Synthesis of a C_3-Symmetric Nanoscale Molecular Platform Based on Marine Cyclopeptides

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Abstract: Efficient synthesis of a conformationally preorganized, C_3-symmetric molecular platform is reported. The rigid scaffold is based on the structure of marine cyclopeptides and presents three functional groups pointing in the same direction. The bicyclic imidazole building blocks were synthesized in seven steps from *trans*-4-hydroxy-(*S*)-proline.

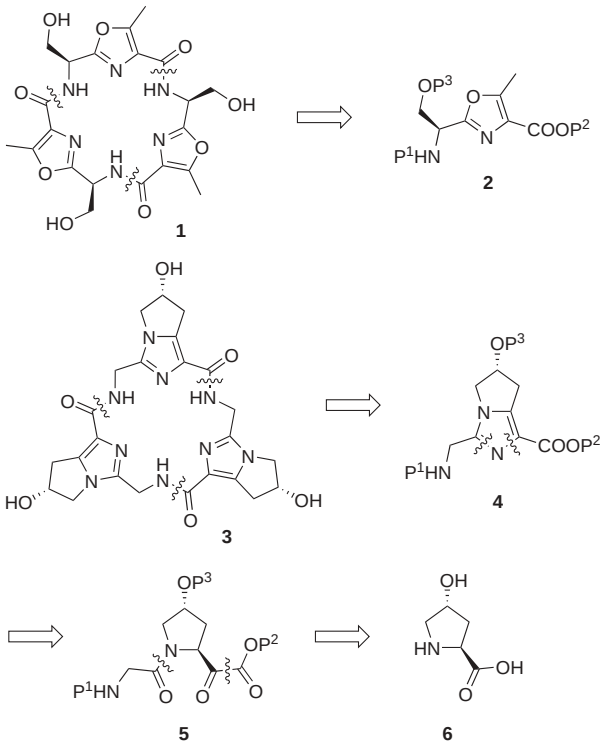
Key words: amino acids, condensation, cyclizations, heterocycles, peptides

Rigid molecular platforms presenting three functional groups in the same direction are useful tools in molecular recognition.[1] The conformationally preorganized nature of these scaffolds allows for pendant functionalities to be specifically spaced and oriented for the attachment of recognition elements. For the application of these systems as synthetic receptors, the distance and the relative orientation of the functional groups play a major role.

We have previously reported the synthesis of functionalized trisoxazole and trisimidazole platforms related to marine cyclopeptides which are characterized by an alternating sequence of oxazole moieties with hydrophobic standard amino acid residues.[2] The average distance between the polar functional groups in the synthetic macrocycles (e.g. the hydroxyl groups in **1**, Scheme 1) amounts to about 7 Å and is independent from the parent azole system. Disadvantageously, the polar functional groups of these platforms are not directly bound to the scaffold, but via methylene units, which leads to a reduced preorganization. Herein we discuss efforts toward the synthesis of a new class of trisimidazole platforms with a distinctly enhanced distance between the hydroxyl groups (**3** in Scheme 1), which are directly connected to the scaffold, making these platforms more suitable for the application in molecular recognition.

The C_3-symmetry of the target macrocyclic triamide **3** suggested a synthetic approach employing the bicyclic imidazole-based, protected amino acid monomer **4** (Scheme 1) for cyclotrimerization. This type of macrolactamization has already been successfully applied to related azole-based cyclotrimers.[3]

Our synthetic plan for accessing the bicyclic imidazole monomer **4** envisaged to form the azole system by cyclocondensation of ammonia with the ketoester **5**, already bearing the five-membered functionlized ring. The latter was expected to be obtainable from *trans*-4-hydroxy-(*S*)-proline (Scheme 1).



Scheme 1

Esterification of hydroxy proline **6** led to the hydrochloride **7**, which was coupled with *Z*-glycine *N*-hydroxysuccinimide ester (Z-Gly-OSu) to the dipetide **8** (Scheme 2). Protection of **8** as its *tert*-butyldimethylsilyl ether was followed by basic hydrolysis to give the acid **9**. From the numerous methods known for the conversion of carboxylic acids to 2-oxo esters[4] we favored a method involving ozonolysis of α-ketocyanophosphoranes originally described by Wasserman and Ho.[5] Treatment of acid **9** with (cyanomethylene)triphenylphosphorane in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) and 4-dimethylaminopyridine (DMAP) yielded the cyano keto phosphorane **10**. The ylide **10** was then oxidatively cleaved with ozone to form an α,β-diketonitrile which was converted in situ with MeOH to the α-keto ester **11**.

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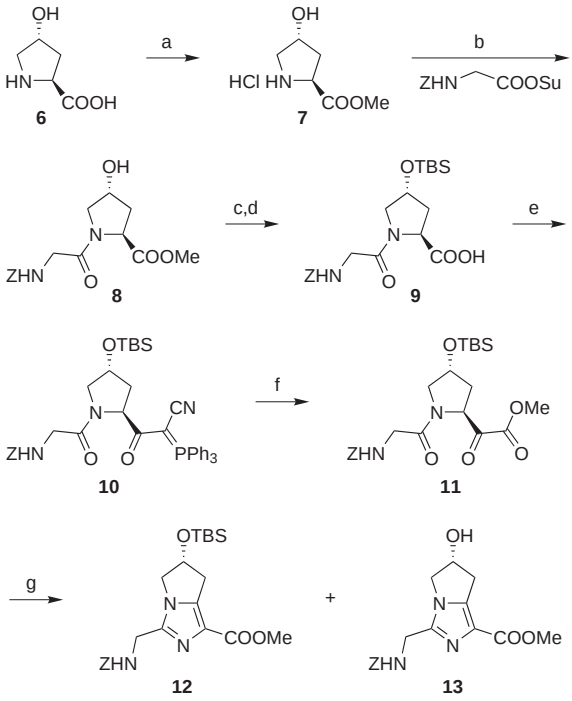
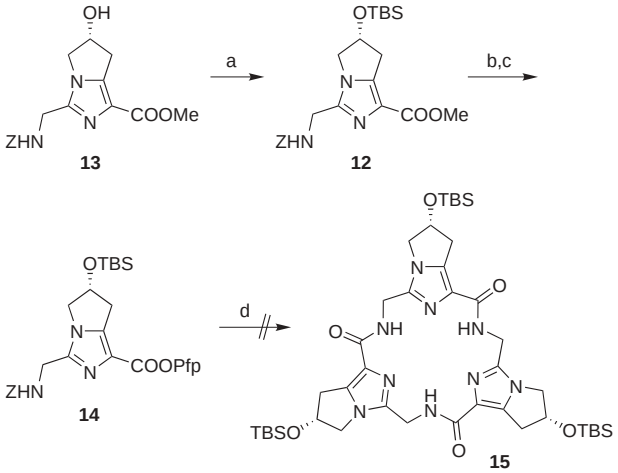


Scheme 2 Reaction conditions: (a) $SOCl_2$, MeOH, 99%; (b) Et_3N, DCM, 65%; (c) TBSCl, DBU, CH_3CN, 95%; (d) NaOH, MeOH, 96%; (e) Ph_3PCHCN, DMAP, EDCI, CH_2Cl_2, 59%; (f) O_3, MeOH–CH_2Cl_2, 80%; (g) TFA, NH_3, xylenes, 130 °C, 47% for **12**, 29% for **13**.

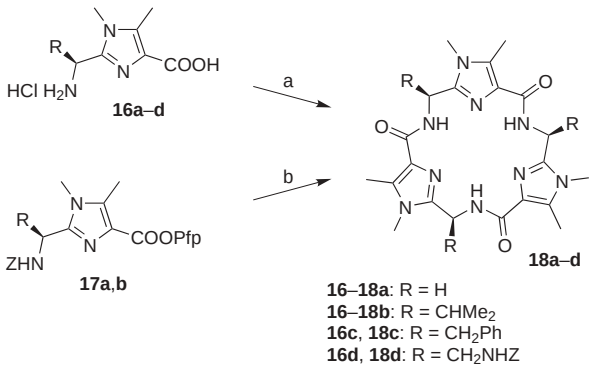
The final cyclocondensation of amidoketone **11** to the bicyclic imidazole **12** was examined with various ammonia reagents. The best yields for the formation of **12** (up to 65%) were obtained when ammonium trifluoroacetate was used in refluxing xylenes with azeotropic removal of water. The yields for the cyclization were even higher (up to 76%) when ammonium trifluoroacetate was formed in situ from methanolic NH_3 and trifluoroacetic acid. However, under these conditions the TBS protective group was partially removed, so that beside **12** (47%), the alcohol **13** (29%) could be isolated.[6] Since **13** could be almost quantitatively reprotected to **12**, the latter synthetic method was nevertheless regarded to be the best (Scheme 3).

Unfortunately, the hydrolysis of the methyl ester functionality of compound **12** proved to be extremely difficult. After examining many reaction conditions,[7] especially basic aqueous solutions, we found that the best method is the non-hydrolytic cleavage of the methyl ester with lithium iodide in pyridine.[8] The resulting acid was subsequently converted into the activated ester **14** employing pentafluorophenyltrifluoroacetate and pyridine in CH_2Cl_2.

The one-pot hydrogenolysis of the *N*-Z function and macrotrimerization were tried to be realized under transfer hydrogenation conditions.[9] Unfortunately, heating a solution of **14** in *tert*-BuOH in the presence of Pd/C, cyclohexadiene, and Hünig's base provided only polymers (Scheme 3). This observation was surprising since the comparable cyclotrimerization of the amino acids **16b–d** had led to the macrocycles **18b–d** in 25–35% yield with only minor influence of the nature of the coupling reagent (Scheme 4).[2a] In order to find out whether the above-mentioned transfer hydrogenation of an active ester is an appropriate method for the synthesis of such trimers, we synthesized the amino acid **16a** and the *N*-Z protected active esters **17a** and **17b** and tried to cyclize them to the corresponding trimers.

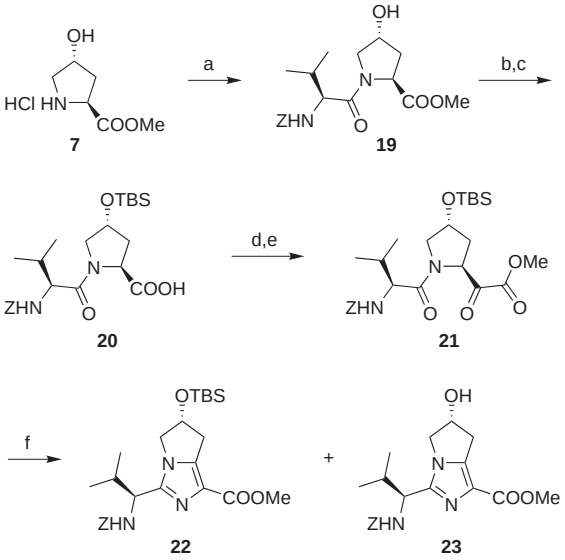


Scheme 3 Reaction conditions: (a) TBSCl, DBU, CH_3CN, 98%; (b) LiI, pyridine, 110 °C; (c) $CF_3COOPfp$, pyridine, CH_2Cl_2, 61% (2 steps); (d) Pd/C, cyclohexadiene, *i*-Pr_2NEt, *t*-BuOH, 85 °C.

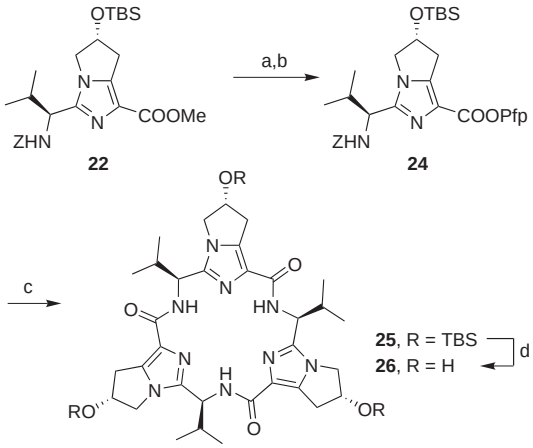


Scheme 4 Reaction conditions: (a) FDPP or DPPA, *i*-Pr_2NEt, CH_3CN, RT, 25–35% for **18b–d**, 0% for **18a**. (b) Pd/C, cyclohexadiene, *i*-Pr_2NEt, *t*-BuOH, 85 °C, 48% for **18b**, 0% for **18a**.

A comparison of the two methods (i.e. steps a and b in Scheme 4) showed that cyclization via hydrogenation of an active ester led to even higher yields for the macrocycles. However, independently from the coupling method, the monomers where the amino acid residue is derived from glycine (i.e. R = H) gave no cyclic trimers at all. Evidently, it is necessary to use monomers derived from amino acids different from glycine (R ≠ H) for a successful cyclotrimerization.



Scheme 5 Reaction conditions: (a) *Z*-Val-OH, HOBt, EDCI, NMM, CH_2Cl_2, 93%; (b) TBSCl, DBU, CH_3CN, 96%; (c) NaOH, MeOH, 94%; (d) Ph_3PCHCN, DMAP, EDCI, CH_2Cl_2, 87%; (e) O_3, MeOH–CH_2Cl_2, 66%; (f) TFA, NH_3, xylenes, 130 °C, 50% for **22**, 35% for **23**.



Scheme 6 Reaction conditions: (a) LiI, pyridine, 110 °C; (b) $CF_3COOPfp$, pyridine, CH_2Cl_2, 65% (2 steps); (c) Pd/C, cyclohexadiene, *i*-Pr_2NEt, *t*-BuOH, 85 °C, 43%; (d) HF, CH_3CN, 90%.

Therefore, we decided to synthesize a bicyclic imidazole monomer, which is based on L-valine. We favored L-valine because monomers derived from this amino acid had given the highest yields in comparable cyclotrimerization reactions.[2a] Furthermore, the L-configuration at the α-C-atom guarantees that in the desired platform, the *iso*-propyl groups of the valine-based moiety point into a direction opposite to the hydroxyl groups.

The revised approach is outlined in Scheme 5. Treatment of hydrochloride **7** with *Z*-Val-OH in the presence of EDCI, 1-hydroxybenztriazole (HOBt) and *N*-methylmorpholine (NMM) gave dipeptide **19** (93%), which was protected as its TBS ether and subsequently hydrolyzed to acid **20**. The transformation of carboxylic acid **20** into the α-keto ester **21** was again performed via the oxidative cleavage of the corresponding α-ketocyanophosphorane. Cyclocondensation of amidoketone **21** with ammonium trifluoroacetate (generated in situ) afforded the bicyclic imidazoles **22** and **23** in an overall yield of 85%.[6] Racemization at the α-C-atom of the L-valine-based moiety which generally occurs during the condensation to related bicyclic imidazoles[10] was not observed.

Methyl ester **22** was converted into the activated ester **24** via ester cleavage with lithium iodide in pyridine and esterification with pentafluorophenyltrifluoroacetate and pyridine (Scheme 6). As expected, the subsequent one-pot hydrogenolysis of the *N*-Z function and macrotrimerization of the modified bicyclic imidazole monomer provided the cyclotrimer **25**[11] in a satisfactory yield (43%). Deprotection of the silyl ethers with aqueous HF in CH_3CN afforded the desired triol platform **26**.[12]

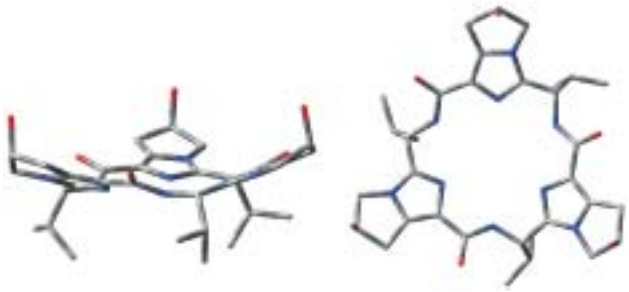


Figure 1 Amber* minimized structure of **26**: side view (left) and top view (right); all hydrogen atoms have been omitted for clarity.

The resonance of the amide protons (δ = 8.19) in the ^1H NMR spectrum of **26** proves that there is an interaction between the lone pairs of the imidazole nitrogen and the hydrogen of the secondary amides. This is consistent with the self-complementary pattern of alternating hydrogen donors and acceptors pointing into the interior of the platform, which has already been observed in the original platforms. Molecular modeling[13] of platform **26** (Figure 1) using MacroModel and the Amber* force field showed that the azole moieties of the macrocycle do not form a single plane but have a cone-like structure. This deviation from planarity is in good agreement with the data obtained from the X-ray crystal structure of the related trisimidazole platform **18b**[2a] and is probably caused by the *iso*-propyl groups of the valine-based moiety. The distance between the hydroxyl groups in the minimized structure amounts to more than 11 Å, which is almost twice that of other tripodal platforms.[14]

In summary, a new class of C_3-symmetric nanoscale molecular platforms has been synthesized in good yield from *trans*-4-hydroxy-(*S*)-proline. While they still realize the basic concept of the original scaffold, these platforms advantageously show an enhanced distance between the functional groups, which are bound directly to the scaffold and thus fixed. The synthetic results show that for a successful cyclotrimerization it is necessary to use monomers derived from amino acids different from glycine.

Acknowledgment

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(6) **Preparation of Compounds 12, 13, 22 and 23**. To a solution of the amidoketone (**11** or **21**; 8.40 mmol) in xylenes (200 mL) were added TFA (3.1 mL, 40.0 mmol) and a solution of NH_3 in MeOH (7 M, 5.7 mL, 40.0 mmol) at r.t. The solution was stirred at 150 °C with azeotropic removal of water for 6 h and then cooled to r.t. The mixture was concentrated and the residue was dissolved in EtOAc, then washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification was accomplished by flash chromatography on silica gel (CH_2Cl_2–EtOAc–MeOH, 75:25:5). Data for **12**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 6 H), 0.87 (s, 9 H), 2.94 (dd, *J* = 4.2, 17.0 Hz, 1 H), 3.31 (dd, *J* = 6.6, 17.0 Hz, 1 H), 3.77–3.89 (m, 4 H), 4.20 (dd, *J* = 6.2, 11.6 Hz, 1 H), 4.37 (d, *J* = 6.1 Hz, 2 H), 4.97–5.12 (m, 3 H), 5.57 (m, 1 H), 7.24–7.36 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.99, –4.87, 17.9, 25.6, 34.7, 37.6, 51.4, 53.6, 67.0, 75.7, 123.9, 128.0, 128.1, 128.5, 136.1, 140.7, 142.8, 156.3, 163.4. HRMS (FAB+): *m*/*z* [M + H$^+$] calcd for $C_{23}H_{34}N_3O_5Si$: 460.2268; found: 460.2260. Data for **13**: Mp 148–150 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.77 (dd, *J* = 2.3, 17.1 Hz, 1 H), 3.18 (dd, *J* = 6.1, 17.1 Hz, 1 H), 3.70 (s, 3 H), 3.80 (dd, *J* = 2.1, 11.8 Hz, 1 H), 4.09 (dd, *J* = 5.3, 11.8 Hz, 1 H), 4.21 (d, *J* = 5.9 Hz, 2 H), 4.88 (s, 1 H), 5.05 (s, 2 H), 5.57 (d, *J* = 4.3 Hz, 1 H), 7.25–7.40 (m, 5 H), 7.88 (t, *J* = 5.9 Hz, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 34.0, 37.2, 50.6, 53.4, 65.5, 74.1, 122.2, 127.6, 127.7, 128.2, 136.9, 141.0, 143.7, 156.1, 162.8. HRMS (FAB+): *m*/*z* [M + H$^+$] calcd for $C_{17}H_{20}N_3O_5$: 346.1403; found: 346.1384. Data for **22**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.10 (s, 6 H), 8.85 (d, *J* = 6.7 Hz, 3 H), 0.88 (s, 9 H), 0.98 (d, *J* = 6.7 Hz, 3 H), 2.15–2.30 (m, 1 H), 2.95 (dd, *J* = 4.2, 17.0 Hz, 1 H), 3.34 (dd, *J* = 6.6, 17.0 Hz, 1 H), 3.85 (s, 3 H), 3.86–3.94 (m, 1 H), 4.07–4.18 (m, 1 H), 4.46 (t, *J* = 8.7 Hz, 1 H), 4.98–5.14 (m, 3 H), 5.56 (d, *J* = 9.1 Hz, 1 H), 7.25–7.37 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.0, –4.9, 17.9, 18.5, 19.4, 25.6, 32.8, 34.7, 51.5, 53.4, 54.0, 66.8, 75.5, 124.1, 127.9, 128.0, 128.4, 136.3, 141.8, 143.9, 156.2, 163.6. HRMS (FAB+): *m*/*z* [M + H$^+$] calcd for $C_{26}H_{40}N_3O_5Si$: 502.2737; found: 502.2736. Data for **23**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.7 Hz, 3 H), 0.98 (d, *J* = 6.7 Hz, 3 H), 2.14–2.28 (m, 1 H), 3.00–3.11 (m, 1 H), 3.32 (dd, *J* = 5.9, 17.5 Hz, 1 H), 3.84 (s, 3 H), 4.08 (m, 2 H), 4.44 (t, *J* = 8.7 Hz, 1 H), 5.00–5.13 (m, 3 H), 5.76 (d, *J* = 9.3 Hz, 1 H), 7.25–7.37 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 19.4, 32.8, 34.5, 51.5, 53.6, 54.2, 66.9, 75.3, 124.1, 127.9, 128.0, 128.5, 136.3, 142.1, 144.2, 156.4, 163.5. HRMS (FAB+): *m*/*z* [M + H$^+$] calcd for $C_{20}H_{26}N_3O_5$: 388.1872; found: 388.1858.

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(11) Data for **25**: Mp 136 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.06 (s, 9 H), 0.07 (s, 9 H), 0.84 (s, 27 H), 1.02 (d, *J* = 6.7 Hz, 9 H), 1.03 (d, *J* = 6.7 Hz, 9 H), 2.06–2.15 (m, 3 H), 2.94 (dd, *J* = 3.7, 16.9 Hz, 3 H), 3.35 (dd, *J* = 6.4, 16.9 Hz, 3 H), 3.74 (dd, *J* = 3.7, 11.2 Hz, 3 H), 4.08 (dd, *J* = 5.8, 11.2 Hz, 3 H), 4.93 (dd, *J* = 6.1, 8.7 Hz, 3 H), 5.02 (m, 3 H), 8.32 (d, *J* = 8.7 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.0, –4.8, 17.9, 18.4, 19.3, 25.7, 34.1, 35.0, 51.3, 53.3, 76.1, 126.5, 138.2, 142.6, 162.8. HRMS (FAB+): *m*/*z* [M + H$^+$] calcd for $C_{51}H_{88}N_9O_6Si_3$: 1006.6165; found: 1006.6116.

(12) Data for **26**: Mp >250 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.7 Hz, 9 H), 1.04 (d, *J* = 6.7 Hz, 9 H), 1.92–2.01 (m, 3 H), 3.22–3.30 (m, 6 H), 3.78 (dd, *J* = 4.4, 11.5 Hz, 3 H), 4.41 (d, *J* = 11.5 Hz, 3 H), 4.64 (dd, *J* = 8.1, 9.6 Hz, 3 H), 5.09 (m, 3 H), 5.38 (s, 3 H), 8.19 (d, *J* = 9.8 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.9, 19.3, 34.1, 35.6, 50.8, 53.3, 75.6, 125.5, 139.2, 142.8, 163.2. HRMS (FAB+): *m*/*z* [M + H$^+$] calcd for $C_{33}H_{46}N_9O_6$: 664.3571; found: 664.3578.

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