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Hydroxy-α-amino acids modified by ionic liquid moieties: recoverable organocatalysts for asymmetric aldol reactions in the presence of water

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ABSTRACT

New chiral ionic liquids bearing proline, serine or threonine moieties were synthesized. Compounds that contain 1-dodecylimidazolium or 4-(5-*n*-nonyl)-pyridinium cations and NTf_2 or PF_6 anions efficiently catalyze the asymmetric aldol reaction between aldehydes and ketones in the presence of water to generate aldols with high distereo- (up to 98:2) and enantioselectivity (up to >99% ee). 4-Hydroxyproline modified by the 4-(5-*n*-nonyl)-pyridinium hexafluorophosphate moiety retains its activity and selectivity over at least eight reaction cycles.

1. Introduction

An asymmetric aldol reaction is one of the most common methods for C–C bond formation in organic molecules. It is extensively applied in the synthesis of carbohydrates, amino sugars, steroids, and other valuable chiral organic compounds.[1] In nature, the reaction is catalyzed by aldolase enzymes.[2] It was ascertained that the reaction could be performed at a higher rate and with higher selectivity under the action of some more elementary organic molecules, so-called 'organocatalysts'. These include proline,[3] its derivatives,[4] other natural amino acids,[5] 2-pyrrolidine derivatives,[6] and small peptides.[5c,7] Note that some of the recently synthesized organocatalysts exceed proline and other amino acids in their activity and selectivity. Unlike aldolases that catalyze the aldol reaction in aqueous medium, the reactions catalyzed by synthetic organocatalysts are normally carried out in an excess of reacting ketone,[3b,4a,b,d,f,l,6c,d,7a,c,e] organic solvents,[3a–d,g,i,n,q,4a,f,h,i,5c,6a,c,d,7a–c,h] or ionic liquids.[3e,j,4c]

Meanwhile there is a group of organocatalysts that allow an aldol reaction in the presence of water,[8,9] i.e., the most low-cost and environment-friendly solvent, which makes it attractive for researchers. An asymmetric aldol reaction in the presence of water has specific features due to the limited solubility of reagents and catalysts in it as well as due to the water impact on the rate of establishing the acid–base equilibrium and on the energy and special architecture of the enamine transition state. The highest conversion and selectivity were achieved in the reactions running under the action of water-insoluble catalysts that include hydrophobic structural moieties such as long-chain hydrocarbon[8b,d] and perfluorohydrocarbon[8a,h] fragments, aryl,[4l,o,8g] siloxy,[8c,e,f] polymeric,[9a–c] or dendrimeric[9d] groups. Of note is that the reactions occur in heterophase systems related to those characterized by Sharpless as the 'on water' reactions.[10a] Reagents and a catalyst in such systems react with each other on the surface or inside of concentrated organic associates (micelles)[10b] where hydrophobic structural moieties protect the chiral transient complex from the racemizing water impact.[10c] The important role of the interfacial region is affirmed by the fact that aldol reactions catalyzed by water-soluble amino acids run in water slowly and less selectively[5d] than where affected by water-insoluble catalysts or performed under PTC-conditions.[3h,10d]

Since many catalysts used for reactions in the presence of water have a rather complex structure, a critical issue here is to develop efficient methods for their regeneration. A solution to this problem may be approached through the introduction of polymer or ionic groups to the catalyst's framework. They facilitate catalyst separation from the reagents and products by reducing the solubility in the reaction system components. However, the synthesis of recoverable catalysts having been designed by now, which comprise either a polymer or dendritic moiety, is quite challenging and demands costly starting compounds.[7f,9d] The activity of more available siloxy ethers of hydroxyproline declines as early as in the third

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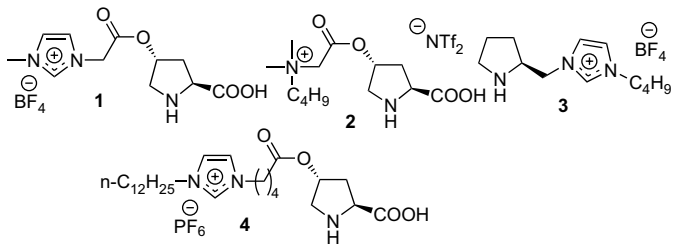


Figure 1. Known organocatalysts bearing ionic liquid moieties.

reaction cycle[8c,e] assumingly because of the Si–O bond hydrolysis and/or good solubility of such catalysts in the organic solvent employed for the products extraction. Systems with acid or surfactant additives were only one-cycle usable.[3h,8b,10d]

Derivatives of proline **1** and **2** bearing an ionic group[11a,b] can act as recoverable catalysts for aldol reactions in organic solvents or ionic liquids (Fig. 1). Ionic catalyst **3** (Fig. 1) was examined in the asymmetric aldol reaction in aqueous medium with AcOH as an additive.[11c] Whereas the aldol reactions catalyzed by **1** and **2** proceeded with satisfactory distereo- and enantioselectivity, these characteristics of the reactions catalyzed by **3** were much lower. Our attempts to perform the aldol reaction under the action of **1** in water failed: compound **1**, readily soluble in water, does not catalyze the aldol reaction under these conditions.

To improve the activity of catalyst **1** in aqueous medium, we recently designed catalyst **4** with a structure close to **1** (Fig. 1). Along with the imidazolium hydrophilic cation, it incorporated hydrophobic alkyl groups containing 4–12 carbon atoms and the hydrophobic anion PF_6.[11d] The catalyst demonstrated high activity and selectivity values in reactions between cycloalkanones and aromatic aldehydes in aqueous media and remained usable for at least five cycles without decrease in conversion and selectivity.

2. Results and discussion

To elucidate the role of hydrophobic interactions in organocatalytic aldol reactions in the presence of water, herein we synthesized a few new amphiphilic compounds **5**–**9** differing from compound **4** by the type of the chiral inductor and the cation or anion (Fig. 2). We examined their catalytic properties in the 'on water' aldol reaction.

The choice of compound **5** bearing the anion NTf_2^- as a research subject was reasoned by the fact that imidazolium salts with such an anion usually have lower solubility in water (more hydrophobic) than their respective salts with the anion PF_6.[12] The incorporation of pyridinium or 4-(5-nonyl)-pyridinium cations to catalysts **6**–**9** was also intended to improve the catalysts' hydrophobic properties that influence the activity through increasing the C/N ratio in the cation structure (pyridine derivatives contain more carbon atoms and fewer nitrogen atoms than imidazole derivatives). Finally, the use of serine and threonine moieties as chiral inductors in compounds **8** and **9** is related with an ability of hydrophobic derivatives of these amino acids, as has been recently stated, to efficiently catalyze the aldol reaction in the presence of water.[8e,f] It should be pinpointed that serine and threonine derivatives bearing ionic liquid moieties had not been earlier studied as organocatalysts for enantioselective organic reactions.

Compound **5** was synthesized by replacing the anion Br^- in bromide **10**, which we had described before,[11d] for the anion NTf_2^- (Scheme 1).

trans-4-Hydroxyproline derivatives **6** and **7** were prepared through the interaction of protected amino acid ester **11** containing the terminal bromoalkyl group[11d] with pyridine or 4-(5-nonyl)-pyridine,[13] the anion metathesis in alkylation products **12a** and **b**, and the removal of protective groups from hexafluorophosphates **13a** and **b** (Scheme 2).

Serine **8** and threonine **9** derivatives bearing the 4-(5-n-nonyl)-pyridinium moiety were synthesized in a similar manner from the respective amino acids protected by Cbz and Bn groups **14a** and **b** (Scheme 3).

Compound **5** is a viscous oil and compounds **6**–**9** are crystalline substances with melting points $<117\,^{\circ}C$, therefore they can be assigned as ionic liquids.

The synthesized compounds **5**–**9** were investigated as organocatalysts in the aldol reaction between cyclohexane **18a** and *p*-nitrobenzaldehyde **19a** in the presence of water. All reaction runs were performed in the presence of 15 mol % of the catalyst at room temperature without an organic solvent and with the use of 3 equiv of ketone **18a**.

Aldol **20a** was synthesized under the action of bis(triflyl)imide salt **5** with the conversion, distereo- and enantioselectivities, which were comparable with the values having been previously obtained in the reaction catalyzed by hexafluorophosphate **4** (Table 1, entry 1).[11d] However, unlike catalyst **4**, the activity of catalyst **5** decreased as early as in the third cycle (Table 1, entries 1–3) due to its washout to the organic solvent used for the product extraction. The NMR spectrum of crude aldol contained signals of catalyst **5**.

Compound **6**, despite the presence of PF_6^-, is significantly water-soluble and does not catalyze the aldol reaction under the examined conditions (Table 1, entry 4). Whereas compound **7**, which has the hydrophobic 5-*n*-nonyl group in the pyridine cycle and given that is actually insoluble in water, displayed high activity and selectivity in the model reaction (Table 1, entry 5). Also, opposite to catalyst **5**, catalyst **7** retained activity and selectivity at least eight reaction cycles (Table 1, entries 5–12).

Catalysts **8** and **9** also showed rather good results in the aldol reaction between compounds **18a** and **19a** in the aqueous medium (Table 1, entries 13 and 14). However, the conversion, distereo- and enantioselectivity values were slightly lower than the values afforded in the reaction catalyzed by **7**.

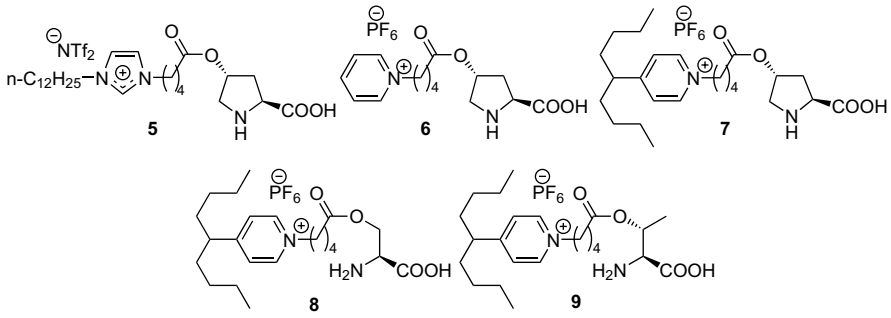
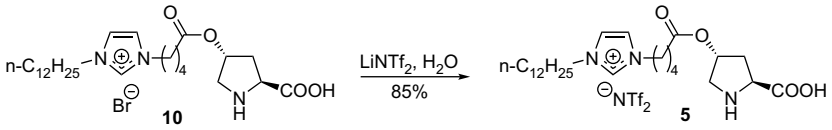
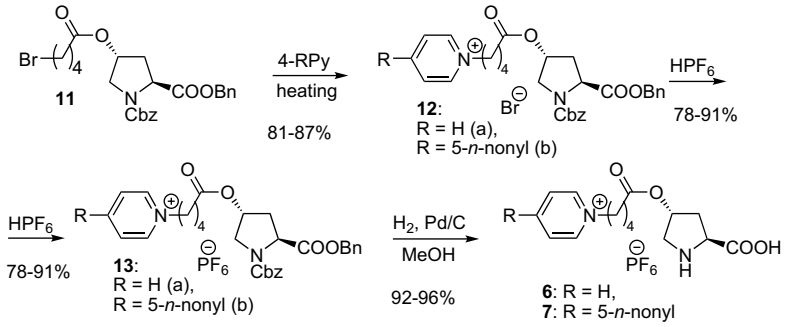


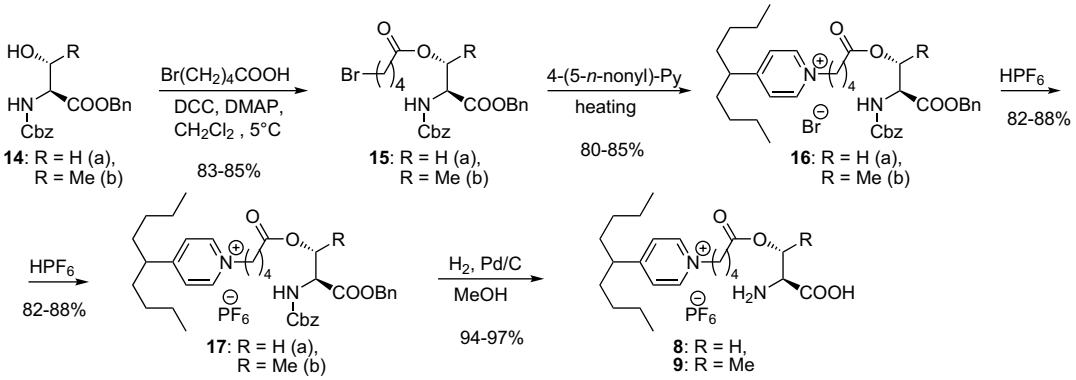
Figure 2. New amphiphilic derivatives of α-amino acids.



Scheme 1. Synthesis of IL-containing catalyst **5** with the NTf_2^- anion.



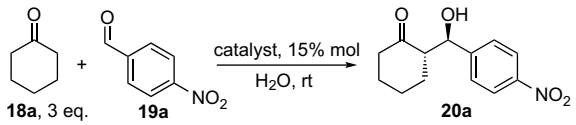
Scheme 2. Synthesis of *trans*-4-hydroxy-(*S*)-proline derivatives **6** and **7** bearing pyridinium moieties.



Scheme 3. Synthesis of serine (**8**) and threonine (**9**) derivatives bearing the 4-(5-*n*-nonyl)-pyridinium moiety.

Of note is that all the investigated catalysts (except for **6**) were efficient in heterophase systems consisting of three phases restrictedly soluble in each other: the eutectic solution of reagents, water phase, and ionic phase of the catalyst is poorly soluble both in the organic layer and in water. Obviously, the catalysts (**5**, **7**–**9**) that incorporate the lipophilic alkyl group, along with the hydrophilic ionic moiety, in these conditions are located on the water/organic solvent interface where the catalytic conversion occurs.

Table 1
Catalytic activities and selectivities of new IL-containing catalysts



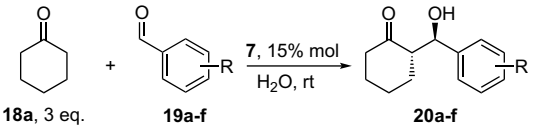
Entry	Catalyst	Time, h	Conv., %	dr, *anti*/*syn*	ee of *anti*, %
1	5	15	>99	98:2	98
2	5 (cycle 2)	15	>99	98:2	>99
3	5 (cycle 3)	15	58	97:3	>99
4	6	15	—	—	—
5	7	15	97	97:3	99
6	7 (cycle 2)	15	98	97:3	>99
7	7 (cycle 3)	15	95	97:3	>99
8	7 (cycle 4)	15	98	96:4	99
9	7 (cycle 5)	15	98	97:3	99
10	7 (cycle 6)	15	96	97:3	99
11	7 (cycle 7)	15	94	97:3	99
12	7 (cycle 8)	15	96	97:3	99
13	8	20	84	87:13	91
14	9	20	89	90:10	97

Conversion and dr were determined by NMR on crude products, ee was determined by HPLC (Chiralcel OJ-H) on crude products.

Higher efficiency of the catalysis in organic solvent/water heterophase systems compared to homogeneous systems may also be associated with special features of hydrophobic molecule solvation in water. Water has a much higher cohesion energy than organic solvents (water—550.2 kcal cm^{-3}, organic solvents—60–380 kcal cm^{-3}). Given that, water-insoluble hydrophobic organic molecules experience water cohesion pressure equal to about 23 kbar in conventional units. This accelerates organic reactions characterized by negative activation volumes, to which the aldol reaction belongs.[14]

Catalyst **7** retained high activity and selectivity during multiple model reaction runs in the aqueous medium and was employed in aldol reactions with the participation of various aldehydes and ketones (Table 2). It appeared that benzaldehyde **19b** and its derivatives **19a**,**c**–**f** bearing electron-withdrawing or electron-donating groups in the aromatic ring entered the reactions with cyclohexanone **18a** catalyzed by **7**. The highest conversion, distereo- and enantioselectivity values were attained in the reactions with benzaldehyde **19b** and aromatic aldehydes with electron-acceptor substituents **19a**,**c**,**d**. Less active in the examined reactions were *m*-phenoxybenzaldehyde **19e** and *p*-methoxybenzaldehyde **19f**. However, in the instance of *m*-phenoxybenzaldehyde **19e**, the long reaction run (90 h) resulted in product **20e** with the high conversion, distereo- and enantioselectivities. These characteristics

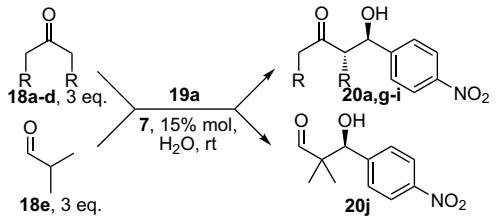
Table 2
The aldol reaction between cyclohexanone and aromatic aldehydes catalyzed by **7**



Entry	R in **19** and **20**	Time, h	Conv.,%	dr, *anti*/*syn*	ee of *anti*, %
1	(**a**) *p*-NO_2	15	97	97:3	99
2	(**b**) H	40	75	95:5	97
3	(**c**) *p*-CN	15	86	97:3	99
4	(**d**) *p*-CO_2CH_3	15	>95	97:3	98
5	(**e**) *m*-OC_6H_5	90	87	96:4	>99
6	(**f**) *p*-OCH_3	110	38	90:10	93

Conversion and dr were determined by NMR on crude products, ee was determined by HPLC (Chiralcel OJ-H) on crude products.

Table 3
The aldol reaction between cycloalkanones/isobutyraldehyde and *p*-nitrobenzaldehyde catalyzed by **7**



Entry	R, R in **18**	Aldol **20**	Time, h	Conv., %	dr, *anti*/*syn*	ee of *anti*, %
1	(**a**) –$(CH_2)_3$–	(**a**)	15	97	97:3	99
2	(**b**) –$(CH_2)_2$–	(**g**)	15	>95	80:20	92
3	(**c**) –CH_2OCH_2–	(**h**)	20	66	97:3	97
4	(**d**) –CH_2SCH_2–	(**i**)	20	78	98:2	99
5	(**e**) —	(**j**)	96	40	—	99

Conversion and dr were determined by NMR on crude products, ee was determined by HPLC (Chiralcel OJ-H, OD-H) on crude products.

of product **20f** of the reaction between cyclohexanone **18a** and *p*-methoxybenzaldehyde **19f** were somewhat lower.

Along with cyclohexanone (**18a**), other cyclic ketones, viz. cyclopentanone (**18b**), tetrahydropyran-4-one (**18c**), and tetrahydrothiopyran-4-one (**18d**), entered the reaction with *p*-nitrobenzaldehyde (**19a**) catalyzed by **7** (Table 3). Also, the reactions with the participation of six-membered heterocycles **18c**,**d** proceeded with high distereo- and enantioselectivities, and in the case of cyclopentanone (**18b**) dr and ee values of aldol **20g** were somewhat lower. Taking isobutyraldehyde (**18e**) as an example, we showed the possibility to introduce aldehyde donors to the aldol reaction catalyzed by **7**. The produced aldol **20j** had high enantiomeric purity although a prolonged reaction period was required to achieve a moderate conversion.

3. Conclusion

New chiral ionic liquids bearing 4-hydroxyproline, serine or threonine moieties, and imidazolium or pyridinium cations capable to catalyze the asymmetric aldol reaction between aldehydes and ketones in the presence of water were synthesized. It was established that the hydrophobic alkyl groups available in organocatalysts improved the reaction efficiency under the examined conditions. The catalyst with the anion PF_6^- can be readily regenerated and utilized multiply without a decline in the conversion, dr, and ee values.

4. Experimental

4.1. Synthesis

*4.1.1. Compound **5***

$LiNTf_2$ solution (65 mg, 0.23 mmol) in water (5 mL) was gradually added to a stirred solution of bromide **10** (0.12 g, 0.23 mmol) in water (5 mL). The aqueous phase was decanted, and the resulting precipitate was washed with water (2×5 mL) and dried in vacuo (0.5 Torr) for 2 h to afford trifluoromethanesulfonimidate **5** (0.14 g, 85%) as colorless viscous oil.

*4.1.2. Compounds **15a** and **15b***

A mixture of corresponding Cbz,Bn-protected amino acid: L-serine (2.00 g, 6.08 mmol) **14a** or L-treonine (2.08 g, 6.06 mmol) **14b**, 5-bromovaleric acid (1.10 g, 6.08 mmol), DCC (1.25 g, 6.08 mmol), and DMAP (40 mg, 0.33 mmol) in CH_2Cl_2 (30 mL) was stirred at 5 °C for 3 h. The resulting precipitate was filtered off and washed with CH_2Cl_2 (3×5 mL). The combined organic extracts were evaporated, and the residue was purified by column chromatography on silica gel (Acros, 0.035–0.070 mm, 60Å, eluent: n-hexane/EtOAc=4:1) to afford **15a** (2.48 g, 83%) or **15b** (2.61 g, 85%) as colorless oil.

*4.1.3. Compounds **12a**, **12b**, **16a**, and **16b***

A mixture of corresponding compound **11** (1.55 g, 3.00 mmol, for **12a**; 1.25 g, 2.41 mmol, for **12b**)/**15a** (1.25 g, 2.54 mmol)/**15b** (1.25 g, 2.47 mmol) and corresponding pyridine (0.26 g, 3.30 mmol, for **12a**)/4-(5-*n*-nonyl)-pyridine (0.52 g, 2.53 mmol, for **12b**; 0.55 g, 2.67 mmol, for **16a**; 0.53 g, 2.59 mmol, for **16b**) was heated at 90 °C for 15 min, cooled to ambient temperature, and washed with Et_2O (6×15 mL). The residue was dissolved in MeOH (3 mL), and Et_2O (20 mL) was added to a stirred solution. The separated oil was dried in vacuo (0.5 Torr) for 3 h to afford **12a** (1.56 g, 87%)/**12b** (1.42 g, 81%)/**16a** (1.51 g, 85%)/**16b** (1.41 g, 80%) as corresponding aggregative states (see Characterization).

*4.1.4. Compounds **13a**, **13b**, **17a**, and **17b***

Solution of corresponding bromide **12a** (1.40 g, 2.34 mmol)/**12b** (1.20 g, 1.66 mmol)/**16a** (1.20g, 1.72 mmol)/**16b** (1.20 g, 1.69 mmol) in water (15 mL) was adjusted to pH ~2–3 with 60% HPF_6 (0.8 mL/0.5 mL/0.5 mL/0.5 mL) at 40–50 °C. The aqueous layer was decanted, and the precipitate washed with water to neutral pH. The residue was dried in vacuo (0.5 Torr) for 3 h to afford **13a** (1.21 g, 78%)/**13b** (1.19 g, 91%)/**17a** (1.15 g, 88%)/**17b** (1.07 g, 82%) as corresponding aggregative states (see Characterization).

*4.1.5. Compounds **6**–**9***

A mixture of corresponding compound **13a** (1.10 g, 1.66 mmol)/**13b** (1.00 g, 1.27 mmol)/**17a** (1.00 g, 1.31 mmol)/**17b** (0.9 g, 1.16 mmol) and Pd/C (5%) (0.30 g) in dry CH_3OH (30 mL) was stirred under H_2 (760 Torr) at ambient temperature for 3 h. The resulting precipitate was filtered off and washed with 10 mL CH_3OH. The combined organic phases were evaporated, and the residue was dried in vacuo (0.5 Torr) for 3 h to afford **6** (0.67 g, 92%)/**7** (0.69 g, 96%)/**8** (0.66 g, 94%)/**9** (0.62 g, 97%) as corresponding aggregative states (see Characterization).

4.1.6. A typical procedure for the aldol reaction

A mixture of the appropriate organocatalyst (0.02 mmol), ketone/aldehyde **18** (0.40 mmol), aldehyde **19** (0.13 mmol), and distilled water (0.3 mL) was stirred at room temperature for the period given in Tables 1–3. Aldol **20** and the remained starting compounds were extracted with Et_2O (2×5 mL), the combined extracts were filtrated through a silica gel pad (1 g) and evaporated in vacuo (15 Torr). Conversion and dr values of aldols **20**

were measured by ^{1}H NMR of the crude reaction mixture, ee values of *anti*-isomers of **20** were determined by HPLC, chiral phase: Chiralcel OD-H, OJ-H.

4.2. Characterization

4.2.1. (4R)-4-((5-(1-Dodecyl-1H-imidazol-3-ium-3-yl)pentanoyl)-oxy)-L-proline trifluoromethanesulfonimide ***5***

Colorless viscous oil. $[\alpha]_D^{27}$ −10.2 (*c* 1, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.20 (1H, s, NC*H*N), 7.80 (2H, s, NC*H*C*H*N), 5.16–5.23 (1H, m, C*H*O), 4.11–4.21 (4H, m, 2CH_2CH_2N), 3.78 (1H, t, *J*=8.9 Hz, CH_2CHN), 3.05–3.48 (2H, m, CHCH_2N), 2.31–2.39 (2H, m, $CH_2CH_2CO_2$), 2.02–2.21 (2H, m, CH_2CHN), 1.72–1.87 (4H, m, 2CH_2CH_2N), 1.40–1.54 (2H, m, C$H_2CH_2CO_2$), 1.22 (18H, s, $CH_3(CH_2)_9$), 0.86 (3H, t, *J*=6.1 Hz, CH_3) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 171.8, 169.8, 135.3, 122.4, 122.3, 73.2, 59.3, 49.9, 48.9, 48.5, 35.0, 32.5, 31.3, 29.3, 29.0, 28.9, 28.8, 28.7, 28.6, 28.4, 25.5, 22.0, 20.7, 13.9 ppm; IR (KBr, cm^{-1}): 3440, 3176, 2928, 2856, 1736, 1628, 1460, 1388, 1312, 1264, 1172, 844, 752. Anal. Calcd for $C_{27}H_{44}F_6N_4O_8S_2$: C, 44.38; H, 6.07; N, 7.67; S, 8.78; F, 15.60. Found: C, 44.27; H, 6.01; N, 7.66; S, 8,80; F, 15.51.

4.2.2. 1-(5-(((3R,5S)-1,5-Bis((benzyloxy)carbonyl)pyrrolidin-3-yl)-oxy)-5-oxopentyl)pyridinium bromide ***12a***

Colorless oil. $[\alpha]_D^{27}$ −17.9 (*c* 1, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.48–9.57 (2H, m, CHC*H*NC*H*CH), 8.39–8.50 (1H, m, $(CH)_2CH(CH)_2$), 8.00–8.10 (2H, m, C*H*CHNCHC*H*), 7.20–7.42 (10H, m, 2C_6H_5), 4.91–5.28 (7H, m, C*H*O, 2CH_2Ph, CH_2CH_2N), 4.41–4.55 (1H, m, C*H*CO_2), 3.60–3.83 (2H, m, CHCH_2N), 2.41 (2H, t, *J*=6.8 Hz, CH_2CO_2), 2.02–2.50 (2H, m, CHCH_2CH), 2.02–2.14 (2H, CH_2CH_2N), 1.62–1.79 (2H, m, C$H_2CH_2CO_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.1, 169.8, 153.5, 144.6, 144.3, 136.9, 136.1, 128.4, 128.2, 128.1, 127.9, 127.8, 127.5, 127.4, 72.9, 65.8, 65.4, 59.9, 56.9, 52.1, 35.3, 32.2, 28.8, 20.4 ppm. Anal. Calcd for $C_{30}H_{33}BrN_2O_6$: C, 60.31; H, 5.57; N, 4.69; Br, 13.37. Found: C, 60.57; H, 5.52; N, 4.78; Br, 13.23.

4.2.3. 1-(5-(((3R,5S)-1,5-Bis((benzyloxy)carbonyl)pyrrolidin-3-yl)-oxy)-5-oxopentyl)pyridinium hexafluorophosphate ***13a***

Colorless oil. $[\alpha]_D^{28}$ −19.6 (*c* 1, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.02–9.11 (2H, m, CHC*H*NC*H*CH), 8.56–8.67 (1H, m, $(CH)_2CH(CH)_2$), 8.11–8.21 (2H, m, C*H*CHNCHC*H*), 7.22–7.41 (10H, m, 2C_6H_5), 5.19–5.27 (1H, m, C*H*O), 5.03–5.17 (4H, m, 2CH_2Ph), 4.57–4.65 (2H, m, CH_2CH_2N), 4.21–4.45 (1H, m, C*H*CO_2), 3.41–3.59 (2H, m, CHCH_2N), 2.33–2.41 (2H, m, CH_2CO_2), 2.05–2.30 (2H, m, CHCH_2CH), 1.87–2.00 (2H, m, CH_2CH_2N), 1.45–1.60 (2H, m, C$H_2CH_2CO_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 172.1, 169.8, 153.8, 145.4, 144.6, 136.4, 135.6, 128.5, 128.2, 127.9, 127.8, 127.6, 127.5, 127.2, 72.4, 66.4, 65.9, 60.3, 57.2, 52.2, 35.8, 32.5, 29.9, 20.6 ppm. Anal. Calcd for $C_{30}H_{33}F_6N_2O_6P$: C, 54.38; H, 5.02; N, 4.23; F, 17.20. Found: C, 54.52; H, 4.94; N, 4.30; F, 17.06.

4.2.4. (4R)-4-((5-Pyridinium-1-ylpentanoyl)oxy)-L-proline hexafluorophosphate ***6***

White solid, mp 113–114 °C. $[\alpha]_D^{29}$ −12.9 (*c* 1, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.09 (2H, d, *J*=6.1 Hz, CHC*H*NC*H*CH), 8.62 (1H, t, *J*=7.8 Hz, $(CH)_2CH(CH)_2$), 8.18 (2H, t, *J*=6.9 Hz, C*H*CHNCHC*H*), 5.18–5.26 (1H, m, C*H*O), 4.61 (2H, t, *J*=6.9 Hz, CH_2CH_2N), 3.80–3.89 (1H, m, C*H*CO_2), 3.08–3.50 (2H, m, CHCH_2N), 2.32–2.41 (2H, m, CH_2CO_2), 2.05–2.25 (2H, m, CHCH_2CH), 1.88–2.00 (2H, m, CH_2CH_2N), 1.45–1.58 (2H, m, C$H_2CH_2CO_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 172.1, 170.3, 145.6, 144.8, 128.2, 73.2, 60.4, 59.3, 50.0, 35.1, 32.6, 30.0, 20.6 ppm; IR (KBr, cm^{-1}): 3416, 2960, 1736, 1636, 1488, 1456, 1396, 1320, 1172, 1064, 840, 776. Anal. Calcd for $C_{15}H_{21}F_6N_2O_4P$: C, 41.10; H, 4.83; N, 6.39; F, 26.01. Found: C, 41.22; H, 4.77; N, 6.43; F, 25.83.

4.2.5. 1-(5-(((3R,5S)-1,5-Bis((benzyloxy)carbonyl)pyrrolidin-3-yl)oxy)-5-oxopentyl)-4-(1-butylpentyl)pyridinium bromide ***12b***

Light yellow oil. $[\alpha]_D^{24}$ −17.2 (*c* 1, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.42 (2H, d, *J*=6.1 Hz, CHC*H*NC*H*CH), 7.73 (2H, d, *J*=6.1 Hz, C*H*CHNCHC*H*), 7.20–7.38 (10H, m, 2C_6H_5), 5.21–5.28 (1H, m, C*H*O), 4.98–5.22 (6H, m, 2CH_2Ph, NCH_2CH_2), 4.45–4.56 (1H, m, C*H*CO_2), 3.60–3.78 (2H, m, CHCH_2N), 2.72–2.83 (1H, m, $(C_2H_5)_2CH$), 2.42 (2H, t, *J*=6.9 Hz, CH_2CO_2), 2.12–2.45 (2H, m, CHCH_2CH), 2.02–2.16 (2H, m, NCH_2CH_2), 1.65–1.81 (2H, m, C$H_2CH_2CO_2$), 1.51–1.64 (4H, m, $(CH_2CH_2)_2CH$), 1.00–1.33 (8H, m, 2$CH_2CH_2CH_3$), 0.84 (6H, t, *J*=6.9 Hz, 2CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.1, 171.8, 167.0, 154.0, 144.4, 135.9, 135.0, 128.4, 128.2, 128.1, 127.9, 127.8, 127.5, 127.0, 71.7, 67.1, 66.8, 60.0, 57.5, 52.4, 46.3, 36.2, 35.1, 33.0, 30.9, 29.3, 22.3, 20.9, 13.6 ppm. Anal. Calcd for $C_{39}H_{51}BrN_2O_6$: C, 64.72; H, 7.10; N, 3.87; Br, 11.04. Found: C, 65.01; H, 7.04; N, 3.93; Br, 10.91.

4.2.6. 11-(5-(((3R,5S)-1,5-Bis((benzyloxy)carbonyl)pyrrolidin-3-yl)oxy)-5-oxopentyl)-4-(1-butylpentyl)pyridinium hexafluorophosphate ***13b***

Colorless oil. $[\alpha]_D^{25}$ −16.0 (*c* 1, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.92 (2H, d, *J*=6.1 Hz, CHC*H*NC*H*CH), 8.02 (2H, d, *J*=6.1 Hz, C*H*CHNCHC*H*), 7.22–7.39 (10H, m, 2C_6H_5), 5.18–5.24 (1H, m, C*H*O), 4.98–5.17 (4H, m, 2CH_2Ph), 4.51 (2H, t, *J*=7.4 Hz, NCH_2CH_2), 4.37–4.45 (1H, m, C*H*CO_2), 3.51–3.72 (2H, m, CHCH_2N), 2.82–2.93 (1H, m, $(C_2H_5)_2CH$), 2.38 (2H, t, *J*=7.4 Hz, CH_2CO_2), 2.12–2.29 (2H, m, CHCH_2CH), 1.84–1.96 (2H, m, CH_2CH_2N), 1.45–1.74 (6H, m, $CH_2CH_2CO_2$, $(CH_2CH_2)_2CH$), 0.93–1.27 (8H, m, 2$CH_2CH_2CH_3$), 0.69 (6H, t, *J*=7.0 Hz, 2CH_3) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 172.1, 171.8, 166.2, 153.7, 144.1, 136.3, 135.5, 128.4, 128.2, 127.9, 127.7, 127.5, 127.4, 126.9, 72.1, 66.5, 66.2, 59.6, 57.2, 52.2, 45.1, 35.8, 34.7, 32.6, 29.8, 28.9, 22.0, 20.7, 13.7 ppm. Anal. Calcd for $C_{39}H_{51}F_6N_2O_6P$: C, 59.38; H, 6.52; N, 3.55; F, 14.45. Found: C, 59.62; H, 6.41; N, 3.60; F, 14.38.

4.2.7. (4R)-4-((5-(4-(1-Butylpentyl)pyridinium-1-yl)-pentanoyl)oxy)-L-proline hexafluorophosphate ***7***

White solid, mp 97–98 °C. $[\alpha]_D^{27}$ −12.7 (*c* 1, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.88 (2H, d, *J*=6.1 Hz, CHC*H*NC*H*CH), 7.99 (2H, d, *J*=6.1 Hz, C*H*CHNCHC*H*), 5.19–5.24 (1H, m, C*H*O), 4.5 (2H, t, *J*=7.4 Hz, NCH_2CH_2), 3.81–3.89 (1H, m, C*H*CO_2), 3.12–3.53 (2H, m, CHCH_2N), 2.81–2.92 (1H, m, $(C_2H_5)_2CH$), 2.37 (2H, t, *J*=7.4 Hz, CH_2CO_2), 2.02–2.30 (2H, m, CHCH_2CH), 1.85–1.97 (2H, m, CH_2CH_2N), 1.45–1.76 (6H, m, C$H_2CH_2CO_2$, $(CH_2CH_2)_2CH$), 0.88–1.28 (8H, m, 2$CH_2CH_2CH_3$), 0.78 (6H, t, *J*=7.0 Hz, 2CH_3) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 172.0, 169.8, 166.1, 144.2, 126.9, 73.2, 59.3, 59.1, 49.8, 44.9, 35.0, 34.6, 32.7, 29.9, 28.8, 21.9, 20.6, 13.7 ppm; IR (KBr, cm^{-1}): 3416, 2936, 2872, 1736, 1640, 1520, 1460, 1384, 1168, 1064, 976, 840. Anal. Calcd for $C_{24}H_{39}F_6N_2O_4P$: C, 51.06; H, 6.96; N, 4.96; F, 20.19. Found: C, 51.21; H, 6.88; N, 4.99; F, 20.07.

4.2.8. Benzyl N-((benzyloxy)carbonyl)-O-(5-bromopentanoyl)-L-serinate ***15a***

Colorless oil. $[\alpha]_D^{27}$ −15.8 (*c* 1, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29–7.42 (10H, m, 2C_6H_5), 5.07 (1H, d, *J*=7.7 Hz, N*H*), 5.11–5.21 (4H, m, 2CH_2Ph), 4.65–4.72 (1H, m, C*H*NH), 4.31–4.55 (2H, m, CH_2CH), 3.38 (2H, t, *J*=6.5 Hz, CH_2Br), 2.18–2.25 (2H, m, CH_2CO_2), 1.77–1.89 (2H, m, CH_2CH_2Br), 1.64–1.75 (2H, m, C$H_2CH_2CO_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.4, 169.2, 155.7, 136.0, 135.0, 128.6, 128.5, 128.5, 128.4, 128.2, 128.1, 67.6, 67.2, 64.0, 53.4, 32.9, 32.7, 31.7, 23.1 ppm. Anal. Calcd for $C_{23}H_{26}BrNO_6$: C, 56.11; H, 5.32; N, 2.84; Br, 16.23. Found: C, 56.38; H, 5.30; N, 2.81; Br, 16.10.

4.2.9. Benzyl N-((benzyloxy)carbonyl)-O-(5-(4-(1-butylpentyl)-pyridinium-1-yl)pentanoyl)-L-serinate bromide ***16a***

Light yellow oil. $[\alpha]_D^{24}$ −9.9 (*c* 1, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.41 (2H, d, *J*=6.1 Hz, CHC*H*NC*H*CH), 7.69 (2H, d, *J*=6.1 Hz,

CHCHNCHCH), 7.25–7.40 (10H, m, 2C$_6H_5$), 5.87 (1H, d, J=7.6 Hz, NH), 5.08–5.22 (4H, m, 2CH$_2$Ph), 4.82–5.02 (2H, m, CH$_2$N), 4.61–4.70 (1H, m, CHNH), 4.36–4.50 (2H, m, CH$_2$CHNH), 2.70–2.81 (1H, m, CH$_2$CHCH$_2$), 2.30–2.39 (2H, m, CH$_2$CO$_2$), 1.99–2.11 (2H, m, CH$_2$CH$_2$N), 1.61–1.80 (4H, m, CH$_2$CHCH$_2$), 1.47–1.60 (2H, m, CH$_2$CH$_2$CO$_2$), 0.96–1.35 (8H, m, 2CH$_2$CH$_2$CH$_3$), 0.84 (6H, t, J=7.1 Hz, 2CH$_3$) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ: 172.2, 169.0, 166.7, 155.7, 144.3, 135.9, 134.7, 129.4, 129.2, 128.3, 127.9, 127.8, 127.6, 126.9, 67.2, 66.6, 63.5, 59.8, 53.2, 46.1, 35.0, 32.4, 30.6, 29.1, 22.2, 20.6, 13.5 ppm. Anal. Calcd for $C_{37}H_{49}BrN_2O_6$: C, 63.69; H, 7.08; N, 4.02; Br, 11.45. Found: C, 63.98; H, 7.02; N, 4.08; Br, 11.35.

4.2.10. Benzyl N-((benzyloxy)carbonyl)-O-(5-(4-(1-butylpentyl)-pyridinium-1-yl)pentanoyl)-L-serinate hexafluorophosphate **17a**

Colorless oil. $[\alpha]_D^{25}$ −8.9 (c 1, CH$_3$OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.92 (2H, d, J=6.1 Hz, CHCHNCHCH), 8.03 (2H, d, J=6.1 Hz, CHCHNCHCH), 7.95 (1H, d, J=8.1 Hz, NH), 7.25–7.41 (10H, m, 2C$_6H_5$), 5.03–5.18 (4H, m, 2CH$_2$Ph), 4.45–4.55 (3H, m, CH$_2$N, CHNH), 4.16–4.41 (2H, m, CH$_2$CHNH), 2.82–2.95 (1H, m, CH$_2$CHCH$_2$), 2.26–2.36 (2H, m, CH$_2$CO$_2$), 1.81–1.94 (2H, m, CH$_2$CH$_2$N), 1.56–1.78 (4H, m, CH$_2$CHCH$_2$), 1.41–1.55 (2H, m, CH$_2$CH$_2$CO$_2$), 0.91–1.30 (8H, m, 2CH$_2$CH$_2$CH$_3$), 0.80 (6H, t, J=7.2 Hz, 2CH$_3$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 172.2, 169.5, 166.2, 156.1, 144.1, 136.8, 135.7, 129.4, 128.9, 128.4, 128.1, 127.8, 127.3, 126.9, 66.4, 65.8, 62.9, 59.6, 53.1, 45.1, 34.7, 32.4, 29.9, 28.9, 22.0, 20.7, 13.7 ppm. Anal. Calcd for $C_{37}H_{49}F_6N_2O_6P$: C, 58.26; H, 6.48; N, 3.67; F, 14.94. Found: C, 58.41; H, 6.38; N, 3.72; F, 14.82.

4.2.11. O-(5-(4-(1-Butylpentyl)pyridinium-1-yl)pentanoyl)-L-serine hexafluorophosphate **8**

White solid, mp 114–115 °C. $[\alpha]_D^{25}$ +4.6 (c 1, CH$_3$OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.08 (2H, d, J=6.1 Hz, CHCHNCHCH), 8.04 (2H, d, J=6.1 Hz, CHCHNCHCH), 4.44–4.61 (2H, m, CH$_2$N), 4.21–4.37 (2H, m, OCH$_2$), 3.51–3.57 (1H, m, CHNH$_2$), 2.83–2.95 (1H, m, CH$_2$CHCH$_2$), 2.32–2.46 (2H, m, CH$_2$CO$_2$), 1.85–1.98 (2H, m, CH$_2$CH$_2$N), 1.48–1.78 (6H, m, CH$_2$CHCH$_2$, CH$_2$CH$_2$CO$_2$), 0.92–1.31 (8H, m, 2CH$_2$CH$_2$CH$_3$), 0.81 (6H, t, J=7.2 Hz, 2CH$_3$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 174.3, 172.4, 166.2, 144.3, 127.0, 63.7, 59.7, 53.1, 45.2, 34.8, 32.7, 30.1, 29.0, 22.1, 20.8, 13.8 ppm; IR (KBr, cm^{-1}): 3400, 2936, 1740, 1640, 1520, 1456, 1412, 1172, 1024, 836. Anal. Calcd for $C_{22}H_{37}F_6N_2O_4P$: C, 49.07; H, 6.93; N, 5.20; F, 21.17. Found: C, 49.28; H, 6.86; N, 5.24; F, 21.02.

4.2.12. Benzyl N-((benzyloxy)carbonyl)-O-(5-bromopentanoyl)-L-threoninate **15b**

Colorless oil. $[\alpha]_D^{27}$ −6.1 (c 1, CH$_3$OH); ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.31–7.42 (10H, m, 2C$_6H_5$), 5.41–5.50 (1H, m, CHCH$_3$), 5.46 (1H, d, J=8.7 Hz, NH), 5.14 (4H, s, 2CH$_2$Ph), 4.54 (1H, dd, J_1=9.7 Hz, J_2=2.3 Hz, CHNH), 3.38 (2H, t, J=6.5 Hz, CH$_2$Br), 2.09–2.19 (2H, m, CH$_2$CO$_2$), 1.75–1.86 (2H, m, CH$_2$CH$_2$Br), 1.60–1.71 (2H, m, CH$_2$CH$_2$CO$_2$), 1.29 (3H, d, J=6.5 Hz, CH$_3$) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ: 171.5, 169.8, 156.3, 136.0, 135.0, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 70.3, 67.8, 66.5, 57.7, 32.9, 32.7, 31.8, 23.2, 16.8 ppm. Anal. Calcd for $C_{24}H_{28}BrNO_6$: C, 56.92; H, 5.57; N, 2.77; Br, 15.78. Found: C, 57.16; H, 5.53; N, 2.73; Br, 15.66.

4.2.13. Benzyl N-((benzyloxy)carbonyl)-O-(5-(4-(1-butylpentyl)-pyridinium-1-yl)pentanoyl)-L-threoninate bromide **16b**

Colorless oil. $[\alpha]_D^{24}$ +0.9 (c 1, CH$_3$OH); ^{1}H NMR (300 MHz, CDCl$_3$) δ: 9.41 (2H, d, J=6.1 Hz, CHCHNCHCH), 7.69 (2H, d, J=6.1 Hz, CHCHNCHCH), 7.29–7.41 (10H, m, 2C$_6H_5$), 5.59 (1H, d, J=9.5 Hz, NH), 5.38–5.48 (1H, m, CHCH$_3$), 5.12 (4H, d, J=10.1 Hz, 2CH$_2$Ph), 4.86–5.04 (2H, m, CH$_2$N), 4.52 (1H, dd, J=9.1 Hz, J=2.3 Hz, CHNH), 2.71–2.82 (1H, m, CH$_2$CHCH$_2$), 2.22–2.32 (2H, m, CH$_2$CO$_2$), 1.94–2.08 (2H, m, CH$_2$CH$_2$N), 1.62–1.82 (4H, m, CH$_2$CHCH$_2$), 1.48–1.62 (2H, m, CH$_2$CH$_2$CO$_2$), 1.29 (3H, d, J=6.5 Hz, CH$_3$CH), 0.96–1.35 (8H, m, 2CH$_2$CH$_2$CH$_3$), 0.84 (6H, t, J=7.2 Hz, 2CH$_2$CH$_3$) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ: 171.4, 169.6, 166.9, 156.3, 144.4, 135.9, 134.8, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.0, 70.1, 67.3, 67.0, 59.9, 57.4, 46.2, 35.1, 32.7, 30.6, 29.2, 22.3, 20.8, 16.7, 13.6 ppm. Anal. Calcd for $C_{38}H_{51}BrN_2O_6$: C, 64.13; H, 7.22; N, 3.94; Br, 11.23. Found: C, 64.43; H, 7.14; N, 4.01; Br, 11.10.

4.2.14. Benzyl N-((benzyloxy)carbonyl)-O-(5-(4-(1-butylpentyl)-pyridinium-1-yl)pentanoyl)-L-threoninate hexafluorophosphate **17b**

Colorless oil. $[\alpha]_D^{24}$ +0.3 (c 1, CH$_3$OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.92 (2H, d, J=6.1 Hz, CHCHNCHCH), 8.03 (2H, d, J=6.1 Hz, CHCHNCHCH), 7.88 (1H, d, J=8.6 Hz, NH), 7.25–7.40 (10H, m, 2C$_6H_5$), 5.16–5.27 (1H, m, CHCH$_3$), 5.09 (4H, s, 2CH$_2$Ph), 4.40–4.52 (3H, m, CH$_2$N, CHNH), 2.81–2.93 (1H, m, CH$_2$CHCH$_2$), 2.13–2.28 (2H, m, CH$_2$CO$_2$), 1.77–1.89 (2H, m, CH$_2$CH$_2$N), 1.54–1.77 (4H, m, CH$_2$CHCH$_2$), 1.38–1.50 (2H, m, CH$_2$CH$_2$CO$_2$), 1.27 (3H, d, J=6.5 Hz, CH$_3$CH), 0.90–1.30 (8H, m, 2CH$_2$CH$_2$CH$_3$), 0.79 (6H, t, J=7.2 Hz, 2CH$_2$CH$_3$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 171.7, 169.7, 166.4, 156.8, 144.2, 136.9, 135.7, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.0, 69.5, 66.5, 66.0, 59.7, 57.6, 45.2, 34.8, 32.7, 29.9, 29.0, 22.1, 20.8, 16.6, 13.8 ppm. Anal. Calcd for $C_{38}H_{51}F_6N_2O_6P$: C, 58.76; H, 6.62; N, 3.61; F, 14.67. Found: C, 58.97; H, 6.50; N, 3.67; F, 14.53.

4.2.15. O-(5-(4-(1-Butylpentyl)pyridinium-1-yl)pentanoyl)-L-threonine hexafluorophosphate **9**

White solid, mp 116–117 °C. $[\alpha]_D^{26}$ +6.5 (c 1, CH$_3$OH); ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.07 (2H, d, J=6.1 Hz, CHCHNCHCH), 8.04 (2H, d, J=6.1 Hz, CHCHNCHCH), 5.21–5.35 (1H, m, CHCH$_3$), 4.51–4.59 (2H, m, CH$_2$N), 3.40–3.48 (1H, m, CHNH$_2$), 2.82–2.96 (1H, m, CH$_2$CHCH$_2$), 2.25–2.32 (2H, m, CH$_2$CO$_2$), 1.85–2.01 (2H, m, CH$_2$CH$_2$N), 1.47–1.78 (6H, m, CH$_2$CHCH$_2$, CH$_2$CH$_2$CO$_2$), 1.28 (3H, d, J=6.5 Hz, CH$_3$CH), 0.91–1.32 (8H, m, 2CH$_2$CH$_2$CH$_3$), 0.81 (6H, t, J=7.2 Hz, 2CH$_2$CH$_3$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 174.5, 171.9, 166.4, 144.3, 127.1, 70.1, 59.7, 57.6, 45.2, 34.8, 33.0, 30.1, 29.1, 22.1, 21.0, 16.9, 13.9 ppm; IR (KBr, cm^{-1}): 3400, 2936, 2872, 1740, 1640, 1520, 1456, 1396, 1340, 1176, 1032, 840. Anal. Calcd for $C_{23}H_{39}F_6N_2O_4P$: C, 50.00; H, 7.11; N, 5.07; F, 20.63. Found: C, 50.16; H, 7.02; N, 5.13; F, 20.51.

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References and notes

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