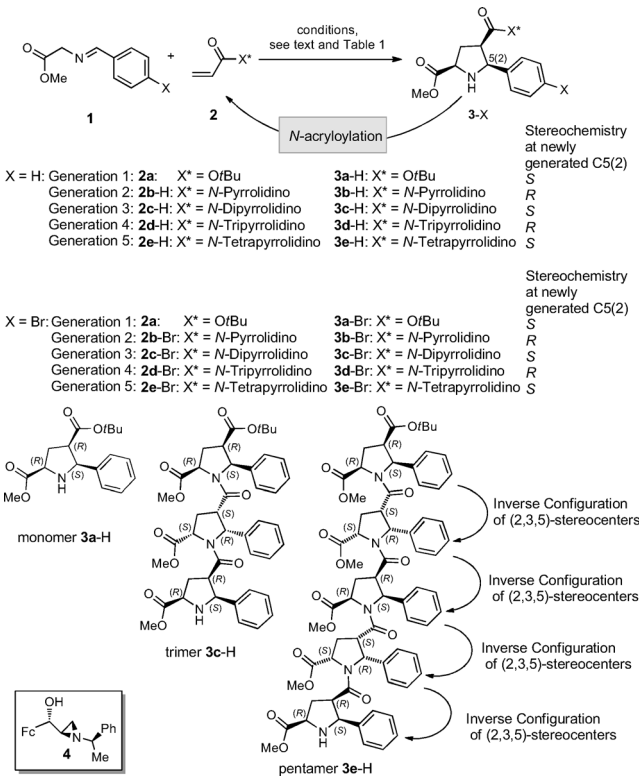


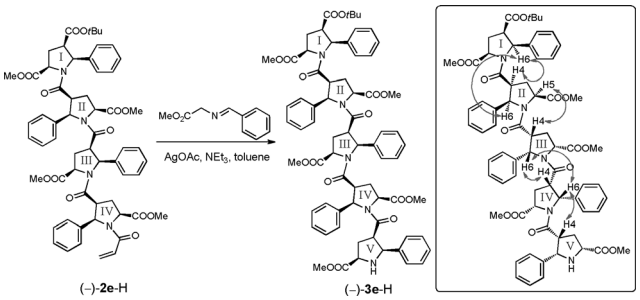
Scheme 1. Synthesis of Pca oligomers by cycloadditive self-inductive oligomerization. Fc = ferrocenyl.

Table 1: Reactions to generate monomers **3a**-X and oligomers **3b–e**.

Entry	1	2	Conditions[a]	3-X	Yield [%]	Conf.[b]
1	**1**-H	**2a**	A	*rac*-**3a**-H	65	*S*(*R*)
2	**1**-H	**2a**	B	(−)-**3a**-H	81	*S*
3	**1**-Br	**2a**	A	*rac*-**3a**-Br	67	*S*(*R*)
4	**1**-H	*rac*-**2b**-H	C	*rac*-**3b**-H	70	*R*(*S*)
5	**1**-H	(−)-**2b**-H	C	(−)-**3b**-H	90	*R*
6	**1**-Br	*rac*-**2b**-Br	C	*rac*-**3b**-Br	82	*R*(*S*)
7	**1**-H	*rac*-**2c**-H	C	*rac*-**3c**-H	94	*S*(*R*)
8	**1**-H	(−)-**2c**-H	C	(+)-**3c**-H	87	*S*
9	**1**-Br	*rac*-**2c**-Br	C	*rac*-**3c**-Br	82	*S*(*R*)
10	**1**-H	*rac*-**2d**-H	C	*rac*-**3d**-H	83	*R*(*S*)
11	**1**-H	(+)-**2d**-H	C	(−)-**3d**-H	85	*R*
12	**1**-Br	*rac*-**2d**-Br	C	*rac*-**3d**-Br	81	*R*(*S*)
13	**1**-H	(−)-**2e**-H	C	(−)-**3e**-H	93	*S*
14	**1**-Br	*rac*-**2e**-Br	C	*rac*-**3e**-Br	85	*S*(*R*)

[a] Conditions: A) LiBr (1.5 equiv), Et_3N (1.2 equiv), THF, 0°C; B) Catalyst **4** (0.1 equiv), $Zn(OTf)_2$ (0.1 equiv), Et_3N (0.1 equiv), THF, −20°C; C) AgOAc (1.5 equiv), Et_3N (1.5 equiv), toluene, RT. [b] Configuration at the newly generated C5(2) center (see Scheme 1).

corresponding pure dimers **3b** indicated more than 95% cycloaddition diastereoselectivity. Compound (−)-**3b**-H has an enantiomeric purity of 97% *ee*. The racemic analogue **3b**-H was characterized by X-ray crystallographic analysis. Repetition of the acroylation/cycloaddition processes gave access to oligomers **3c–e** with up to five pyrrolidine units in good yields (Table 1, entries 7–14 and the Supporting Information). The enantiomerically pure pentamer (−)-**3e**-H



Scheme 2. Synthesis of pentamer (−)-**3e**-H and its dominant solution conformation (in box) as determined by NMR spectroscopy (for details, see Table 1, entry 13, text, and the Supporting Information). NOE interactions are shown with double-headed arrows.

(Scheme 2) did not rotate polarized light in CH_2Cl_2 solution but its methanol solution is characterized by anticlockwise rotation.

The intriguing issue of the stereochemistry of newly generated stereogenic centers at the pyrrolidine rings under developed cycloadditive oligomerization process was underpinned by certain structural investigations. We succeeded in evaluation of several oligomeric molecules **3** by single-crystal diffraction.[9] The results confirmed without doubt that the newly formed 5-methoxycarbonyl-2-phenylpyrrolidine fragment has exactly inverse configuration of three new stereogenic centers beside the adjacent parent monomer unit, as shown for the pentamer (−)-**3e**-H in Scheme 2. For discussion purposes, the pyrrolidine rings are numbered with Roman figures according the order of introducing in an oligomer chain (Scheme 2). All of the bond lengths and angles of studied molecules have typical values for organic compounds. The molecular backbone of racemic dimer **3b**-H consists of two pyrrolidine rings linked by an amide group (see the Supporting Information).

The central amide fragment O1-C18-N1-C1-C4-C20 of **3b**-H is planar to within 0.108(1) Å. Both pyrrolidine cycles in dimer **3b**-H adopt an envelope conformation. Flap atoms C2 and C20 of **3b**-H are displaced from the base planes of other four atoms in pyrrolidine cycles by 0.628(2) and 0.555(3) Å, respectively. The molecular backbone of racemic trimer **3c**-Br consists of three pyrrolidine rings linked by two amide units (Figure 1). Bridging amide fragments C18-O5-N1-C1-C4-C20 and C31-O8-N2-C19-C22-C34 are planar within 0.084(2) and 0.081(3) Å, respectively. All three of the pyrrolidine rings adopt an envelope conformation. The displacements of flap atoms from the base planes are 0.576(6) Å for C3, 0.557(7) Å for C21, and 0.536(7) Å for C34. In the crystal, the adjacent molecules of **3c**-Br are combined in chains along the *c* axis by weak hydrogen bonds between amino and methoxy groups N3−H1···O3($1-x$, $1-y$, $0.5+z$) with N···O distances equal to 3.576 Å. There are wide, solvent-accessible channels passing along the *a* axis with an approximate diameter of 5.2 Å (see the Supporting Information).

The molecular geometry of chiral trimer (+)-**3c**-H was also determined by X-ray studies and is very similar to the bromophenyl trimer **3c**-Br (Figure 1). The only noticeable differences were observed in rotations of methoxycarbonyl

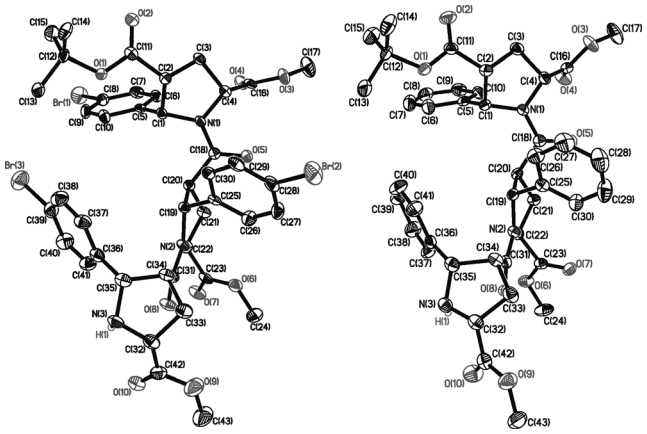


Figure 1. Molecular structures of trimers **3c**-Br (left) and (+)-**3c**-H (right).

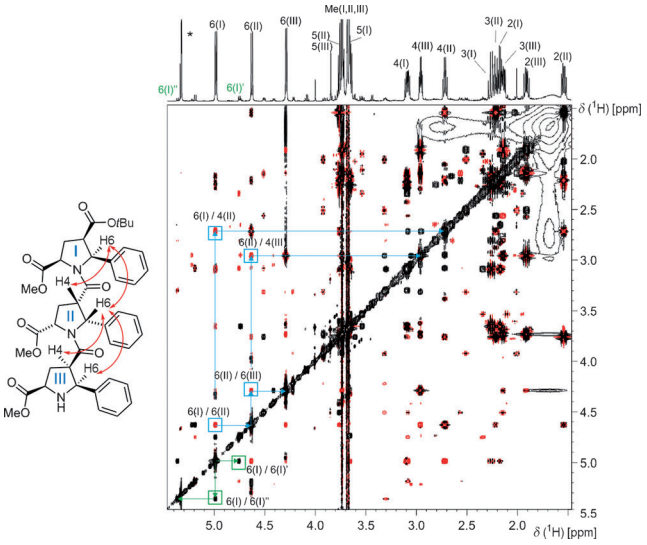
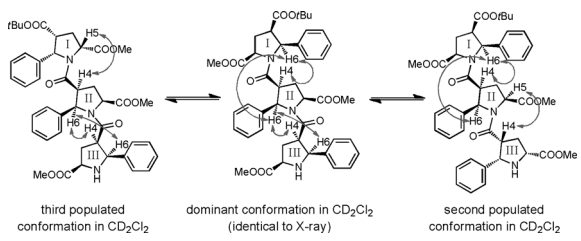


Figure 2. Relevant NOE contacts in the trimer *rac*-**3c**-H. Part of a ^{1}H–^{1}H-NOESY with 400 ms mixing time showing the pyrrolidine proton region. The assignment is indicated in the 1D-spectrum above (⋆ indicates residual $CHDCl_2$). Characteristic NOEs between the rings are boxed (cyan), with the assignment given in the spectrum. Peaks arising from chemical exchange between major and minor conformations appear with opposite sign. Exemplified are exchange peaks between H6(I) (major conformation) and H6(I)′ (1st minor) or H6(I) major and H6(I)″ (2nd minor; green boxes).

groups along C4–C16 and C32–C42 single bonds. However, the crystal packing of (+)-**3c**-H is completely different. In (+)-**3c**-H, amino hydrogen atom H1 does not participate in any hydrogen bonding and the crystal is built by van der Waals interactions only. In contrast to **3c**-Br, in the structure of (+)-**3c**-H no solvent-accessible voids are observed.

An NMR study of well-ordered oligomers **3** of the phenyl series (X = H, Scheme 1) elucidated their structural preferences in solution. Assignment of the ^{1}H and ^{13}C NMR signals can be found in the Supporting Information, Table S1. Based on pyrrolidine ring-proton spin couplings, the dihedral angles were calculated[10] and correlated with the corresponding X-ray data for the racemic dimer **3b**-H and the trimer (+)-**3c**-H. This demonstrated almost full consistency between the main conformations in solution and the crystal structures (Supporting Information, Table S2). Further study of conformational modes of the racemic trimer **3c**-H in CD_2Cl_2 solution was assessed by correlating 2D ^{1}H NMR experiments (Figure 2).

In the trimer *rac*-**3c**-H we observed at least three stable conformations with relative intensities of 89.7/7.2/2.7. The minor conformations were in dynamic exchange with the main conformation, as demonstrated by exchange peaks with opposite intensity than the conventional NOEs. Within a temperature range from 0 °C to 40 °C the relative intensities of the observed *rac*-**3c**-H conformations did not change. The spatial arrangement of pyrrolidine units in the minor conformers was determined by a detailed analysis of the corresponding NOEs (Figure 2, Scheme 3). *Cis*/*trans* amide bond isomerization[5d,11] is an evident reason of the detected conformational exchange. The major regular solution conformation for oligomers *rac*-**3b**-H, *rac*-**3c**-H, and (−)-**3d**-H is characterized by NOEs between the pyrrolidine rings protons H6(*i*)/H6(*i*+1) and H4(*i*)/H6(*i*+1) corresponding to *cis* β-peptide bond with an alternating arrangement of the phenyl substituents, as observed in the crystalline state for trimers *rac*-**3c**-Br and (+)-**3c**-H. Increasing the number of pyrrolidine units in oligomers leads to an increase in *cis*/*trans* amide bond isomerization cases and complication of conformational balance. The dominant conformer of pentamer (−)-**3e**-H in CD_2Cl_2 solution deviates from all *cis* β-peptide bond conformation and shows a *trans* β-peptide bond between the second and third pyrrolidine ring (Scheme 2). Using the described method, we performed conformational analysis of the phenyl series of oligomers **3** (Scheme 3; Supporting Information, Table S3). Tenfold dilution of CD_2Cl_2 solution of pentamer (−)-**3e**-H did not change the ^{1}H NMR (see the Supporting Information), indicating negligible influence of intermolecular interactions on conformer population. We also performed atomic force microscopy studies of tetramers *rac*-**3d**-H, (−)-**3d**-H, and *rac*-**3d**-Br to detect supramolecular organization in solid state, but no ordering was observed (see the Supporting Information). At the current stage it is difficult to make a statement about the definite type of folding of the Pca oligomers **3** synthesized herein. Undoubtedly an appropriate selection of aryl substituents and carboxylic functions (for example, COOH instead of COOMe) would be a powerful way to design intra- and intermolecular interactions in Pca oligomers **3**.



Scheme 3. Conformers of the trimer *rac*-**3c**-H in CD_2Cl_2 solution as determined by NMR spectroscopy.

The enantiopure set of polypyrrolidines **3** was studied by CD spectroscopy. CD spectra were recorded in the far UV area from 300 nm to 190 nm, a region of essential absorbance

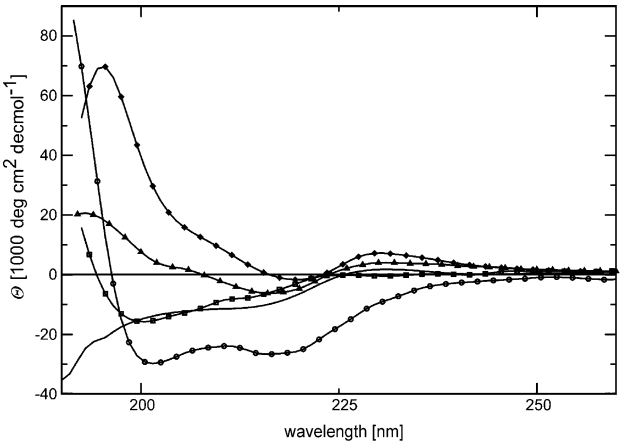


Figure 3. CD spectra of monomer (−)-**3a**-H (no symbol) and oligomers (−)-**3b**-H (○), (+)-**3c**-H (◇), (−)-**3d**-H (□), and (−)-**3e**-H (△).

of the amide and ester groups and to a lesser extent of aromatic groups. The CD spectrum of the dimer (−)-**3b**-H shows a maximum at 190 nm and two minima at 201 and 217 nm (Figure 3). By analogy to other peptoids and peptides, the band at 217 nm was assigned to the $n\rightarrow\pi^*$ transition[11b] of the amide and ester chromophores and the other two bands to the exciton-split π^* transition. In the higher oligomers, the position of these bands change and the relative intensities vary considerably. In the trimer (+)-**3c**-H, the absorption is mainly positive, in the tetramer (−)-**3d**-H it is negative, and in the pentamer (−)-**3e**-H it was found that any true extrema can no longer be distinguished (Figure 3). In contrast to peptoids and peptides with uniform chirality, the alternating *R*/*S* configurations in adjacent pyrrolidine units of enantiomerically pure oligomers **3** seemingly lead to bands of opposite intensities, which partially compensate each other and thus cause the flattening of the curves.

In conclusion, a unique set of racemic and chiral oligomers based on the Pca scaffold was efficiently synthesized by an efficient cycloadditive oligomerization approach. A specific feature of the developed synthetic method is the self-generation of new stereogenic centers with a high degree of stereoselectivity. Owing to the rigidity of poly(5-arylpyrrolidine-2-carboxylic acid) systems, we aim to produce well-organized oligomeric nanosized objects having various functional groups in a confined spatial arrangement for biological, catalytic, and materials applications. Theoretical studies of the stereochemical course of the observed reversal under chain growth will be also performed.

Experimental Section

The general procedure for the synthesis of oligomers is illustrated by example of trimer (+)-**3c**-H: Et_3N (0.423 g, 583 μL, 4.18 mmol) was added to a solution of (−)-**3b**-H (1.400 g, 2.61 mmol) in CH_2Cl_2 (50 mL) at 0 °C. Acryloyl chloride (353 mg, 310 μL, 3.92 mmol) was added dropwise to the reaction mixture under an argon atmosphere at 0 °C. After 15 min, the reaction mixture was allowed to warm to ambient temperature and stirred for 24 h. After washing with water (25 mL), saturated $NaHCO_3$ solution (25 mL), and brine (25 mL), an organic phase was dried over Na_2SO_4 and evaporated. Acrylamide (−)-**2c**-H was purified by column chromatography on silica gel (eluent CH_2Cl_2/MeOH 100:1) and isolated as yellowish crystals in 78% yield (for spectroscopic data, see the Supporting Information). (−)-**2c**-H (1.100 g, 1.86 mmol) was dissolved in anhydrous toluene (20 mL) under an argon atmosphere. The reaction flask was protected from the light with aluminum foil. A solution of **1**-H (0.395 g, 2.23 mmol) in anhydrous toluene (20 mL) and AgOAc (500 mg, 2.79 mmol) were added sequentially. Et_3N (0.283 g, 390 μL, 2.79 mmol) was added dropwise to the reaction mixture and stirred at the ambient temperature for 24 h. The volatiles were removed under vacuum and the residue was redissolved in CH_2Cl_2 (50 mL) and filtered. The organic phase was washed with water (25 mL), brine (25 mL), and then dried over Na_2SO_4. The residue after solvent evaporation was subjected to purification by column chromatography on silica gel (eluent CH_2Cl_2/MeOH 100:1). Trimer (+)-**3c**-H was isolated as yellowish crystals, 1.241 g, yield 87%; m.p. 144–146 °C; 95% *ee* (Chiralpack IB column, heptane/*i*PrOH 75:25, 0.7 mL min^{-1}, t_R(major) = 18.99 min); $[\alpha]_D^{26}$ +22.07° (*c* 0.97, CH_2Cl_2). H NMR (300 MHz, $CDCl_3$, 293 K, dominant conformer signals): $\delta = 1.17$ (s, 9H), 1.58–1.69 (m, 1H), 1.94–1.97 (m, 1H), 2.16–2.24 (m, 1H), 2.25–2.35 (m, 3H), 2.71–2.74 (m, 1H), 2.97–3.00 (m, 1H), 3.07–3.11 (m, 1H), 3.66–3.81 (m, 13H), 4.33 (d, $J = 7.4$ Hz, 1H), 4.66 (d, $J = 8.9$ Hz, 1H), 5.01 (d, $J = 8.5$ Hz, 1H), 7.32–7.46 (m, 13H, H_{Ar}), 7.60 ppm (d, $J = 6.4$ Hz, 2H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$, 293 K, dominant conformer signals): $\delta = 27.69$, 28.44, 29.56, 34.62, 47.40, 47.83, 50.63, 52.11, 52.15, 52.24, 59.09, 59.17, 60.12, 62.65, 62.76, 66.55, 82.07, 127.03, 127.06, 128.04, 128.24, 128.55, 128.65, 128.96, 137.53, 138.61, 138.93, 167.45, 167.45, 167.99, 177.65, 171.72, 172.77 ppm. HRMS (FAB): $[M+H]^+$ calculated for $C_{43}H_{50}N_3O_{10}$ 768.3496, found 768.3497.

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