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The Synthesis of D-Trihydroxyllysine-Based Oligopeptides as a Hydrophilic Scaffold and its Application to the Synthesis of Bifunctional Chelating Agents for Use as Bone Tracers

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Abstract: An effective hydrophilic scaffold composed of D-trihydroxyllysine-based oligopeptides and its application in the synthesis of the various ^{111}In–DTPA conjugates with mono- to penta-bisphosphonate units for use as bone tracers are described. The D-trihydroxyllysine derivative with three orthogonal protecting groups was conjugated with functional devices at the γ position and allowed oligomerization based on peptide chemistry. The radiopharmaceutical complexes of $^{111}In^{III}$ with selected chelators, **4** and **8**, were suitable for bone imaging. These results show that D-trihydroxyllysine **2** was an effective building block for the synthesis of multivalent ligands applicable to medical use.

Keywords: bisphosphonate · chemical biology · indium · molecular imaging · oligopeptides

Introduction

Molecular imaging is a powerful method not only for analysis of biological phenomena but also for diagnosis.[1] Bifunctional chelating agents composed of metal-chelating, and molecular recognition devices serve as effective platforms for development of new and effective contrast agents. Complexing various paramagnetic metals with the metal chelater allows one to trace the bifunctional chelating agents in vivo.[2] Bakker et al. have reported on the synthesis of an ^{111}In–DTPA-conjugated somatostatin derivative (DTPA = diethylenetriamine-*N*,*N*,*N*′,*N*″,*N*″-pentaacetic acid) as a cancer-contrast agent for single photon emission computed tomography.[3] Recently Fukase and co-workers developed an effective method for the conjugation of proteins with chelating agents through 6π-azaelectrocyclization.[4] The resulting protein-conjugated chelaters were used for positron emission tomography imaging by chelating with Ga^{3+} ions.

Chitosan and its hydrolysates composed of β(1,4)-linked glucosamines have served as effective hydrophilic scaffolds for the synthesis of biocompatible materials adaptable to medicinal use.[5] The amino groups at the C2 position are amenable to conjugation with various functional devices. Multiple hydroxy groups also contribute to their biocompatibility.[6] In addition, the glycosidic linkages are resistant to metabolism in the human body. We have recently reported the synthesis of MRI contrast agents composed of multiple DTPA–Gd complexes on chitosan hydrolysates.[7] The number of DTPA monosaccharide units was critical for enhancing the relative signal intensity of water protons per Gd atom. However, tuning the number of ligands and the structure of the oligosaccharide backbone requires laborious synthetic processes involving protection/deprotection and stereoselective glycosylation. Therefore, development of a chitosan-like biocompatible multivalent scaffold whose number of ligands is tunable by simple protocols would strongly assist the synthesis of various multifunctional chelating agents. Herein, we describe the development of D-trihydroxyllysine-based oligopeptides as effective platforms for the synthesis of various bifunctional chelating agents and their application to the synthesis of a series of bifunctional chelating agents with variable numbers of bisphosphonate units for use as bone tracers.

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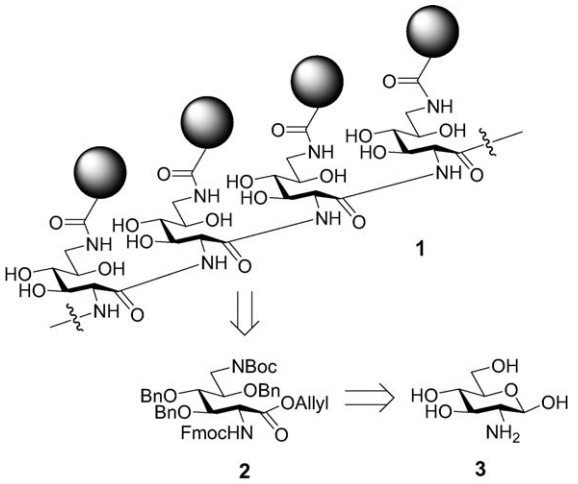
Results and Discussion

The D-trihydroxyllysine-based oligopeptide **1** with multiple ligands at the γ position, in order to reduce non-specific interactions, was designed as a multivalent platform for molec-

ular imaging (Scheme 1). The multiple hydroxy groups make it highly hydrophilic, which could thereby reduce the undesired interactions of peptide **1** with abundant hydro-



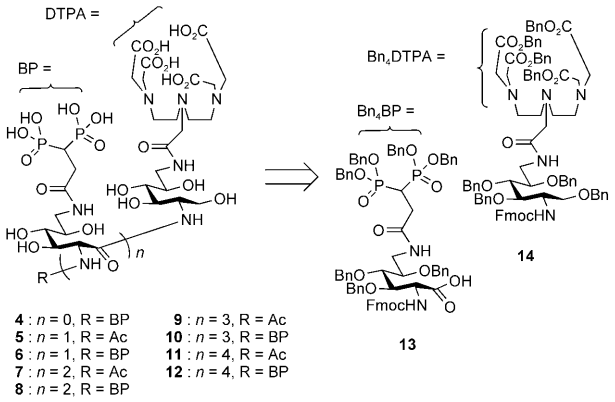
Scheme 1. D-Trihydroxyllysine-based oligopeptide **1** as a multivalent platform for contrast agents. Boc = *tert*-butyloxycarbonyl, Fmoc = 9-fluorenylmethoxycarbonyl.

philic biomolecules.[6] In addition, the synthetic D-amino acid based oligopeptide may be resistant to in vivo metabolism.[3,8] The D-trihydroxyllysine unit **2**, with three orthogonal protecting groups on two amino groups and a carboxylic acid group, was used as a building block to allow incorporation of various functional devices at the γ position and oligomerization by means of the established peptide chemistry.[9] The D-trihydroxyllysine unit **2** can be prepared from D-glucosamine (**3**).

The feasibility of the scaffold was demonstrated by the synthesis of a series of DTPA derivatives **4–12** by varying the number of bisphosphonate (BP) units as bifunctional chelating agents for bone scintigraphy[10] (Scheme 2). DTPA is widely used as an iron chelate in hydroponic solutions. The DTPA unit can complex with various metals that are detectable by clinical imaging modalities, such as Gd, Tc,

Abstract in Japanese:

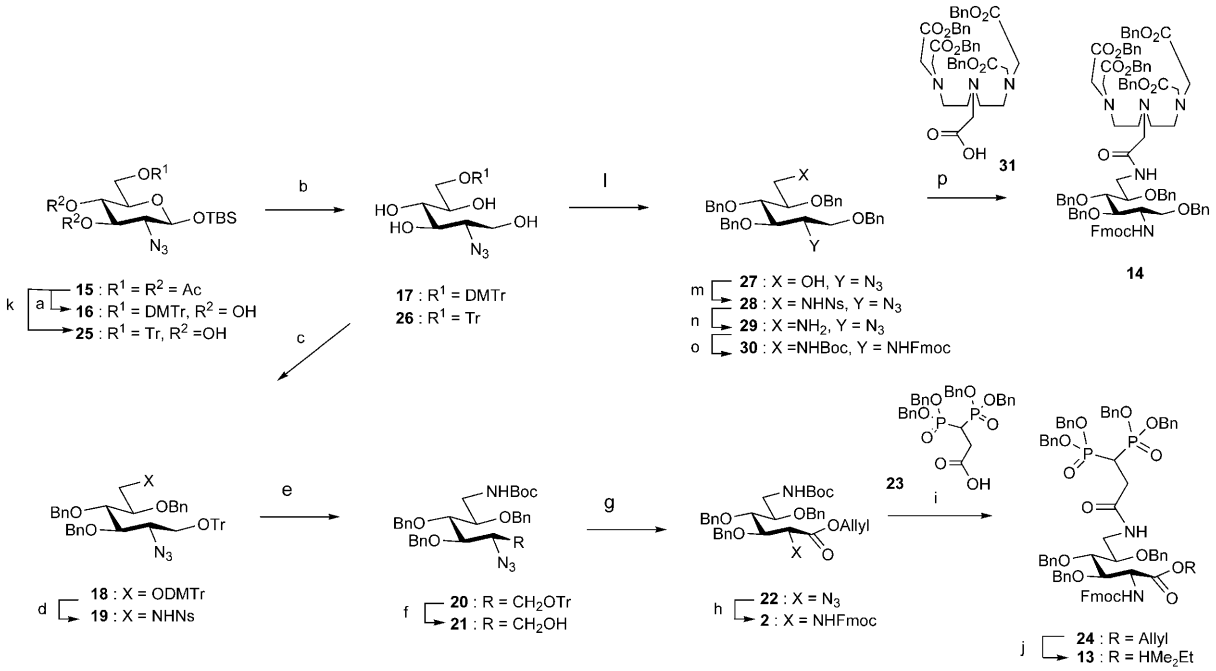
本研究は、トリヒドロキシルD-リジンからなるオリゴペプチド構造を有する水溶性テンプレートを利用した骨イメージング用ケミカルプローブの合成とその評価について述べる。側鎖部に様々な官能基を導入可能なトリヒドロキシルリジン誘導体を合成した。本アミノ酸を用いて、DTPA基と複数のビスホスホナート基を有する骨シンチグラフィー用分子プローブを合成した。合成したプローブを ^{111}In(III)を用いて標識しラット骨のイメージングを行った結果、最も小さなプローブによって良好な骨のイメージングが可能であることを見いだした。



Scheme 2. DTPA derivates **4–12** with multi-bisphosphonate units.

and In, and reduces the toxicity of these metals.[11] The BP unit has a very high affinity for bone tissue, and is known to be rapidly absorbed onto the bone surface. The metal chelaters conjugated with the BP unit have been reported to act as bone tracers.[12] The series of DTPA derivatives **4–12** with multiple BP units would be useful for elucidating the effect of the number of BP units to the affinity of contrast agents to bone.[13] Bisphosphonate derivatives were prepared from the D-amino acid of **13** with a bisphosphonate unit and the DTPA unit of **14**.

Preparation of the key intermediate **2** and the building blocks **13** and **14** is outlined in Scheme 3. The β-silyl 2-azidoglycoside **15** prepared from glucosamine (**3**) by the established procedure[14] was used as the starting material. Hydrolysis of the acetyl group of **15**, followed by dimethoxytritylation at the primary hydroxy group provided dimethoxytrityl ether **16**. Hydrolysis of the silyl ether at the anomeric position of **16**, followed by reduction at the anomeric position provided tetraol **17**. The regioselective tritylation at the resulting primary hydroxy group of **17**, followed by benzylation of the remaining hydroxy groups provided the tribenzyl ether **18** in 47% yield from **15**. Chemoselective deprotection of the dimethoxytrityl group in the presence of the trityl group, mesylation of the resulting primary alcohol, then N-alkylation of the mesylate with nosylamide[15] provided the N-alkyl nosylamide **19** in 63% from **18**. Removal of the nosyl protecting group, followed by protection of the resulting amine with a *tert*-butyloxycarbonyl (Boc) group provided the *N*-Boc derivative **20** in 86% yield. Removal of the trityl group under the acidic conditions provided the primary alcohol **21**. Oxidation of the primary alcohol with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO),[16] followed by O-allylation yielded **22** in 73% yield. Reduction of azide **22** to amine, followed by protection of the amine with the 9-fluorenylmethoxycarbonyl (Fmoc) group provided the *N*-Fmoc derivative **2**. The nosyl derivative obtained from **22** was not a suitable substrate for the oxidation. Selective removal of the *N*-Boc group in **2**, followed by acylation of the resulting amine with the carboxylic acid **23**,[13c] bearing a bisphosphonate unit, provided the γ acylated lysine **24** in 81% yield. Deprotection of the allyl group in **24** by using a

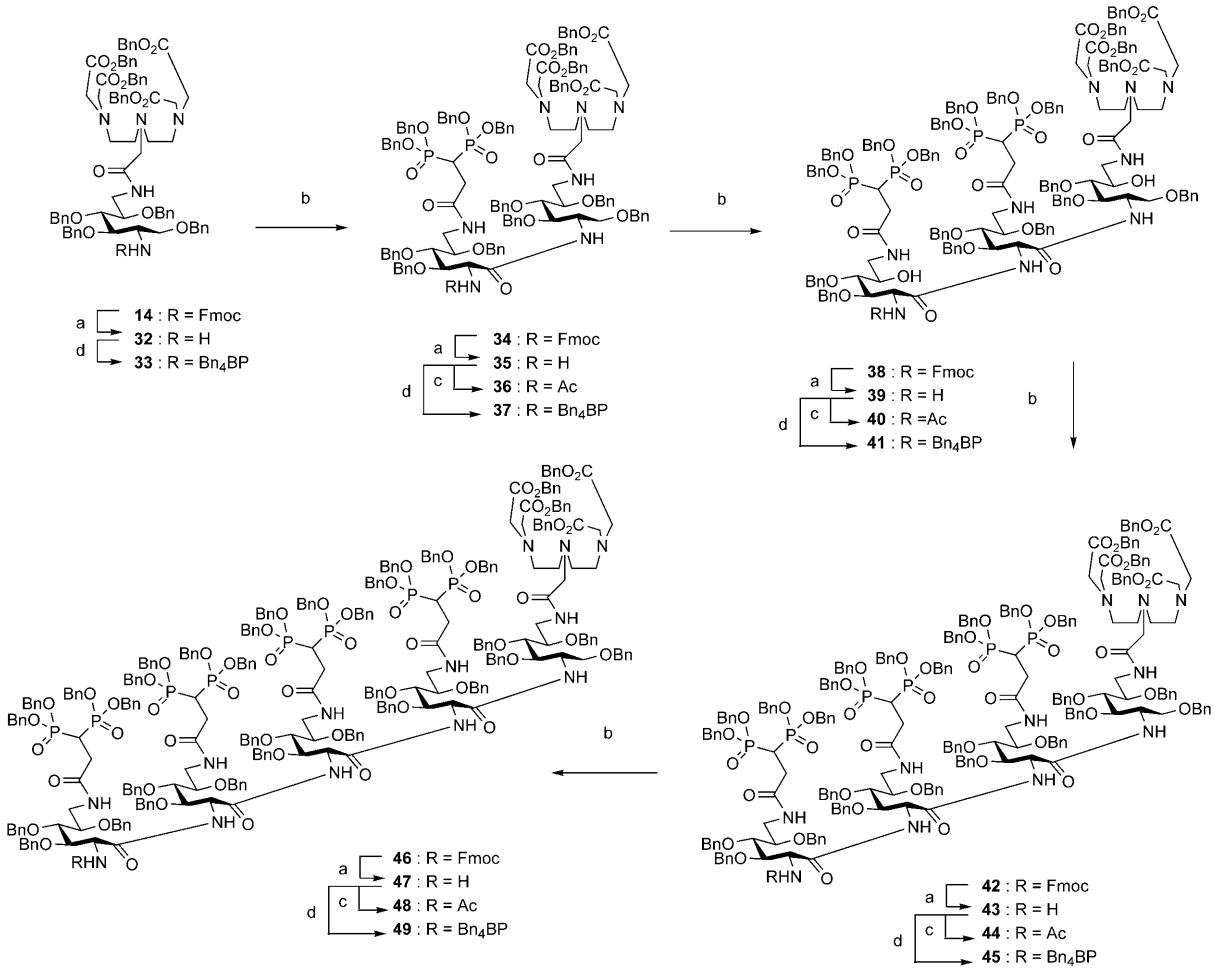


Scheme 3. Reagents and conditions: a) i) NaOMe, MeOH; ii) DMTrCl, Py.; b) i) HF/Py., Py.; ii) $NaBH_4$, EtOH, 87% for **26**; c) i) TrCl, DBU, CH_2Cl_2; ii) BnBr, NaH, TBAI, DMF, 47% from **15**; d) i) AcOH/THF/H_2O; ii) MsCl, NEt_3, CH_2Cl_2; iii) $NsNH_2$, Cs_2CO_3, DMF, 63%; e) i) PhSH, Cs_2CO_3, CH_3CN; ii) Boc_2O, $NaHCO_3$ aq. dioxane, 86%; f) CSA, MeOH, 90%; g) i) NaOCl, TEMPO, KBr, TBAB, $NaHCO_3$ aq., CH_2Cl_2; ii) AllylBr, $NaHCO_3$, DMF, 73%; h) PPh_3, H_2O, THF, 60 °C then $NaHCO_3$ aq., FmocCl, RT, 91%; i) 4 M HCl/dioxane; ii) **31**, HATU, DIEA, CH_2Cl_2, 81%; j) i) $Pd(PPh_3)_4$, *N*-methylaniline, THF, 88%; k) i) NaOMe, MeOH; ii) TrCl, Py.; l) i) BnBr, NaH, TBAI, DMF; ii) CSA, MeOH; m) i) MsCl, NEt_3, CH_2Cl_2; ii) $NsNH_2$, Cs_2CO_3, DMF, 79%; n) PhSH, Cs_2CO_3, CH_3CN, 88%; o) i) Boc_2O, $NaHCO_3$, dioxane, ii) PPh_3, H_2O, THF, 60 °C then $NaHCO_3$ aq., FmocCl, RT, 93%; p) i) 4 M HCl/dioxane; ii) **23**, HATU, DIEA, CH_2Cl_2, 90%. DMF = *N*,*N*-dimethylformamide, DMTrCl = *para*-dimethoxytrityl chloride, TBAB = tetrabutylammonium bromide, TBAI = tetrabutylammonium iodide.

palladium catalyst afforded the BP-conjugated D-trihydroxyllysine unit **13** in 88% yield. The synthesis of the DTPA-conjugated building block **14** was conducted. Hydrolysis of the acetyl group of **15**, followed by tritylation at the primary hydroxy group provided trityl ether **25**. Hydrolysis of the silyl ether at the anomeric position of **25**, followed by reduction at the anomeric position provided tetraol **26** in 87% yield from **15**. Benzylation of all the hydroxy groups, followed by cleavage of the tritylether provided the primary alcohol **27** in 98% yield. Mesylation of the primary alcohol **27**, followed by N-alkylation with a nosylamide provided the *N*-alkyl nosylamide **28** in 79%. Removal of the nosyl protecting group with thiophenol provided the primary amine **29** in 88% yield. Protection of the resulting amine with a Boc group, followed by conversion of the azido group to an *N*-Fmoc group provided the *N*-Fmoc derivative **30** in 93% yield. Selective removal of the *N*-Boc group in **30**, followed by acylation of the resulting amine with the carboxylic acid **31**, bearing a DTPA unit, provided the DTPA derivative **14** in 98% yield.

The synthesis of the chelators **4**–**12** with one to five bisphosphonate units is shown in Scheme 4 and Table 1. Treatment of the *N*-Fmoc derivative **14** with diethylamine provided the amine **32**. Subsequent acylation with the lysine derivative **13** gave the amidated product **34** in 90% yield. The same protocol was used for acylation of **34**, **38**, and **42** to provide the di-, tri-, and tetra-peptides **38**, **42**, and **46** in 84, 81, and 62% yields, respectively. The coupling reactions proceeded smoothly using 1.1 equivalents of the trihydroxyllysine **13** except for the coupling with **42**. The acetamide derivatives **36**, **40**, **44**, and **48** were prepared from **34**, **38**, **42**, and **46** by removal of the Fmoc group and subsequent acetylation of the resulting amine. The bisphosphonate derivatives **33**, **37**, **41**, **45**, and **49** were prepared by the same protocols by using acid **23** instead of the amino acid **13**. Deprotection of the BP derivatives **33**, **36**, **37**, **40**, **41**, **44**, **45**, **48**, and **49** was achieved by hydrogenolysis with a Pd catalyst. Purification of the crude materials by reverse-phase column chromatography and gel filtration gave the DTPA-conjugated BP derivatives **4**–**12** in moderate yields (Table 1). The use of ethanol as an amphiphilic co-solvent was critical for the deprotection of the tetra- and pentamers **44**, **45**, **48**, and **49** owing to their enhanced hydrophobicity.

Ligand-competition experiments involving inhibition of the ligands **4**–**12** on [^{14}C]-citric acid bound to synthetic hydroxyapatite were examined for elucidation of the binding affinity of the multiple BP ligands **4**–**12** to bone surfaces (Table 2). Citric acid is known to compete with bisphosphonates for binding hydroxyapatite, which are materials located on the bone surface.[17] The inhibitory effects of the ligands were determined by measuring free [^{14}C]-citric acid by liquid scintillation spectroscopy. Methylenediphospho-

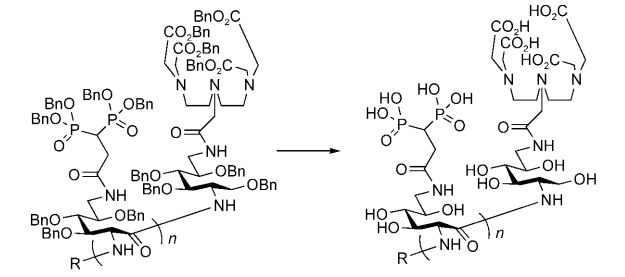


Scheme 4. Reagents and conditions: (a) diethylamine, CH_3CN (b) **13**, HATU, DIEA, CH_2Cl_2, 84% for **34** from **14**, 84% for **38** from **34**, 81% for **42** from **38**, 62% for **46** from **42**; (c) Ac_2O, DIEA, CH_2Cl_2, 97% for **36** from **34**, 96% for **40** from **38**, 80% for **44** from **42**, 72% for **48** from **46**; (d) **23**, HATU, DIEA, CH_2Cl_2, 90% for **33** from **14**, 91% for **37** from **34**, 89% for **41** from **38**, 76% for **45** from **42**, 71% for **49** from **46**.

nate (MDP) was used as a positive control. The pentamer **12** with five bisphosphonate units, and the monomer **4** with one bisphosphonate unit showed the strongest inhibitory effect among derivatives **4**–**12** and were comparable to MDP. However, surprisingly the di- to tetramers **5**–**10** with two to four bisphosphonate units showed weaker inhibitory activities than that of monomer **4**. The displacement of the acetyl group to the bisphosphonate unit improved the inhibitory effects. However, a reduced inhibitory activity of **5** was observed in comparison with that of **4**. We speculated that an enhanced number of the BP-conjugated amino acid units resulted in both positive and negative effects on the binding to hydroxyapatite. The positive effect would be derived from multivalent interactions of the BP units and hydroxyapatite. The negative effect would be caused by the enhanced hydrophilicity. In total, the positive multivalent effects would be observed in the case of the trimer **8**, which contains three BP units in comparison with the trimer **7**, which contains two BP units.

We next examined the ability of $^{111}In^{III}$ complexes with selected chelators, monomer **4**, trimer **8**, and pentamer **12**, that form radiopharmaceuticals for use in bone scintigraphy of normal rats. We focused on the effects of molecular weight or size and binding affinity of the bifunctional chelators to hydroxyapatite on the imaging ability of bone. The chelators **4** and **12** showed the strongest binding affinity for hydroxyapatite among **4**–**12** and are the smallest and biggest chelaters, respectively. The binding affinity of the tri--bisphosphonate derivative **8**, having a median molecular weight, to hydroxyapatite is one of the weakest binders among them. The radioactive complexes were prepared by using a large excess of the chelators **4**, **8**, and **12**. The radiochemical yield for complex formation between $^{111}In^{III}$ and the selected chelators **4**, **8**, and **12** was estimated by using the cellulose acetate membrane to be quantitative (see the Supporting Information). Figure 1 shows planar bone scintigraphy of rats after intravenous administration of $^{111}In^{III}$ complexes with the chelaters **4**, **8**, and **12**. To quantify accumulation of the $^{111}In^{III}$ complexes in the femur, region of interest (ROI) analysis was performed. None of the $^{111}In^{III}$ complexes showed any significant toxicity or degradability in vivo during the examination. The chelators **4** and **8** accu-

Table 1. Deprotection of the protected BP derivatives **33**, **36**, **37**, **40**, **41**, **44**, **45**, **48**, and **49** to **4**–**12**.



33 : n = 0, R = Bn_4BP **44** : n = 3, R = Ac
36 : n = 1, R = Ac **45** : n = 3, R = Bn_4BP
37 : n = 1, R = Bn_4BP **48** : n = 4, R = Ac
40 : n = 2, R = Ac **49** : n = 4, R = Bn_4BP
41 : n = 2, R = Bn_4BP

4 : n = 0, R = BP **9** : n = 3, R = Ac
5 : n = 1, R = Ac **10** : n = 3, R = BP
6 : n = 1, R = BP **11** : n = 4, R = Ac
7 : n = 2, R = Ac **12** : n = 4, R = BP
8 : n = 2, R = BP

Entry	Substrate	Product	Conditions[a]	Yield [%]
1	**33**	**4**	A	68
2	**36**	**5**	A	93
3	**37**	**6**	A	35
3	**40**	**7**	A	91
4	**41**	**8**	A	35
5	**44**	**9**	B	42
6	**45**	**10**	B	62
7	**48**	**11**	B	58
8	**49**	**12**	B	55

[a] The condition A: H_2 (1 atm), $Pd(OH)_2$, EtOAc, MeOH, H_2O. The condition B: H_2 (1 atm), $Pd(OH)_2$, EtOAc, EtOH, MeOH, H_2O.

Table 2. Competitive binding of the 1 μM ligands to hydroxyapatite against 50 nM [^{14}C]-citric acids. Data are the mean percentage of the vehicle ±SD of three separate experiments.

Entry	Substrate	[^{14}C]-citric acid binding [% of vehicle]
1	Vehicle	100.0±5.14
2	MDP	61.8±2.91
3	**4**	65.2±5.03
3	**5**	87.1±6.54
4	**6**	81.3±4.96
5	**7**	95.4±5.08
6	**8**	87.4±5.86
7	**9**	79.1±0.80
8	**10**	91.2±3.42
9	**11**	63.7±5.29
10	**12**	51.6±3.65

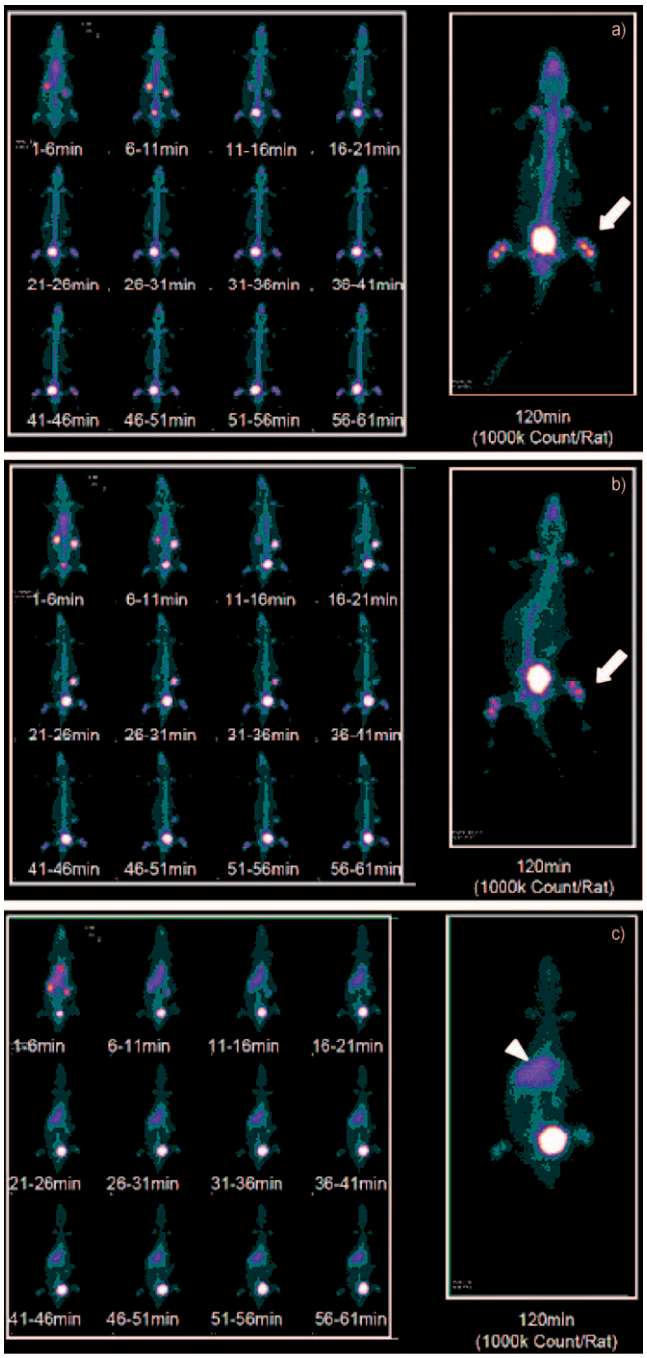


Figure 1. The bone scintigraphy two hours after intravenous administration of $^{111}In^{III}$ complexed with selected chelators, **4**, **8**, and **12**. a) **4**, b) **8**, c) **12**. Arrows indicate accumulation sites $^{111}In^{III}$ complexes in rat femurs. Arrowhead shows the accumulation of $^{111}In^{III}$ with the chelator **12** in liver.

mulated in the femur within 20 min. The unaccumulating chelators were excreted by the kidneys. The trimer **8**, which has three bisphosphonate units, also acted as an effective bone tracer. However, trimer **8** was easier to be excreted by the kidneys than **4**. The high hydrophilicity derived from the multiple hydroxy group backbone would promote the excretion. On the other hand, a percentage of pentamer **12** also accumulated in the liver after 2 h, and all of the chelators **4**, **8**, and **12** initially provided a strong signal around liver. In addition, most of **12** was excreted by the kidneys except for a small percentage which remained in the liver. These results suggest that the pentamer **12**, which demonstrated high binding affinity for hydroxyapatite in vitro, was easily trapped in the liver and was unable to diffuse through the blood vessel walls owing to its large molecular weight.

The biodistribution of the $^{111}In^{III}$ complexed with the selected chelators, **4**, **8**, and **12** after 2 hours is shown in Figure 2 as a percentage of injected dose per gram. The chelators **4** showed a significantly higher accumulation in the femur than chelators **8** and **12**. The chelators **12** accumulat-

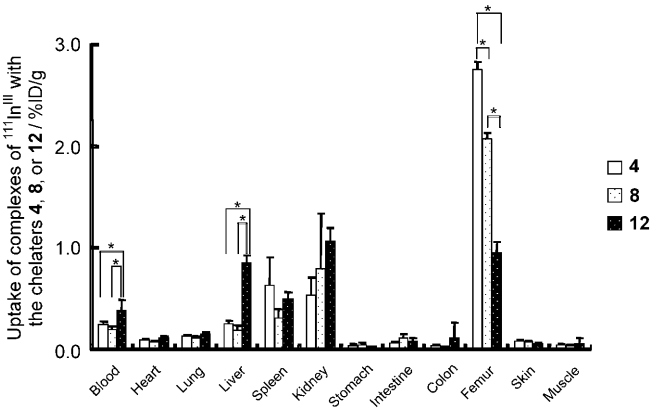


Figure 2. Biodistribution of the complexes of $^{111}In^{III}$ with the chelaters **4**, **8**, or **12** in rats 2 h after intravenous administration. Data are expressed as mean ±SD for four rats. These results were statistically analyzed by using a one-way ANOVA followed by Sheffe's post-hoc test. Differences were considered statically significant when p values were less than 0.05.

ed in liver and blood in significantly larger amounts than chelators **4** and **8**, which is caused by the larger molecular weight of chelator **12**. These results were comparable with those from the scintigraphy images. In total, the smallest chelator **4** exhibited the best performance as a radiopharmaceutical suitable for bone scintigraphy.

Conclusions

In conclusion, this paper describes an effective biocompatible multivalent scaffold, which is composed of the D-trihydroxyllysine-based oligopeptides, and its application in the synthesis of various ^{111}In–DTPA conjugates with mono- to penta-bisphosphonate units for use as bone tracers. The D-trihydroxyllysine derivative with three orthogonal protecting groups was conjugated with functional devices at the γ position. The D-lysine derivative with a protected bisphosphonate unit allowed oligomerization in good yields. None of the $^{111}In^{III}$ complexes showed any significant toxicity or degradation in vivo during the examination. The complexes of $^{111}In^{III}$ with the chelators **4** and **8** were suitable for bone imaging. These results show that D-trihydroxyllysine **2** was an effective building block for the synthesis of multivalent ligands applicable to medical use.

Experimental Section

General Techniques

NMR spectra were recorded on a JEOL Model EX-270 (270 MHz for ^1H, 67.8 MHz for ^{13}C) or a JEOL Model ECP-400 (400 MHz for ^1H, 100 MHz for ^{13}C, 160 MHz for ^{31}P) instrument in the indicated solvent. Chemical shifts are reported in parts per million (ppm) relative to the signal (0 ppm) for internal tetramethylsilane for solutions in $CDCl_3$. ^1H NMR spectrum data are reported as follows: $CDCl_3$ (7.26 ppm) or D_2O (HOD (4.8654 ppm at 285 K, 4.7015 ppm at 303 K, 4.6201 ppm at 311 K, and 4.3560 ppm at 339 K as the internal standard by using 3-(trimethylsilyl)-1-propanesulfonicacid sodium salt as external standard)). ^{13}C NMR spectral data are reported as follows: $CDCl_3$ (77.0 ppm) as the internal standard for $CDCl_3$ and $[D_6]$acetone (30.3 ppm) or $[D_3]$acetonitrile (1.3 ppm) as the internal standard for D_2O. Multiplicities are reported by using the following abbreviations: s singlet, d doublet, t triplet, q quartet, m multiplet, br broad; J coupling constants in Hertz. IR spectra were recorded on a Perkin–Elmer Spectrum One FTIR spectrophotometer. Only the strongest and/or structurally important peaks are reported as the IR data given in cm^{-1}. Optical rotations were measured on a JASCO model P-1020 polarimeter. All reactions were monitored by thin-layer chromatography carried out on 0.2 mm E. Merck silica gel plates (60F-254) with UV light, visualized by 10% ethanolic phosphomolybdic acid, p-anisaldehyde solution or 0.5% ninhydrin n-butanol solution. Daiso silica gel, Chlomatorex NH-silica gel, or Merck silica gel was used for column chromatography. Gel permeation chromatography (GPC) for qualitative analysis were performed on Japan Analytical Industry Model LC908 (recycling preparative HPLC), on a Japan Analytical Industry Model RI-5 refractive index detector, and on a Japan Analytical Industry Model 310 UV detector with a polystylene gel column (JAIGEL-1 H, 20 mm × 600 mm) using chloroform as the solvent (3.5 mL min^{-1}). High performance liquid chromatography (HPLC) was performed on a Waters 2695 apparatus by using a Senshu Pak Silica 3301-N Column with a Waters 2996 photodiode array detector at 254 nm (normal phase). HPLC was performed on a Senshu Scientific apparatus by using a Develosil ODS-UG-5 column or an Inertsil ODS-3 column (4.6 mm × 25 cm for analysis) with a Senshu Scientific photodiode array detector at 214 or 254 nm (reverse phase). HPLC was also performed on a Gilson 506C system by using a Develosil ODS-UG-5 column or an Inertsil ODS-3 column (4.6 mm × 25 cm for analysis, 2 cm × 25 cm for collection) with a Gilson UV/Vis-151 photodiode array detector at 214 or 254 nm or Shimadzu ELSD-LT evaporative light-scattering detactor (reverse phase). ESI-TOF mass spectra were measured with P. E. Biosystems TK-3500 Biospectrometry Workstation. ESI mass spectra were measured with Bruker esquire 3000 plus 07. Dry THF, dry hexane, dry diethylether, and dry DME were distilled from sodium and were contained with a catalytic amount of benzophenone. Dry benzene and dry toluene were distilled from a lump of sodium. Dry dichloromethane was distilled from P_2O_5. Dry DMF, dry triethylamine, and dry pyridine were distilled from CaH_2. Dry methanol and dry ethanol were distilled from magnesium contained with a catalytic amount of iodine.

Synthesis

18: Sodium (130 mg, 5.60 mmol,) was added at room temperature (RT) to a stirred solution of **15** (50.0 g, 112 mmol) in MeOH (300 mL). After being stirred at RT for 5.5 h, the reaction mixture was concentrated in vacuo and mixed with toluene. The residue was used for the next reaction without further purification. To a stirred solution of the residue in pyridine (300 mL) was added dimethoxytritylchloride (3.79 g, 112 mmol) at RT. After being stirred at RT for 4 h, the reaction mixture was poured into ice-cooled water. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with ice-cooled 1 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was used for the next reaction without further purification. Hydrogen fluoride-pyridine (30.0 mL) was added to a stirred solution of the residue in pyridine (150 mL) at 0 °C. After being stirred at RT for 6 h, the reaction mixture was poured into ice-cooled saturated aqueous $NaHCO_3$. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was used for the next reaction without further purification. A solution of the residue in dry EtOH (125 mL) was added at 0 °C to a stirred solution of $NaBH_4$ (5.07 g, 134 mmol) in dry EtOH (25.0 mL). After being stirred at RT for 4 h, the reaction mixture was poured into ice-cooled saturated aqueous NH_4Cl. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with aqueous NH_4Cl and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was used for the next reaction without further purification. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 25.1 mL, 168 mmol) and tritylchloride (31.2 g, 112 mmol) was

added to a stirred solution of the residue in CH_2Cl_2 (200 mL) at RT. After being stirred at 40 °C for 6 h, the reaction mixture was poured into ice-cooled water. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with ice-cooled 1 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was used for the next reaction without further purification.

A solution of the residue in dry *N*,*N*-dimethylformamide (150 mL) was added at 0 °C to a stirred solution of 55% sodium hydride (22.0 g, 504 mmol) which was washed twice with dry hexane and the reaction mixture was stirred at the same temperature for 30 min. Then benzyl bromide (40.0 mL, 336 mol) and a catalytic amount of nBu$_4$NI were added to the reaction mixture at 0 °C. After being stirred at RT for 2 h, the reaction mixture was poured into saturated aqueous NH_4Cl. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified with chromatography with 85:15 hexane/ethyl acetate to give **18** (53.0 g, 52.7 mmol, 6 steps 47%) as a pale-yellow oil. $[\alpha]_D^{27} = -6.2$ (c = 1.12, $CHCl_3$); IR (KBr) $\tilde{\nu}$ = 3087, 3061, 3032, 2932, 2836, 2097, 1607, 1584, 1509, 1449, 1251, 1176, 1031, 831, 751, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14–7.45 (m, 35H, Ar), 6.90–7.00 (m, 4H, Ar), 6.70–6.74 (m, 4H), 4.73 (d, 1H, J_{gem} = 12.1 Hz), 4.55 (d, 1H, J_{gem} = 11.6 Hz), 4.47 (d, 1H, J_{gem} = 12.1 Hz), 4.41 (d, 1H, J_{gem} = 11.1 Hz), 4.36 (d, 1H, J_{gem} = 11.6 Hz), 4.34 (d, 1H, J_{gem} = 11.1 Hz), 3.91 (dd, 1H, J = 5.8 Hz, 5.8 Hz), 3.67–3.79 (m, 9H), 3.52 (dd, J = 3.4 Hz, J_{gem} = 10.6 Hz), 3.33–3.39 (m, 1H, 6-H), 3,32 (dd, 1H, J = 5.3 Hz, J_{gem} = 10.6 Hz), 3.23 ppm (dd, 1H, J = 3.9 Hz, J_{gem} = 9.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.4, 144.9, 143.5, 138.3, 138.1, 136.1, 136.0, 130.1, 128.6, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.5, 127.34, 127.27, 127.0, 126.7, 113.1, 87.2, 86.2, 79.2, 79.0, 78.8, 74.6, 74.1, 72.0, 63.7, 63.2, 62.5, 55.1 ppm.

19: AcOH (16.0 mL) and H_2O (4.00 mL) were added at RT to a stirred solution of **18** (2.47 g, 2.42 mmol) in THF (8.0 mL). After being stirred at RT for 24 h, the reaction mixture was poured into ice-cooled 1 M NaOH. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M NaOH and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was used for the next reaction without further purification.

NEt_3 (2.02 mL, 14.5 mmol) and methanesulfonyl chloride (562 μL, 7.26 mmol) were added at 0 °C to a stirred solution of the residue in CH_2Cl_2 (15.0 mL). After being stirred at RT for 1 h, the reaction mixture was poured into ice-cooled water. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was used for the next reaction without further purification. Cs_2CO_3 (3.15 g, 9.68 mmol) and 2-nitrobenzenesulfonylamide (979 mg, 4.84 mmol) were added at RT to a stirred solution of the residue in *N*,*N*-dimethylformamide (15.0 mL). After being stirred at 80 °C for 20 h, the reaction mixture was poured into ice-cooled 1 M HCl. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. Silica gel column purification with 70:30 hexane/ethyl acetate gave **19** (1.26 g, 1.52 mmol, 3 steps 63%) as a yellow oil. $[\alpha]_D^{19} = -5.4$ (c = 1.11, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3345, 3089, 3064, 3032, 2879, 2098, 1539, 1361, 1070, 748, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, 1H, J = 7.7 Hz), 7.78 (d, 1H, J = 7.7 Hz), 7.63 (dd, 1H, J = 7.7, 7.7 Hz), 7.55 (dd, 1H, J = 7.7, 7.7 Hz), 7.11–7.41 (m, 30H, Ar), 5.69 (dd, 1H, J = 5.8, 5.8 Hz), 4.59 (d, 1H, J_{gem} = 11.1 Hz), 4.58 (d, 1H, J_{gem} = 11.1 Hz), 4.49 (d, 1H, J_{gem} = 11.1 Hz), 4.38 (d, 1H, J_{gem} = 11.6 Hz), 4.32 (d, 1H, J_{gem} = 11.1 Hz), 4.31 (d, 1H, J_{gem} = 11.6 Hz), 3.76 (dd, 1H, J = 5.3, 4.3 Hz), 3.68 (dd, 1H, J = 5.3, 4.3 Hz), 3.59 (m, 1H), 3.55 (m, 1H), 3.36 (m, 2H), 3.30 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.9, 143.4, 137.7, 137.6, 137.0, 133.4, 133.3, 132.6, 131.0, 128.54, 128.51, 128.30, 128.3, 127.9, 127.8, 127.7, 127.2, 125.3, 87.2, 78.5, 78.4, 78.2, 74.57, 74.55, 71.8, 63.0, 62.2, 43.3 ppm.

20: Cs_2CO_3 (84.1 mg, 0.258 mmol) and thiophenol (33.2 μL, 0.323 mmol) were added at RT to a stirred solution of **19** (178 mg, 0.215 mmol) in CH_3CN (3.00 mL). After being stirred at RT for 2 h, the reaction mixture was filtered through a pad of Celite and evaporated in vacuo. The residue was used for the next reaction without further purification. $(Boc)_2O$ (70.5 mg, 0.323 mmol) was added at RT to a stirred solution of the residue in 1,4-dioxane (2.00 mL) and saturated aqueous $NaHCO_3$ (200 μL). After being stirred at RT for 1 h, the reaction mixture was poured into ice-cooled water. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. Silica gel column purification with 80:20 hexane/ethyl acetate gave **20** (151 mg, 0.184 mmol, 2 steps 86%) as a colorless oil. $[\alpha]_D^{26} = +14.4$ (c = 0.95, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3089, 3063, 2977, 2876, 2097, 1713, 1496, 1068, 747, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05–7.42 (m, 30H, Ar), 4.84 (m, 1H), 4.65 (d, 1H, J_{gem} = 11.1 Hz), 4.63 (d, 1H, J_{gem} = 11.1 Hz), 4.54 (d, 1H, J_{gem} = 11.6 Hz), 4.48 (d, 1H, J_{gem} = 11.6 Hz), 4.45 (d, 1H, J_{gem} = 11.1 Hz), 4.42 (d, 1H, J_{gem} = 11.1 Hz), 3.79–3.80 (m, 1H), 3.69–3.72 (m, 2H), 3.56 (ddd, 1H, J = 4.8, 4.3, 4.3 Hz), 3.44–3.48 (m, 1H), 3.40 (dd, 1H, J_{gem} = 9.2, 6.8 Hz), 3.30–3.36 (m, 2H), 1.43 ppm (s, 9H, tBu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 143.5, 138.1, 137.8, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 127.5, 127.1, 87.1, 79.7, 79.1, 78.9, 78.1, 74.9, 74.7, 71.3, 63.3, 62.3, 40.0, 28.4 ppm.

21: 10-Camphorsulfonic acid (15.4 mg, 0.0664 mmol) was added at RT to a stirred solution of **20** (544 mg, 0.664 mmol) in MeOH (5.00 mL). After being stirred at the same temperature for 24 h, the reaction mixture was evaporated in vacuo. Silica gel column purification with 55:45 hexane:ethyl acetate gave **21** (344 mg, 0.597 mmol, 90%) as a colorless oil. $[\alpha]_D^{25} = +47.8$ (c = 1.07, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3431, 2978, 2932, 2111, 1694, 1498, 1254, 1169, 1060, 736, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.36 (m, 15H, Ar), 4.89 (m, 1H), 4.78 (d, 1H, J_{gem} = 11.1 Hz), 4.77 (d, 1H, J_{gem} = 11.6 Hz), 4.67 (d, 1H, J_{gem} = 11.1 Hz), 4.63 (d, 1H, J_{gem} = 11.6 Hz), 4.56 (m, 2H), 3.94 (dd, 1H, J = 3.4, 5.8 Hz), 3.71–3.76 (m, 3H), 3.64 (ddd, 1H, J = 5.8, 3.9, 3.9 Hz), 3.52 (ddd, 1H, J = 5.3, 5.3, 5.3 Hz), 3.44 (br dd, 1H, J = 3.9 Hz, J_{gem} = 14.5 Hz), 3.34 (br dd, 1H, J = 3.9 Hz, J_{gem} = 14.5 Hz), 2.32 (m, 1H), 1.42 ppm (s, 9H, tBu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 138.0, 137.8, 137.7, 128.5, 128.43, 128.40, 128.1, 128.0, 127.9, 127.83, 127.79, 79.4, 79.0, 78.3, 75.0, 74.6, 71.7, 63.5, 62.1, 40.3, 28.4 ppm.

22: A catalytic amount of TEMPO, TBAB and KBr, and aqueous NaOCl (2.96 mL) was added to a stirred solution of **21** (299 mg, 0.518 mmol) in CH_2Cl_2 (3.00 mL) and saturated aqueous $NaHCO_3$ (1.50 mL) at 0 °C. After being stirred at the same temperature for 30 min, the reaction mixture was poured into ice-cooled 1 M HCl. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was used for the next reaction without further purification. $NaHCO_3$ (218 mg, 2.59 mmol) and allyl bromide (107 μL, 1.24 mmol) were added at 0 °C to a stirred solution of the residue in DMF (5.00 mL). After being stirred at RT for 6 h, the reaction mixture was poured into ice-cooled 1 M HCl. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. Silica gel column purification with 75:25 hexane/ethyl acetate gave **22** (239 mg, 0.379 mmol, 2 steps 73%) as a colorless oil. $[\alpha]_D^{24} = +17.5$ (c = 1.15, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3436, 3032, 3007, 2979, 2933, 2113, 1749, 1713, 1498, 1173, 737, 698 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3): δ = 7.20–7.32 (m, 15H, Ar), 5.83 (dddd, 1H, J = 5.8, 10.6, 17.4 Hz), 5.30 (dd, 1H, J = 10, 17.4 Hz), 5.21 (d, 1H, J = 10.6 Hz), 4.83 (d, 1H, J_{gem} = 11.6 Hz), 4.80 (m, 1H), 4.75 (d, 1H, J_{gem} = 10.6 Hz), 4.71 (d, 1H, J_{gem} = 10.6 Hz), 4.60 (d, 1H, J_{gem} = 11.6 Hz), 4.57–4.63 (m, 1H), 4.56 (d, 1H, J_{gem} = 11.6 Hz), 4.54 (d, 1H, J_{gem} = 11.6 Hz), 4.49 (dd, 1H, J = 5.8 Hz, J_{gem} = 13.0 Hz), 4.17 (dd, 1H, J = 2.4, 7.7 Hz), 4.06 (m, 1H), 3.95 (dd, 1H, J = 7.7 Hz, J = 4.8 Hz), 3.62 (m, 1H), 3.39–3.42 (m, 2H), 1.42 ppm (s, 9H, tBu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 155.9, 137.8, 137.4, 131.0, 128.3, 128.23, 128.18, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 127.3, 127.2, 119.3, 81.2, 79.3, 79.1, 78.2, 75.1, 74.9, 71.5, 66.3, 62.8, 39.9, 28.2 ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 653.2946, found 653.2946.

2: H_2O (2.00 mL) and triphenylphosphine (873 mg, 3.33 mmol) were added at RT to a stirred solution of **22** (1.40 g, 2.22 mmol) in THF

(100 mL). After being stirred at 60 °C for 8 h, the reaction mixture was added to saturated aqueous $NaHCO_3$ (3.00 mL) and 9-fluorenylmethyl chloroformate (861 mg, 3.33 mmol) at RT. After being stirred at the same temperature for 1 h, the reaction mixture was poured into ice-cooled water. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. Silica gel column purification with 75:25 hexane/ethyl acetate gave **2** (1.68 g, 2.03 mmol, 91 %) as a colorless amorphous solid. $[\alpha]_D^{21} = -0.9$ ($c = 0.99$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3436$, 3032, 2978, 2932, 1715, 1505, 1171, 1068, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.74$–7.76 (m, 2H, Fmoc), 7.58–7.64 (m, 2H, Fmoc), 7.18–7.47 (m, 19H, Ar), 5.82 (dddd, 1H $J = 5.8$, 10.1, 17.4 Hz), 5.69 (br d, 1H, $J = 9.2$ Hz), 5.29 (d, 1H, $J = 17.4$ Hz), 5.20 (d, 1H, $J = 10.1$ Hz), 4.97 (m, 1H), 4.76 (d, 1H, $J_{gem} = 11.1$ Hz), 4.69 (m, 2H), 4.61–4.66 (m, 1H), 4.56–4.58 (m, 2H), 4.46–4.51 (m, 4H), 4.32 (dd, 1H, $J = 10.1$ Hz, $J_{gem} = 7.7$ Hz), 4.19–4.26 (m, 2H), 3.82 (m, 1H), 3.68–3.69 (m, 1H), 3.41–3.50 (m, 2H), 1.33 ppm (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.2$, 156.6, 156.0, 143.9, 143.5, 141.22, 141.19, 138.0, 137.7, 137.7, 131.3, 128.3, 128.1, 127.7, 127.8, 127.71, 127.66, 127.0, 125.1, 125.0, 119.9, 119.2, 79.8, 79.3, 79.1, 78.3, 75.1, 75.0, 71.5, 67.3, 66.2, 56.0, 47.0, 39.7, 28.3 ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 849.3722, found 849.3722.

24: To a solution of **2** (1.68 g, 2.03 mmol) in 1,4-dioxane (5.00 mL) was added 4 M HCl/1,4-dioxane (15 mL) at RT. After being stirred at the same temperature for 2 h, the reaction mixture was concentrated in vacuo. The residue was used for the next reaction without further purification. *N,N*-diisopropylethylamine (DIEA; 1.06 mL, 6.10 mmol) and 2-(1-hydroxy-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU; 1.16 g, 3.05 mmol) were added at RT to a solution of the residue and **23** (1.33 g, 2.23 mmol) in CH_2Cl_2 (10.0 mL). After being stirred at the same temperature for 2 h, the reaction mixture was concentrated in vacuo. NH-silica gel column purification with $CHCl_3$ and further purification by GPC gave **24** (2.01 g, 1.54 mmol, 2 steps 87 %) as a colorless oil. $[\alpha]_D^{23} = +2.7$ ($c = 0.94$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3300$, 3065, 3033, 2949, 1728, 1674, 1455, 1252, 1008, 738, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.71$–7.74 (m, 2H, Fmoc), 7.55–7.61 (m, 2H, Fmoc), 7.18–7.44 (m, 39H, Ar), 5.89 (dd, 1H, $J = 4.8$, 9.2 Hz), 5.80 (dddd, 1H, $J = 5.8$, 6.3, 10.1, 17.4 Hz), 5.68 (d, 1H, $J = 10.1$ Hz), 5.27 (d, 1H, $J = 17.4$ Hz), 5.18 (d, 1H, $J = 10.1$ Hz), 4.92–5.07 (m, 8H,P-Bn), 4.75 (d, 1H, $J_{gem} = 10.6$ Hz), 4.68 (d, 1H, $J_{gem} = 11.1$ Hz), 4.62 (d, 1H, $J = 8.7$ Hz), 4.60 (d, 1H, $J_{gem} = 11.1$ Hz), 4.55 (dd, 1H, $J = 5.8$ Hz, $J_{gem} = 13.0$ Hz), 4.46 (dd, 1H, $J = 6.3$ Hz, $J_{gem} = 13.0$ Hz), 4.46 (d, 1H, $J_{gem} = 10.6$ Hz), 4.45–4.49 (m, 1H), 4.42 (d, 1H, $J_{gem} = 11.6$ Hz), 4.38 (d, 1H, $J_{gem} = 11.6$ Hz), 4.27 (dd, 1H, $J = 7.2$ Hz, $J_{gem} = 10.1$ Hz), 4.18 (m, 1H), 4.12–4.14 (m, 1H), 3.76 (dd, 1H, $J = 4.3$, 8.2 Hz), 3.59–3.61 (m, 1H), 3.43–3.57 (m, 2H), 3.31 (ddd, 1H, $J = 4.8$, 4.8 Hz, $J_{gem} = 9.2$ Hz), 2.58 ppm (ddt, 2H, $J = 6.8$ Hz, $J_{gem} = 9.2$ Hz, $J_{H,P} = 15.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.1$, 169.1 (t, $J_{C,P} = 8.4$ Hz), 156.6, 143.9, 143.5, 141.2, 137.9, 137.7, 137.6, 136.1, 136.1, 136.0, 131.3, 128.4, 128.4, 128.2, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.1, 127.0, 125.1, 125.0, 119.9, 119.4, 79.5, 79.4, 77.7, 75.1, 75.0, 71.4, 68.3 (d, $J_{C,P} = 6.1$ Hz), 68.0 (d, $J_{C,P} = 6.1$ Hz), 67.3, 66.3, 56.0, 47.0, 38.9, 32.7 (t, $J_{C,P} = 135$ Hz), 31.7 ppm; ^{31}P NMR (160 MHz, $CDCl_3$): $\delta = 24.31$ ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 1325.4664, found 1325.4644.

13: *N*-methylaniline (142 mL, 1.31 mmol) and $Pd(PPh_3)_4$ (144 mg, 0.125 mmol) were added at RT to a stirred solution of **24** (1.63 g, 1.25 mmol) in THF (30.0 mL). After being stirred at the same temperature for 2.5 h, the reaction mixture was evaporated in vacuo. Silica gel column purification with 97:3 $CHCl_3$/MeOH and 0.5 % Me_2NEt gave **13** (1.59 g, 1.25 mmol, 95 %) as a pale-brown oil. $[\alpha]_D^{19} = -7.7$ ($c = 0.99$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.58$–7.74 (m, 4H, Fmoc), 7.05–7.45 (m, 39H, Ar), 6.27 (br s, 1H), 5.86 (d, 1H, $J = 8.7$ Hz), 4.96–5.05 (m, 8H, P−Bn), 4.78 (d, 1H, $J_{gem} = 11.1$ Hz), 4.46 (m, 2H), 4.33 (d, 1H, $J = 8.2$ Hz), 4.19–4.30 (m, 4H), 3.94 (dd, 1H, $J = 1.4$, 8.7 Hz), 3.85 (m, 1H), 3.68 (br dd, 1H, $J = 5.3$ Hz, $J_{gem} = 13.0$ Hz), 3.54 (ddt, 1H, $J = 5.3$, 5.3 Hz, $J_{H,P} = 23.7$ Hz), 3.41 (br dd, 1H, $J = 4.3$ Hz, $J_{gem} = 13.0$ Hz), 2.85 (q, 2H, $J = 7.2$ Hz), 2.57–2.63 (m, 2H), 2.52 (s, 6H), 1.18 ppm (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.5$, 168.9 (t, $J_{C,P} = 7.6$ Hz), 156.8, 144.1, 138.6, 138.3, 136.3, 136.1, 136.0, 132.0, 129.0, 128.7, 128.4, 128.25, 128.20, 128.15, 128.0, 127.9, 127.79, 127.79, 127.75, 127.5, 127.5, 127.4, 127.0, 126.9, 125.3, 125.1, 119.8, 81.04, 81.00, 75.3, 71.2, 68.2 (d, $J_{C,P} = 4.6$ Hz), 68.0 (d, $J_{C,P} = 6.1$ Hz), 67.1, 56.2, 51.8, 47.1, 41.5, 39.1, 32.5 (t, $J_{C,P} = 135$ Hz), 31.5, 9.2 ppm; ^{31}P NMR (160 MHz, $CDCl_3$): $\delta = 24.35$ ppm; IR (KBr): $\tilde{\nu} = 3304$, 3065, 3034, 2948, 2894, 1721, 1673, 1498, 1455, 1250, 998, 736, 698 cm^{-1}; HRMS (ESI-TOF) $[M+H]^+$ calcd. 1285.4351, found 1285.4351.

26: To a stirred solution of **15** (5.00 g, 11.2 mmol) in MeOH (50 mL) was added sodium (10.0 mg) at RT. After being stirred at the same temperature for 2 h, the reaction mixture was concentrated in vacuo and mixed with toluene. The residue was used for the next reaction without further purification. To a stirred solution of the residue in pyridine (50.0 mL) was added tritylchloride (4.68 g, 16.8 mmol) at RT. After being stirred at 85 °C for 24 h, the reaction mixture was poured into ice-cooled water and the aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was used for the next reaction without further purification. To a stirred solution of the residue in pyridine (25.0 mL) was added hydrogen fluoride-pyridine (2.50 mL) at 0 °C. After being stirred at RT for 6 h, the reaction mixture was poured into ice-cooled saturated aqueous $NaHCO_3$. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was used for the next reaction without further purification. To a stirred solution of $NaBH_4$ (507 mg, 13.4 mmol) in dry EtOH (20.0 mL) was added a solution of the residue in dry EtOH (40.0 mL) at 0 °C. After being stirred at RT for 3 h, the reaction mixture was poured into ice-cooled saturated aqueous NH_4Cl and the aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with aqueous NH_4Cl and brine, dried over $MgSO_4$, filtered and evaporated in vacuo. Silica gel column purificationl with 94:6 $CHCl_3$/MeOH gave **26** (4.40 g, 9.79 mmol, 4 steps 87 %) as a white amorphous solid. $[\alpha]_D^{21} = -1.5$ ($c = 1.28$, MeOH); IR (KBr): $\tilde{\nu} = 3378$, 2109, 1449, 1074, 748, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.24$–7.48 (m, 15H, Ar), 3.93 (dd, 1H, $J = 4.8$, 5.3 Hz), 3.81–3.85 (m, 3H), 3.69 (dd, 1H, $J = 5.3$, 5.8 Hz), 3.63 (dd, 1H, $J = 4.6$, 4.8 Hz), 3.39 (dd, 1H, $J = 4.8$ Hz, $J_{gem} = 9.7$ Hz), 3.34 (dd, 1H, $J = 5$,8 Hz, $J_{gem} = 9.7$ Hz), 2.98 (d, 1H, $J = 5.8$ Hz), 2.92 (d, 1H, $J = 5.8$ Hz), 2.64 (d, 1H, $J = 5.8$ Hz), 2.30 ppm (t, 1H, $J = 5.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 143.4$, 128.5, 127.9, 127.2, 87.2, 71.3, 71.0, 69.9, 65.2, 64.8, 61.7 ppm.

27: A solution of **26** (1.11 g, 2.47 mmol) in dry *N,N*-dimethylformamide (15 mL) was added at 0 °C to a stirred 55 % sodium hydride (355 mg, 14.8 mmol) solution, which was washed twice with dry hexane and the reaction mixture was stirred at the same temperature for 30 min. Then, benzyl bromide (1.42 mL, 11.9 mmol) and a catalytic amount of nBu_4NI were added to the reaction mixture at 0 °C. After being stirred at RT for 3 h, the reaction mixture was poured into saturated aqueous NH_4Cl and the aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was used for the next reaction without further purification. To a stirred solution of the residue in THF (7.50 mL) and MeOH (15.0 mL) was added 10-camphorsulfonic acid (57.4 mg, 0.247 mmol) at RT. After being stirred at RT, the reaction mixture was quenched with NEt_3 and evaporated in vacuo. Silica gel column purification with 75:25 hexane/ethyl acetate gave **27** (1.37 g, 2.41 mmol, 2 steps 98 %) as a colorless oil. $[\alpha]_D^{16} = +11.6$ ($c = 1.22$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3469$, 3089, 3065, 3032, 2869, 2098, 1497, 1454, 1093, 1067, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$–7,40 (m, 20H, Ar), 4.76 (d, 1H, $J_{gem} = 11.1$ Hz), 4.71 (d, 1H, $J_{gem} = 11.1$ Hz), 4.66 (d, 1H, $J_{gem} = 11.1$ Hz), 4.58 (d, 1H, $J_{gem} = 11.1$ Hz), 4.58 (d, 1H, $J_{gem} = 11.6$ Hz), 4.52 (d, 1H, $J_{gem} = 11.6$ Hz), 4.43 (m, 2H), 3.92 (dd, 1H, $J = 4.4$, 5.3 Hz), 3.77–3.87 (m, 2H), 3.73 (dd, 1H, $J = 4.4$, 5.8 Hz), 3.62–3.69 (m, 2H), 3.55 (d, 2H, $J = 5.8$ Hz), 2.10 ppm (dd, 1H, $J = 5.8$, 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 138.0$, 137.8, 137.7, 137.5, 128.5, 128.40, 128.38, 128.35, 128.1, 127.9, 127.8, 127.8, 127.7, 79.7, 78.9, 78.7, 74.8, 74.5, 73.3, 71.7, 69.4, 61.8, 60.8 ppm.

28: To a stirred solution of **27** (2.64 g, 4.65 mmol) in CH_2Cl_2 (25 mL) was added NEt_3 (1.42 mL, 10.2 mmol) and methanesulfonyl chloride (396 μL,

5.12 mmol) at 0 °C. After being stirred at RT for 3 h, the reaction mixture was poured into ice-cooled water. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was used for the next reaction without further purification. To a stirred solution of the residue in *N,N*-dimethylformamide (25 mL) was added Cs_2CO_3 (6.06 g, 18.6 mmol) and 2-nitrobenzenesulfonylamide (1.88 g, 9.30 mmol) at RT. After being stirred at 80 °C for 10 h, the reaction mixture was poured into ice-cooled 1 M HCl. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with 1 M HCl and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. Silica gel column purification with 75:25 hexane/ethyl acetate gave **28** (2.76 g, 3.67 mmol, 2 steps 79 %) as a yellow oil. $[\alpha]_D^{15} = +13.7$ ($c = 0.93$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3345$, 3090, 3065, 3032, 2870, 2100, 1539, 1362, 1171, 1092, 739, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.98$ (d, 1H, $J = 7.7$ Hz), 7.77 (d, 1H, $J = 7.7$ Hz), 7.63 (dd, 1H, $J = 7.2$, 7.7 Hz), 7.55 (dd, 1H, $J = 7.2$, 7.7 Hz), 7.23–7.36 (m, 20H, Ar), 5.73 (dd, 1H, NH, $J = 5.3$, 5.8 Hz), 4.70 (d, 1H, $J_{gem} = 11.1$ Hz), 4.68 (d, 1H, $J_{gem} = 11.1$ Hz), 4.59 (d, 1H, $J_{gem} = 11.1$ Hz), 4.56 (d, 1H, $J_{gem} = 11.1$ Hz), 4.44 (d, 1H, $J_{gem} = 11.1$ Hz), 4.44 (m, 2H), 4.39 (d, 1H, $J_{gem} = 11.1$ Hz), 3.89 (dd, 1H, $J = 4.3$, 4.3 Hz), 3.63–3.68 (m, 2H), 3.56 (m, 3H), 3.35 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.8$, 137.7, 137.6, 137.5, 137.1, 133.4, 133.3, 132.6, 130.9, 128.42, 128.38, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 125.2, 78.4, 78.4, 78.3, 74.6, 74.4, 73.2, 71.9, 69.1, 61.2, 43.4 ppm.

29: Cs_2CO_3 (1.40 g, 4.30 mmol) and thiophenol (442 mL, 4.30 mmol) were added at RT to a stirred solution of **28** (2.69 g, 3.58 mmol) in CH_3CN (30 mL). After being stirred at the same temperature for 6 h, the reaction mixture was filtered through a pad of Celite and evaporated in vacuo. Silica gel column purification with 97:3 $CHCl_3$/MeOH and 0.5 % $iPrNH_2$ gave **29** (1.78 g, 3.14 mmol, 88 %) as a yellow oil. $[\alpha]_D^{18} = +26.6$ ($c = 1.22$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3031$, 2866, 2098, 1454, 1093, 1068, 736, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.24$–7.30 (m, 20H, Ar), 4.77 (d, 1H, $J_{gem} = 11.1$ Hz), 4.75 (d, 1H, $J_{gem} = 11.6$ Hz), 4.68 (d, 1H, $J_{gem} = 11.1$ Hz), 4.55 (d, 1H, $J_{gem} = 11.6$ Hz), 4.55 (d, 1H, $J_{gem} = 11.6$ Hz), 4.54 (d, 1H, $J_{gem} = 11.6$ Hz), 4.43 (m, 2H), 3.93–3.96 (m, 1H), 3.70–3.73 (m, 1H), 3.62–3.67 (m, 1H), 3.55–3.60 (m, 2H), 3.51–3.55 (m, 1H), 2.97 (dd, 1H, $J = 5.8$ Hz, $J_{gem} = 13.5$ Hz), 2.89 ppm (dd, 1H, $J = 3.9$ Hz, $J_{gem} = 13.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 138.2$, 138.0, 137.6, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.6, 81.5, 78.9, 78.6, 74.8, 74.1, 73.2, 71.7, 69.4, 61.7, 41.4 ppm.

30: $(Boc)_2O$ (328 mg, 1.50 mmol) was added at RT to a stirred solution of **29** (810 mg, 1.43 mmol) in 1,4-dioxane (12 mL) and saturated aqueous $NaHCO_3$ (1.20 mL). After being stirred at the same temperature for 1 h, the reaction mixture was then poured into ice-cooled water. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was used for the next reaction after briefly purifying it through chromatography on silica gel. To a stirred solution of the residue in THF (50.0 mL) was added H_2O (1.00 mL) and triphenylphosphine (564 mg, 2.15 mmol) at RT. After being stirred at 60 °C for 10 h, saturated aqueous $NaHCO_3$ (4.00 mL) and 9-fluorenylmethyl chloroformate (406 mg, 1.57 mmol) was added to the reaction mixture at RT. After being stirred at the same temperature for 2 h, the reaction mixture was poured into ice-cooled water. The aqueous layer was extracted with two portions of ethyl acetate. The combined extract was washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. Silica gel column purification with 75:25 hexane/ethyl acetate gave **30** (1.14 g, 1.32 mmol, 93 %) as a colorless oil. $[\alpha]_D^{19} = +15.8$ ($c = 0.985$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3437$, 3031, 2977, 2868, 1715, 1505, 1453, 1089, 740, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.72$–7.74 (m, 2H, $J = 7.7$ Hz), 7.54–7.57 (m, 2H), 7.11–7.38 (m, 24H, Ar), 5.18 (d, 1H, $J = 9.1$ Hz), 5.01 (m, 1H), 4.79 (d, 1H, $J_{gem} = 11.1$ Hz), 4.73 (d, 1H, $J_{gem} = 11.1$ Hz), 4.66 (d, 1H, $J_{gem} = 11.1$ Hz), 4.54 (d, 1H, $J_{gem} = 11.6$ Hz), 4.46–4.56 (m, 2H), 4.43 (d, 1H, $J_{gem} = 11.1$ Hz), 4.42 (d, 1H, $J_{gem} = 10.1$ Hz), 4.33–4.43 (m, 2H), 4.17 (t, 1H, $J = 6.8$ Hz), 4.06–4.12 (m, 1H), 3.88–3.90 (m, 1H), 3.79–3.83 (m, 1H), 3.69–3.70 (m, 1H), 3.52 (m, 1H), 3.39–3.47 (m, 3H), 1.42 ppm (s, 9H, *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.2$, 156.0, 143.9, 141.3, 138.4, 138.2, 138.2, 138.0, 128.4, 128.3, 128.2, 128.0, 127.8, 127.73, 127.66, 127.58, 127.0, 125.0, 124.9, 120.0, 80.6, 79.0, 78.4, 75.4, 74.96, 73.0, 71.5, 69.3, 66.8, 51.4, 47.2, 39.9, 28.4 ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 885.4085, found 885.4085.

14: 4 M HCl/1,4-dioxane (7.50 mL) was added at RT to a solution of **30** (500 mg, 0.579 mmol) in 1,4-dioxane (2.50 mL). After being stirred at the same temperature for 2 h, the reaction mixture was concentrated in vacuo. The residue was used for the next reaction without further purification. To a solution of the residue and **31** (480 mg, 0.637 mmol) in CH_2Cl_2 (10.0 mL) was added DIEA (604 μL, 3.47 mmol) and HATU (330 mg, 0.869 mmol) at RT. After being stirred at the same temperature for 2 h, the reaction mixture was concentrated in vacuo. NH–silica gel column purification with $CHCl_3$ and further purified by GPC gave **14** (868 mg, 0.579 mmol, 2 steps 98 %) as a colorless oil. $[\alpha]_D^{21} = +9.7$ ($c = 1.20$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3305$, 3033, 2948, 2865, 1745, 1668, 1498, 1454, 1172, 1128, 741, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.96$ (dd, 1H, $J = 5.3$, 5.3 Hz), 7.70–7.72 (m, 2H), 7.51–7.54 (m, 2H), 7.09–7.36 (m, 44H, Ar), 5.24 (d, 1H, $J = 9.7$ Hz), 5.04–5.07 (m, 8H), 4.82 (d, 1H, $J_{gem} = 11.1$ Hz), 4.79 (d, 1H, $J_{gem} = 11.1$ Hz), 4.69 (d, 1H, $J_{gem} = 11.1$ Hz), 4.52 (m, 2H), 4.47 (d, 1H, $J_{gem} = 12.1$ Hz), 4.44 (d, 1H, $J_{gem} = 11.1$ Hz), 4.42 (d, 1H, $J_{gem} = 12.1$ Hz), 4.37 (dd, 1H, $J = 7.2$ Hz, $J_{gem} = 10.6$ Hz), 4.28 (dd, 1H, $J = 6.8$ Hz, $J_{gem} = 10.6$ Hz), 4.18–4.24 (m, 1H), 4.14 (dd, 1H, $J = 6.8$, 7.2 Hz), 3.90–3.93 (m, 3H), 3.66 (br ddd, 1H, $J = 3.4$, 5.3 Hz, $J_{gem} = 13.0$ Hz), 3.57 (br ddd, 1H, $J = 5.3$, 5.8 Hz, $J_{gem} = 13.0$ Hz), 3.44–3.47 (m, 10H), 3.08 (s, 2H), 2.71–2.72 (m, 4H), 2.52–2.55 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.8$, 170.8, 156.1, 143.9, 141.2, 138.7, 138.5, 138.3, 138.0, 135.6, 128.5, 128.28, 128.25, 128.17, 127.8, 127.8, 127.6, 127.6, 127.54, 127.50, 127.3, 127.0, 125.01, 124.95, 119.9, 80.5, 79.2, 77.7, 75.4, 74.6, 72.9, 71.7, 69.4, 66.8, 66.2, 58.5, 55.0, 53.3, 51.9, 51.4, 47.2, 39.4 ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 1498.6897, found 1498.6897.

33: Et_2NH (200 μL) was added at RT to a solution of **14** (66.0 mg, 0.0440 mmol) in CH_3CN (1.80 mL). After being stirred at the same temperature for 2 h, the reaction mixture was concentrated in vacuo and the residue was used for the next reaction without further purification. DIEA (23.0 μL, 0.132 mmol) and HATU (25.1 mg, 0.660 mmol) were added to a solution of the residue and **31** (28.8 mg, 0.0484 mmol) in CH_2Cl_2 (2.00 mL) at RT. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated in vacuo. NH–silica gel column purification with $CHCl_3$ and further purified by GPC gave **33** (73.2 mg, 0.0395 mmol, two steps 90 %) as a colorless oil. $[\alpha]_D^{18} = +10.7$ ($c = 1.15$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3295$, 3065, 3033, 2952, 2892, 1743, 1674, 1498, 1455, 1255, 1173, 997, 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.90$ (dd, 1H, $J = 5.3$, 5.8 Hz), 7.08–7.33 (m, 60H, Ar), 6.04 (d, 1H, $J = 9.2$ Hz), 5.04–5.07 (m, 8H), 4.90–5.02 (m, 8H, P–Bn), 4.78 (d, 1H, $J_{gem} = 11.1$ Hz), 4.78 (d, 1H, $J_{gem} = 10.6$ Hz), 4.65 (d, 1H, $J_{gem} = 11.6$ Hz), 4,56 (d, 1H, $J_{gem} = 12.1$ Hz), 4.45 (d, 1H, $J_{gem} = 12.1$ Hz), 4.41 (d, 1H, $J_{gem} = 10.6$ Hz), 4.40–4.47 (m, 1H), 4.37 (d, 1H, $J_{gem} = 12.1$ Hz), 4.23 (d, 1H, $J_{gem} = 12.1$ Hz), 3.85–3.91 (m, 3H), 3.64 (ddd, 1H, $J = 3.4$, 5.8 Hz, $J_{gem} = 13.0$ Hz), 3.45–3.56 (m, 10H), 3.26–3.35 (m, 2H), 3.03 (s, 2H), 2.59–2.75 (m, 6H), 2.49–2.52 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.6$, 170.8, 168.8 (dd, $J_{C,P} = 6.8$, 16.0 Hz), 138.8, 138.6, 138.3, 138.0, 136.14, 136.07, 136.01, 135.97, 135.6, 128.5, 128.4, 128.3, 128.2, 128.02, 127.96, 127.8, 127.7, 127.6, 127.5, 127.3, 80.4, 78.7, 77.8, 77.5, 76.4, 75.3, 74.6, 72.8, 71.6, 68.7, 68.22, 68.15, 68.1, 68.03, 67.97, 67.83, 67.76, 66.2, 58.4, 54.9, 53.2, 51.8, 49.7, 39.4, 32.6 (t, $J_{C,P} = 135$ Hz), 31.8 ppm (t, $J_{C,P} = 3.0$ Hz); ^{31}P NMR (160 MHz, $CDCl_3$): $\delta = 24.44$ ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 1852.7683, found 1852.7684.

34: According to the method for the synthesis of **33**, **14** (457 mg, 0.305 mmol) in CH_3CN (9.00 mL) was treated with Et_2NH (1.00 mL) to give an amine. The amine and **13** (449 mg, 0.336 mmol) in CH_2Cl_2 (10.0 mL) were treated with DIEA (176 μL, 1.01 mmol) and HATU (191 mg, 0.503 mmol) to give the coupling product **34** (643 mg, 0.255 mmol, 2 steps 84 %). $[\alpha]_D^{12} = +10.0$ ($c = 1.35$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3301$, 3065, 3033, 2922, 1743, 1674, 1498, 1455, 1250, 1061, 996, 737, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.89$ (br t, 1H), 7.68–7.69 (m, 2H, Fmoc), 7.44–7.52 (m, 2H, Fmoc), 7.11–7.31 (m, 80H, Ar and 2NH), 6.14 (br d, 1H, $J = 5.8$ Hz), 5.76 (m, 1H), 5.03 (m, 8H, DTPA–Bn), 4.88–4.99 (m, 8H, P–Bn), 4.74 (d, 1H, $J_{gem} = 11.1$ Hz), 4.69 (d, 1H, $J_{gem} = 11.1$ Hz), 4.57 (d, 1H, $J_{gem} = 11.1$ Hz), 4.52 Hz (d, 1H, $J_{gem} = 11.1$ Hz),

4.50–4.57 (m, 2H), 4.46 (d, 1H, J_{gem}=11.1 Hz), 4.43 (d, 1H, J_{gem}= 11.1 Hz), 4.42–4.47 (m, 2H), 4.11–4.35 (m, 9H), 4.05 (brt, 1H, J= 6.3 Hz), 3.88–3.90 (m, 2H), 3.81–3.82 (m, 1H), 3.72 (m, 1H), 3.45–3.63 (m, 5H), 3.45 (s, 8H), 3.36–3.40 (m, 1H), 3.19–3.34 (m, 2H), 2.99–3.08 (m, 2H), 2.68–2.69 (m, 4H), 2.43–2.52 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.7, 170.8, 169.5, 169.0, 156.4, 143.9, 143.7, 141.2, 138.7, 138.5, 138.4, 137.92, 137.86, 137.6, 136.2, 136.1, 136.0, 135.6, 128.5, 128.43, 128.36, 128.31, 128.28, 128.26, 128.18, 128.14, 128.05, 128.0, 127.94, 127.89, 127.86, 127.7, 127.6, 127.5, 127.4, 127.3, 127.1, 125.2, 119.9, 80.7, 79.4, 79.1, 78.8, 78.1, 77.5, 76.3, 75.1, 74.8, 74.6, 74.5, 72.78, 71.75, 71.4, 68.8, 68.3 (d, $J_{C,P}$=6.8 Hz), 68.2 (d, $J_{C,P}$=6.8 Hz), 68.02 (d, $J_{C,P}$= 6.8 Hz), 67.95 (d, $J_{C,P}$=6.8 Hz), 67.3, 66.2, 58.6, 55.0, 54.8, 53.2, 51.9, 49.9, 45.0, 39.5, 32.7 (t, $J_{C,P}$=131 Hz), 31.8 ppm; ^{31}P NMR (160 MHz, $CDCl_3$): δ=24.31 ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 2521.0575, found 2521.0613.

38: According to the method for the synthesis of **33**, **34** (448 mg, 0.178 mmol) in CH_3CN (9.00 mL) was treated with Et_2NH (1.00 mL) to give an amine. The amine and **13** (261 mg, 0.196 mmol) in CH_2Cl_2 (5.0 mL) were treated with DIEA (102 μL, 0.588 mmol) and HATU (112 mg, 0.294 mmol) to give the coupling product **38** (531 mg, 0.150 mmol, 2 steps 84%). $[\alpha]_D^{19}$=+11.3 (c=1.06, $CHCl_3$); IR (KBr): $\tilde{\nu}$= 3300, 3065, 3033, 2948, 2893, 1743, 1670, 1498, 1455, 1256, 996, 736, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.86 (m, 1H), 7.75 (d, 1H, J= 4.8 Hz), 7.65 (d, 2H, Fmoc, J=6.6 Hz), 7.51 (d, 1H, Fmoc, J=6.8 Hz), 7.43 (d, 1H, Fmoc, J=7.2 Hz), 7.05–7.28 (m, 115H, Ar and 2NH), 6.44 (m, 1H), 5.78 (m, 2H), 5.04 (s, 8H, DTPA–Bn), 4.82–5.04 (m, 16H,P-Bn), 4.71 (d, 1H, J_{gem}=10.6 Hz), 4.70 (d, 1H, J_{gem}=10.6 Hz), 4.01–4.59 (m, 27H,), 3.80–3.93 (m, 2H), 3.74 (m, 2H), 3.42 (s, 8H), 3.38–3.67 (m, 8H), 3.10–3.24 (m, 4H), 3.00 (s, 2H), 2.59–2.69 (m, 4H), 2.45 ppm (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.5, 170.7, 170.4, 168.9, 168.8, 156.6, 143.8, 143.5, 141.0, 138.7, 138.5, 138.4, 138.0, 137.9, 137.8, 137.7, 137.4, 136.01, 135.99, 135.95, 135.8, 135.5, 128.7, 128.4, 128.3, 128.2, 128.2, 128.04, 127.95, 127.9, 127.84, 127.80, 127.7, 127.64, 127.56, 127.3, 127.2, 127.01, 126.98, 125.0, 125.1, 119.8, 80.6, 79.6, 79.4, 79.1, 78.8, 78.2, 78.1, 77.6, 75.0, 74.8, 74.6, 73.9, 72.6, 71.6, 71.4, 71.1, 68.5, 68.1, 67.9, 67.8, 67.2, 66.1, 58.4, 55.5, 54.9, 53.0, 51.7, 50.1, 46.8, 39.6, 39.4, 38.9, 32.5×2 (t, $J_{C,P}$=135 Hz), 31.6 ppm; ^{31}P NMR (160 MHz, $CDCl_3$): δ=24.44 ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 3543.4248, found 3543.4260.

42: According to the method for the synthesis of **33**, **38** (142 mg, 0.0401 mmol) in CH_3CN (4.50 mL) was treated with Et_2NH (500 mL) to give an amine. The amine and **13** (58.9 mg, 0.0441 mmol) in CH_2Cl_2 (5.00 mL) were treated with DIEA (23.0 μL, 0.132 mmol) and HATU (25.2 mg, 0.0662 mmol) to give **42** (149 mg, 0.0326 mmol, two steps 81%). $[\alpha]_D^{21}$=+9.9 (c=1.06, $CHCl_3$); IR (solid): $\tilde{\nu}$=3306, 3065, 3033, 2893, 1744, 1673, 1497, 1455, 1258, 998, 735, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.88 (m, 1H), 7.77–7.80 (m, 2H), 7.63 (d, 2H, Fmoc, J=7.2 Hz), 7.01–7.50 (m, 151H, Ar), 6.15 (m, 1H), 5.77–5.87 (m, 3H), 5.01 (s, 8H, DTPA–Bn), 4.81–4.99 (m, 24H,P-Bn), 3.92–4.69 (m, 37H), 3.41 (s, 8H), 3.15–3.82 (m, 21H), 3.00 (s, 2H), 2.45–2.67 ppm (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.3, 170.7, 169.7, 169.2, 169.1, 168.9, 168.8, 168.7, 168.6, 156.7, 143.8, 143.5, 141.0, 138.8, 138.6, 138.4, 138.3, 138.2, 138.0, 137.9, 137.8, 137.7, 137.5, 137.1, 136.04, 135.97, 135.9, 135.7, 135.5, 128.4, 128.3, 128.22, 128.17, 128.0, 128.0, 127.94, 127.92, 127.90, 127.87, 127.83, 127.80, 127.6, 127.5, 127.5, 127.4, 127.2, 127.13, 127.07, 125.3, 125.2, 125.0, 119.7, 80.8, 79.4, 78.8, 78.6, 78.1, 75.1, 75.01, 74.97, 74.9, 74.6, 72.5, 71.6, 71.5, 71.2, 68.4, 68.1, 67.9, 67.8, 67.4, 66.0, 58.50, 58.45, 55.7, 54.9, 53.1, 52.9, 51.7, 50.1, 50.04, 49.99, 46.7, 40.0, 39.3, 33.9, 33.8, 32.5, 32.41, 32.36, 31.6, 31.54, 31.49, 31.4, 31.11, 31.09, 29.6 ppm; ^{31}P NMR (160 MHz, $CDCl_3$): δ=24.52 ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 4565.7920, found 4565.8003.

46: According to the method for the synthesis of **33**, **42** (39.8 mg, 8.71 mmol) in CH_3CN (1.80 mL) was treated with Et_2NH (200 μL) to give an amine. The amine and **13** (23.3 mg, 0.0174 mmol) in CH_2Cl_2 (2.00 mL) were treated with DIEA (9.11 μL, 0.0523 mmol) and HATU (9.92 mg, 0.0261 mmol) to **46** (30.3 mg, 5.42 mmol, two steps 62%). $[\alpha]_D^{18}$=+6.8 (c=1.35, $CHCl_3$); IR (solid): $\tilde{\nu}$=3301, 3064, 3032, 2893, 1742, 1672, 1497, 1455, 1255, 1062, 992, 732, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.72–7.83 (m, 4H), 7.62 (d, 2H, Fmoc, J=6.8 Hz), 6.97–7.26 (m, 186H, Ar), 5.80–6.04 (m, 5H), 5.00 (s, 8H, DTPA–Bn), 4.79–4.97 (m, 32H, P–Bn), 3.40 (s, 8H), 2.97–4.61 (m, 71H), 2.43–2.61 ppm (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.2, 170.7, 170.1, 170.0, 169.9, 169.1, 169.0, 168.92, 168.85, 168.8, 168.7, 168.6, 168.6, 156.7, 143.8, 143.5, 141.0, 138.7, 138.5, 138.4, 138.3, 138.2, 138.1, 138.0, 137.9, 137.7, 137.5, 137.0, 136.0, 135.5, 129.3, 128.4, 128.3, 128.2, 127.9, 127.8, 127.8, 127.5, 127.0, 125.1, 119.7, 80.9, 80.3, 79.8, 79.7, 79.6, 79.5, 79.4, 78.9, 78.2, 78.0, 77.7, 75.0, 74.8, 74.7, 74.5, 74.39, 72.42, 71.5, 71.43, 71.35, 71.2, 68.6, 68.1, 69.0, 67.3, 66.1, 58.4, 55.8, 54.87, 52.90, 51.7, 50.1, 46.7, 40.2, 39.3, 39.1, 33.9, 33.8, 33.7, 32.53, 32.46, 32.4, 31.5, 31.23, 31.17, 31.1, 29.6 ppm; ^{31}P NMR (160 MHz, $CDCl_3$): δ=24.48 ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 5588.1592, found 5588.1543.

37: According to the method for the synthesis of **33**, **34** (122 mg, 0.0484 mmol) in CH_3CN (2.70 mL) was treated with Et_2NH (300 μL) to give an amine. The amine and **23** (31.6 mg, 0.0532 mmol) in CH_2Cl_2 (2.00 mL) were treated with DIEA (25.3 μL, 0.145 mmol) and HATU (27.6 mg, 0.0726 mmol) to give **37** (126 mg, 0.0438 mmol, two steps 91%). $[\alpha]_D^{21}$=+7.9 (c=1.28, $CHCl_3$); IR (KBr): $\tilde{\nu}$=3300, 3065, 3033, 2944, 2892, 1745, 1669, 1498, 1455, 1255, 997, 736, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.86 (dd, 1H, J=5.3, 5.3 Hz), 7.08–7.29 (m, 96H), 6.83 (d, 1H, J=5.8 Hz), 6.58 (brdd, 1H), 5.03 (s, 8H, DTPA–Bn), 4.76–5.03 (m, 16H, P−Bn), 4.72 (d, 1H, J_{gem}=11.6 Hz), 4.69 (d, 1H, J_{gem}=11.6 Hz), 4.60 (d, 1H, J_{gem}=11.6 Hz), 4.49 (d, 1H, J_{gem}=11.6 Hz), 4.48–4.61 (m, 5H), 4.38–4.48 (m, 5H), 4.35 (dd, 1H, J=2.4, 5.3 Hz), 4.20 (d, 1H, J_{gem}= 11.6 Hz), 4.09 (d, 1H, J_{gem}=11.6 Hz), 3.95 −3.96 (m, 1H), 3.89 (brd, 1H, J=8.2 Hz), 3.89 (brd, 1H, J=8.2 Hz), 3.79–3.82 (m, 2H), 3.63–3.70 (m, 2H), 3.45 (s, 8H), 3.37–3.60 (m, 5H), 3.32–3.35 (m, 2H), 3.03 (s, 2H), 2.63–2.71 (m, 6H), 2.48–2.63 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.48, 170.73, 169.50, 169.33, 169.27, 169.19, 169.09, 169.01, 168.93, 138.75, 138.57, 138.54, 138.18, 138.02, 137.53, 136.10, 136.06, 136.00, 135.94, 135.88, 135.82, 135.78, 135.54, 128.45, 128.34, 128.22, 128.15, 128.09, 128.03, 127.96, 127.80, 127.75, 127.58, 127.50, 127.47, 127.31, 127.16, 80.12, 78.50, 77.88, 77.64, 74.87, 74.61, 74.45, 73.95, 72.49, 71.62, 71.24, 68.45, 68.19, 68.13, 68.05, 67.99, 67.96, 67.94, 67.88, 67.85, 66.11, 58.48, 54.91, 53.22, 53.06, 51.74, 50.07, 39.59, 39.19, 32.63 (t, $J_{C,P}$= 135 Hz), 32.34 (t, $J_{C,P}$=135 Hz), 30.81, 31.71, 31.50, 31.35, 29.59 ppm; ^{31}P NMR (160 MHz, $CDCl_3$): δ=24.61, 24.09 ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 2875.1361, found 2875.1499.

41: According to the method for the synthesis of **33**, **38** (92.3 mg, 0.0260 mmol) in CH_3CN (2.70 mL) was treated with Et_2NH (300 μL) to give an amine. The amine and **23** (17.0 mg, 0.0286 mmol) in CH_2Cl_2 (3.00 mL) were treated with DIEA (13.6 mL, 0.0780 mmol) and HATU (14.8 mg, 0.0390 mmol) to give coupling product **41** (89.7 mg, 0.0230 mmol, 2 steps 89%). $[\alpha]_D^{20}$=+10.9 (c=0.96, $CHCl_3$); IR (KBr) 3302, 3065, 3033, 2950, 2893, 1745, 1673, 1455, 1254, 997, 735, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.81–7.83 (m, 2H), 7.07–7.27 (m, 130H, Ar), 6.96 (brd, 1H, J=6.8 Hz), 6.85 (brs, 1H), 5.89 (brs, 1H), 5.01 (s, 8H, DTPA−Bn), 4.69–4.97 (m, 24H, P−Bn), 4.69–4.78 (m, 2H), 4.39–4.60 (m, 14H), 4.26–4.30 (m, 5H), 4.09–4.12 (m, 3H), 3.94 (d, 1H, J_{gem}= 12.1 Hz), 3.86 (m, 4H), 3.73 (brs, 1H), 3.55–3.63 (m, 4H), 3.41 (s, 8H), 3.27–3.54 (m, 6H), 3.18–3.22 (m, 1H), 3.10–3.11 (m, 2H), 3.00 (s, 2H), 2.57–2.73 (m, 8H), 2.40–2.47 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.46, 170.72, 170.23, 169.43, 129.28, 129.20, 168.90, 168.82, 168.73, 138.81, 138.57, 138.46, 138.28, 138.12, 138.02, 137.96, 137.93, 137.78, 137.43, 136.04, 136.00, 135.94, 135.88, 135.82, 135.77, 135.71, 135.56, 128.45, 128.32, 128.25, 128.21, 128.15, 128.08, 127.97, 127.92, 127.84, 127.77, 127.75, 127.70, 127.65, 127.59, 127.39, 127.31, 127.19, 80.87, 79.05, 78.82, 78.23, 77.61, 74.97, 74.80, 73.77, 73.59, 72.54, 71.72, 71.36, 70.98, 68.58, 68.40, 68.17, 68.12, 67.93, 67.86, 66.09, 58.44, 54.90, 53.56, 53.13, 52.99, 51.71, 50.00, 39.74, 39.26, 32.45×2, (t, $J_{C,P}$=135 Hz), 33.00 (t, $J_{C,P}$= 135 Hz), 31.59, 31.39, 29.59 ppm; ^{31}P NMR (160 MHz, $CDCl_3$): δ=24.61, 24.44 ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 3897.5034, found 3897.5210.

45: According to the method for the synthesis of **33**, **42** (72.4 mg, 0.0158 mmol) in CH_3CN (2.70 mL) was treated with Et_2NH (300 μL) to give an amine. The amine and **23** (10.3 mg, 0.0174 mmol) in CH_2Cl_2 (3.00 mL) was treated with DIEA (8.26 μL, 0.0474 mmol) and HATU (9.01 mg, 0.0237 mmol) to give **45** (59.1 mg, 0.0120 mmol, two steps

76%). $[\alpha]_D^{21} = +7.3$ ($c = 1.23$, $CHCl_3$); IR (solid): $\tilde{\nu} = 3303$, 3064, 3033, 2948, 2892, 1744, 1675, 1498, 1456, 1255, 1057, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.73$–7.85 (m, 3H), 6.98–7.27 (m, 166H), 5.82–5.90 (m, 2H), 5.01 (s, 8H, DTPA–Bn), 4.79–4.99 (m, 32H, P–Bn), 4.32–4.74 (m, 30H), 3.40 (s, 8H), 2.99 (s, 2H), 2.96–4.25 (m, 26H), 2.44–2.66 ppm (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.2$, 170.6, 170.4, 169.79, 169.76, 169.1, 169.03, 168.95, 168.9, 168.7, 168.67, 168.66, 168.6, 168.61, 168.57, 138.7, 138.5, 138.4, 138.2, 138.1, 137.9, 137.8, 137.6, 137.5, 136.0, 135.8, 135.7, 135.5, 128.4, 128.3, 128.1, 128.0, 127.91, 127.89, 127.86, 127.8, 127.72, 127.69, 127.6, 127.5, 127.3, 80.8, 79.4, 78.9, 78.0, 74.9, 74.6, 74.3, 73.6, 72.4, 71.6, 71.4, 71.2, 68.1, 67.9, 67.9, 67.8, 66.2, 66.0, 58.4, 54.8, 53.6, 52.9, 51.6, 49.9, 40.1, 39.7, 39.0, 33.7, 33.6, 32.3, 32.2, 31.5, 31.4, 31.3, 31.10, 31.06, 31.0, 30.91, 30.85, 29.5 ppm; ^{31}P NMR (160 MHz, $CDCl_3$): $\delta = 24.61$ ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 4919.8706, found 4919.8804.

49: According to the method for the synthesis of **33**, **46** (34.5 mg, 6.17 mmol) in CH_3CN (1.80 mL) was treated with Et_2NH (200 μL) to give an amine. The amine and **23** (5.51 mg, 9.26 mmol) in CH_2Cl_2 (1.00 mL) were treated with DIEA (3.22 μL, 0.0185 mmol) and HATU (4.68 mg, 0.0123 mmol) to give **49** (26.0 mg, 4.37 mmol, two steps 71%). $[\alpha]_D^{26} = +9.7$ ($c = 1.09$, $CHCl_3$); IR (solid): $\tilde{\nu} = 3415$, 3065, 2830, 1744, 1669, 1498, 1252, 1008, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.66$–7.89 (m, 4H), 6.96–7.30 (m, 200H, aromatic), 5.01 (s, 8H, DTPA–Bn), 4.80–4.96 (m, 40H, P–Bn), 3.39 (s, 8H, a), 2.97 (s, 2H, d), 2.91–4.71 (m, 69H), 2.43–2.63 ppm (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.3$, 170.7, 170.10 169.96, 169.2, 169.12, 169.06, 169.0, 169.0, 168.9, 168.8, 168.7, 168.6, 138.7, 138.5, 138.4, 138.3, 138.2, 138.1, 138.0, 137.8, 137.4, 136.0, 135.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.5, 127.3, 127.2, 79.2, 79.1, 79.0, 78.93, 78.87, 78.7, 78.6, 78.0, 77.93, 77.88, 75.03, 74.99, 74.9, 74.8, 74.71, 74.65, 74.5, 73.5, 73.4, 71.5, 71.4, 71.30, 71.25, 71.2, 71.14, 71.09, 68.1, 67.9, 66.0, 58.4, 54.8, 53.7, 52.9, 51.7, 51.6, 50.0, 39.8, 39.0, 33.74, 33.67, 32.4, 32.2, 31.4, 31.0, 30.9, 29.5 ppm; ^{31}P NMR (160 MHz, $CDCl_3$): $\delta = 24.54$ ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 5942.2378, found 5942.2402.

36: **34** (110 mg, 0.0436 mmol) in CH_3CN (2.70 mL) was added Et_2NH (300 μL) at RT. After being stirred at the same temperature for 1 h, the reaction mixture was evaporated in vacuo. The residue was used for the next reaction without further purification. To a stirred solution of the residue in CH_2Cl_2 (10.0 mL) was added DIEA (22.8 μL, 0.131 mmol) and acetic anhydride (4.93 mg, 0.0523 mmol) at RT. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated in vacuo. NH–silica gel column purification with $CHCl_3$ and further purified by GPC to give **36** (94.1 mg, 0.0402 mmol, two steps 92%) as a colorless oil. $[\alpha]_D^{23} = +10.3$ ($c = 1.06$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3301$, 3090, 3065, 3033, 2949, 2892, 1744, 1668, 1498, 1455, 1256, 1132, 997, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.89$ (dd, 1H, $J = 5.3$, 5.8 Hz), 7.10–7.30 (m, 75H, Ar), 6.99 (d, 1H, $J = 8.7$ Hz), 6.81 (d, 1H, $J = 7.2$ Hz), 5.78 (dd, 1H, $J = 3.9$, 5.8 Hz), 5.03 (s, 8H, DTPA−Bn), 4.92–5.03 (m, 8H, P−Bn), 4.74 (d, 1H, $J_{gem} = 11.1$ Hz), 4.69 (d, 1H, $J_{gem} = 11.1$ Hz), 4.64 (dd, 1H, $J = 2.4$, 8.7 Hz), 4.57 (d, 1H, $J_{gem} = 11.1$ Hz), 4.56–4.61 (m, 2H), 4.52 (d, 1H, $J_{gem} = 11.1$ Hz), 4.51–4.57 (m, 2H), 4.47 (d, 1H, $J_{gem} = 11.1$ Hz), 4.44 (d, 1H, $J_{gem} = 11.1$ Hz), 4.40–4.43 (m, 1H), 4.30 (d, 1H, $J_{gem} = 11.6$ Hz), 4.29–4.33 (m, 2H), 4.21 (d, 1H, $J_{gem} = 11.6$ Hz), 4.10 (dd, 1H, $J = 2.4$ Hz, $J = 6.3$ Hz), 3.88–3.90 (m, 2H), 3.77 (dd, 1H, $J = 1.9$, 7.7 Hz), 3.60–3.66 (m, 3H), 3.45 (s, 8H), 3.37–3.55 (m, 5H), 3.25–3.29 (m, 1H), 3.13–3.19 (m, 1H), 3.03 (s, 2H), 2.66–2.73 (m, 4H), 2.45–2.56 (m, 6H), 1.77 ppm (s, 3H, Ac); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.7$, 170.8, 170.5, 169.3, 169.0 (dd, $J_{C,P} = 6.8$, 9.9 Hz), 138.6, 138.5, 138.3, 138.0, 137.9, 137.8, 137.60, 136.03, 135.97, 135.9, 135.5, 128.8, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.73, 127.68, 127.63, 127.60, 127.5, 127.4, 127.34, 127.27, 80.5, 79.3, 78.0, 78.6, 77.8, 74.9, 74.7, 74.4, 74.3, 72.8, 71.7, 71.3, 68.7, 68.5 (d, $J_{C,P} = 6.8$ Hz), 68.4 (d, $J_{C,P} = 6.8$ Hz), 68.3 (d, $J_{C,P} = 6.1$ Hz), 68.2 (d, $J_{C,P} = 6.1$ Hz), 66.1, 58.5, 54.9, 53.2, 53.1, 51.8, 49.7, 39.4, 39.3, 32.7 (t, $J_{C,P} = 135$ Hz), 31.6 (t, $J_{C,P} = 3.7$ Hz), 22.8 ppm; ^{31}P NMR (160 MHz, $CDCl_3$): $\delta = 24.35$; HRMS (ESI-TOF) $[M+H]^+$ calcd. 2341.0000, found 2340.9980.

40: According to the method for the synthesis of **36**, **38** (77.1 mg, 0.0217 mmol) in CH_3CN (2.70 mL) was treated with Et_2NH (300 μL) to give an amine. The amine in CH_2Cl_2 (3.00 mL) was treated with DIEA (11.3 μL, 0.0651 mmol) and acetic anhydride (2.45 μL, 0.0260 mmol) to give **40** (70.3 mg, 0.0209 mmol, 2 steps 96%). $[\alpha]_D^{20} = +16.9$ ($c = 1.05$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3296$, 3065, 3034, 2891, 2838, 1747, 1669, 1515, 1498, 1251, 995, 734, 697 cm^{-1}; IR (solid): $\tilde{\nu} = 3303$, 3064, 3033, 2945, 2892, 1744, 1666, 1497, 1255, 1027, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.86$ (br dd, 1H, $J = 4.8$ Hz), 7.47 (d, 1H, $J = 5.8$ Hz), 7.06–7.32 (m, 111H), 5.91 (m, 1H), 5.84 (m, 1H), 5.02 (s, 8H, DTPA−Bn), 4.86–5.05 (m, 16H, P−Bn), 4.70 (d, 1H, $J_{gem} = 11.6$ Hz), 4.69 (d, 1H, $J_{gem} = 10.6$ Hz), 4.68–4.72 (m, 1H), 4.55 (d, 1H, $J_{gem} = 11.6$ Hz), 4.48 (d, 1H, $J_{gem} = 11.6$ Hz), 4.45 (d, 1H, $J_{gem} = 11.6$ Hz), 4.40–4.65 (m, 8H), 4.33–4.38 (m, 1H), 4.27–4.38 (m, 6H), 4.27–4.28 (m, 1H), 4.18 (d, 1H, $J_{gem} = 12.1$ Hz), 4.05 (d, 1H, $J_{gem} = 12.1$ Hz), 3.94–3.99 (m, 2H), 3.85 (br d, 1H, $J = 8.2$ Hz), 3.78 (br d, 1H, $J = 8.2$ Hz), 3.63–3.72 (m, 3H), 3.51–3.57 (m, 2H), 3.43 (s, 8H), 3.34–3.48 (m, 4H), 3.28–3.54 (m, 2H), 3.28–3.29 (m, 1H), 3.19–3.22 (m, 2H), 3.00 (s, 2H), 2.61–2.71 (m, 4H), 2.43 (m, 8H), 1.78 ppm (s, 3H, Ac); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.6$, 171.0, 170.8, 170.3, 169.14, 169.06, 169.0, 168.9, 138.7, 138.5, 138.4, 138.2, 138.1, 137.93, 137.87, 137.8, 137.5, 136.1, 136.04, 136.01, 136.0, 135.9, 135.8, 135.6, 128.5, 128.4, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6, 127.4, 127.3, 80.7, 79.9, 79.5, 79.3, 78.6, 78.4, 75.1, 74.9, 74.8, 74.7, 74.6, 73.8, 72.7, 71.7, 71.5, 71.1, 68.6, 68.32, 68.27, 68.2, 68.1, 67.99, 67.96, 66.2, 58.5, 54.9, 54.4, 53.2, 53.1, 51.8, 50.4, 39.4, 39.2, 39.0, 32.7 (t, $J_{C,P} = 135$ Hz), 32.6 (t, $J_{C,P} = 135$ Hz), 31.6, 22.6 ppm; ^{31}P NMR (160 MHz, $CDCl_3$): $\delta = 24.39$ ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 3363.3673, found 3363.3742.

44: According to the method for the synthesis of **36**, **42** (65.7 mg, 0.0144 mmol) in CH_3CN (2.70 mL) was treated with Et_2NH (300 μL) to give an amine. The amine in CH_2Cl_2 (3.00 mL) was treated with DIEA (7.53 μL, 0.0432 mmol) and acetic anhydride (1.63 μL, 0.0173 mmol) to give **44** (50.3 mg, 0.0115 mmol, 2 steps 80%). $[\alpha]_D^{21} = +12.0$ ($c = 0.91$, $CHCl_3$); IR (solid): $\tilde{\nu} = 3303$, 3064, 3033, 2945, 2892, 1744, 1666, 1497, 1255, 1027, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.78$ (m, 3H), 7.00–7.47 (m, 145H, Ar), 5.84–6.04 (m, 3H), 5.02 (s, 8H, DTPA−Bn), 4.85–5.00 (m, 24H, P−Bn), 4.02–4.76 (m, 31H), 3.41 (s, 8H), 3.01–3.97 (m, 24H), 2.99 (s, 2H), 2.45–2.67 (m, 10H), 1.73 ppm (s, 3H, Ac); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.5$, 171.4, 171.34, 171.30, 171.1, 170.7, 170.3, 169.7, 169.28, 169.25, 169.2, 169.11, 169.06, 169.02, 168.96, 168.9, 168.8, 168.74, 168.69, 138.7, 138.5, 138.4, 138.3, 138.2, 138.02, 137.96, 137.9, 137.6, 137.5, 137.3, 137.2, 136.0, 135.7, 135.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 127.2, 80.8, 80.2, 79.3, 78.9, 78.8, 78.8, 78.22, 78.17, 74.93, 74.91, 74.6, 74.49, 74.45, 72.3, 72.5, 71.7, 71.5, 71.4, 71.2, 71.1, 71.03, 70.95, 68.5, 68.2, 68.1, 67.9, 67.8, 66.1, 58.4, 54.9, 54.4, 52.9, 51.6, 50.1, 39.9, 39.22, 39.19, 33.9, 33.8, 32.5, 32.4, 31.51, 31.50, 31.41, 31.35, 31.1, 31.1, 29.6, 22.54, 22.47, 22.4 ppm; ^{31}P NMR (160 MHz, $CDCl_3$): $\delta = 24.52$ ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 4385.7345, found 4385.7461.

48: According to the method for the synthesis of **36**, **46** (99.4 mg, 0.0178 mmol) in CH_3CN (1.80 mL) was treated with Et_2NH (200 μL) to give an amine. The amine in CH_2Cl_2 (2.00 mL) was treated with DIEA (12.4 μL, 0.0712 mmol) and acetic anhydride (3.36 μL, 0.0356 mmol) to give acetylamide **48** (69.7 mg, 0.0129 mmol, 2 steps 72%). $[\alpha]_D^{26} = +10.7$ ($c = 1.28$, $CHCl_3$); IR (solid): $\tilde{\nu} = 3306$, 3065, 2896, 1744, 1669, 1498, 1456, 1253, 998, 737, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.70$–7.86 (m, 4H), 7.00–7.29 (m, 180H, Ar), 5.77–6.25 (m, 4H), 5.01 (s, 8H, DTPA–Bn), 4.84–4.99 (m, 32H, P–Bn), 3.40 (s, 8H), 3.05–4.74 (m, 68H), 2.97 (s, 2H), 2.43–2.63 (m, 16H), 1.61 ppm (s, 3H, Ac); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.3$, 171.2, 170.7, 170.6, 169.2, 169.1, 169.0, 168.9, 168.80, 168.76, 168.73, 138.70, 138.5, 138.4, 138.24, 138.19, 138.18, 138.0, 138.0, 137.9, 137.83, 137.79, 137.7, 137.6, 137.5, 136.2, 136.0, 135.8, 135.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.5, 79.6, 79.6, 79.1, 78.9, 78.84, 78.79, 78.1, 78.0, 75.0, 74.84, 74.80, 74.7, 74.64, 74.61, 74.58, 74.4, 72.4, 71.6, 71.2, 71.0, 68.6, 68.1, 67.9, 66.1, 58.4, 54.86, 52.90, 51.6, 50.1, 40.1, 39.1, 33.8, 32.4, 31.4, 31.1, 29.6, 22.4 ppm; ^{31}P NMR (160 MHz, $CDCl_3$): $\delta = 24.41$ ppm; HRMS (ESI-TOF) $[M+H]^+$ calcd. 5408.1017, found 5408.0991.

4: $Pd(OH)_2$ (20.0 mg) at RT to a stirred solution of **33** (19.4 mg, 0.0105 mmol) in ethyl acetate (0.250 mL), MeOH (1.70 mL) and H_2O (0.500 mL). The reaction mixture was hydrogenated for 6 h under H_2 gas

atmosphere. The reaction mixture was filtered through a pad of cotton and the filtrate was concentrated in vacuo and azeotroped with toluene. The residue was purified by reverse-phase column chromatography (Bond Elute-C18) and further purified by size-exclusion column chromatography on Sephadex LH-20 with H_2O to give **4** (5.50 mg, 7.13 mmol, 68%). $[\alpha]_D^{25} = +1.8$ ($c = 0.18$, H_2O); IR (KBr): $\tilde{\nu} = 3253$, 1627, 1400, 1143, 1079 cm^{-1}; ^1H NMR (400 MHz, D_2O): $\delta = 4.07$ (br ddd, 1H, $J = 1.9$, 4.3, 6.3 Hz), 3.97 (dd, 1H, $J = 1.9$, 6.8 Hz), 3.81 (s, 8H), 3.79–3.83 (m, 1H), 3.71 (dd, 1H, $J = 4.3$ Hz, $J_{gem} = 12.1$ Hz), 3.63 (dd, 1H, $J = 2.9$ Hz, $J_{gem} = 14.0$ Hz), 3.61 (dd, 1H, $J = 6.3$ Hz, $J_{gem} = 12.1$ Hz), 3.53 (dd, 1H, $J = 2.4$, 6.8 Hz), 3.41 (t, 4H, $J = 6.8$ Hz), 3.39 (s, 2H), 3.30 (dd, 1H, $J = 7.7$ Hz, $J_{gem} = 14.0$ Hz), 3.03 (t, 4H, $J = 6.8$ Hz), 2.72 (dt, 2H, $J = 6.8$ Hz, $J_{H,P} = 15.5$ Hz), 2.52 ppm (tt, 1H, $J = 6.8$ Hz, $J_{H,P} = 21.3$ Hz); ^{13}C NMR (100 MHz, D_2O): $\delta = 175.7$, 173.9, 171.1, 72.6, 70.3, 69.1, 61.7, 58.1, 57.22, 55.20, 53.4, 49.7, 43.07, 42.95, 36.9 (t, $J_{C,P} = 118$ Hz), 33.8 ppm; ^{31}P NMR (160 MHz, D_2O): $\delta = 19.0$, 18.9 ppm; MS(ESI-TOF) $[M+H]^+$ calcd. 772.2049, found 772.2243.

5: According to the method for the synthesis of **4**, **36** (9.50 mg, 4.05 mmol) in ethyl acetate (0.250 mL), MeOH (1.50 mL) and H_2O (0.50 mL) were treated with $Pd(OH)_2$ (15.0 mg) and hydrogenated under H_2 gas atmosphere to give **5** (3.70 mg, 3.74 mmol, 93%). $[\alpha]_D^{23} = +10.3$ ($c = 1.06$, H_2O); IR (KBr): $\tilde{\nu} = 3263$, 1637, 1401, 1100, 747, 595 cm^{-1}; ^1H NMR (400 MHz, D_2O): $\delta = 4.52$ (d, 1H, $J = 6.4$ Hz), 4.20 (dd, 1H, $J = 1.9$, 6.4 Hz), 4.10 (dd, 1H, $J = 5.8$ Hz), 4.00 (dd, 1H, $J = 2.4$, 5.8 Hz), 3.82 (s, 8H), 3.75–3.82 (m, 2H), 3.69–3.73 (m, 1H), 3.57–3.65 (m, 3H), 3.54 (dd, 1H, $J = 2.4$, 7.7 Hz), 3.48 (dd, 1H, $J = 1.9$, 8.2 Hz), 3.41 (t, 4H, $J = 6.8$ Hz), 3.39 (s, 2H), 3.31 (dd, 1H, $J = 8.2$ Hz, $J_{gem} = 14.0$ Hz), 3.21 (dd, 1H, $J = 7.7$ Hz, $J_{gem} = 14.0$ Hz), 3.02 (t, 4H, $J = 6.8$ Hz), 2.70 (dt, 2H, $J = 6.8$ Hz, $J_{H,P} = 15.5$ Hz), 2.50 (tt, 1H, $J = 6.8$ Hz, $J_{H,P} = 21.3$ Hz), 2.05 ppm (s, 3H, Ac); ^{13}C NMR (100 MHz, D_2O): $\delta = 175.5$, 175.4, 173.9, 172.8, 171.1, 73.0, 72.9, 70.4, 70.1, 69.9, 68.9, 61.6, 58.1, 54.8, 49.7, 43.7, 43.0, 36.8, 33.6, 22.8 ppm; ^{31}P NMR (160 MHz, D_2O): $\delta = 19.1$, 19.0 ppm; MS-(ESI) $[M-H]^-$ calcd. 988.29, found 988.9, $[M-2H]^{2-}$ calcd. 493.6, found 493.6.

6: According to the method for the synthesis of **4**, **37** (23.1 mg, 8.63 mmol) in ethyl acetate (0.250 mL), MeOH (1.80 mL) and H_2O (0.200 mL) were treated with $Pd(OH)_2$ (20.0 mg) and hydrogenated under H_2 gas atmosphere to give **6** (3.50 mg, 3.01 mmol, 35%). $[\alpha]_D^{26} = +3.2$ ($c = 0.11$, H_2O); IR (solid): $\tilde{\nu} = 3292$, 1637, 1402, 1160, 1057 cm^{-1}; ^1H NMR (400 MHz, D_2O): $\delta = 4.57$ (d, 1H, $J = 4.8$ Hz), 4.30 (dd, 1H, $J = 2.4$, 4.8 Hz), 4.09–4.11 (m, 1H), 4.00 (dd, 1H, $J = 1.9$, 6.3 Hz), 3.83 (s, 8H), 3.61 (dd, 1H, $J = 3.4$ Hz, $J_{gem} = 10.6$ Hz), 3.52–3.83 (m, 7H), 3.42 (t, 4H, $J = 6.8$ Hz), 3.40 (s, 2H), 3.31 (dd, 1H, $J = 8.2$ Hz, $J_{gem} = 14.0$ Hz), 3.22 (dd, 1H, $J = 7.7$ Hz, $J_{gem} = 14.0$ Hz), 3.04 (t, 4H, $J = 6.8$ Hz), 2.70 (dt, 2H, $J = 6.8$ Hz, $J_{H,P} = 15.0$ Hz), 2.66–2.82 (m, 2H, g), 2.47–2.63 ppm (m, 2H); ^{31}P NMR (160 MHz, D_2O): $\delta = 19.2$, 19.0 ppm; MS(ESI) $[M-H]^-$ calcd. 1162.24, found 1162.5, $[M-2H]^{2-}$ calcd. 580.6, found 580.4, $[M-3H]^{3-}$ calcd. 386.7, found 386.6.

7: According to the method for the synthesis of **4**, **40** (16.0 mg, 4.76 mmol) in ethyl acetate (0.250 mL), MeOH (1.70 mL) and H_2O (0.300 mL) was treated with $Pd(OH)_2$ (20.0 mg) and hydrogenated under H_2 gas atmosphere to give deprotected compound **7** (6.00 mg, 4.34 mmol, 91%). $[\alpha]_D^{25} = +3.5$ ($c = 0.12$, H_2O); IR (solid): $\tilde{\nu} = 3285$, 1630, 1554, 1403, 1084 cm^{-1}; ^1H NMR (400 MHz, D_2O): $\delta = 4.56$ (d, 2H, $J = 5.3$ Hz), 4.28 (dd, 1H, $J = 2.4$, 5.3 Hz), 4.24 (dd, 1H, $J = 2.4$, 5.3 Hz), 4.09 (m, 1H), 3.99 (dd, 1H, $J = 2.4$, 6.3 Hz), 3.82 (s, 8H), 3.75–3.82 (m, 3H), 3.71 (dd, 1H, $J = 4.8$ Hz, $J_{gem} = 9.1$ Hz), 3.62–3.65 (m, 2H), 3.59–3.60 (m, 2H), 3.50–3.55 (m, 3H), 3.41 (t, 4H, $J = 6.3$ Hz), 3.39 (s, 2H), 3.31 (dd, 1H, $J = 8.2$ Hz, $J_{gem} = 14.0$ Hz), 3.20–3.26 (m, 2H), 3.03 (t, 4H, $J = 6.3$ Hz), 2.70 (dt, 4H, $J = 6.8$, 15.5 Hz), 2.51 (t, 2H, $J = 6.8$, 21.3 Hz), 2.08 ppm (s, 3H, Ac); ^{31}P NMR (160 MHz, D_2O): $\delta = 19.1$ ppm; MS (ESI) $[M-H]^-$ calcd. 1380.33, found 1380.4, $[M-2H]^{2-}$ calcd. 689.7, found 689.7, $[M-3H]^{3-}$ calcd. 459.4, found 459.4.

8: According to the method for the synthesis of **4**, **41** (23.4 mg, 6.00 mmol, 1.00 equiv) in ethyl acetate (0.250 mL), MeOH (1.70 mL) and H_2O (0.200 mL) were treated with $Pd(OH)_2$ (20.0 mg) and hydrogenated under H_2 gas atmosphere to give **8** (3.30 mg, 2.12 mmol, 35%). $[\alpha]_D^{26} = +10.7$ ($c = 0.05$, H_2O); IR (solid) 3292, 1640, 1560, 1404, 1141, 1071, 902, 751, 568 cm^{-1}; ^1H NMR (400 MHz, D_2O): $\delta = 4.56$ (d, 1H, $J = 4.3$ Hz), 4.54 (d, 1H, $J = 5.3$ Hz), 4.34 (dd, 1H, $J = 2.4$, 4.3 Hz), 4.27 (dd, 1H, $J = 2.4$, 5.3 Hz), 4.08–4.11 (m, 1H), 3.99 (dd, 1H, $J = 2.4$, 6.8 Hz), 3.82 (s, 8H), 3.74–3.82 (m, 3H), 3.68–3.72 (m, 1H), 3.49–3.66 (m, 7H), 3.42 (t, 4H, $J = 6.3$ Hz), 3.40 (s, 2H), 3.31 (dd, 1H, $J = 5.8$ Hz, $J_{gem} = 9.7$ Hz), 3.21–3.27 (m, 2H), 3.04 (t, 4H, $J = 6.3$ Hz), 2.73–2.98 (m, 2H), 2.71 (dt, 4H, $J = 6.8$ Hz, $J_{H,P} = 15.5$ Hz), 2.49–2.61 (m, 1H), 2.48 ppm (tt, 2H, $J = 6.8$ Hz, $J_{H,P} = 21.7$ Hz); ^{31}P NMR (160 MHz, D_2O): $\delta = 19.1$, 19.0 ppm; MS(ESI) $[M-2H]^{2-}$ calcd. 776.6, found 776.9, $[M-3H]^{3-}$ calcd. 517.4, found 517.3.

9: According to the method for the synthesis of **4**, **44** (29.4 mg, 6.70 mmol) in ethyl acetate (0.250 mL), EtOH (0.250 mL), MeOH (1.50 mL), and H_2O (0.25 mL) were treated with $Pd(OH)_2$ (20.0 mg) and hydrogenated under H_2 gas atmosphere to give **9** (5.00 mg, 2.82 mmol, 42%). $[\alpha]_D^{25} = +10.8$ ($c = 0.05$, H_2O); IR (solid): $\tilde{\nu} = 3271$, 1631, 1403, 1167, 1055, 876, 620 cm^{-1}; ^1H NMR (400 MHz, D_2O): $\delta = 4.55$–4.59 (m, 3H), 4.23–2.30 (m, 3H), 4.08–4.11 (m, 1H), 4.00 (dd, 1H, $J = 1.9$. 6.8 Hz), 3.82 (s, 8H), 3.76–3.79 (m, 4H), 3.71 (m, 1H), 3.53–3.66 (m, 9H), 3.42 (t, 4H, $J = 6.3$ Hz), 3.40 (s, 2H), 3.31 (dd, 1H, $J = 7.7$ Hz, $J_{gem} = 14.0$ Hz), 3.20–3.29 (m, 3H), 3.03 (t, 4H, $J = 6.3$ Hz), 2.71 (dt, 6H, $J = 6.3$ Hz, $J_{H,P} = 15.0$ Hz), 2.51 (tt, 3H, $J = 6.3$ Hz, $J_{H,P} = 21.7$ Hz), 2.09 ppm (s, 3H, Ac); ^{31}P NMR (160 MHz, D_2O): $\delta = 19.11$, 19.02 ppm; MS(ESI) $[M+Na-3H]^{2-}$ calcd. 896.7, found 896.7.

10: According to the method for the synthesis of **4**, **45** (22.1 mg, 4.49 mmol) in ethyl acetate (0.250 mL), EtOH (0.250 mL), MeOH (1.50 mL) and H_2O (0.250 mL) was treated with $Pd(OH)_2$ (20.0 mg) and hydrogenated under H_2 gas atmosphere to give **10** (5.10 mg, 2.62 mmol, 58%). $[\alpha]_D^{25} = +2.7$ ($c = 0.15$, H_2O); IR (solid): $\tilde{\nu} = 3147$, 1637, 1522, 1401, 1161, 1053, 881, 670, 524 cm^{-1}; ^1H NMR (400 MHz, D_2O): $\delta = 4.52$–4.59 (m, 3H), 4.34 (dd, 1H, $J = 2.4$, 4.8 Hz), 4.22–4.29 (m, 2H), 4.09–4.11 (m, 1H), 3.99 (dd, 1H, $J = 1.9$, 6.8 Hz), 3.82 (s, 8H), 3.76–3.82 (m, 4H), 3.70–3.73 (m, 1H), 3.49–3.65 (m, 9H), 3.41 (t, 4H, $J = 6.3$ Hz), 3.40 (s, 2H), 3.30–3.33 (m, 1H), 3.20–3.25 (m, 3H), 3.04 (t, 4H, $J = 6.3$ Hz), 2.74–2.83 (m, 2H), 2.71 (dt, 6H, $J = 6.8$ Hz, $J_{H,P} = 15.5$ Hz), 2.55–2.63 (m, 1H), 2.51 ppm (tt, 3H, $J = 6.8$ Hz, $J_{H,P} = 20.8$ Hz); ^{31}P NMR (160 MHz, D_2O): $\delta = 19.06$ ppm; MS(ESI) $[M+Na-3H]^{2-}$ calcd. 983.7, found 983.7.

11: According to the method for the synthesis of **4**, **48** (23.6 mg, 4.36 mmol) in ethyl acetate (0.250 mL), EtOH (0.250 mL), MeOH (2.10 mL), and H_2O (0.250 mL) was treated with $Pd(OH)_2$ (20.0 mg) and hydrogenated under H_2 gas atmosphere to give **11** (5.90 mg, 2.72 mmol, 62%). $[\alpha]_D^{25} = +25.9$ ($c = 0.05$, H_2O); IR (solid): $\tilde{\nu} = 3258$, 1632, 1555, 1403, 1084, 903, 748, 579 cm^{-1}; ^1H NMR (400 MHz, D_2O): $\delta = 4.57$–4.60 (m, 4H), 4.27–4.29 (m, 4H), 4.10 (m, 1H), 3.99 (dd, 1H, $J = 1.9$, 6.8 Hz), 3.82 (s, 8H), 3.76–3.82 (m, 5H), 3.69–3.71 (m, 1H), 3.53–3.66 (m, 11H), 3.41–3.43 (m, 6H), 3.31 (dd, 1H, $J = 8.2$ Hz, $J_{gem} = 14.5$ Hz), 3.20–3.25 (m, 4H), 3.04 (t, 4H, $J = 5.8$ Hz), 2.71 (dt, 8H, $J = 6.3$ Hz, $J_{H,P} = 15.5$ Hz), 2.50 (tt, 4H, $J = 6.3$ Hz, JCP = 21.3 Hz), 2.09 ppm (s, 3H, Ac); ^{31}P NMR (160 MHz, D_2O): $\delta = 19.2$, 19.1 ppm; MS (ESI) $[M+Na-3H]^{2-}$ calcd. 1092.7, found 1092.6.

12: According to the method for the synthesis of **4**, **49** (21.5 mg, 3.62 mmol) in ethyl acetate (0.250 mL), EtOH (0.250 mL), MeOH (2.90 mL), and H_2O (0.250 mL) was treated with $Pd(OH)_2$ (20.0 mg) and hydrogenated under H_2 gas atmosphere to give **12** (4.70 mg, 2.01 mmol, 55%). $[\alpha]_D^{25} = +18.9$ ($c = 0.10$, H_2O); IR (solid): $\tilde{\nu} = 3209$, 1637, 1411, 1094, 960, 753, 542 cm^{-1}; ^1H NMR (400 MHz, D_2O): $\delta = 4.55$–4.59 (m, 4H), 4.35–4.37 (m, 1H), 4.27–4.28 (m, 3H), 4.09–4.11 (m, 1H), 3.99–4.00 (m, 1H), 3.81 (s, 8H), 3.72–3.81 (m, 6H), 3.53–3.65 (m, 11H), 3.39–3.42 (m, 6H), 3.31 (dd, 1H, $J = 5.8$ Hz, $J_{gem} = 13.5$ Hz), 3.19–3.25 (m, 4H), 3.04 (t, 4H, $J = 5.8$ Hz), 2.74–2.84 (m, 2H), 2.71 (dt, 8H, $J = 6.3$ Hz, $J_{H,P} = 15.0$ Hz), 2.57–2.59 (m, 1H), 2.50 ppm (tt, 4H, $J = 6.3$ Hz, $J_{H,P} = 21.3$ Hz); ^{31}P NMR (160 MHz, D_2O): $\delta = 19.1$ ppm; MS (ESI) $[M+Na-3H]^{2-}$ calcd. 1179.7, found 1179.4.

Hydroxyapatite Binding Assay

Hydroxyapatite binding assay using [^{14}C]-citric acid was performed according to procedures described previously with a slight modification.[17] In brief, 50 nM [^{14}C]-citric acid (Moravec Biochemicals, Inc.) and 1 μM tested compound were added to 50 mM Tris/HCl buffer solution (pH 7.4).

In vehicle group, [^{14}C]-citric acid and water were added. Binding reaction was initiated by addition of 0.02 mg mL^{-1} hydroxyapatite at RT. After 20 min, the binding reaction terminated by filtration through Whatman GF/B filters. Filters were washed twice with ice-cold Tris/HCl buffer solution and placed in scintillation vials. Bound radioactivity was determined using liquid scintillation spectroscopy. Nonspecific binding was defined in the presence of 10 μM hydroxymethylenediphosphonate (HMDP). Therefore, specific bound [^{14}C]-citric acid was defined as the difference between total bound [^{14}C]-citric acid minus [^{14}C]-citric acid in the presence of 10 μM HMDP.

Preparation of complexes of $^{111}In^{III}$ with the chelaters **4** , **8**, and **12**: Chelaters **4**, **8**, and **12** (0.1 mmol) were dissolved in 1.0 mL of 50 mM acetate buffer solution (1.0 mL, 50 mM, pH 5.0) and then, $^{111}In^{III+}$ (37 MBq) was added. To confirm that there was no presence of free $^{111}In^{III+}$ in the reaction mixture, reaction mixtures were applied to the cellulose acetate membrane (SEPARAX, Fuji Photo Film) and electrophoresis was performed. After the electrophoresis, the radioactivity was detected by the TLC scanner (Rita star, Ray test). Positive control ($^{111}In^{III}$) was prepared using the same procedure without any chelaters.

Imaging study of complexes of $^{111}In^{III}$ with the chelaters **4**, **8** and **12**: Animal experimental procedures were approved by the Nihon Mediphysics Animal Care Committee. The rats were anesthetized with 50 mg kg^{-1} pentobarbital intraperitoneally and then, 200 μCi of the complexes of $^{111}In^{III}$ with the chelaters **4**, **8**, or **12** was administered into the tail vein to male SD rats (7 weeks). Imaging data was obtained by using a gamma camera (GE Millenium MG, GE Healthcare) after administration.

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