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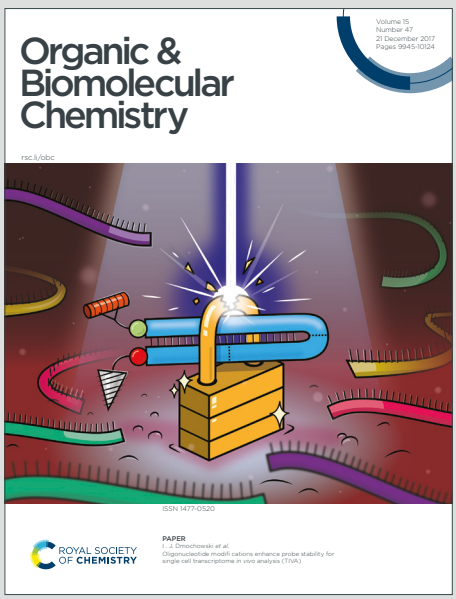

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ARTICLE

An Alternative Approach to the Synthesis of the Three Fragments of Anachelin H

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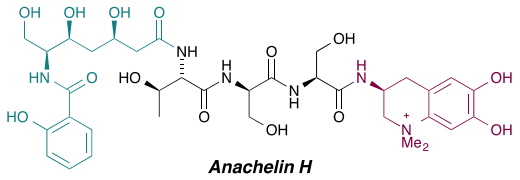
The synthesis of the fully protected peptide, polyketide and alkaloid fragments of Anachelin H are presented. The peptide fragment was prepared using a liquid phase peptide synthesis; the polyketide fragment was synthetized using a cross metathesis and an intramolecular oxa-Michael reaction as the key steps to introduce the desired stereochemistry; finally, the alkaloid fragment was obtained by an oxidative cyclization of a catechol derivative using potassium ferricyanide. The synthesis of all fragments was based on the use of natural aminoacids as sources of asymmetry. The independent synthesis of the three fragments should allow more efficient biological studies, on the fragments instead the whole natural product. Experiments to illustrate the coupling of fragments and the effectiveness of the convergent strategy are also described.

Introduction

Antimicrobial resistance is one of the largest public health problems worldwide.[1] Generally bacteria and other microorganisms evolve quickly enough to develop resistance in just a few years (even months) after the antibiotic drug is on the market;[2] in consequence multiple strategies to develop new antibiotics are highly important in medical, biological and chemical research, among others.[3] Anachelin H (Figure 1) is a naturally occurring iron chelator (siderophore) that was isolated from the freshwater blue green algae *Anabaena cylindrica* in 2000.[4] It has shown moderate antibacterial activity against the respiratory track pathogen *Moraxella catarrhalis*;[5] on the other hand it has been demonstrated that anachelin H enhances growth of the cyanobacterium *Microcystis aeruginosa* with simultaneous allelopathic activity against green algae *Kirchneriella contorta*, thus suggesting a dual mode of action.[6] Finally, the alkaloid fragment of anachelin H has been used in biomimetic surface modifications showing amazing results.[7]

Having in mind the aforementioned properties of anachelin H, its specific function as siderophore, as well as its particular and uncommon structure (composed of three fragments, polyketide, peptide and alkaloid), it seems plausible to assume that an expeditious synthesis of the natural product will derive in more conclusive and advanced biological studies, in order to determine the potential applications of anachelin H and its fragments. In consequence, the development of new synthetic strategies for molecules that can act as siderophores or sideromycins is highly desirable;[8] unfortunately, the complex structure of anachelin H translates into a challenge for synthetic organic chemists and it is also responsible for the very few synthetic reports described to date.



Anachelin H

Figure 1. Structure of *anachelin H*, highlighting the three fragments.

Gademann and coworkers described its total synthesis in 2004,[9] then some additional studies culminated with improvements in the synthesis of some fragments;[5-6,10] it is noteworthy to mention that some of those fragments may also act as siderophores and have shown interesting properties.

Inspired by those features, we decided to study the synthesis of anachelin H fragments, since a shorter and more efficient synthesis of the fragments will make them available for biological trials. Herein we detail our approaches and some unsuccessful strategies to construct independent fragments of anachelin H, a new synthesis of the polyketide unit and a significant improvement in the alkaloid portion synthesis. All our approaches are based on naturally occurring amino acids as source of asymmetry.

Results and Discussion

Our retrosynthetic analysis is based on the independent synthesis of the three fragments (see Figure 1). The synthesis of peptide **2** was accomplished in gram scale and 70% overall yield, starting with commercially available *O*-benzyl-L-serine methyl ester **1** and using subsequent couplings of D-serine and L-threonine by the BOP strategy (Scheme 1);[11] as this is a common

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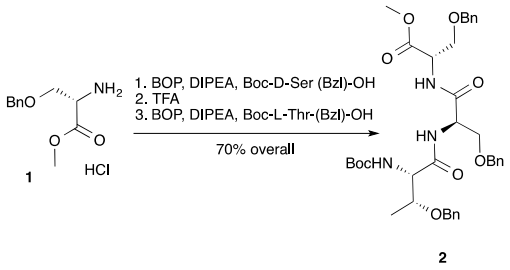
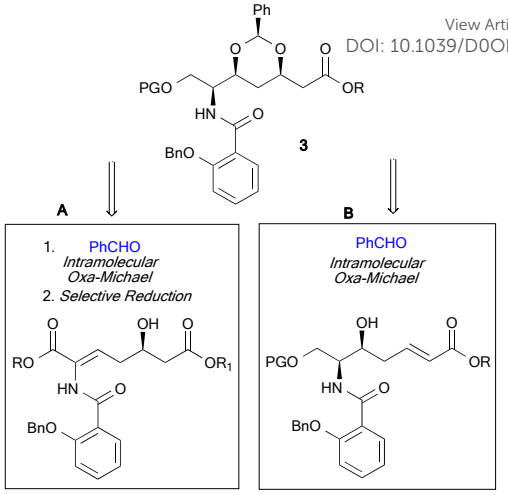
and well documented peptide synthesis we will not discuss it here.



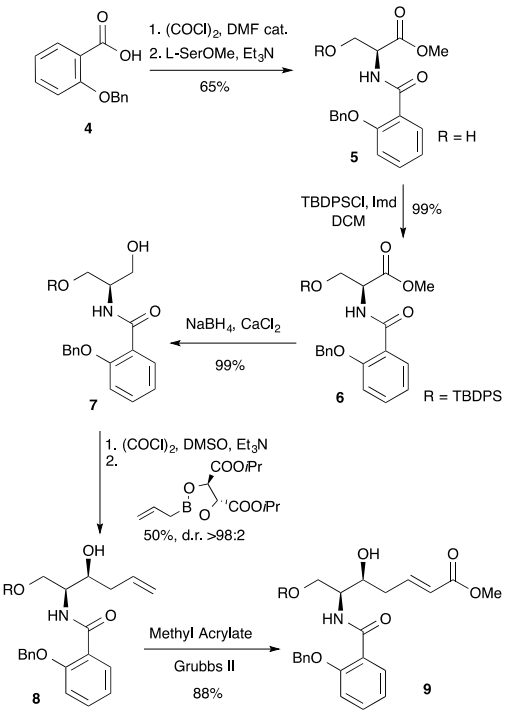
Scheme 1 Synthesis of fully protected peptide fragment **2**.

More challenging was the polyketide fragment; since one of our research topics is the diastereoselective construction of *syn* 1,3-diols using intramolecular oxa-Michael reactions (so-called Evans-Prunet reaction),[12] we envisaged to use this method to generate the desired stereochemistry in the fully protected polyketide fragment **3**.

The retrosynthetic analysis in Scheme 2 shows two possibilities. In route **A**, two stereogenic centers may be installed in a single step. However, our previous studies with similar molecules showed that highly electrophilic aldehydes or ketones - such as *p*-nirobenzaldehyde or trifluoroacetophenone - are the only suitable carbonyl substrates for the desired transformation,[13] and even if the desired stereochemistry was obtained, the stability of the corresponding acetals would make route **A** risky. In consequence, we turned our attention to route **B** and started our investigation using commercially available benzyloxy benzoic acid **4** and L-serine methyl ester (Scheme 3). The first step was the generation of the acyl chloride using oxalyl chloride and catalytic DMF, and the crude acid chloride reacted *in situ* with the amino acid ester to afford compound **5** in good yield. Because of future transformations the protection of the primary alcohol is mandatory; this was accomplished by installing a *tert*-butyldiphenylsilyl group under classic conditions yielding compound **6** quantitatively. The reduction of the methyl ester in **6** with DIBAL-H proved complicated and not reproducible, presumably because of the instability of the aldehyde, so complete reduction and further oxidation was a plausible alternative.



Scheme 2 Retrosynthetic analysis for polyketide fragment.

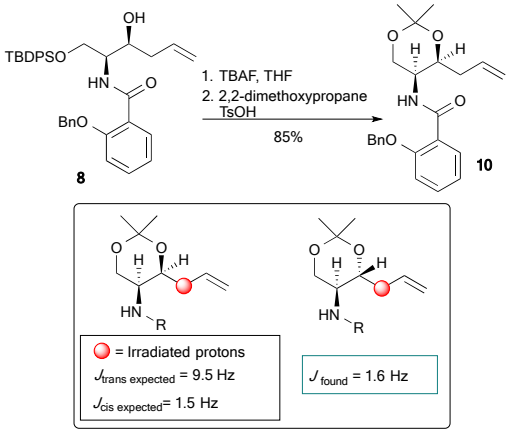


Scheme 3 Synthesis of polyketide precursor.

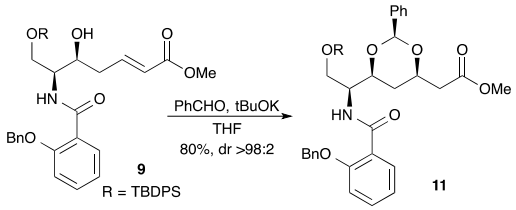
After trying different conditions, the reduction using calcium borohydride[14] (formed *in situ*) afforded the best results and the alcohol **7** was obtained in 99% yield. Unfortunately, oxidation to the aldehyde showed similar problems to those observed for the ester reduction, which means the aldehyde is difficult to purify and degradation is observed during the chromatography, no matter the oxidant used. However, Swern oxidation[15] produced the cleanest crude aldehyde product, which was used directly in the allylation step without further purification.

The literature describes allylation reactions on similar substrates giving the *syn* 1,2-amino alcohol, generally using Osomi-Sakurai allylation.[16] In our hands, the desired *syn* isomer was obtained as the major product but the best diastereomeric

ratio was only 1.6:1 using $SnCl_4$, and after separation of the isomers by flash chromatography compound **8** was obtained in 35% yield. All other attempts (direct allylation with allyl halides and metals) to perform a diastereoselective allylation were impractical, commonly the diastereoselectivity was low, consequently, we decided to try a matched Roush allylation[17] for better results, and the *syn* isomer **8** was the only isolated product in 50% yield over two steps. To investigate the stereochemical integrity of compound **8**, we performed TDBPS cleavage followed by acetonide formation (Scheme 4). The coupling constant in ketal **10** (obtained by homonuclear decoupling ^{1}H NMR experiments) proved unequivocally the *syn* 1,2-stereochemistry; *trans* coupling constants are typically between 9 and 9.5 Hz and *cis* coupling constants are less than 2.0 Hz;[18] in our case the measured constant was 1.6 Hz which is in entire agreement with the literature values. Cross metathesis of compound **8** and methyl acrylate provided product **9** in 88% yield.

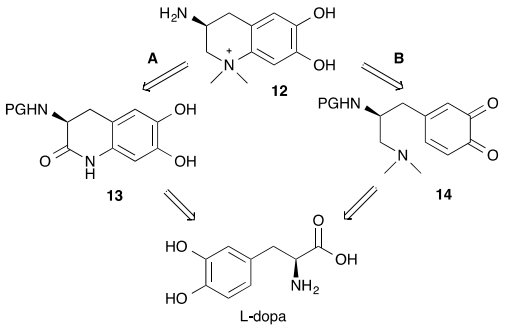


Scheme 4 Confirmation of stereocenters.

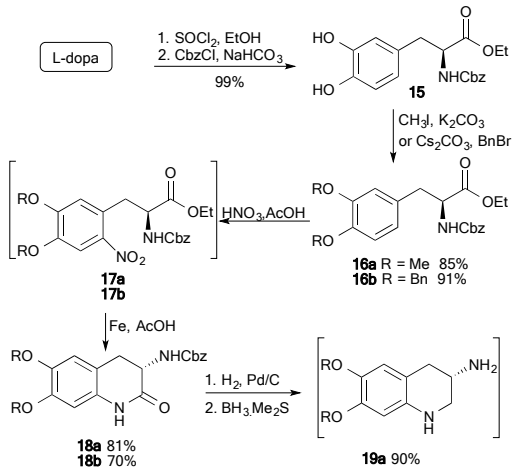


Scheme 5 Intramolecular oxa-Michael reaction performed on compound **9**.

The intramolecular oxa-Michael reaction is usually performed with substoichiometric amounts of base and an excess of benzaldehyde. In this case, the amide proton is acidic enough[19] to react with the base, producing undesirable byproducts; in consequence, a variation to the typical procedure was necessary. First, we used one equivalent of base to ensure the complete deprotonation of the amide followed by successive additions of base and benzaldehyde as is usual in this reaction; to our delight the benzylidene acetal **11** was obtained as a single diastereomer and in very good yield (Scheme 5). In summary, the synthesis of the fully protected polyketide fragment of anachelin H was accomplished in 22.4% overall yield, which is superior to the yield of the previous synthesis by Gademann. We then turned our attention to the synthesis of the alkaloid fragment **12**. It is noteworthy to mention that the 3-aminohydroquinolines are common fragments in natural products with a variety of biological activities,[20] so we decided to explore two alternative routes starting from L-dopa (Scheme 6).



Scheme 6 Plausible precursors for alkaloid **12**.



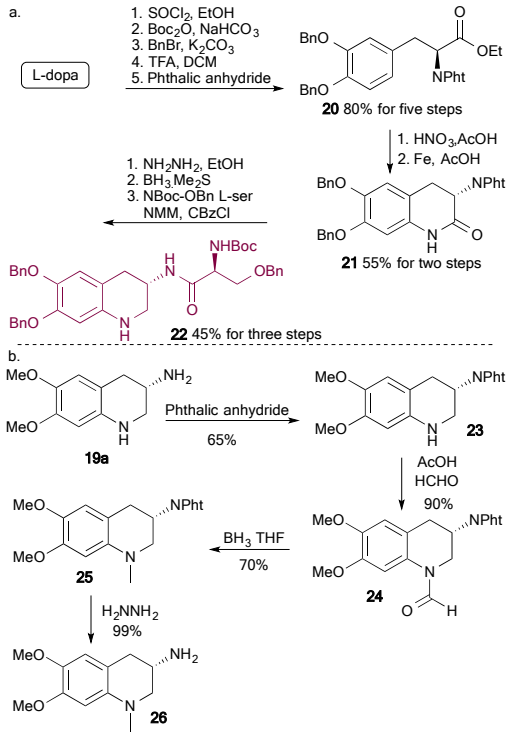
Scheme 7 Synthesis of alkaloid core **19a**.

Both approaches are founded on intramolecular cyclizations, route A is based on a reductive lactamization reaction from the nitro derivative of L-dopa; on the other hand, an intramolecular Michael reaction performed with the oxidized intermediate 14 should provide the desired alkaloid (route b, Scheme 6)

Route A (Scheme 7) started with esterification of L-dopa using the acyl chloride formed *in situ*, followed by protection of the amine to provide compound **15** in 99% yield. We then installed two different protecting groups on the aromatic hydroxyls, and both methyl **16a** and benzyl **16b** ethers where obtained in excellent yields. The literature emphasizes the role of nitrogen protecting group for the following nitration and reductive cyclization; apparently Alloc is the only group compatible with this sequence,[21] but in our case the Cbz proved adequate and the nitro compounds **17a** and **17b** were obtained in excellent yields.

Compounds **17a** and **17b** were used without further purification in the cyclisation step; in both cases the reductive cyclisation proceeded smoothly and compounds **18a** and **18b** were isolated in good overall yields. The lactam reduction on compound **18b** proved difficult and complex mixtures of products were obtained in all cases; besides all the attempts for selective cleavage of the carbamate on the same compound were also unsuccessful. In consequence, compound **18a** was deprotected with subsequent reduction of the lactam to afford the alkaloid core **19a**, which was used in subsequent reactions without any purification. Unfortunately, the high stability of the methyl ethers may be anticipated as a big issue in deprotection experiments, thus taking us to study an alternative route for the benzylated analogue (Scheme 8a).

Direct protection of the amine in L-dopa or its corresponding ester with a phthaloyl group was very complicated, so we were forced to perform the following sequence: esterification, then protection of the amine with a Boc, followed by benzylation and Boc cleavage, and finally the free amino group was protected using phthalic anhydride to give compound **20** in 80% yield over the five steps (Scheme 8a).



Scheme 8 *a.* Alternative route to alkaloid fragment. *b.* methylation of secondary nitrogen.

The nitration and successive reductive cyclisation provided the protected lactam **21** in good yield. All our attempts to reduce the lactam were ineffective, with reduction of the phthalimide as a side reaction. We thus cleaved the phthaloyl group, reduced the lactam and inserted the L-serine fragment using the mixed anhydride technique[22] with CbzCl, producing an advanced fragment of anachelin H in 45% yield (compound **22**), but a significant amount of the regioisomer was observed. We then tried the formation of the quaternary salt of anachelin H without any success. Accordingly, we moved back to compound **19a** (see Scheme 8b), which may be used without any purification. Protection of the amine gave compound **23**, which was formylated to afford compound **24**; the formamide group was selectively reduced with BH_3.THF complex yielding the methylated alkaloid **25**, and **26** was obtained after phthaloyl cleavage. Efforts to obtain the quaternary salts of compounds **22**, **23** and **25** were absolutely impractical, so we started our investigation of route B (see Scheme 6).

Route B (Scheme 9) started with protection and amidation of L-dopa, which produced dimethyl amide **27** in 65% yield over two steps. Then benzylation of the phenols and a sequence of Boc cleavage, amide reduction and protection of the primary amine provided the diamine **29** in good overall yield. According to literature precedents, the ring closure using free hydroxyl groups and dianisyl tellurium oxide (DTO) as the oxidant proceeded by a Michael-rearomatization reaction.[23] Having in mind the toxicity of the tellurium derivative and that its preparation is mandatory and also requires two steps from commercial starting materials,[24] we decided to explore other oxidants. Habitually, the oxidation of catechols is accomplished using $NaIO_4$[25] or Ag_2O;[26] however, those reagents as well as hypervalent iodine reagents were inactive with our substrate. Inspired by the work of ElSohly and Francis,[27] we used $K_3[Fe(CN)_6]$, observing the desired hydroquinoline salt by ^{1}H NMR of the crude reaction mixture, but its isolation was problematic. Freeze-drying of the aqueous phase followed by benzylation afforded the Boc protected quaternary salt in higher yield compared with the use of DTO.

At this point we had in hand the three fragments of anachelin H and some analogues, particularly the tertiary amine **26**. Previous works on anachelin H synthesis are based on the construction of alkaloid-peptide fragment by growing the peptide using the alkaloid as a template, which means the alkaloid fragment is usually obtained with one amino acid attached to it (similar to compound **22**), then a dipeptide is introduced to produce the desired fragment, and posterior coupling with the polyketide leads to the synthesis of the natural product. Having this in mind, we were interested in the coupling of the alkaloid and peptide fragments, in order to demonstrate that our strategy is more convergent than the previously reported approaches.

We prepared the alkaloid-peptide fragment of anachelin H using carbonyl imidazole as the coupling auxiliary, leading to compound **31** in reasonable yield (Scheme 10a). We also performed the saponification of the polyketide ester to acid **32**, followed by its coupling with a dipeptide to afford compound **33**, which illustrates the potential construction of the natural product following a convergent strategy based on the independent construction of the three fragments. The same coupling between the alkaloid analogue **26** and peptide **2** was performed, yielding fragment **34**; this could be linked to the polyketide fragment in acceptable yield, to produce the fully protected analogue **35**. It is noteworthy to mention that transformations in Schemes 10 and 11 help to demonstrate coupling of fragments, affording advanced material in the potential synthesis of the natural product

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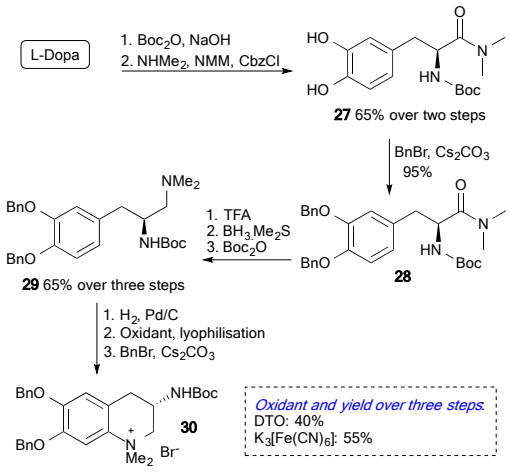
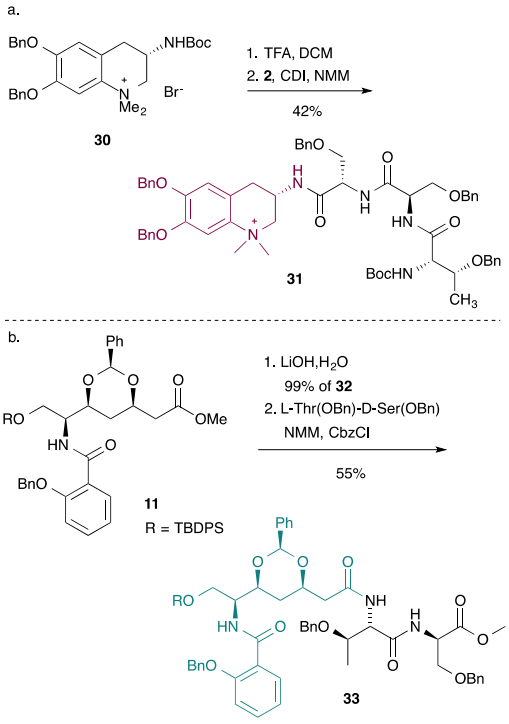


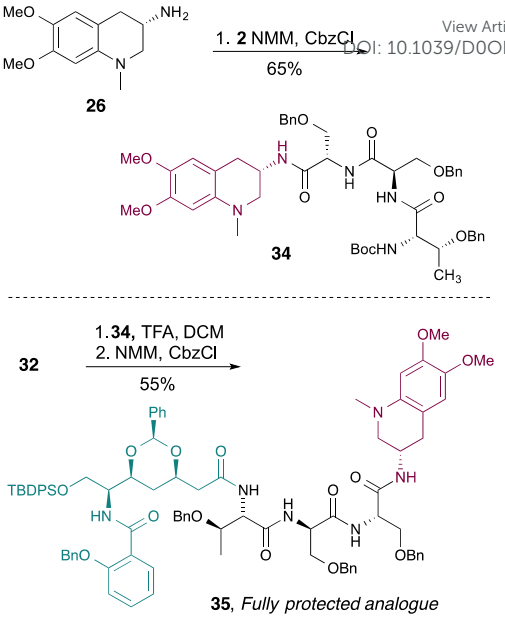
Scheme 9 Synthesis of alkaloid fragment of anachelin H.



Scheme 10 Coupling experiments.

Conclusions

The synthesis of all three fragments of anachelin H was completed, along with the synthesis of advanced portions of the target molecule. The preparation of all the fragments was achieved using amino acids as starting materials, thus making this route inexpensive and potentially scalable. We also described the use potassium ferricyanide - a cheaper and less toxic reagent - as an alternative to the use of DTO (dianisyl tellurium oxide) for the crucial cyclisation step in the alkaloid synthesis. The synthesis of the fully protected polyketide fragment is also described by a shorter reaction sequence compared with previous reports.



Scheme 11 Coupling experiments.

Experimental section

General information. All reactions were performed under argon atmosphere. All solvents were distilled from appropriate drying agents prior to use. All reagents were used as received from commercial suppliers. Reactions progress was monitored by thin layer chromatography (TLC) performed on aluminum plates coated with silica gel F_{254} with 0.2 mm thickness. Flash column chromatography was performed using silica gel 60 (230-400 mesh). Neat infrared spectra were recorded using a THERMO NICOLET-NEXUS (FT-IR) with PIKE MIRacle ATR cell. Wavenumbers (vmax) are reported in cm^{-1}. High Resolution Mass spectrometry was recorded using a Finnigan MAT 8200 or (70 eV) or an Agilent 5973 (70 eV) spectrometer, using electrospray ionization (ESI). All ^1H NMR and ^{13}C NMR spectra were recorded using a BRUKER Avance III HD Ascend 400 spectrometer. Chemical shifts were given in parts per million (ppm, δ), referenced to the TMS, solvent peak of $CDCl_3$ defined at δ = 7.26 ppm (^1H NMR) and δ = 77.16 (^{13}C NMR). Coupling constants are quoted in Hz (J). ^1H NMR splitting patterns were designated as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), double quartet (dq), and multiplet (m). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m).

L-Ser(OBn)-D-Ser(OBn)-BocL-Thr(OBn) methyl ester (2). Boc-D-Ser-(Bzl)-OH (960 mg, 3.25 mmol) was dissolved in dry DMF (6.0 mL), and BOP reagent (1.36 g, 2.95 mmol) and *O*-Bzl-L-Serine methyl ester (730 mg, 2.95 mmol) were successively added. After 5 min, DIPEA (1.42 mL, 8.12 mmol) was added, and the reaction mixture was stirred at room temperature for 24 hours, then saturated aqueous $NaHCO_3$ was added. The mixture was extracted with DCM (3 x 20 mL), the organic phases were combined, washed three times with water, brine, aqueous $KHSO_4$ (1.0 M), dried over anhydrous Na_2SO_4 filtered and

concentrated *in vacuo*. The crude dipeptide was used without further purification. It was dissolved in dry DCM (15 mL), then cooled to 0 °C, and TFA (3.5 mL, 45 mmol) was slowly added. The reaction mixture was stirred for 2.5 hours, the volatiles were evaporated. The crude product was directly used in the next step, dissolving it in dry DMF (6.0 mL) and mixing it with BOP Reagent (1.43 g, 3.25 mmol). Then Boc-L-Thr-(Bzl)-OH (1.05 g, 3.25 mmol) and DIPEA (1.42 mL, 8.12 mmol) were successively added, the reaction mixture was stirred for 12 hours, and saturated aqueous $NaHCO_3$ was added. The mixture was extracted with DCM (3 x 20 mL), the organic phases were combined, washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (DCM : EtOAc 30:1) to give the desired compound as a white solid. Melting point 127-129 °C. (1.54 g, 70% yield). $[\alpha]_D^{21.7}$: +19.8 (*c* 0.66, $CHCl_3$). IR (neat): 3294, 2926, 1747, 1635, 1390, 1247, 1056 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 7.17 – 7.42 (m, 17 H), 5.50 (d, *J* = 7.1 Hz, 1H), 4.70 – 4.77 (m, 1H), 4.66 (m, 1H), 4.54 (m, 2H), 4.50 (s, 1H), 4.38 - 4.48 (m, 3H), 4.30 (d, *J* = 5.5 Hz, 1H), 4.18 (d, *J* = 4.3 Hz, 1H), 3.86 (m, 2H), 3.68 (s, 3H), 3.64 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.54 (dd, *J* = 9.3, 6.7 Hz, 1H), 1.44 (s, 9H), 1.14 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 170.4, 170.2, 169.5, 155.9, 137.9, 137.5, 137.4, 128.4, 128.3, 128.3, 127.8, 127.8, 127.7, 127.7, 127.6, 80.2, 74.3, 73.4, 73.2, 71.5, 69.3, 69.1, 58.1, 52.9, 52.8, 52.5, 28.3, 15.8. HRMS (ESI-TOF) m/z: [M+H] Calcd for $C_{37}H_{48}N_3O_9$ 678.3385; found 678.3380.

Methyl (2-(benzyloxy)benzoyl)-L-serinate (5). To a 0 °C solution of 2-benzyloxy benzoic acid (3.75 g, 15.7 mmol) in cyclohexane (60 mL), DMF (0.10 mL) was added, and after 2 min oxalyl chloride (4.20 mL, 50 mmol) was added dropwise. The reaction mixture was then refluxed for 12 hours, and the crude acid chloride obtained after concentration was dissolved in 25 mL of dry dioxane. The L-serine methyl ester hydrochloride (2.44 g, 15.7 mmol) was dissolved in 100 mL of dry dioxane and freshly distilled triethylamine (7.60 mL, 55 mmol) was slowly added, then the initial solution of the acid chloride was slowly added and the reaction mixture was stirred at room temperature for 12 hours. It was filtered and extracted with DCM (3 x 20 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (DCM : EtOAc 2:10) to give the desired compound as a yellow solid. (3.36 g, 65 % yield). The spectroscopy data and physical constants of (**5**) were in good agreement with those reported in the literature.[28] Melting point: 130°C. lit. 129°C. [28] $[\alpha]_D^{21.7}$: +26.4 (*c* 1.0, $CHCl_3$). Lit. $[\alpha]_D^{26}$: +25.33 (*c* 1.4, MeOH). ^1H NMR (400 MHz, $CDCl_3$), δ: 8.70 (d, *J* = 6.5 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.29 – 7.44 (m, 6H), 7.01 (m, 2H), 5.21 – 5.13 (m, 2H), 4.77 (dt, *J* = 7.5, 3.9 Hz, 1H), 3.83 (dd, *J* = 9.1, 4.8 Hz, 2H), 3.62 (s, 3H), 2.11 (s, 1H).

Methyl *N*-(2-(benzyloxy)benzoyl)-*O*-(tert-butyldiphenylsilyl)-L-serinate (6). To a stirred solution of the L-serine ester derivative (5) (1.66 g, 5 mmol) in dry DCM (20 mL), imidazole (410 mg, 6 mmol) and TBDPSCl (1.50 mL, 5.5 mmol) were successively added, and the reaction mixture was stirred at room temperature for 24 hours. Then saturated aqueous $NaHCO_3$ was added, and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*, and the crude product was purified by flash chromatography (CHX : DCM 1 : 10) to give the titled compound as a colorless oil (2.85 g, 99% yield). $[\alpha]_D^{21.7}$: -1.4 (*c* 1.0, $CHCl_3$). IR (neat): 3392, 2953, 2931, 2856, 1745, 1651, 1209, 1047, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 8.91 (d, *J* = 7.7 Hz, 1H), 8.18 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.49 – 7.59 (m, 4H), 7.20 – 7.42 (m, 12H), 7.05 (m, 1H), 6.95 (dd, *J* = 8.4, 1 Hz, 1H), 5.23 (q, *J* = 12.8 Hz, 2H), 4.92 – 4.97 (m, 1H), 4.10 (dd, *J* = 10.1, 3.3 Hz, 1H), 3.97 (dd, *J* = 10.1, 3.3 Hz, 1H), 3.68 (s, 3H), 0.95 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 171.0, 164.8, 156.9, 135.8, 135.5, 135.4, 133.1, 132.9, 132.5, 129.8, 129.7, 128.7, 128.1, 127.7, 127.6, 127.2, 121.4, 113.2, 70.9, 64.4, 60.4, 54.9, 52.2, 26.9, 26.6, 19.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{34}H_{38}NO_5Si$ 568.2514; found 568.2510.

(*R*)-2-(Benzyloxy)-*N*-(1-((tert-butyldiphenylsilyl)oxy)-3-hydroxypropan-2-yl)benzamide (7). To a 0 °C solution of the protected L-serine methyl ester derivative (6) (2.02 g, 3.5 mmol), in dry ethanol (13.0 mL), was added $CaCl_2$ (800 mg, 7 mmol), keeping the same temperature, and $NaBH_4$ (540 mg, 14 mmol). The reaction mixture was slowly warmed up to room temperature and stirred for 18 hours, poured into ice/citric acid mixture and extracted with AcOEt (3 x 20 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent afforded the product as a colorless oil (1.92 g, 99 % yield). $[\alpha]_D^{21.7}$: -22.8 (*c* 1.0, $CHCl_3$). IR (neat): 3392, 2854, 1639, 1520, 1228, 1112, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 8.26 (d, *J* = 7.7 Hz, 1H), 8.09 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.50 (dd, *J* = 9.6, 8.0 Hz, 4H), 7.11 – 7.32 (m, 12H), 6.95 (t, *J* = 7.6 Hz, 1H) 6.87 (d, *J* = 8.3 Hz, 1H), 5.00 (d, *J* = 1.8 Hz, 2H), 4.11 – 4.22 (m, 1H), 3.50 – 3.75 (m, 4H), 2.65 – 2.92 (bs, 1H), 0.90 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 165.7, 156.8, 135.6, 135.5, 135.5, 133.1, 132.9, 132.8, 132.4, 129.8, 129.8, 128.7, 128.5, 127.8, 127.7, 127.6, 121.8, 121.6, 112.9, 71.3, 63.6, 63.6, 60.4, 52.8, 26.8, 19.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{33}H_{38}NO_4Si$ 540.2565; found 540.2550.

2-(Benzyloxy)-*N*-((2*S*,3*S*)-1-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxyhex-5-en-2-yl)benzamide (8). a) *Swern oxidation.* To a solution of oxalyl chloride (0.13 mL, 1.56 mmol) in dry DCM (2.0 mL) at -63 ºC was slowly added dry dimethyl sulfoxide (0.14 mL, 2.07 mmol) dissolved in dry DCM (1.0 mL). The reaction mixture was stirred at -63 °C for 30 min, then a solution of L-serine derivative alcohol (**7**) (280 mg, 0.52 mmol) in dry DCM (1.0 mL) was added dropwise. The mixture was stirred for 2 hours keeping the same temperature, after that, freshly distilled triethylamine (0.43 mL, 3.12 mmol) was slowly added, and the reaction mixture was slowly warmed up to room temperature. It was then diluted with DCM and washed with 10% aqueous HCl, then saturated aqueous $NaHCO_3$, and brine. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude aldehyde was kept at -20 °C and directly used without further purification. b) *Roush allylation.* The crude aldehyde (280 mg, 0.52 mmol) was dissolved in dry toluene (3.0 mL), and warmed up to room

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temperature, then 0.15 g of activated 4 Å molecular sieves were added, and the mixture was stirred for 30 min. It was then cooled to -78 °C and Roush allylboronate solution[29] (approx. 0.54 mmol of Roush allyboronate per milliliter, 1.85 mL, 1 mmol) was added dropwise. The reaction mixture was stirred for 8 hours at –78 °C, and slowly warmed up to room temperature and stirred for 3 hours. The residue was filtered, diluted with ether and mixed with 30 mL of 1 M aqueous NaOH, under vigorous stirring for 1 hour. The phases were separated and the aqueous one was extracted with ether, the combined organic phases were washed with $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (CHX : DCM 1 : 80) to give the desired compound as a colorless oil and as a single diastereomer (150 mg, 50% yield). $[\alpha]_D^{21.7}$: + 22.0 (*c* 1.0, $CHCl_3$). IR (neat): 3391, 2955, 2928, 2856, 1639, 1619, 1427, 1111, 997 cm $^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.46 (d, *J* = 8.3 Hz, 1H), 8.20 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.56 – 7.63 (m, 4H), 7.19 – 7.44 (m, 14H), 5.73 – 5.85 (m, 1H), 5.20 (q, *J* = 11.8 Hz, 2H), 5.00 – 5.08 (m, 2H), 4.16 – 4.24 (m, 1H), 4.06 (t, *J* = 6.7 Hz, 1H), 3.85 (qd, *J* = 10.3, 4.5 Hz, 2H), 2.78 (d, *J* = 2.3 Hz, 1H), 2.20 (t, *J* = 6.8 Hz, 2H), 1.00 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 165.3, 156.8, 135.5, 135.4, 134.5, 132.7, 132.6, 132.5, 129.8, 129.7, 128.7, 128.4, 127.9, 127.8, 127.7, 121.9, 121.4, 117.7, 112.7, 71.4, 71.1, 65.6, 53.2, 38.6, 29.7, 26.8, 19.1. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{36}H_{42}NO_4Si$ 580.2878; found 580.2880.

Methyl (5*S*,6*S*,E)-6-(2-(benzyloxy)benzamido)-7-((*tert*-butyldiphenylsilyl)oxy)-5-hydroxyhept-2-enoate (9). To a room temperature solution of the homoallylic alcohol (**8**) (380 mg, 0.66 mmol), in dry DCM (12 mL), methyl acrylate (0.3 mL, 3.3 mmol) and Grubbs II catalyst (30 mg, 0.02 mmol) were successively added, and the reaction mixture was refluxed for 12 hours. It was then concentrated *in vacuo* and directly purified by flash chromatography (DCM : EtOAc 1:20), affording the product as a colorless oil (370 mg, 88% yield). $[\alpha]_D^{21.7}$: +3.0 (*c* 1.0, $CHCl_3$). IR (neat). 3358, 2933, 2901, 2866, 1697, 1573, 1411, 1284, 1188, 995, 740. cm $^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.38 (d, *J* = 8.2 Hz, 1H), 8.11 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.46 – 7.56 (m, 4H), 7.13 – 7.37 (m, 12H), 6.95 – 7.04 (m, 2H), 6.80 - 6.93 (m, 1H), 5.74 (d, *J* = 15.6 Hz, 1H), 5.10 (q, *J* = 11.6 Hz, 2H), 4.01 – 4.12 (m, 2H), 3.76 (d, *J* = 4.4 Hz, 2H), 3.61 (s, 3H), 2.82 (d, *J* = 2.9 Hz, 1H), 2.22 (t, *J* = 6.7 Hz, 2H), 0.93 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 166.7, 165.4, 156.9, 145.4, 135.5, 135.5, 135.4, 132.9, 132.7, 132.6, 132.5, 129.9, 129.9, 128.8, 128.6, 128.0, 127.8, 127.8, 127.7, 127.7, 123.1, 121.7, 121.4, 112.7, 71.2, 70.6, 65.4, 53.8, 51.3, 37.1, 26.9, 19.1. HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{38}H_{43}NO_6Si$ 637.2860; found 637.2862.

***N*-((4S,5S)-4-allyl-2,2-dimethyl-1,3-dioxan-5-yl)-2-(benzyloxy)benzamide (10).** To solution of the protected alcohol (**8**) (210 mg, 0.36 mmol) in dry THF (4 mL) at 0 ºC, 1.0 M TBAF in THF (0.6 mL, 0.6 mmol) was slowly added. The reaction mixture was stirred for 4 hours at the same temperature, slowly warmed up to room temperature, diluted with water and extracted four times with AcOEt. The combined organic phases were washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was directly dissolved in 4 mL of dry THF, then, at room temperature, 2,2 dimethoxypropane (0.35 mL, 2.88 mmol) and *p*-toluenesulfonic acid (7 mg, 0.03 mmol) were successively added, and the reaction mixture was stirred for 24 hours. Then saturated aqueous $NaHCO_3$ was added, and the aqueous phase was extracted with AcOEt (3 x 10 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (DCM: EtOAc 6:1) to give the title compound as a yellow oil (120 mg, 85% yield). $[\alpha]_D^{19}$: +6.6 (*c* 2.4, $CHCl_3$). IR (neat): 3321, 2891, 1655 516, 1308, 1212 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.58 (d, *J* = 8.7 Hz, 1H), 8.21 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.30 – 7.45 (m, 6H,), 6.93 – 7.16 (m, 2H), 5.61 – 5.88 (m, 1H), 5.28 (s, 2H), 5.05 (d, *J* = 5.7 Hz, 1H), 5.02 (s, 1H), 4.06 – 4.19 (m, 2H), 4.01 (t, *J* = 6.2 Hz, 1H), 3.84 (d, *J* = 11.9 Hz, 1H), 2.14 (t, *J* = 6.9 Hz, 2H), 1.44 (s, 3H), 1.22 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ: 165.1, 156.7, 135.5, 133.7, 132.7, 132.4, 128.9, 128.4, 127.9, 122.0, 121.4, 117.4, 112.8, 98.9, 71.1, 71.1, 64.9, 45.7, 36.4, 29.7, 18.6. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{28}NO_4$ 382.2013; found 382.2020.

Methyl 2-((2*S*,4*R*,6*S*)-6-((*S*)-1-(2-(benzyloxy)benzamido)-2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)acetate (11). To a 0°C stirred solution of the homoallylic alcohol (**9**) (100 mg, 0.15 mmol) in dry THF (1.5 mL) was added freshly distilled benzaldehyde (0.02 mL, 0.17 mmol). After 5 min *t*-BuOK (20 mg, 0.15 mmol) was added, the mixture was stirred at the same temperature for 20 min, after that, benzaldehyde (0.02 mL, 0.17 mmol) was added followed by *t*-BuOK (2 mg, 0.01 mmol). The resulting solution was stirred for 15 min at 0 °C. This sequence (addition/stirring) was repeated three times. The reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (DCM) to give the titled compound as a yellow oil (90 mg, 80% yield). $[\alpha]_D^{21.7}$: +13.6 (*c*. 0.8 $CHCl_3$). IR (neat): 3210, 2981, 2821, 2832, 1721, 1511, 1256, 1238, 859, 741cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.18 (dd, *J* = 15.8, 8.4 Hz, 2H), 7.63 (dd, *J* = 18.9, 7.1 Hz, 4H), 7.00 – 7.42 (m, 18H), 6.90 (d, *J* = 8.3 Hz, 1H), 5.53 (s, 1H), 4.99 (m, 2H), 4.43 – 4.58 (m, 2H), 4.38 (m, 1H), 3.61 – 3.81 (m, 5H), 2.66 (dd, *J* = 15.8, 7.5 Hz, 1H), 2.48 (dd, *J* = 15.8, 5.4 Hz, 1H), 1.64 – 1.77 (m, 2H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 171.1, 165.4, 156.6, 138.3, 135.6, 135.6, 135.5, 133.4, 133.3, 132.7, 132.3, 129.7, 129.6, 128.6, 128.2, 128.0, 127.7, 127.7, 127.1, 126.0, 121.9, 121.4, 113.0, 100.4, 73.6, 73.2, 70.8, 61.5, 53.6, 51.7, 40.8, 32.9, 26.9, 19.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{45}H_{50}NO_7Si$ 744.3351; found 744.3367.

Ethyl (*S*)-2-(((benzyloxy)carbonyl)amino)-3-(3,4-dihydroxyphenyl)propanoate (15). To a 0 °C stirred suspension of L-dopa (1.5 g, 7.6 mmol) in dry EtOH (40.0 mL) was dropwise added thionyl chloride (1 mL, 13.7 mmol). After 15 min, the mixture was refluxed for 24 hours, then, the excess of thionyl chloride was removed under an air flux and the resulting white solid was dried for 3 hours under high vacuum. The solid was dissolved in water (50 mL), and $NaHCO_3$ (1.27 g, 15.2 mmol) and benzyl chloroformate (1.2 mL, 9.12 mmol) dissolved in THF (20 mL), were successively added. The reaction mixture was stirred

for 24 hours. The volatiles were evaporated, and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with water, 5% aqueous HCl, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*, affording the title compound as a colorless oil (2.72 g, 99 % yield). $[\alpha]_D^{18}$: + 28.2 (*c*. 2,8 $CHCl_3$). IR (neat): 3250, 2981, 1731, 1511, 1223, 1157 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 7.15 – 7.45 (m, 5H), 6.56 – 6.78 (m, 2H), 6.47 (dd, *J* = 8.0, 1.5 Hz, 1H), 5.42 – 5.52 (m, 1H), 5.05 (s, 2H), 4.49 – 4.62 (m, 1H), 4.06 – 4.18 (m, 2H), 2.94 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 172.0, 156.1, 143.9, 143.2, 136.0, 128.5, 128.2, 128.1, 127.9, 121.5, 116.2, 115.3, 67.2, 61.8, 55.0, 37.6, 14.1. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{22}NO_6$ 360.1442; found 360.1439.

Ethyl (*S*)-2-(((benzyloxy)carbonyl)amino)-3-(3,4-dimethoxyphenyl)propanoate (16a). *N*-Cbz L-dopa ethyl ester (**15**) (470 g, 1.30 mmol) was dissolved in dry acetone (20 mL), then dry K_2CO_3 (1.55 g, 11.1 mmol) was added, and after 5 min, iodomethane (1.38 mL, 22 mmol) was added dropwise. The reaction mixture was stirred at reflux for 6 hours. Then it was filtered, and the filtrate was concentrated *in vacuo* then dissolved in EtOAc. This organic phase was washed with water, brine, dried over anhydrous Na_2SO_4, affording the product as a colorless oil (420 mg, 85% yield). $[\alpha]_D^{18}$: +34.0 (*c* 4.4, $CHCl_3$), δ: IR: 1747, 1695, 1516, 1456, 1271, 1139, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 7.25 – 7.40 (m, 5H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.58 – 6.70 (m, 2H), 5.24 (d, *J* = 7.7 Hz, 1H), 5.10 (m, 2H), 4.52 – 4.68 (m, 1H), 4.17 (dd, *J* = 14.3, 7.2 Hz, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 3.06 (t, *J* = 5.8 Hz, 2H), 1.25 (t, *J* = 7.1, Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 171.8, 155.9, 148.9, 148.1, 136.5, 128.5, 128.4, 128.0, 127.9, 121.4, 112.5, 111.3, 111.0, 66.7, 61.4, 55.7, 55.6, 55.2, 37.6, 14.1. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{25}NNaO_6$ 410.1574; found 410.1595.

Ethyl (*S*)-2-(((benzyloxy)carbonyl)amino)-3-(3,4-*bis*(benzyloxy)phenyl)propanoate (16b). *N*-Cbz L-dopa ethyl ester (**15**) (1.20 g, 3.33 mmol) was dissolved in dry acetone (50.0 mL), then K_2CO_3 (1.55 g, 13.3 mmol) was added, and after 5 min benzyl bromide (1.4 mL, 11.6 mmol) and NaI (0.05 g, 0.33 mmol) were successively added. The reaction mixture was stirred at reflux for 30 hours. The solvent was evaporated, the residue was dissolved in DCM, washed with water, 5% HCl and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (CHX : DCM 1:1) to give the title compound as a white solid (1.60 g, 91% yield). Melting point: 140°C. $[\alpha]_D^{18}$: +25.3 (*c* 0.6, $CHCl_3$). IR: 1747, 1681, 1523, 1454, 1276 cm^{-1}. ^1H NMR (400 MHz,), δ: 7.36 (m, 15H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.72 (s, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 5.02 – 5.20 (m, 7H), 4.57 (d, *J* = 6.6 Hz, 1H), 4.00 – 4.15 (m, 2H), 3.00 (d, *J* = 5.3 Hz, 2H), 1.18 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 171.5, 155.6, 148.9, 148.2, 137.3, 137.1, 136.2, 129.0, 128.5, 128.5, 128.2, 128.1, 127.8, 127.8, 127.3, 127.3, 122.4, 116.2, 115.1, 71.3, 66.9, 61.4, 54.8, 37.8, 14.1. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{33}H_{34}NO_6$ 540.2381; found 540.2377.

Benzyl (*S*)-(6,7-dimethoxy-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate (18a). The protected L-dopa derivative (**16a**) (420 mg, 1.08 mmol) was dissolved at 0 °C in glacial acetic acid (2.2 mL), then, concentrated aqueous nitric acid (0.80 mL, 13.3 mmol) dissolved in glacial acetic acid (2 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 2 hours, water was added, and the mixture was filtered. The obtained solid was dried under high vacuum and directly dissolved in glacial acetic acid (4 mL). The mixture was heated at 80 °C, then iron powder (1.09 g, 19.5 mmol) was added in three portions. After 2 hours of reflux, the cold reaction mixture was filtered through a pad of celite, poured into water and 6 M aqueous NaOH was added until pH 14. The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained after column chromatography (DCM : EtOAc 10:3) as a white solid (310 mg, 81% yield). Melting point: 171°C. $[\alpha]_D^{18}$: - 28.8 (*c* 0.3, $CHCl_3$). IR: 16725, 1698, 1505, 1260, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 9.20 (s, 1H), 7.24 – 7.44 (m, 5H), 6.68 (s, 1H), 6.42 (s, 1H), 6.03 (d, *J* = 5.3 Hz, 1H), 5.14 (s, 2H), 4.38 (m, 1H), 3.82 (s, 3H), 3.83 (s, 3H), 3.36 (dd, *J* = 12.9, 6.1 Hz, 1H), 2.78 (t, *J* = 5.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 169.6, 157.2, 156.2, 148.7, 145.2, 136.2, 128.5, 128.2, 128.1, 114.0, 111.9, 100.7, 67.0, 56.3, 56.2, 50.5, 31.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{21}N_2O_5$ 357.1445; found 357.1454.

Benzyl (*S*)-(6,7-*bis*(benzyloxy)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)carbamate (18b). The protected L-dopa derivative (**16b**) (120 mg, 0.22 mmol) was dissolved at 0 °C in glacial acetic acid (1.0 mL), then concentrated aqueous nitric acid (0.15 mL, 13.3 mmol) dissolved in glacial acetic acid (1.0 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 3 hours, water was added, and the mixture was filtered. The obtained solid was dried under high vacuum and directly dissolved in glacial acetic acid (2.0 mL). The mixture was heated at 80 °C, and iron powder (220 mg, 3.9 mmol) was added in one portion. After 1.5 hours of reflux, the cold reaction mixture was filtered through a pad of celite, poured into water, and 6 M aqueous NaOH was added until pH 14. The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained after column chromatography (DCM : EtOAc 10:1) as a brown oil (79 mg, 70% yield). $[\alpha]_D^{18}$: +12.6 (*c* 0.6, $CHCl_3$). IR (neat): 1716, 1685, 1508, 1388, 1226 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 7.74 (s, 1H), 7.22 – 7.48 (m, 15H), 6.78 (s, 1H), 6.37 (s, 1H), 5.85 (s, 1H), 5.11 (m, 6H), 4.34 (m, 1H), 3.36 (dd, *J* = 14.3, 5.2 Hz, 1H), 2.74 (t, *J* = 14.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 169.4, 156.1, 148.7, 145.1, 137.1, 136.8, 136.2, 130.0, 128.6, 128.6, 128.2, 128.2, 128.1, 128.0, 127.4, 127.3, 116.0, 115.0, 103.8, 72.0, 71.5, 67.0, 50.4, 31.8.

HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{29}N_2O_5$ 509.2071; found 509.2073.

Ethyl 3-(3,4-*bis*(benzyloxy)phenyl)-2-(1,3-dioxoisoindolin-2-yl)propanoate (20). To a 0 °C stirred suspension of L-dopa (1.5 g, 7.6 mmol) in dry EtOH (40 mL) was added dropwise thionyl chloride (1 mL, 13.7 mmol). After 15 min, the mixture was refluxed for 24 hours, then, the excess of thionyl chloride was removed with an airflow and the resulting white solid was dried for 3 hours under vacuum. It was then dissolved in water (50 mL) and $NaHCO_3$ (1.3 g, 15.2 mmol) and Boc_2O (1.84 g, 8.4

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mmol), previously dissolved in 25 mL of THF, were successively added. The reaction mixture was stirred at room temperature for 16 hours, the volatiles were evaporated, and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with water, 5% aqueous HCl, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*, affording *N*-protected L-dopa ester intermediate, which was directly dissolved in acetone (35 mL). K_2CO_3 (2.6 g, 19 mmol) and BnBr (2 mL, 16.7 mmol) were successively added, and the reaction mixture was refluxed for 48 hours. The solvent was evaporated, the residue was dissolved in DCM, and the organic phase was washed with water, brine and concentrated *in vacuo*. The obtained solid was repeatedly washed with cold MeOH (-15 °C), dried under high vacuum and directly dissolved in dry DCM (40 mL). The solution was cooled to 0 °C and TFA (6.2 mL, 80 mmol) was slowly added. The reaction mixture was stirred at this temperature for 2 hours, warmed up to room temperature and stirred for 24 hours. The volatiles were evaporated, and the residue was dissolved in DCM, then saturated aqueous $NaHCO_3$ was added until pH 10, and the mixture was extracted with EtOAc (3 x 10 mL). The organic phases were washed with brine and concentrated *in vacuo*. The obtained crude free amine was dissolved in dry toluene (40.0 mL), and phthalic anhydride (1.2 g, 8.3 mmol) was added. The reaction mixture was refluxed for 24 hours, the solvent was evaporated, and the crude product purified by flash chromatography (CHX : DCM 2:1) to give the desired compound as a colorless oil (3.25 g, 80% yield). $[\alpha]_D^{18}$: -64.4 (*c* 0.3, $CHCl_3$). IR (neat): 3299, 1721, 1621, 1544, 1289, 1060 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 7.78 (dd, *J* = 5.1, 3.3 Hz, 2H), 7.68 (dd, *J* = 5.1, 3.3 Hz, 2H), 7.21– 7.39 (m, 10H), 6.75 (d, *J* = 8.1Hz, 2H), 6.69 (d, *J* = 8.1 Hz, 1H), 5.10 (dd, *J* = 10.9, 5.7 Hz, 1H), 5.02 (s, 2H), 4.93 (q, *J* = 11.9 Hz, 2H), 4.24 (m, 2H), 3.48 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 167.6, 166.7 166.6, 149.0, 145.0, 137.1, 136.7, 134.2, 132.0, 130.5, 128.5, 128.5, 128.0, 127.9, 127.5, 127.4, 123.5, 116.4, 114.1, 103.8, 72.4, 71.6, 49.6, 48.8, 29.7, 14.1. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{33}H_{30}NO_6$ 536.2068; found 536.2077.

(S)-2-(6,7-*bis*(benzyloxy)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)isoindoline-1,3-dione (21). The protected L-dopa derivative (**20**) (250 mg, 0.47 mmol) was dissolved at 0 °C in glacial acetic acid (1.0 mL), then, concentrated aqueous nitric acid (0.35 mL, 5.8 mmol) dissolved in glacial acetic acid (1.0 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1.5 hours, water was added, and the mixture was filtered. The obtained solid was dried under high vacuum and directly dissolved in glacial acetic acid (2.0 mL). The mixture was heated at 80 °C, iron powder (470 mg, 8.4 mmol) was added in three portions, and after 1.5 hours of reflux, the cold reaction mixture was filtered through a pad of celite, poured into water, and 6 M aqueous NaOH was added until pH 14. The aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained after column chromatography (DCM : EtOAc 10:1) as a yellow solid. (130 mg, 55% yield). Melting point 190 °C, lit. 192 °C.[21].$[\alpha]_D^{18}$: - 22.8 (*c* 0.4, $CHCl_3$), lit. $[\alpha]_D$ - 1.4 (*c* 5, DMF).[21] IR (neat): 1716, 1689, 1512, 1454, 1388, 1261 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 8.02 (s, 1H), 7.86 (dd, *J* = 5.1, 3.2 Hz, 2H), 7.71 (dd, *J* = 5.1, 3.2 Hz, 2H), 7.36 (m, 10H), 6.73 (s, 1H), 6.38 (s, 1H), 5.10 (m, 5H), 3.87 (t, *J* = 15.0 Hz, 1H), 2.84 (dd, *J* = 14.9, 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 167.7, 166.4, 148.9, 144.8, 137.1, 136.7, 134.2, 131.9, 130.5, 128.6, 128.5, 128.0, 127.9, 127.4, 127.4, 123.6, 116.2, 114.0, 103.6, 72.3, 71.5, 48.7, 29.4. HRMS (ESI-TOF) m/z: $[M+H]^+$Calcd for $C_{31}H_{25}N_2O_5$ 505.1758; found 505.1763.

***tert*-Butyl ((*S*)-3-(benzyloxy)-1-(((*S*)-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroquinolin-3-yl)amino)-1-oxopropan-2-yl)carbamate (22).** The protected tetrahydroquinolin derivative (**21**) (136 mg, 0.27 mmol) was dissolved in dry EtOH (5.0 mL), then hydrazine hydrate (0.1 mL, 3.2 mmol) was added. The reaction mixture was refluxed for 40 hours, cooled and diluted with EtOH, then it was filtered. The filtrate was concentrated *in vacuo* and the deprotected product was directly dissolved in dry THF (10.0 mL) and the resulting solution cooled at 0 °C. Then 2 M BH_3-SMe_2 in THF (1 mL, 2 mmol) was slowly added, and the reaction mixture was refluxed for 30 hours. It was then cooled at 0 °C and 5 mL of 10% aqueous HCl were added. The mixture was refluxed for 1 hour, cooled to 0 °C and basified with 3 M aqueous NaOH. The aqueous phase was extracted with EtOAc (3 x 10 mL), and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude diamine was used without any further purification. NBoc L serine (OBn) (80 mg, 0.27 mmol) was dissolved in dry DCM (1.5 mL) and cooled to -78 °C, then NMM (0.03 mL, 0.27 mmol) and CbzCl (0.04 mL, 0.27 mmol) were successively added. After 15 min, the crude diamine dissolved in DCM (2.0 mL) was added dropwise, the reaction mixture was stirred at -78 °C for 2 hours, and slowly warmed up to room temperature and stirred for 4 hours. The solvent was evaporated, and the crude product was directly purified by flash chromatography (Pentane : EtOAc 1:2) to give the desired compound as a yellow oil (78 mg, 45% yield). $[\alpha]_D^{18}$: + 6.8 (*c* 1, $CHCl_3$). IR (neat): 3094, 1778, 1693, 1357, 961 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 7.18 – 7.52 (m, 16H), 6.57 (s, 1H), 6.09 (s, 1H), 5.39 (s, 1H), 5.01 (m, 4H), 4.30 – 4.41 (m, 3H), 4.21 (bs, 1H), 3.77 – 3.92 (m, 1H), 3.51 – 3.60 (m, 1H), 3.43 (bs, 1H) 3.25 (m, 1H), 3.01 – 3.15 (m, 1H), 2.88 – 3.00 (m, 1H), 2.57 (d, *J* = 16.7 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 169.8, 169.8, 155.4, 149.0, 149.0, 141.8, 138.4, 138.3, 137.9, 137.5, 137.5, 137.4, 128.5, 128.4, 128.4, 128.3, 127.8, 127.8, 127.7, 127.6, 127.6, 127.2, 127.2, 119.2, 110.7, 102.5, 80.1, 73.4, 73.0, 71.4, 70.2, 45.4, 42.5, 42.4, 32.1, 28.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{38}H_{44}N_3O_6$ 638.3225; found 638.3229.

(*S*)-2-(6,7-Dimethoxy-1,2,3,4-tetrahydroquinolin-3-yl)isoindoline-1,3-dione (23). The protected tetrahydroquinoline carbamate (**18a**) (360 mg, 1.03 mmol) was dissolved in methanol (10.0 mL), and under hydrogen atmosphere, Pd/C (90 mg) was added. The reaction mixture was stirred under hydrogen at room temperature for 6 hours and filtered through celite. Solvent evaporation afforded the free amide intermediate, which was directly dissolved in dry THF (12.0 mL). Then at 0°C, 2 M BH_3-SMe_2 in THF (4.12 mL, 8.2 mmol) was slowly added, the reaction mixture was refluxed during 24 hours, cooled to 0 °C, and 10% HCl (8 mL) was slowly added, the reaction mixture was refluxed during 2 hours, cooled and basified with 8 M aqueous NaOH. The aqueous phase was

extracted with EtOAc (3 x 5 mL), and the combined organic phases were concentrated *in vacuo*. The resulting free diamine was dissolved in dry toluene (3.0 mL) and dry DMF (0.3 mL), then phthalic anhydride (160 mg, 1.1 mmol) was added. The reaction mixture was refluxed for 12 hours, the solvent was evaporated, and the crude product purified by flash chromatography (DCM : EtOAc 20:1) to give the desired compound as a yellow oil (220 mg, 70% yield). $[\alpha]_D^{19}$: + 48.4 (*c* 0.76, $CHCl_3$). IR (neat): 2929, 1722, 1627, 1386, 1228, 1062 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 7.85 (m, 2H), 7.73 (m, 2H), 6.52 (s, 1H), 6.20 (s, 1H), 4.74 (m, 1H), 3.97 (t, *J* = 10.8 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.65 (dd, *J* = 15.4, 11.3 Hz, 1H), 3.24 – 3.31 (m, 1H), 2.78 (dd, *J* = 15.3, 6.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 168.1, 148.6, 142.0, 137.5, 134.0, 131.9, 123.4, 123.2, 113.7, 111.0, 100.0, 56.7, 55.9, 46.6, 44.0, 29.8. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{19}N_2O_4$ 339.1339; found 339.1350.

(*S*)-3-(1,3-Dioxoisoindolin-2-yl)-6,7-dimethoxy-3,4-dihydroquinoline-1(2H)-carbaldehyde (24). The protected diamine (**23**) (120 mg, 0.35 mmol) was refluxed with formic acid (0.50 mL, 14 mmol) and acetic anhydride (0.50 mL, 5.24 mmol) for 1.5 hours, and the cold mixture was diluted with DCM. The volatiles were evaporated, and the product was obtained after column chromatography (DCM : EtOAc 10:1) as a yellow oil (110 mg, 90 % yield). $[\alpha]_D^{18}$: +14.85(*c* 0.6, $CHCl_3$). IR (neat): 3211, 1703, 1649, 1528, 1330, 1257, 1116, 1060 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 8.74 (s, 1H), 7.86 (m, 2H), 7.76 (m, 2H), 6.69 (s, 1H), 6.68 (s, 1H), 4.63 (m, 1H), 4.45 (dd, *J* = 12.2, 4.5 Hz, 1H), 4.02 (d, *J* = 12.2 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.56 (dd, *J* = 12.1, 10.9 Hz, 1H), 2.98 (dd, *J* = 15.9, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 167.8, 160.6, 148.5, 147.0, 134.4, 134.2, 131.7, 129.5, 123.5, 123.4, 118.3, 112.4, 102.0, 56.2, 56.2, 45.5, 40.9, 30.4. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{19}N_2O_5$ 367.1288; found 367.1290.

(*S*)-2-(6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroquinolin-3-yl)isoindoline-1,3-dione (25). The formylated amide (**24**) (100 mg, 0.29 mmol) was dissolved in dry THF (5.0 mL) and 1 M BH_3.THF in THF (3.4 mL, 3.4 mmol) was added dropwise. The reaction mixture was stirred under argon atmosphere for 12 hours, then 2.5 M aqueous NaOH was added dropwise until the release of gas stopped. The mixture was extracted with DCM, the combined organic phases were washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was mixed with 0.5 mL of acetic acid and 3 mL of 10% aqueous HCl and it was stirred at room temperature for 24 hours, cooled to 0 °C and basified with aqueous NH_3. The aqueous phase was extracted with DCM (3 x 5 mL), and the combined organic phases were washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (DCM : EtOAc 20:1) to give the desired compound as a yellow oil (71 mg, 70% yield). $[\alpha]_D^{19}$: +12.75 (*c* 0.13, $CHCl_3$). IR (neat): 1719, 1667, 1433, 1199, 1008 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 7.84 (bs, 2H), 7.73 (bs, 2H), 6.57 (s, 1H), 6.33 (s, 1H), 4.82 (s, 1H), 3.84 (m, 7H), 3.61– 3.73 (m, 1H), 3.14 (d, *J* = 8.4 Hz, 1H), 2.90 (s, 3H), 2.81 (dd, *J* = 14.9, 4.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 168.1, 148.6, 141.3, 140.6, 134.0, 131.8, 123.2, 114.1, 112.5, 98.2, 56.8, 56.1, 52.8, 46.0, 39.9, 30.6. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{21}N_2O_4$ 353.1496; found 353.1501.

(*S*)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroquinolin-3-amine (26). The methylated diamine (**25**) (60 mg, 0.17 mmol) was dissolved in EtOH (2.0 mL), then hydrazine hydrate (0.03 mL, 0.42 mmol) was added. The reaction mixture was refluxed 24 hours and concentrated *in vacuo*. Purification by column chromatography (DCM : EtOAc 10:1) afforded the product as a yellow oil (38 mg, 99 % yield). $[\alpha]_D^{19}$: + 22.4 (*c* 0.55, $CHCl_3$). IR (neat): 3296, 2958, 2926, 1523, 1465, 1386, 1286, 1072 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 6.52 (s, 1H), 6.20 (s, 1H), 3.80 (s, 3H) 3.77 (m, 4H), 3.24 (s, 2H), 3.08 (dd, *J* = 16.3, 3.7 Hz, 1H), 2.84 (m, 4H), 1.90 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 148.7, 141.6, 140.0, 114.2, 109.7, 97.7, 56.6, 56.0, 53.9, 44.8, 39.4, 32.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{19}N_2O_2$ 223.1441; found 223.1451.

***tert*-Butyl (*S*)-(3-(3,4-dihydroxyphenyl)-1-(dimethylamino)-1-oxopropan-2-yl)carbamate (27):** L-dopa (1g, 5 mmol) was suspended in dioxane (8 mL), then water (5 mL) and 1M aqueous NaOH (5.6 mL, 5.6 mmol) were successively added. After 5 minutes, $(Boc)_2O$ (1.22 g, 5.6 mmol) previously dissolved in dioxane (3.0 mL) was added and the reaction mixture was stirred overnight. The volatiles were evaporated, and the aqueous residue was acidified with 5% aqueous HCl and extracted with EtOAc. The organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was directly used in the next step without further purification. The protected L-dopa was dissolved in THF (20 mL) and cooled to -78 °C, then NMM (0.66 mL, 6 mmol) and CbzCl (0.86 mL, 6 mmol) were successively added. The reaction mixture was stirred for 20 min and 1 M dimethylamine (11 mL, 11 mmol) in THF was dropwise added. The reaction mixture was stirred at -78 °C for 1 hour and then it was slowly warmed up to room temperature and stirred for 12 hours. The solvent was evaporated, and the obtained residue was dissolved in ethyl acetate, washed three times with 10% aqueous citric acid, saturated aqueous $NaHCO_3$ and brine. The solvent was evaporated, and the product was purified by column chromatography (DCM : EtOAc 1:1) affording the product as a white solid (1.05 g, 65% yield). The spectroscopy data and physical constants of (**27**) were in good agreement with those reported in the literature.[10c] Melting point: 157°C, lit. 156 – 157 °C. $[\alpha]_D^{18}$: + 46.7 (*c* 0.15, $CHCl_3$). lit. $[\alpha]_D^{25}$: + 56.8 (*c* 1, $CHCl_3$).^1H NMR (400 MHz, $CDCl_3$), δ: 7.78 (bs, 1H), 6.69 – 6.83 (m, 2H), 6.61 (d, *J* = 6.6 Hz, 1H), 6.25 (bs, 1H), 5.42 (d, *J* = 7.0 Hz, 1H), 4.80 (s, 1H), 2.62 – 2.94 (m, 8H), 1.42 (s, 9H).

***tert*-Butyl (*S*)-(3-(3,4-bis(benzyloxy)phenyl)-1-(dimethylamino)-1-oxopropan-2-yl)carbamate (28).** The protected L-dopa amide derivative (**27**) (0.86 g, 2.6 mmol) was dissolved in acetone (20 mL), then Cs_2CO_3 (2.6 g, 8 mmol) was added, and the mixture was stirred at room temperature for 15 min. Then BnBr (0.95 mL, 8 mmol) was added and the reaction mixture was refluxed for 4 hours. The solvent was evaporated, and the residue was dissolved in EtOAc, washed three times with 10 % aqueous citric acid, saturated aqueous $NaHCO_3$ and brine. The solvent was evaporated, and the product was purified by column chromatography (EtOAc : DCM 1:10)

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affording the product as a white solid. (1.27 g, 95% yield). The spectroscopy data and physical constants of (**28**) were in good agreement with those reported in the literature.[9] Melting point: 89°C. lit. 85 – 88 °C. $[\alpha]_D^{19}$: +33.1 (*c* 0.4, $CHCl_3$). lit. $[\alpha]_D^{28.5}$: + 27.5 (*c* 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.20 – 7.52 (m, 10H), 6.84 (d, *J* = 8.3 Hz, 2H), 6.69 (dd, *J* = 8.1, 1.4 Hz, 1H), 5.39 (d, *J* = 8.4 Hz, 1H), 5.12 (s, 2H) 5.13 (s, 2H), 4.73 (dd, *J* = 14.7, 8.9 Hz, 1H), 2.78 – 3.02 (m, 2H), 2.77 (s, 3H), 2.47 (s, 3H), 1.42 (s, 9H).

***tert*-Butyl (*S*)-(1-(3,4-*bis*(benzyloxy)phenyl)-3-(dimethylamino)propan-2-yl)carbamate (29).** At 0 °C the amide product (**28**) (1.18 g, 2,3 mmol) was dissolved in dry DCM (10.0 mL), then TFA (1.8 mL, 23 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1 hour, slowly warmed up to room temperature and stirred for 12 hours. The solvent was evaporated and the residue was redissolved in water and basified by the addition of 10% aqueous NaOH. The aqueous phase was extracted with EtOAc (3 x 15 mL), and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude deprotected product was directly dissolved in dry THF (10 mL) and cooled to 0°C, then 2 M BH_3-SMe_2 in THF (6.5 mL, 13 mmol) was added dropwise and the reaction was refluxed for 16 hours, cooled to 0°C and 10% aqueous HCl was slowly added until pH 2. The mixture was refluxed for 1 hour, cooled to room temperature and 2M aqueous NaOH was added to reach pH 13. The basic phase was extracted with EtOAc (3 x 10 mL), the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude free diamine was dissolved in water (3.5 mL) and dioxane (2.5 mL) was added, then $(Boc)_2O$ (620 mg, 2,8 mmol) and 1M aqueous NaOH (2.6 mL, 2.6 mmol) were successively added and the mixture was stirred at room temperature for 24 hours. The organic solvent was evaporated and the aqueous phase was extracted with EtOAc (3 x 5 mL). the combined organic phases were washed with brine and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc : MeOH 1:10) affording the product as colorless oil. (730 mg, 65% yield). The spectroscopy data and physical constants of (**29**) were in good agreement with those reported in the literature.[9] $[\alpha]_D^{19}$: + 19.7 (*c* 0.9, $CHCl_3$). lit. $[\alpha]_D^{27.1}$ + 19.95 (*c* 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.21 – 7.53 (m, 10H), 6.77 – 6.96 (m, 2H), 6.69 (d, *J* = 8.1 Hz, 1H), 5.14 (s, 2H), 5,12 (s, 2H) 4.64 (bs, 1H), 3.79 (bs, 1H), 2.83 (d, *J* = 12.3 Hz, 1H), 2.71 (dd, *J* = 13.6, 6.4 Hz, 1H) , 2.17 (m, 8H), 1.43 (s, 9H).

(*S*)-6,7-*bis*(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-1,1-dimethyl-1,2,3,4-tetrahydroquinolin-1-ium (30). The benzylated diamine (**29**) (200 mg, 0.41 mmol) was dissolved in MeOH (5.0 mL), then, under hydrogen atmosphere, catalytic Pd/C (0.04 g) was added. The reaction mixture was stirred under hydrogen at room temperature for 24 hours, filtered through Celite and eluted with hot MeOH. Solvent evaporation afforded the deprotected diamine intermediate.

a) *Oxidation with dianisyltellurium oxide.* The deprotected diamine intermediate (60 mg, 0.19 mmol) was directly dissolved in dry DCM (7.0 mL) under argon atmosphere, then dianisyltellurium oxide (72 mg, 0.21 mmol) (prepared according to the procedure described by Silberman[24]), was added and the reaction mixture was stirred at room temperature for three hours. The reaction mixture was then extracted with water (4 x 5 mL), the aqueous phase was washed with DCM, and lyophilized affording the expected intermediate tetrahydroquinolinium compound. This compound was dissolved in dry acetone (10.0 mL), and Cs_2CO_3 (185 mg, 0.57 mmol) and BnBr (0.07 mL, 0.57 mmol) were successively added. The mixture was stirred at reflux for 16 hours, and the solvent was evaporated. The residue was dissolved in water and extracted with EtOAc (4 x 5 mL), the organic phase was washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (DCM: MeOH 15:1) to give the desired compound as a white solid (43 mg, 40%). The spectroscopy data and physical constants of (**30**) were in good agreement with those reported in the literature.[9] $[\alpha]_D^{18}$ + 7.4 (*c* 0.9, $CHCl_3$). lit. $[\alpha]_D^{25.6}$: + 8.16 (*c* 1 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.65 (s, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.23 – 7.43 (m, 8H), 6.60 (s,1H), 6.18 (s, 1H), 5.40 (d, *J* = 6.6 Hz, 2H), 5.07 – 5.15 (d, 2H), 3.99 – 4.30 (m, 2H), 3.91 (s, 3H), 3.76 (s,3H), 3.15 – 3.31 (m, 1H), 2.98 (m, 1H), 2.10 (s,1H), 1.43 (s,9H).

b) *Oxidation with $K_3[Fe(CN)_6]$*. The deprotected diamine intermediate (60 mg, 0.19 mmol) was directly dissolved in acetonitrile (1 mL) and mixed with 45 mL of buffer solution (pH 6.5 NaH_2PO_4/Na_2HPO_4, 0.008M). Then $K_3[Fe(CN)_6]$ (625 mg, 1.9 mmol) was added, the reaction mixture was stirred at room temperature for two hours, and lyophilization gave the intermediate tetrahydroquinolinium compound. The solid intermediate was dissolved in dry acetone (20.0 mL) and Cs_2CO_3 (185 mg, 0.57 mmol) and BnBr (0.07 mL, 0.57 mmol) were successively added. The mixture was stirred at reflux for 16 hours, and the solvent was evaporated. The residue was dissolved in water and extracted with EtOAc (4 x 5 mL), the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (DCM: MeOH 15:1) to give the desired compound as a white solid (59 mg, 55%).

(*S*)-3-Amino-6,7-*bis*(OBn)-1,1-dimethyl-1,2,3,4-tetrahydroquinolin-1-ium L-ser(OBn)-D-Ser (OBn)-BocL-Thr(OBn) (31). To a 0 °C stirred solution of the compound (**30**) (58 mg, 0.1 mmol) in dry DCM (2 mL) was added dropwise TFA (0.2 mL, 2.5 mmol). The reaction mixture was stirred for 1 hour keeping the same temperature and then it was slowly heated to room temperature and stirred for 12 hours. The solvent was evaporated, and the free amine product was dried under high vacuum.

To a 0 °C stirred solution of the ester (**2**) (67 g, 0.098 mmol) in methanol (2.0 mL) was added in small portions 1M aqueous NaOH (1 mL, 1 mmol). The reaction mixture was stirred for 1 hour keeping the same temperature and then it was slowly warmed up to room temperature and stirred for 6 hours. Then the mixture was diluted with water and acidified with 5% aqueous HCl. The aqueous phase was extracted with EtOAc (4 x 5 mL), and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude carboxylic acid was directly dissolved in dry DCM (1.5

mL) and CDI (25 mg, 0.15 mmol) was added. The reaction mixture was stirred at room temperature for 45 min, then the free amine (0.1 mmol) previously mixed with NMM (0.05 mL, 0.45 mmol) in dry DCM (1.5 mL), was added. The reaction mixture was stirred at room temperature for 24 hours. The solvent was evaporated, and the crude product was directly purified by column chromatography, (DCM : MeOH:20:1) affording the product as a colorless oil (43 mg, 42% yield). The spectroscopy data and physical constants of (**35**) were in good agreement with those reported in the literature [9] $[\alpha]_D^{18}$ +6.29 (*c* 0.2, $CHCl_3$). lit. $[\alpha]_D^{25.1}$ +4.36 (*c* 1.82, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.37 (d, *J* = 7.0 Hz, 1H), 8.22 (d, *J* = 6.6 Hz, 1H), 7.26 (m, 31H), 6.56 (s, 1H), 5.70 – 5.61 (m, 1H), 5.30 (m, 2H), 5.11 (m, 2H), 4.76 (m, 2H), 4.43 (m, 7H), 4.08 (s, 2H), 3.93 – 3.71 (m, 3H), 3.67 – 3.50 (m, 3H), 3.39 (s, 2H), 3.24 – 3.04 (m, 1H), 2.81 (m, 1H), 1.35 (s, 9H), 1.13 (d, *J* = 5.6 Hz, 3H).

2-((2*S*,4*R*,6*S*)-6-((*S*)-1-(2-(OBn)benzamido)-2-((TBDPS)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)acetic acid-L-Thr(OBn)-D-Ser(OBn) (33). To a 0°C stirred solution of NBoc L-Thr (OBn)-D-Ser(OBn) methyl ester (60 mg, 0.12 mmol), prepared according to Gademann *et al.*[10c] in dry DCM (2 mL), was slowly added TFA (0.1 mL, 1.3 mmol). The reaction mixture was stirred for 1 hour keeping the same temperature and then it was slowly warmed up to room temperature and stirred for 12 hours. The solvent was evaporated, and the free NH_2 dipeptide product was dried under high vacuum.

To a 0 °C stirred solution of the ester (**11**) (80 mg, 0.10 mmol) in methanol (2.0 mL) was added in small portions 1M aqueous NaOH (1 mL, 1 mmol). The reaction mixture was stirred for 1 hour keeping the same temperature and then it was slowly warmed up to room temperature and stirred for 6 hours. Then, the mixture was diluted with water and acidified with 5% aqueous HCl, and extracted with EtOAc (3 x 5 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude carboxylic acid was directly cooled to -78 °C and dissolved in dry DCM (2 mL) then NMM (0.011 mL, 0.10 mmol) and CbzCl (0.014 mL, 0.10 mmol) were successively added. The reaction mixture was stirred for 20 min. then the free NH_2 dipeptide (50 mg, 0.12 mmol), dissolved in DCM (1.5 mL) was added. The reaction mixture was stirred at -78 °C for 1 hour, then it was slowly warmed up to room temperature and stirred for 6 hours. The crude product was directly purified by column chromatography (EtOAc : DCM 2:10) affording the product as a yellow oil (61 mg, 55% yield). $[\alpha]_D^{18}$ +3.87 (*c* 1.2, $CHCl_3$). IR (neat): 3301, 2989, 1881, 1731, 1650, 1158 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.17 (d, *J* = 6.7 Hz, 2H), 7.62 (dd, *J* = 22.6, 7.1 Hz, 4H), 7.10 – 7.42 (m, 22H), 7.04 (dd, *J* = 15.4, 7.6 Hz, 5H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.71 (d, *J* = 6.8 Hz, 1H), 5.53 (s, 1H), 4.91 – 5.09 (m, 2H), 4.69 – 4.76 (m, 1H), 4.62 – 4.69 (m, 1H), 4.33 – 4.61 (m, 7H), 4.05 – 4.17 (m, 1H), 3.78 – 3.88 (m, 1H), 3.58 – 3.75 (m, 6H), 2.39 (m, 2H), 1.66 (m, 2H), 1.26 (bs, 2H) 1.03 (s, 9H), 0.96 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 163.2, 163.0, 161.9, 158.2, 149.4, 128.3, 126.0, 125.9, 125.5, 125.1, 121.4, 121.1, 121.1, 121.0, 120.7, 120.6, 120.5, 120.4, 120.3, 119.8, 118.8, 114.6, 114.2, 105.6, 93.1, 66.6, 66.4, 65.9, 64.2, 63.4, 62.1, 54.0, 48.9, 46.2, 45.5, 45.3, 19.6, 12.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{66}H_{74}N_3O_{11}Si$ 1112.5087; found 1112. 5096.

(*S*)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroquinolin-3-amine-L-ser (OBn)-D-Ser(OBn)-BocL-Thr(OBn) (34). To a 0 °C stirred solution of the ester (**2**) (110 mg, 0.16 mmol) in methanol (2.0 mL) was added in small portions 1M aqueous NaOH (2 mL, 2 mmol). The reaction mixture was stirred for 1 hour keeping the same temperature and then it was slowly heated to room temperature and stirred for 6 hours. Then the mixture was diluted with water and acidified with 5% aqueous HCl. The aqueous phase was extracted with EtOAc (3 x 5 mL), and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude carboxylic acid was directly dissolved in dry DCM (2.0 mL), and cooled to -78°C, then NMM (0.017 mL, 0.16 mmol) was added dropwise. After 5 min, CbzCl (0.023 mL, 0.16 mmol) was added dropwise, keeping the same temperature, and after 10 min a solution of the diamine (26) (0.038 g, 0.17 mmol) dissolved in dry DCM (1.5 mL) was added. The reaction mixture was stirred at –78 °C for one hour, slowly warmed up to room temperature and filtered. The crude material was directly purified by flash chromatography (Pentane : EtOAc 1:1) to give the desired compound as a colorless oil (80 mg, 65% yield). $[\alpha]_D^{18}$ - 34.0 (*c* 0.73, $CHCl_3$). IR (neat): 3310, 2927, 1707, 1651, 1519, 1215 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.04 – 7.50 (m, 17H), 6.87 (dd, *J* = 18.6, 7.9 Hz, 1H), 6.49 (d, *J* = 4.3 Hz, 1H), 6.20 (s, 1H), 5.49 (dd, *J* = 15.8, 7.2 Hz, 1H), 4.32 – 4.67 (m, 8H), 4.10 – 4.36 (m, 2H), 3.62 - 4.06 (m, 9H), 3.32 – 3.58 (m, 2H), 3.18 (t, *J* = 11.6 Hz, 1H), 2.97 (dd, *J* = 15.9, 5.4 Hz, 1H), 2.88 (dd, *J* = 11.5, 5.5 Hz, 1H), 2.68 – 2.79 (m, 3H) 2.63 (dd, *J* = 16.2, 4.8 Hz, 1H), 1.43 (s, 9H), 1.13 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 170.5, 169.0, 155.8, 148.4, 141.3, 140.3, 137.8, 137.3, 137.2, 128.4, 128.4, 128.4, 127.8, 127.7, 127.6, 127.5, 127.3, 114.2, 114.2, 111.2, 103.3, 97.6, 80.2, 73.4, 73.3, 73.3, 73.1, 71.3, 69.4, 68.9, 56.6, 56.0, 54.7, 53.3, 52.6, 43.3, 39.6, 39.5, 32.9, 29.7, 28.2, 15.7. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{48}H_{62}N_5O_{10}$ 868.4491; found 868.4490.

2-((2*S*,4*R*,6*S*)-6-(*S*)-1-(2-(OBn)benzamido)-2-((TBDPS)oxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)acetic acid-L-Thr OBn)-D-Ser(OBn)-L-Ser(OBn)-(S)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroquinolin -3-amine (35). To a 0 °C stirred solution of the compound (**34**) (30 mg, 0.039 mmol) in dry DCM (2 mL) was added TFA (0.04 mL, 0.54 mmol). The reaction mixture was stirred for 1 hour keeping the same temperature and then it was slowly heated to room temperature and stirred for 12 hours. The solvent was evaporated, and the free amine product was dried under high vacuum.

To a 0 °C stirred solution of the ester (**11**) (28 mg, 0.037 mmol) in methanol (1.0 mL) was added in small portions 1 M aqueous NaOH (0.37 mL, 0.37 mmol). The reaction mixture was stirred for 1 hour keeping the same temperature and then it was slowly heated to room temperature and stirred for 6 hours. Then the mixture was diluted with water and acidified with 5% aqueous HCl, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude carboxylic acid was directly cooled to -78 °C and dissolved in dry

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DCM (1.0 mL) then NMM (0.004 mL, 0.037 mmol) and CbzCl (0.005 mL, 0.037 mmol) were successively added. The reaction mixture was stirred for 20 min and the free amine dissolved in dry DCM (2.0 mL) was added. The reaction mixture was stirred at -78 °C for 1 hour, then it was slowly warmed up to room temperature and stirred for 6 hours. The crude product was directly purified by column chromatography (Pentane : EtOAc :1:1) affording the product as a yellow oil (30 mg, 55% yield). $[\alpha]_D^{18}$ +3.29 (*c* 0.2, $CHCl_3$). IR (neat): 3201, 2989, 1881, 1701, 1008, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 8.15 – 8.28 (m, 1H), 7.59 – 7.72 (m, 2H), 7.16 – 7.47 (m, 34H), 7.07 (d, *J* = 6.4 Hz, 2H), 6.87 – 6.99 (m, 2H), 6.53 (d, *J* = 5.2 Hz, 1H), 6.24 (d, *J* = 13.6 Hz, 1H), 5.85 (dd, *J* = 20.1, 6.7 Hz, 1H), 5.00 – 5.21 (m, 4H), 4.29 – 4.56 (m, 8H), 4.10 – 4.18 (m, 2H), 3.69 – 3.93 (m, 14H), 3.46 – 3.62 (m, 2H), 3.20 (m, 1H), 2.88 – 3.08 (m, 3H), 2.63 – 2.78 (m, 4H), 2,53 (m, 1H) 2.22 – 2.40 (m, 1H), 1.99 – 2.12 (m, 1H), 1.72 (m, 1H), 1.09 – 1.40 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 170.5, 170.0, 169.9, 169.4, 169.1, 165.4, 156.6, 156.3, 148.4, 141.34, 141.3, 140.3, 138.4, 138.3, 137.7, 137.4, 137.3, 135.6, 135.5, 133.3, 133.2, 132.7, 132.3, 132.1, 129.7, 129.6, 128.8, 128.7, 128.57, 128.55, 128.52, 128.46, 128.44, 128.42, 128.40, 128.38, 128.33, 128.3, 128.26, 128.22, 128.2, 128.11, 128.1, 128.0, 127.9, 127.81, 127.8, 127.7, 127.67, 127.62, 127.59, 127.5, 127.4, 127.3, 127.1, 126.1, 121.8, 121.4, 114.3, 114.2, 113.0, 111.2, 106.8, 100.4, 97.7, 74.0, 73.6, 73.4, 73.4, 73.3, 73.2, 73.0, 71.4, 71.1, 70.8, 69.5, 69.4, 68.9, 67.2, 66.8, 61.5, 58.7, 58.3, 56.7, 56.6, 56.0, 55.9, 54.7, 53.6, 53.4, 52.7, 43.4, 39.7, 39.6, 38.7, 32.9, 32.8, 31.9, 31.2, 30.3, 29.7, 29.3, 28.2, 27.2, 26.8, 26.8, 22.6, 19.2, 16.1, 15.5, 14.1.

HRMS (ESI-TOF) m/z: $[M+H]^+$: Calcd for $C_{87}H_{99}N_6O_{14}Si$, 1479. 6983; found: 1479.6991

Conflicts of interest

There are no conflicts to declare.

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