Tetrahedron 83 (2021) 131953

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Copper-catalyzed cross-coupling of amino acid-derived amides with (*Z*)-vinyl iodides: Unexpected solvent effect and preparation of plocabulin

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ARTICLE INFO

Article history:
Received 7 December 2020
Received in revised form
11 January 2021
Accepted 15 January 2021
Available online 19 January 2021

Keywords:
Natural products
Enamides
(Z)-vinyl iodide
Buchwald coupling
Plocabulin

ABSTRACT

A copper-catalyzed cross-coupling reaction of amino acid-derived amides and (Z)-vinyl iodide was studied to improve a key step in the synthesis of plocabulin, a novel microtubule destabilizer agent of marine origin. The study revealed a profound solvent effect with 1,2-dimethoxyethane (DME), which gave consistently high yields across a large variety of the amide and (Z)-vinyl iodide substrates. The protocol was successfully utilized in the preparation of plocabulin and provided a significantly improved yield.

1. Introduction

Enamides are a diverse family of synthetic intermediates and represent important structural components in many biologically active marine natural products (Fig. 1) [1–5]. The seemingly simple enamide unit possesses unique physical and chemical properties, such as a polar carbon-carbon double bond, configuration with trans or cis orientation, roughly planar conformation, and as well as hydrogen-bond acceptor or donor. To a large extent, these properties impart interesting activities to those natural products that contain an enamide unit [6–13]. Recently, bio-assay guided investigations on marine-origin natural products have unveiled a viable opportunity to identify new targets for cancer therapy as well as dissimilar modes of action within typical classes drugs [14]. Thus, plocabulin (PM060184), originally isolated from the marine sponge Lithoplocamia lithistoides, deserves much attention [15–17]. As a novel and potent tubulin-binding agent with an IC_{50} value of up to pM range, this molecule targets the recently described maytansine site on β-tubulin different from that of vinca alkakloids, taxanes or eribulin, and can induce microtubule depolymerization through a distinct mechanism [18–20]. Especially, a recent study by Schöffski has revealed that plocabulin also exhibits promising antitumor effects in patients with advanced solid tumors [21].

Our ongoing project requires a substantial supply for extensive investigation of plocabulin biological activities. However, currently plocabulin has to be produced by total synthesis due to its resource rarity. Although a reliable synthetic approach has been reported by C. Cuevas and co-workers to overcome this supply shortage, the stereoselective assembly of the (*Z*)-enamide unit still appears to be a major problem (poor yield: less than 44%) using the advanced intermediate (vinyl iodide) and the appropriate amide (see Fig. 1) [15]. As part of our ongoing project, we herein report an improved copper-catalyzed cross-coupling reaction of amides and vinyl iodides for the construction of (*Z*)-enamides. A remarkable solvent effect was observed for the reaction, where DME provided unexpectedly yet consistently high yields across a large variety of the amide and vinyl iodide substrates. The reaction protocol was successfully utilized in the key step for the preparation of plocabulin and provided a significantly improved yield.

2. Results and discussion

Although there are a variety of protocols for accessing enamide

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https://doi.org/10.1016/j.tet.2021.131953
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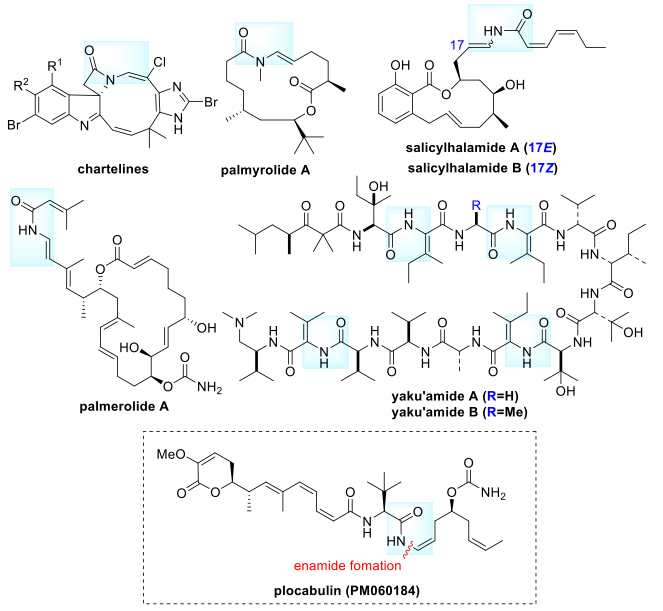


Fig. 1. The representative antitumor active marine natural products containing enamide structural units.

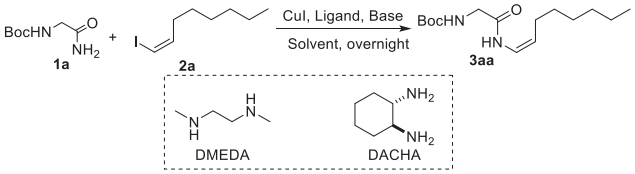
compounds, the most attractive one is the modern copper-catalyzed cross-coupling of amides and vinyl halides in conjunction with diamine or amino acid as the catalyst's ligand [22–26]. Such coupling reactions feature good stereoselectivities, mild conditions, cheap catalysts/ligands, wide substrate scope and high functional group tolerance. Therefore, they have been widely applied in the synthesis of natural products, pharmaceuticals and novel materials [27].

The enamide in plocabulin is representative of linear enamides derived from amides of amino acids and (*Z*)-vinyl iodides. A literature survey found few examples of such enamides except those of cyclic analogues via copper-catalyzed coupling in an intramolecular manner [28–35]. R. R. Cesati III and co-workers have reported that a series of enantiomerically pure amino amides could successfully couple with (*E*)-1,2-disubstituted vinyl iodide without a sacrifice of stereochemistry under the standard Buchwald condition (CuI/$MeNHCH_2CH_2NHMe$ (DMEDA)/Cs_2CO_3, THF, 70 °C, 16 h), affording the enamides with yields ranging from 30% to 87% [36]. In contrast to (*E*)-vinyl iodides, in the same study (*Z*)-vinyl iodides gave much lower yield, as exemplified by the coupling of H-Leu-NH_2 (50%). In addition, the authors suggested that the solvent THF might need to be replaced when certain amino amides were used, possibly due to their solubility.

To improve the (*Z*)-enamide formation and thus facilitate the synthesis of plocabulin, we started to study the model reaction of Boc-Gly-NH_2 (**1a**) and (*Z*)-1-iodooct-1-ene (**2a**) with the Buchwald's protocol [22]. As shown in Table 1, under the standard Buchwald condition, the desired coupling product **3aa** was obtained in THF with a yield of 63% (Entry 1). Similar yields were observed when using other common conditions for the coupling reaction (Entries 2, 3) [28,37]. Notably, Inoue and co-workers suggested that 1,4-dioxane was the best solvent for a related coupling reaction in their total synthesis of Yaku'amide A or B [10]. However, in our case the yield was discouraging (Entry 4, 43%). This result is reminiscent of their experience, namely, "amounts of the reagents, solvent, and concentration had to be carefully tuned to obtain high-yielding transformations".

Not satisfied with the yield, we set out to optimize the reaction

Table 1
The optimization on the copper-catalyzed coupling reaction.



Entry	Ligand	Base	Solvent	T (°C)	Yield (%)[a,b]
1	DMEDA	Cs_2CO_3	THF	70	63
2	DACHA	CsF	Tol	95	63
3	DMEDA	K_2CO_3	DMF	90	61
4	DMEDA	Cs_2CO_3	1,4-Dioxane	55	43
5	DMEDA	Cs_2CO_3	CH_3CN	55	42
6	DMEDA	Cs_2CO_3	DMF	55	66
7	DMEDA	Cs_2CO_3	DMSO	55	80
8	DMEDA	Cs_2CO_3	MTBE	55	84
9	DMEDA	K_2CO_3	MTBE	55	21
10	DMEDA	Li_2CO_3	MTBE	55	8
11	DMEDA	CsF	MTBE	55	22
12	DMEDA	Cs_2CO_3	DME	55	92
13	DMEDA	Cs_2CO_3	DME	65	90
14	DMEDA	Cs_2CO_3	DME	45	89
15	–	Cs_2CO_3	DME	55	trace
16	DMEDA	Cs_2CO_3	DME (H_2O, 5.0 eq.)	55	92

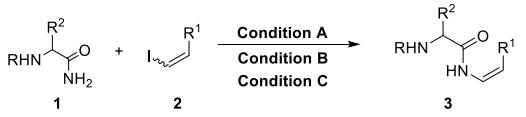
[a] Reaction conditions: a solution of **1a** (2.0 eq.), **2a** (1.0 eq.), CuI (0.3 eq.), the diamine ligand (0.6 eq.) and a suitable base (2.0 eq.) in the solvent (6 mL) noted in table was stirred overnight at an appreciate temperature under N_2.

[b] **2a** was contaminated by minor (*E*)-isomer, and the *E*/*Z* isomer ratio was 13 : 87. The isolated yield was based on (*Z*)-**2a**.

conditions by further screening various solvents and bases (Entries 5-–8). Initial experiments showed that DMSO and methyl *t*-butyl ether (MTBE) appeared to be suitable solvents, especially MTBE, with which a much improved yield of 84% was observed (Entry 8). However, efforts toward further improving the reaction by varying base and temperature were not fruitful (Entries 8–11). To our surprise, when the solvent was switched to 1,2-dimethoxyethane (DME), the conversion became almost quantitative at 55 °C with an isolated yield of 92% (Entry 12). It was further noticed that the reaction was not sensitive to the temperature from 45 to 65 °C when carried out overnight (Entries 12–14). A control experiment indicated that use of ligand DMEDA was required for the reaction, suggesting DME not playing any role as a ligand (Entry 15) [22]. Interestingly, with DME the reaction was also found insensitive to residual water (Entry 16). Even the commercially obtained DME worked well without pre-treatment for drying, and still gave sustained high yields, implying a user-friendly feature for easy adoption. The specific mechanism of how DME enhanced the coupling reaction still needs to be explained and may merit a separate study in the future. That being said, we have reasons to believe that the enhancement is likely caused by the Cs^+ ion complexing property of DME. In a study by Carvajal et al. [38], Cs^+ ion coordinated with DME but not with THF. Such complexing plus a just-right polarity of DME would lead to increased solubility of the inorganic base and the corresponding amides, therefore, a favorable effect on the oxidative addition step in the coupling reaction.

Having established the optimal reaction condition, we then explored the substrate scope. The results are summarized in Table 2. First, a series of Boc-protected amino acids (**1a-g**) were tested to couple with **2a**. All of them gave excellent yields using DME as solvent (**3aa-3ga**: around 90%). For comparsion and further verification, some of the reactions were run in parallel with DME being replaced by DMSO or MTBE as solvent. In such cases, the reactions in DMSO (**3aa**, **3ba** and **3ga**) and MTBE (**3aa, 3da** and **3ea**)

Table 2
The substrate scope: the amides of protected amino acids and vinyl iodides.



1 2 3

1	**1a**	**2a**	**3aa** (92%[a], 80%[b], 84%[c])
2	**1b**	**2a**	**3ba** (87%[a], 69%[b])
3	**1c**	**2a**	**3ca** (93%[a])
4	**1d**	**2a**	**3da** (89%[a], 51%[c])
5	**1e**	**2a**	**3ea** (89%[a], 33%[c])
6	**1f**	**2a**	**3fa** (93%[a])
7	**1g**	**2a**	**3ga** (93%[a], 33%[b])
8	**1a**	**2b**[d]	**3ab** (91%[a])
9	**1a**	**2c**[e]	**3ac** (91%[a])
10	**1e**	**2d**	**3ed** (93%[a])
11	**1e**	**2e**	**3ee** (92%[a])
12	**1h**	**13**	**3h** (86%[a])

[a] Reaction condition **A**: a solution of **1** (2.0 eq.), **2** (1.0 eq.), CuI (0.3 eq.), DMEDA (0.6 eq.) and Cs_2CO_3 (2.0 eq.) in DME (6 mL) was stirred overnight at 55 °C under N_2. The isolated yields were based on (*Z*)-vinyl iodide if contaminated with (*E*)-vinyl iodide.

[b] Condition **B**: the reaction was run in anhydrous DMSO.

[c] Condition **C**: the reaction was run in anhydrous MTBE.

[d] The *Z*/*E* ratio of **2b** was 80 : 20.

[e] The *Z*/*E* ratio of **2c** was 84 : 16.

produced much lower yields.

Next, several other vinyl iodides were examined. Coupling reaction of **2b** or **2c** with **2a** afforded consistently high yields (**3 ab**, **3ac**). Notably, the C=C bond in **3ac** did not isomerize under the reaction conditions. In order to scrutinize the stereospecificity of the coupling reaction, we prepared (*Z*)- and (*E*)-vinyl iodide (**2d** and **2e**) according to a previously reported method [39,40]. When **2d** or **2e** were coupled with **1e** under the current improved condition, both reactions proceeded to afford the corresponding product in excellent yields (**3ed** or **3ee**) with full configuration retention. These results indicated that the reaction underwent in a stereospecific manner.

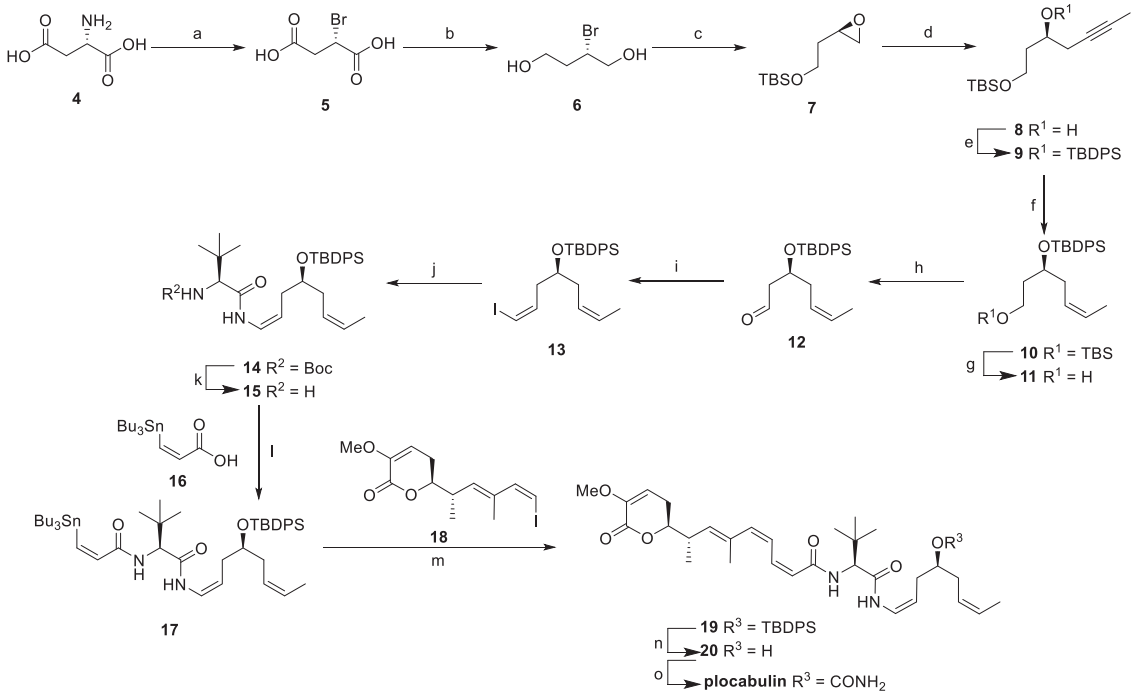
Encouraged by the above achievements, we then attempted to apply the improved coupling reaction for preparation of the target plocabulin according to the reported approach [15]. The synthetic route was depicted in Scheme 1. In the original approach [15], the enantiomerically pure epoxide (**7**) was prepared from racemic **7** by Jacobsen's hydrolytic kinetic resolution, while the other isomer was abandoned. To overcome this shortcoming, we prepared the optically active epoxide **7** according to the modified Rapoport's protocol [41].

Compound **7** could be easily obtained in about 55% yield through a 3-step sequence. Starting from (*S*)-aspartic acid **4**, the bromo di-acid **5** was prepared by treatment with sodium nitrite in hydrobromide aqueous solution, which was then reduced to the diol **6** with diborane in THF. In the presence of an excess amount of NaH, **6** was easily converted into the epoxide, and concurrently trapped by TBSCl, resulting in the protected epoxide **7**.

The epoxide was subjected to ring opening by treatment with prop-1-yn-1-yl lithium in the presence of $BF_3 \cdot OEt_2$, affording the homopropargyl alcohol **8** in 85% yield. After protection of the hydroxyl group in **8** with TBDPS group, the alkyne bond within the resultant OH-TBDPS protected **9** was stereoselectively reduced to the *cis*-alkene **10** quantitatively through Lindlar catalytic hydrogenation in ethyl acetate. After that, careful treatment of **10** with PPTS in ethanol released the primary alcohol **11**, which was subsequently subjected to oxidation under the Piancatelli's condition [42] in the presence of BAIB ($PhI(OAc)_2$) and a catalytic amount of TEMPO (2,2,6,6-tetramethylpiperidinin-1-yl)oxyl), affording aldehyde **12** in 82% yield. Wittig reaction of **12** with the ylide solution *in situ* prepared from $(Ph_3PCH_2I)^+I^-$ salt and KHMDS in anhydrous THF successfully furnished vinyl iodide **13** in 82% yield.

With intermediate **13** in hand, the construction of enamide moiety was then undertaken. As illustrated in Scheme 1, Boc-*t*Bu-Gly-NH_2 (**1e**) and (*Z*)-vinyl iodide (**13**) were allowed to react under our improved copper-catalytic coupling reaction conditions. The reaction proceeded smoothly to provide the desired enamide product **14** in 85% yield. This yield was remarkably increased as compared to that of the original coupling reaction (85% *vs* 44%), a good demonstration of the utility of our coupling reaction in synthesizing enamide-containing biologically active molecules. In addition, Cbz-*t*Bu-Gly-NH_2 (**1h**, Entry 12 in Table 2) gave the almost same result as **1e**.

With Compound **14** readily made in sufficient quantity, the synthesis of plocabulin was completed according to previously reported method [15] and is described in the following. Because of the acidic sensitivity of TBDPS group, the selective removal of the Boc group in **14** had to be performed by employing pyrolysis condition. To this end, a solution of **14** in ethylene glycol was heated at 200 °C for a short time (about 15 min), producing the amine **15** in 72% yield. To avoid the possible epimerization, condensation of the optically active **15** with (*Z*)-3-(tributylstannyl) acrylic acid was carried out in the HOAt/HATU/DIPEA system, which was routinely used in peptide synthesis, leading to **17** in 91% yield. The vinyl iodide **18** [15] was coupled with the stannane **17** under Liebeskind



Scheme 1. The synthesis of plocabulin. *Reagents and conditions*: (a) KBr, $NaNO_2$, H_2SO_4, −5 °C, 2 h, 89%. (b) BH_3·THF, THF, 25 °C, 18 h, 96%. (c) NaH, TBSCl, 25 °C, 18 h, 64%. (d) Propyne, *n*-BuLi, BF_3·Et_2O, THF, −78 °C, 1 h, 85%. (e) TBDPSCl, DMAP, DCM, 25 °C, 18 h, 91%. (f) H_2, quinoline, lindlar catalyst, EtOAc, 25 °C, 7 h, 97%. (g) PPTS, EtOH, 25 °C, 7 h, 98%. (h) BAIB, TEMPO, DCM, 25 °C, 18 h, 82%. (i) Ph_3P^+-CH_2I I^-, KHMDS, THF, −78 °C, 90 min, 82%. (j) Boc-*t*-Bu-Gly-NH_2, CuI, Cs_2CO_3, DMEDA, DME, 55 °C, 18 h, 85%. (k) Ethyleneglycol, 200 °C, 15 min, 72%. (l) **16**, DIPEA, HOAt, HATU, DCM, DMF, 0 °C, 30 min, 91%. (m) **18**, copper(I) thiophene-2-carboxylate (CuTc), NMP, 25 °C, 18 h, 73%. (n) TBAF, THF, 25 °C, 60 min, 66%. (o) (i) Trichloroacetyl isocyanate, DCM, 0 °C, 30 min; (ii) Al_2O_3, 0 °C, 30 min, 68%.

condition [43], smoothly providing **19** in 73% yield. Upon treating with TBAF in THF, the TBDPS group in **19** was removed to release the corresponding alcohol **20**. Compound **20** was then carbonated with trichloroacetyl isocyanate in CH_2Cl_2 followed by removal of the trichloroacetyl group through treatment with neutral alumina, yielding the target plocabulin with an overall yield of 45% in the last three steps.

3. Conclusion

In summary, we have developed an efficient copper-catalyzed cross-coupling reaction of amino acid-derived amides and (Z)-vinyl iodide, where the solvent effect has demonstrated to be a pivotal factor. Using DME as solvent, the reaction furnished a series of enamide products with consistently high yields and full preservation of the vinyl stereo-configuration. The method displayed wide substrate scope and has been utilized to successfully improve the key step for the total synthesis of plocabulin. The study on an evolutionary approach to plocabulin and its extensive biological activities is in progress, and will be reported in due course.

4. Experimental

4.1. General information

The chemicals and reagents were purchased from Acros, Alfa Aesar, and National Chemical Reagent Group Co. Ltd., P. R. China, and used as received without further purification. Anhydrous solvents (THF, MeOH, DMF, DCM, and CH_3CN) used in the reactions were dried and freshly distilled before use. Petroleum ether (PE) used had a boiling range of 60−90 °C. All the reactions were carried out under N_2 atmosphere, unless otherwise stated. Oxygen and/or moisture sensitive solids and liquids were transferred appropriately. Concentration of solutions in *vacuo* was accomplished using a rotary evaporator fitted with a water aspirator. Residual solvents were removed under high vacuum (0.1−0.2 mm Hg). The progress of the reactions was monitored by TLC (silica-coated glass plates) and visualized under UV light, and by using iodine, ceric ammonium molybdate stain or phosphomolybdic acid. ^1H NMR and ^{13}C NMR spectra were recorded either on a 400 MHz Varian Instrument at 25 °C or 600 MHz Bruker Instrument at 25 °C, using TMS as an internal standard, respectively. Multiplicity is tabulated as s for singlet, d for doublet, dd for doublet of doublet, t for triplet, and m for multiplet. Coupling constants (*J*) are reported in Hertz. ^{13}C NMR spectra were completely hetero-decoupled and measured at 150 MHz. HRMS spectra were recorded on Finnigan-Mat-95 mass spectrometer, equipped with ESI source.

4.2. General procedure of condition A in the coupling reaction

A resealable Schlenk tube was charged with vinyl iodide (0.5 mmol, 1.0 eq.) and amide (1.0 mmol, 2.0 eq.), evacuated and backfilled with N_2. 1,2-dimethoxyethane (DME) (6.0 mL), Cs_2CO_3 (326 mg, 1.0 mmol, 2.0 eq.), *N*,*N*′-dimethylethylene-diamine (DMEDA) (32 μL, 0.30 mmol, 0.6 eq.) and CuI (29 mg, 0.15 mmol, 0.3 eq.) were added under N_2. The Schlenk tube was sealed with a Teflon valve, immersed in a preheated oil bath; the reaction mixture was stirred at 55 °C overnight. The reaction vessel was removed from the oil bath and the resulting pale tan suspension was allowed to reach rt, then, it was filtered over Celite, eluting with ethyl acetate (20 mL). The filtrate was concentrated and the residue was purified by column chromatography on silica gel (PE/EA) to afford the desired product. While some vinyl iodides with inseparable (*Z*)- and (*E*)-isomers were used, the corresponding (*Z*)- and (*E*)-coupling products were easy to isolate by column chromatography on silica gel.

4.3. Synthetic studies

4.3.1. 1-Iodooct-1-ene (**2a**)

To a suspension of iodomethyl triphenylphosphonium iodide (15.9 g, 30.0 mmol, 1.2 eq.) in anhydrous THF (160 mL) at 0 °C, a solution of potassium hexamethyldisilazane (KHMDS) (1.0 M in THF, 30.0 mL, 30.0 mmol, 1.2 eq.) was slowly added over a period of 10 min. After stirring for an additional 5 min, the solution was cooled to −78 °C and then 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (7.5 mL, 62.0 mmol, 2.5 eq.) was added, followed by the addition of heptaldehyde (2.85 g, 25.0 mmol, 1.0 eq.) dissolved in THF (30 mL). The temperature was kept at −78 °C while the reaction mixture was stirred for 30 min. Then the reaction system was allowed to warm up to 0 °C in 1 h. When the reaction was completed, the reaction mixture was quenched with sat. *aq*. $NaHCO_3$ and extracted with petroleum ether. The organic layer was collected and concentrated. Column chromatography gave the product (4.77 g, 57% yield). The *Z*/*E* isomer ratio (*Z*/*E* = 87 : 13) was determined by ^{1}H NMR analysis. Major peaks in ^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.20−6.13 (m, 2H), 2.17−2.09 (m, 2H), 1.47−1.19 (m, 8H), 0.92−0.84 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 141.5, 82.1, 34.7, 31.7, 28.8, 27.9, 22.59, 14.1. The spectra data were in agreement with the literature [44].

4.3.2. (2-Iodovinyl)benzene (**2b**)

To a suspension of iodomethyl triphenylphosphonium iodide (6.36 g, 12.0 mmol, 1.2 eq.) in anhydrous THF (65 mL) at 0 °C, a solution of KHMDS in THF (1.0 M, 12.0 mL, 12.0 mmol, 1.2 eq.) was slowly added. After stirring for an additional 5 min, the solution was cooled to −78 °C and then DMPU (3.2 mL, 26.5 mmol, 2.7 eq.) was added, followed by the addition of benzaldehyde (1.06 g, 10.0 mmol, 1.0 eq.) dissolved in anhydrous THF (12 mL). The temperature was kept at −78 °C while the reaction mixture was stirred for 30 min. Then the reaction system was allowed to warm up to 0 °C. When the reaction was completed, the reaction mixture was quenched with sat. *aq*. $NaHCO_3$ and extracted with PE. The organic layers were collected and concentrated. Column chromatography gave the product (1.39 g, 60% yield). The *Z*/*E* isomer ratio (*Z*/*E* = 80 : 20) was determined by ^{1}H NMR analysis. Major peaks in ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.69−7.64 (m, 2H), 7.45−7.31 (m, 4H), 6.61 (d, 1H, *J* = 8.4 Hz). The spectra data were in agreement with those reported in the literature [45].

4.3.3. (3-Iodoallyl)benzene (**2c**)

To a suspension of iodomethyl triphenylphosphonium iodide (6.36 g, 12.0 mmol, 1.2 eq.) in THF (65 mL) at 0 °C, a solution of KHMDS (1.0 M in THF, 12.0 mL, 12.0 mmol, 1.2 eq.) was slowly added over a period of 10 min. After stirring for an additional 5 min, the solution was cooled to −78 °C and DMPU (3.2 mL, 26.5 mmol, 2.7 eq.) was then added, followed by the addition of phenylacetaldehyde (1.20 g, 10.0 mmol, 1.0 eq.) dissolved in THF (12 mL). The temperature was kept at −78 °C while the reaction mixture was stirred for 30 min. Then the reaction system was allowed to warm up to 0 °C over 1 h. When the reaction was completed, the reaction mixture was quenched with sat. *aq*. $NaHCO_3$ and extracted with petroleum ether. The organic layers were collected and concentrated. Column chromatography gave the product (1.03 g, 42% yield). The *Z*/*E* isomer ratio (*Z*/*E* = 84 : 16) was determined by ^{1}H NMR analysis. Major peaks in ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.33−7.19 (m, 5H), 6.39−6.32 (m, 2H), 3.54−3.46 (m, 2H). The spectra data were in agreement with those reported in the literature [46].

4.3.4. (Z)-Tert-butyl((4-iodo-3-methylbut-3-en-1-yl)oxy) dimethylsilane (**2d**)

In a 250 mL round-bottom flask purged and maintained with an inert atmosphere of N_2, was placed $ZrCp_2Cl_2$ (1.10 g, 3.75 mmol, 0.25 eq.) followed by the addition of 1,2-dichloroethane (DCE) (50 mL), and the resultant solution was allowed to stir for 30 min at rt. To this solution was added $AlMe_3$ (2.0 M in hexane, 22.5 mL, 45.0 mmol, 3.0 eq.) at 0 °C, followed by the addition of alkyne 3-butyn-1-ol (1051 mg, 15.0 mmol, 1.0 eq.) in DCE (5.2 mL) and then the reaction was allowed to stir for 18 h at rt. The solution was then heated to 86 °C and gently refluxed for 4 days. After the allotted reaction time, the solution was cooled to −30 °C and then I_2 (5.71 g, 22.5 mmol, 1.5 eq.) in THF (30 mL) was added and the reaction was further stirred for 30 min at rt. The reaction mixture was then quenched by the addition of half sat. *aq*. K_2CO_3 (100 mL), then it was filtered over Celite, eluting with EA (100 mL). The aqueous phase was extracted with EA (2 × 100 mL).The combined organic phases were concentrated and the residue was purified by column chromatography on silica gel (PE/EA) affording (*Z*)-4-Iodo-3-methylbut-3-en-1-ol as a yellow oil (1394 mg, 44%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.00 (q, 1H, *J* = 1.8 Hz), 3.77 (t, 2H, *J* = 6.6 Hz), 2.53 (t, 2H, *J* = 6.6 Hz), 1.95 (d, 3H, *J* = 1.8 Hz), 1.84 (br s, 1H).

To a solution of (*Z*)-vinyl iodide (1.39 g, 6.57 mmol, 1.0 eq.) in DMF (35 mL), TBSCl (1.29 g, 8.55 mmol, 1.3 eq.) and imidazole (895 mg, 13.1 mmol, 2.0 eq.) was added at 0 °C, then the reaction was allowed to warm to rt and stirred overnight. The reaction was quenched with half sat. *aq*. $NaHCO_3$ (100 mL) and the mixture was extracted with PE/EA (*v*/*v* 1:2, 100 mL). After washed with water (2 × 65 mL), the organic layers were concentrated and the residue was purified by column chromatography on silica gel (PE/EA) affording the desired product **2d** as a colorless oil (2109 mg, 98%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.92 (q, 1H, *J* = 1.2 Hz), 3.71 (t, 2H, *J* = 7.2 Hz), 2.44 (t, 2H, *J* = 7.2 Hz), 1.93 (d, 3H, *J* = 1.2 Hz), 0.90 (s, 9H), 0.075 (s, 6H). The spectra data were in agreement with those reported in the literature [39].

4.3.5. (E)-Tert-butyl((4-iodo-3-methylbut-3-en-1-yl)oxy) dimethylsilane (**2e**)

In a 250 mL round-bottom flask purged and maintained with an inert atmosphere of N_2, was placed $ZrCp_2Cl_2$ (1.10 g, 3.75 mmol, 0.25 eq.) followed by the addition of DCM (52.5 mL) and the resultant solution was allowed to stir for 30 min at rt. To this solution was added $AlMe_3$ (2.0 M in hexane, 22.5 mL, 45.0 mmol, 3.0 eq.) at 0 °C, followed by the addition of 3-butyn-1-ol (1051 mg, 15.0 mmol, 1.0 eq.) in DCM (5.2 mL) and then the reaction was allowed to stir for 18 h at rt. After the allotted reaction time, the solution was cooled to −30 °C and then I_2 (5.71 g, 22.5 mmol, 1.5 eq.) in THF (30 mL) was added and the reaction was continuously stirred for 30 min at rt. The reaction mixture was then quenched by the addition of half sat. *aq*. K_2CO_3 (100 mL), then it was filtered over Celite, eluting with EA (100 mL). The aqueous phase was extracted with EA (2 × 100 mL). The combined extracts were concentrated and the residue was purified by column chromatography on silica gel (PE/EA) affording (*E*)-4-iodo-3-methylbut-3-en-1-ol as a colorless oil (2.37 g, 75%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.02 (q, 1H, *J* = 1.2 Hz), 3.72 (t, 2H, *J* = 6.0 Hz), 2.48 (td, 2H, *J* = 6.6, 0.6 Hz), 1.88 (d, 3H, *J* = 1.2 Hz).

To a solution of (*E*)-vinyl iodide (2.37 g, 11.2 mmol, 1.0 eq.) in DMF (55 mL), TBSCl (2.19 g, 14.5 mmol, 1.3 eq.) and imidazole (1.52 g, 22.4 mmol, 2.0 eq.) was added at 0 °C, then the reaction was allowed to warm to rt. and stirred overnight. The reaction was quenched with half sat. *aq*. $NaHCO_3$ (170 mL) and the mixture was extracted with PE: EA 1:2 (170 mL). After washed with water (2 × 110 mL), the organic layers were concentrated and the residue was purified by column chromatography on silica gel (PE/EA) to

afford the desired product **2e** as a colorless oil (3.10 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.93 (s, 1H), 3.69 (t, 2H, J = 6.8 Hz), 2.42 (t, 2H, J = 6.8 Hz), 1.85 (s, 3H), 0.88 (s, 9H), 0.038 (s, 6H). The spectra data were in agreement with those reported in the literature [40].

*4.3.6. Compound **3** in Table 2*

*4.3.6.1. Tert-butyl (Z)-(2-(oct-1-en-1-ylamino)-2-oxoethyl)carbamate (**3aa**).* R_f = 0.51 (PE: EA = 2 : 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.32 (s, 1H), 6.64 (dd, 1H, J = 10.2, 9.6 Hz), 5.70 (s, 1H), 4.77 (dt, 1H, J = 7.8, 7.2 Hz), 3.83 (d, 2H, J = 6.0 Hz), 2.06–1.97 (m, 2H), 1.46 (s, 9H), 1.42–1.23 (m, 8H), 0.88 (t, 3H, J = 6.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.5, 156.8, 120.3, 112.8, 80.5, 44.8, 31.7, 29.3, 28.9, 28.3, 25.8, 22.6, 14.1. HRMS (*m/z*): 307.1994 $[M+Na]^+$ ($C_{15}H_{28}N_2O_3$), required 307.1992.

*4.3.6.2. Tert-butyl (S,Z)-(1-(oct-1-en-1-ylamino)-1-oxo-3-phenylpropan-2-yl)carbamate (**3ba**).* R_f = 0.33 (PE: EA = 10 : 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.50 (s, 1H), 7.33–7.27 (m, 2H), 7.26–7.19 (m, 3H), 6.59 (dd, 1H, J = 9.6, 9.6 Hz), 5.20 (s, 1H), 4.71 (dt, 1H, J = 7.8, 7.2 Hz), 4.38 (s, 1H), 3.18–2.99 (m, 2H), 1.80–1.69 (m, 2H), 1.42 (s, 9H), 1.32–1.18 (m, 8H), 0.88 (t, 3H, J = 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.5, 155.8, 136.7, 129.3, 128. 8, 127.0, 120.1, 112.8, 80.4, 55.9, 38.1, 31.6, 29.2, 28.9, 28.3, 25.5, 22.6, 14.1. HRMS (*m/z*): 397.2464 $[M+Na]^+$ ($C_{22}H_{34}N_2O_3$), required 397.2462.

*4.3.6.3. Tert-butyl (S,Z)-(3-(4-chlorophenyl)-1-(oct-1-en-1-ylamino)-1-oxopropan-2-yl)carbamate (**3ca**).* R_f = 0.30 (PE: EA = 10 : 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.88 (s, 1H), 7.25 (d, 2H, J = 8.4 Hz), 7.15 (d, 2H, J = 7.8 Hz), 6.58 (dd, 1H, J = 9.6, 9.6 Hz), 5.41 (d, 1H, J = 7.8 Hz), 4.74 (dt, 1H, J = 7.8, 7.2 Hz), 4.41 (s, 1H), 2.95–3.14 (m, 2H), 1.89–1.78 (m, 2H), 1.41 (s, 9H), 1.34–1.19 (m, 8H), 0.88 (t, 3H, J = 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.7, 155.9, 135.3, 132.8, 130.7, 128.8, 120.1, 113.2, 80.5, 55.7, 37.4, 31.7, 29.2, 28.9, 28.3, 25.6, 22.6, 14.1. HRMS (*m/z*): 431.2069 $[M+Na]^+$ ($C_{22}H_{33}N_2O_3Cl$), required 431.2072.

*4.3.6.4. Tert-butyl (S,Z)-(1-(oct-1-en-1-ylamino)-1-oxopropan-2-yl) carbamate (**3da**).* R_f = 0.46 (PE: EA = 5 : 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.32 (s, 1H), 6.64 (dd, 1H, J = 10.8, 9.0 Hz), 5.29 (s, 1H), 4.75 (dt, 1H, J = 7.8, 7.8 Hz), 4.26 (s, 1H), 2.07–1.95 (m, 2H), 1.46 (s, 9H), 1.38 (d, 3H, J = 7.2 Hz), 1.41–1.21 (m, 8H), 0.88 (t, 3H, J = 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.1, 156.2, 120.6, 112.5, 80.4, 49.8, 31.7, 29.3, 28.9, 28.3, 25.8, 22.6, 17.2, 14.1. HRMS (*m/z*): 321.2149 $[M+Na]^+$ ($C_{16}H_{30}N_2O_3$), required 321.2149.

(*E*)-**3da**: R_f = 0.32 (PE: EA = 5 : 1). ^{1}H NMR (600 MHz, $CDCl_3$): 7.75 (s, 1H), 6.68 (dd, 1H, J = 13.8, 10.8 Hz), 5.19 (dt, 1H, J = 14.4, 7.2 Hz), 5.07 (s, 1H), 4.19 (s, 1H), 2.04–1.96 (m, 2H), 1.45 (s, 9H), 1.37 (d, 3H, J = 7.2 Hz), 1.41–1.22 (m, 8H), 0.88 (t, 3H, J = 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 169.7, 155.8, 122.0, 114.5, 80.4, 50.0, 31.7, 29.75, 29.72, 28.8, 28.3, 22.6, 18.0, 14.1.

*4.3.6.5. Tert-butyl (S,Z)-(3,3-dimethyl-1-(oct-1-en-1-ylamino)-1-oxobutan-2-yl)carbamate (**3ea**).* R_f = 0.50 (PE: EA = 10 : 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.41 (d, 1H, J = 10.2 Hz), 6.65 (dd, 1H, J = 10.2, 9.6 Hz), 5.40 (d, 1H, J = 9.0 Hz), 4.77 (dt, 1H, J = 7.8, 7.8 Hz), 3.95 (d, 1H, J = 9.0 Hz), 2.02–1.93 (m, 2H), 1.43 (s, 9H), 1.41–1.20 (m, 8H), 1.02 (s, 9H), 0.89 (t, 3H, J = 6.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.4, 156.0, 120.2, 112.7, 79.8, 62.4, 34.6, 31.7, 29.3, 28.9, 28.3, 26.5, 25.8, 22.6, 14.1. HRMS (*m/z*): 363.2617 $[M+Na]^+$ ($C_{19}H_{36}N_2O_3$), required 363.2618.

*4.3.6.6. Tert-butyl (Z)-(1-(oct-1-en-1-ylcarbamoyl)cyclopsentyl) carbamate (**3fa**).* R_f = 0.25 (PE: EA = 10 : 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.96 (s, 1H), 6.67 (m, 1H), 4.77 (s, 1H), 4.73 (dt, 1H, J = 7.8, 7.2 Hz), 2.24–2.38 (m, 2H), 2.08–1.67 (m, 8H), 1.45 (s, 9H), 1.41–1.23 (m, 8H), 0.88 (t, 3H, J = 6.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 171.4, 155.9, 121.2, 111.7, 80.6, 67.3, 36.6, 31.7, 30.3, 29.4, 29.0, 28.3, 25.9, 22.6, 14.1. HRMS (*m/z*): 361.2462 $[M+Na]^+$ ($C_{19}H_{34}N_2O_3$), required 361.2462.

*4.3.6.7. Tert-butyl (S,Z)-(2-(oct-1-en-1-ylamino)-2-oxo-1-phenylethyl)carbamate (**3ga**).* R_f = 0.35 (PE: EA = 10 : 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.52 (s, 1H), 7.40–7.29 (m, 5H), 6.63 (m, 1H), 5.88 (s, 1H), 5.26 (s, 1H), 4.76 (dt, 1H, J = 7.2, 7.2 Hz), 1.93–1.74 (m, 2H), 1.41 (s, 9H), 1.32–1.13 (m, 8H), 0.87 (t, 3H, J = 6.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.6, 155.4, 137.7, 129.1, 128.5, 127.0, 120.4, 113.0, 80.3, 58.6, 31.6, 29.1, 28.8, 28.3, 25.6, 22.6, 14.1. HRMS (*m/z*): 383.2307 $[M+Na]^+$ ($C_{21}H_{32}N_2O_3$), required 383.2305.

*4.3.6.8. Tert-butyl (Z)-(2-oxo-2-(styrylamino)ethyl)carbamate (**3ab**).* R_f = 0.53 (PE: EA = 2 : 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.51 (s, 1H), 7.39–7.33 (m, 2H), 7.30–7.20 (m, 3H), 6.90 (dd, 1H, J = 10.8, 10.2 Hz), 5.77 (d, 2H, J = 9.6 Hz), 5.33 (s, 1H), 3.82 (d, 2H, J = 5.4 Hz), 1.41 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.6, 156.3, 135.4, 129.0, 127.9, 127.0, 121.2, 111.0, 80.6, 44.7, 28.2. HRMS (*m/z*): 299.1369 $[M+Na]^+$ ($C_{15}H_{20}N_2O_3$), required 299.1366.

*4.3.6.9. Tert-butyl (Z)-(2-oxo-2-((3-phenylprop-1-en-1-yl)amino)-ethyl)carbamate (**3ac**).* R_f = 0.45 (PE: EA = 2 : 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.33 (br s, 1H), 7.32–7.26 (m, 2H), 7.24–7.16 (m, 3H), 6.78 (dd, 1H, J = 9.6, 9.6 Hz), 5.38 (br s, 1H), 5.00 (m, 1H), 3.80 (d, 2H, J = 5.4 Hz), 3.39 (d, 2H, J = 7.8 Hz), 1.44 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.4, 156.7, 139.6, 128.7, 128.2, 126.3, 121.4, 110.5, 80.7, 44.8, 31.9, 28.3. HRMS (*m/z*): 313.1520 $[M+Na]^+$ ($C_{16}H_{22}N_2O_3$), required 313.1523.

*4.3.6.10. Tert-butyl (S,Z)-(1-((4-((tert-butyldimethylsilyl)oxy-2-methylbut-1-en-1-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**3ed**).* R_f = 0.48 (PE: EA = 10 : 1). $[\alpha]_D^{20}$ +22.6 (c = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.95 (d, 1H, J = 8.4 Hz), 6.55 (d, 1H, J = 9.0 Hz), 5.33 (d, 1H, J = 8.4 Hz), 3.84 (d, 1H, J = 9.6 Hz), 3.79 (m, 1H), 3.70 (m, 1H), 2.33 (m, 1H), 2.14 (m, 1H), 1.72 (s, 3H), 1.43 (s, 9H), 1.00 (s, 9H), 0.90 (s, 9H), 0.10 (s, 3H), 0.083 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.3, 155.5, 119.4, 118.8, 79.4, 62.4, 62.1, 34.9, 34.9, 28.3, 26.6, 26.1, 21.0, 18.6, −5.2. HRMS (*m/z*): 451.2963 $[M+Na]^+$ ($C_{22}H_{44}N_2O_4Si$), required 451.2963.

*4.3.6.11. Tert-butyl (S,E)-(1-((4-((tert-butyldimethylsilyl)oxy)-2-methylbut-1-en-1-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**3ee**).* R_f = 0.36 (PE: EA = 10 : 1). $[\alpha]_D^{20}$ +15.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.17 (d, 1H, J = 9.0 Hz), 6.54 (d, 1H, J = 10.2 Hz), 5.32 (d, 1H, J = 7.2 Hz), 3.90 (d, 1H, J = 9.0 Hz), 3.66 (t, 1H, J = 7.2 Hz), 2.22 (t, 1H, J = 7.2 Hz), 1.64 (s, 3H), 1.43 (s, 9H), 1.01 (s, 9H), 0.88 (s, 9H), 0.036 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.0, 117.9, 117.0, 79.9, 62.4, 62.2, 40.0, 34.5, 28.3, 26.5, 25.9, 18.3, 15.3, −5.3. HRMS (*m/z*): 429.3144 $[M+H]^+$ ($C_{22}H_{44}N_2O_4Si$), required 429.3143.

*4.3.6.12. Benzyl ((S)-1-(((S,1Z,6Z)-4-((tert-butyldiphenylsilyl)oxy) -octa-1,6-dien-1-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**3h**).* $[\alpha]_D^{20}$ +7.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.71–7.64 (m, 4H), 7.46–7.27 (m, 11H), 7.02 (d, 1H, J = 10.2 Hz), 6.66 (dd, 1H, J = 10.2, 9.0 Hz), 5.54 (d, 1H, J = 9.0 Hz), 5.51 (m, 1H), 5.33 (m, 1H), 5.09 (d, 2H, J = 9.0 Hz), 4.82 (dt, 1H, J = 9.0, 7.8 Hz), 3.88 (d, 1H, J = 9.6 Hz), 3.85 (m, 1H), 2.29–1.99 (m, 4H), 1.44 (d, 3H, J = 6.6 Hz), 1.06 (s, 9H), 0.96 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.9, 156.3, 136.2, 135.9, 134.1, 129.8, 129.7, 128.5, 128.2, 128.1, 127.63, 127.60, 126.5, 125.9, 121.6, 108.7, 72.4, 67.1, 62.9, 34.8, 33.8, 32.5, 27.0, 26.4, 19.3, 13.0. HRMS (*m/z*): 627.3616 $[M+H]^+$ ($C_{38}H_{50}N_2O_4Si$), required 627.3613.

*4.3.7. (S)-2-Bromosuccinic acid (**5**)*

A 500 mL 3-necked round-bottomed flask (charged with 2 washing bottles connected in series with the first one empty and the second one filled with 2 M NaOH) was charged with aspartic acid **4** (13.3 g, 100 mmol, 1.00 eq.) and KBr (51.4 g, 432 mmol, 4.32 eq.). An *aq*. solution of H_2SO_4 (2.5 M, 212 mL) was added in one portion and then the solution was cooled to − 5 °C. A solution of sodium nitrite (11.9 g, 172 mmol, 1.72 eq.) in H_2O (28 mL) was added with careful temperature monitoring, such that the reaction temperature was maintained below 0 °C. After completion of the addition of $NaNO_2$ the resulting dark brown reaction mixture was stirred for 2 h at −5 °C and then extracted with EA (2 × 140 mL). The combined organic extracts were washed with half sat. *aq.* NaCl (140 mL), then dried over Na_2SO_4 and concentrated under reduced pressure to yield the desired product **5** as a white solid that was used in the next step without further purification (17.5 g, 89%). $R_f = 0.15$ (PE: EA: EtOH = 6 : 6: 1).

*4.3.8. (S)-2-Bromobutane-1,4-diol (**6**)*

To a cooled (0 °C) solution of **5** (12.0 g, 61.0 mmol, 1.0 eq) in THF (125 mL) was added $BH_3 \cdot THF$ (1.0 M in THF, 183 mL, 183 mmol, 3.0 eq) over a period of 1 h. After the addition, the cooling bath was removed and the light-yellow solution was stirred for 15 min, resulting in the formation of a thick, milky-white suspension. Stirring was continued at rt overnight, then the reaction mixture was cooled to 0 °C and quenched by dropwise (!) addition of H_2O (5.02 g) (formation of a clear solution). K_2CO_3 (5.02 g) was then added to the reaction mixture and solids were removed by filtration over Celite. The solid residue was washed with MTBE (140 mL) and the combined original filtrate and MTBE washes were concentrated to an oily, yellow residue. This material was purified by column chromatography on silica gel (PE/EA/EtOH) affording the desired product **6** as a yellow oil (9.86 g, 96%). $R_f = 0.33$ (PE: EA: EtOH = 6 : 6: 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.34 (m, 1H), 3.94−3.76 (m, 4H), 2.19−2.05 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 67.1, 60.0, 54.9, 37.8.

*4.3.9. (R)-Tert-butyldimethyl(2-(oxiran-2-yl)ethoxy)silane (**7**)*

To a cooled (−5 °C) suspension of NaH (60% in mineral oil, 6.94 g, 174 mmol, 3.2 eq.) in THF (90 mL) and DMF (90 mL) was added a solution of **6** (9.17 g, 54.3 mmol, 1.0 eq.) in THF (92 mL) over 15 min. After 3 h of stirring at −5 °C, a solution of TBSCl (12.3 g, 81.6 mmol, 1.5 eq.) in THF (90 mL) was added over 10 min and the suspension was stirred for further 5 min at −5 °C. Then the reaction mixture was warmed to rt and stirred overnight. When it was completed, it was quenched with half sat. *aq*. NH_4Cl (180 mL) below 0 °C carefully (!). The aqueous solution was extracted with EA (180 mL). The combined organic extracts were concentrated and the residue was purified by column chromatography on silica gel (PE/EA) affording the desired product **7** as a colorless oil (7.05 g, 64%). $R_f = 0.39$ (PE: EA = 20 : 1). $[\alpha]_D^{20}$ +14.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.81−3.75 (m, 2H), 3.05 (m, 1H), 2.78 (dd, 1H, J = 5.4, 4.2 Hz), 2.52 (dd, 1H, J = 5.4, 3.0 Hz), 1.79 (m, 1H), 1.70 (m, 1H), 0.90 (s, 9H), 0.069 (s, 3H), 0.067 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 59.9, 49.9, 47.1, 35.8, 25.8, 18.2, −5.5. HRMS (*m/z*): 203.1460 $[M+H]^+$ ($C_{10}H_{22}O_2Si$), required 203.1462.

*4.3.10. (S)-1-((Tert-butyldimethylsilyl)oxy)hept-5-yn-3-ol (**8**)*

Propyne (1.0 M in THF, 40.3 mL, 40.3 mmol, 2.0 eq.) was dissolved in anhydrous THF (30 mL) and condensed at −78 °C. *n*-Butyllithium (2.5 M in hexanes, 16.1 mL, 40.3 mmol, 2.0 eq) was added dropwise over 1 h, and the resultant white suspension was stirred for additional 60 min at −78 °C. A solution of epoxide **7** (4.08 g, 20.2 mmol) in anhydrous THF (22 mL) was then added dropwise followed by addition of $BF_3 \cdot Et_2O$ (5.1 mL, 40.3 mmol, 2.0 eq). The mixture was stirred for 1 h at −78 °C and for an additional hour at 0 °C. The reaction mixture was quenched with half sat. *aq*. NH_4Cl (50 mL) and extracted with EA/MTBE 1: 1 (3 × 50 mL). The combined organic layers were concentrated and the residue was purified by column chromatography on silica gel (PE/EA) to furnish the desired product **8** as a colorless oil (4.16 g, 85%). $R_f = 0.25$ (PE: EA = 20 : 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.98−3.87 (m, 2H), 3.83 (m, 1H), 3.46 (br s, 1H), 2.42−2.27 (m, 2H), 1.80, (t, 3H, J = 2.4 Hz), 1.83−1.69 (m, 2H), 0.90 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 77.7, 75.6, 70.6, 62.3, 37.4, 27.5, 25.9, 18.1, 3.6, −5.5, −5.6. HRMS (*m/z*): 243.1776 $[M+H]^+$ ($C_{13}H_{26}O_2Si$), required 243.1775.

*4.3.11. (S)-5-(But-2-yn-1-yl)-2,2,9,9,10,10-hexamethyl-3,3-diphenyl-4,8-dioxa-3,9-disilaundecane (**9**)*

To a cooled (0 °C) solution of alcohol **8** (5.05 g, 20.8 mmol, 1.0 eq.), imidazole (3.33 g, 48.9 mmol, 2.4 eq.) and 4-(dimethylamino) pyridine (DMAP) (127 mg, 1.04 mmol, 0.05 eq.) in DCM (126 mL), *tert*-butyldiphenylsilyl chloride (TBDPSCl) (12.2 mL, 46.8 mmol, 2.3 eq.) was added, then the suspension was stirred at rt overnight. The mixture was quenched with sat. *aq*. NH_4Cl (55 mL) and extracted with MTBE (2 × 55 mL). The combined organic layers were concentrated and the residue was purified by column chromatography on silica gel (PE) affording the desired product **9** as a colorless oil (9.08 g, 91%). R_f = 0.41 (PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.73−7.65 (m, 4H), 7.45−7.32 (m, 6H), 3.98 (m, 1H), 3.73−3.60 (m, 2H), 2.27−2.17 (m, 2H), 1.90−1.78 (m, 2H), 1.70 (t, 3H, J = 2.4 Hz), 1.06 (s, 9H), 0.85 (s, 9H), −0.002 (s, 3H), −0.007 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 135.9, 135.9, 134.4, 134.0, 129.6, 129.5, 127.6, 127.4, 77.4, 76.0, 69.7, 59.8, 39.4, 27.3, 27.0, 25.9, 19.4, 18.3, 3.5, −5.3. HRMS (*m/z*): 481.2966 $[M+H]^+$ ($C_{29}H_{44}O_2Si_2$), required 481.2953.

*4.3.12. (S,Z)-5-(But-2-en-1-yl)-2,2,9,9,10,10-hexamethyl-3,3-diphenyl-4,8-dioxa-3,9-disilaundecane (**10**)*

A flask containing a mixture of **9** (10.1 g, 21.0 mmol, 1.0 eq.), quinoline (2.71 g, 21.0 mmol, 1.0 eq.) and Lindlar's catalyst (2.52 g) in EA (200 mL) was evacuated and flushed with H_2. The reaction mixture was stirred at rt under H_2 (1 atm) for 7 h and then filtered through a plug of Celite. The plug was rinsed with EA (20 mL). The combined organic layers were concentrated and the residue was purified by column chromatography on silica gel (PE) affording the desired product **10** as a colorless oil (9.78 g, 97%). $R_f = 0.59$ (PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.71−7.65 (m, 4H), 7.43−7.32 (m, 6H), 5.42 (m, 1H), 5.30 (m, 1H), 3.92 (m, 1H), 3.66 (m, 1H),3.59 (m, 1H), 2.16 (dd, 2H, J = 6.6, 6.6 Hz), 1.75−1.64 (m, 2H), 1.41 (dd, 3H, J = 7.2, 1.2 Hz), 1.05 (s, 9H), 0.84 (s, 9H), −0.02 (s, 3H), −0.03 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 135.9, 134.6, 134.3, 129.5, 129.4, 127.5, 127.4, 126.2, 125.6, 70.6, 60.1, 39.3, 34.5, 27.0, 25.9, 19.4, 18.3, 12.9, −5.3. HRMS (*m/z*): 483.3116 $[M+H]^+$ ($C_{29}H_{46}O_2Si_2$), required 483.3109.

*4.3.13. (S,Z)-3-((Tert-butyldiphenylsilyl)oxy)hept-5-en-1-ol (**11**)*

PPTS (2.08 g, 8.3 mmol, 0.4 eq.) was added in one portion to a solution of **10** (9.99 g, 20.7 mmol, 1.0 eq.) in ethanol (95%, 200 mL). The reaction mixture was stirred at rt overnight and then was concentrated. The residue was diluted in MTBE (200 mL) and washed sequentially with sat. *aq*. $NaHCO_3$ (2 × 100 mL), water (100 mL), *aq.* HCl (0.3 M, 100 mL) and water (2 × 100 mL). The organic layer was concentrated and the residue was purified by column chromatography on silica gel (PE/EA) affording the desired product **11** as a colorless oil (7.48 g, 98%). $R_f = 0.40$ (PE: EA = 10 : 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.73−7.67 (m, 4H), 7.46−7.35 (m, 6H), 5.41 (m, 1H), 5.21 (m, 1H), 3.98 (m, 1H), 3.79 (m, 1H), 3.68 (m,1H), 2.27 (m,1H), 2.20 (m, 1H), 1.98 (br s, 1H), 1.83 (m, 1H), 1.66 (m, 1H), 1.38 (dt, 3H, J = 7.2, 1.2 Hz), 1.07 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ:

136.0, 135.9, 134.0, 133.7, 129.81, 129.75, 127.7, 127.6, 126.1, 125.6, 72.1, 59.9, 37.5, 34.1, 27.0, 19.3, 12.8. HRMS (*m/z*): 369.2243 $[M+H]^+$ ($C_{23}H_{32}O_2Si$), required 369.2244.

*4.3.14. (S,Z)-3-((Tert-butyldiphenylsilyl)oxy)hept-5-enal (**12**)*

(Diacetoxyiodo)benzene (BAIB) (6.28 g, 19.5 mmol, 1.1 eq.) was added to a solution of **11** (6.53 g, 17.7 mmol, 1.0 eq.) and (2,2,6,6-tetramethylpiperidinin-1-yl)oxyl (TEMPO) (277 mg, 1.77 mmol, 0.1 eq.) in DCM (80 mL) at 0 °C. The reaction mixture was stirred at rt overnight and then quenched with half sat. *aq*. NH_4Cl (40 mL). The organic layer was washed with sat. *aq.* $NaHCO_3$ (40 mL) and water (40 mL), then it was concentrated. The residue was purified by column chromatography on silica gel (PE/EA) affording the desired product **12** as a colorless oil (5.30 g, 82%). R_f = 0.65 (PE: EA = 20 : 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.71 (t, 1H, J = 2.4 Hz), 7.72–7.64 (m, 4H), 7.46–7.35 (m, 6H), 5.49 (m, 1H), 5.27 (m, 1H), 4.25 (m, 1H), 2.52–2.43 (m, 2H), 2.33–2.30 (m, 2H), 1.43 (dd, 3H, *J* = 6.6, 0.6 Hz), 1.05 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 202.0, 135.9, 133.8, 133.5, 129.9, 129.8, 127.8, 127.6, 127.2, 124.9, 69.2, 49.9, 34.9, 26.9, 19.3, 12.9. HRMS (*m/z*): 367.2090 $[M+H]^+$ ($C_{23}H_{30}O_2Si$), required 367.2088.

*4.3.15. Tert-butyl(((S,1Z,6Z)-1-iodoocta-1,6-dien-4-yl)oxy)diphenylsilane (**13**)*

To a suspension of iodomethyltriphenylphosphorane iodide (14.9 g, 28.0 mmol, 1.7 eq.) in THF (60 mL) was slowly added a 1 M solution of KHMDS(28.0 mL, 28.0 mmol, 1.7 eq.) in THF (160 mL) at 0 °C. After being stirred for 10 min, the yellow mixture was cooled to −78 °C and a solution of **12** (6.04 g, 16.5 mmol, 1.0 eq.) in THF (60 mL) was then added. The reaction mixture was stirred at −78 °C for 90 min, then at rt for 5 min, quenched with half sat. *aq*. NH_4Cl (220 mL), diluted with PE (160 mL) and filtered through a plug of Celite. The plug was rinsed with PE (60 mL). The combined organic phase was concentrated and the residue was purified by column chromatography on silica gel (PE) to afford the desired product as a pink oil (6.64 g, 82%). R_f = 0.67 (PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.72–7.64 (m, 4H), 7.45–7.34 (m, 6H), 6.27 (dt, 1H, *J* = 7.2, 7.2 Hz), 6.22 (dt, 1H, *J* = 7.2, 1.2 Hz), 5.46 (m, 1H), 5.32 (m, 1H), 3.90 (m, 1H), 2.33–2.26 (m, 2H), 2.22–2.13 (m, 2H), 1.44 (d, 3H, J = 6.6 Hz), 1.06 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 137.9, 135.9, 134.2, 134.0, 129.62, 129.60, 127.6, 127.5, 126.2, 125.8, 83.9, 71.7, 41.4, 34.2, 27.0, 19.3, 12.9. HRMS (*m/z*): 513.1086 $[M+Na]^+$ ($C_{24}H_{31}IOSi$), required 513.1081.

*4.3.16. Tert-butyl ((S)-1-(((S,1Z,6Z)-4-((tert-butyldiphenylsilyl)-oxy)octa-1,6-dien-1-yl)amino) -3,3-dimethyl-1-oxobutan-2-yl)carbamate (**14**)*

A resealable Schlenk tube was charged with vinyl iodide **13** (491 mg, 1.00 mmol, 1.0 eq.) and **1e** (461 mg, 2.00 mmol, 2.0 eq), evacuated and back filled with N_2. DME (7.5 mL), Cs_2CO_3 (652 mg, 2.00 mmol, 2.0 eq.), DMEDA (65 μL, 0.60 mmol, 0.6 eq.) and CuI (57 mg, 0.30 mmol, 0.3 eq.) were added under N_2. The Schlenk tube was sealed with a teflon valve, immerse in a preheated oil bath; the reaction mixture was stirred at 55 °C for 12 h. The reaction vessel was removed from the oil bath and the resulting suspension was allowed to reach room temperature, then, it was filtered through Celite, eluting with EA (30 mL). The filtrate was concentrated and the residue was purified by column chromatography on silica gel (PE/EA) affording the desired product **14** as a colorless oil (505 mg, 85%). R_f = 0.50 (PE: EA = 10 : 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.71–7.64 (m, 4H), 7.47–7.35 (m, 6H), 7.03 (d, 1H, *J* = 10.2 Hz), 6.66 (dd, 1H, *J* = 10.2, 10.2 Hz), 5.51 (m, 1H), 5.33 (m, 1H), 5.24 (d, 1H, *J* = 9.0 Hz), 4.81 (dt, 1H, *J* = 8.4, 7.8 Hz), 3.85 (m, 1H), 3.79 (d, 1H, *J* = 9.0 Hz) 2.28–1.99 (m, 4H), 1.45 (d, 3H, *J* = 7.8 Hz), 1.43 (s, 9H), 1.06 (s, 9H), 0.96 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.3, 155.7, 135.9, 134.1, 134.1, 129.73, 129.70, 127.62, 127.59, 126.5, 125.9, 121.6, 108.5, 79.8, 72.4, 62.4, 34.8, 33.9, 32.4, 28.3, 27.0, 26.5, 19.3, 13.0. HRMS (*m/z*): 593.3772 $[M+H]^+$ ($C_{35}H_{52}N_2O_4Si$), required 593.3769.

*4.3.17. (S)-2-Amino-N-((S,1Z,6Z)-4-((tert-butyldiphenylsilyl)ox-y) octa-1,6-dien-1-yl)-3,3-dimethylbutanamide (**15**)*

A solution of the amino-protected derivative **14** (1096 mg, 1.85 mmol) in ethylene glycol (60 mL) was heated at 200 °C for only 15 min. The reaction mixture was then cooled at rt, diluted with EA (600 mL), washed with water (3 × 300 mL). The organic layer was concentrated and the residue was purified by column chromatography on silica gel (PE/EA) affording the desired product **15** as a yellow oil (655 mg, 72%). R_f = 0.41 (EA & 5% triethylamine). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.49 (d, 1H, *J* = 10.8 Hz), 7.72–7.64 (m, 4H), 7.45–7.33 (m, 6H), 6.71 (dd, 1H, *J* = 11.4, 9.6 Hz), 5.45 (m, 1H), 5.33 (m, 1H), 4.79 (dt, 1H, *J* = 9.0, 7.2 Hz), 3.86 (m, 1H), 3.09 (s, 1H), 2.25–2.08 (m, 4H), 1.44 (d, 3H, *J* = 6.0 Hz), 1.06 (s, 9H), 0.97 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.8, 135.9, 134.3, 134.2, 129.61, 129.59, 127.5, 126.1, 125.9, 121.9, 107.4, 72.4, 64.2, 34.2, 33.8, 32.5, 27.0, 26.7, 19.4, 12.9. HRMS (*m/z*): 493.3249 $[M+H]^+$ ($C_{30}H_{44}N_2O_2Si$), required 493.3245.

*4.3.18. (Z)-3-(Tributylstannyl)acrylic acid (**16**)*

$HSnBu_3$ (32.0 g, 110 mmol, 1.1 eq.) was added to a solution of ethyl propiolate (9.80 g, 100 mmol, 1.0 eq) in toluene (Tol.) (350 mL) at −78 °C, then Et_3B (1.0 M in THF, 20.0 mL, 20 mmol 0.2 eq.) was added. The reaction mixture was stirred from −78 °C to room temperature for 18 h. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (PE/EA) to afford the desired intermediate ethyl (*Z*)-3-(tributylstannyl)acrylate as a colorless oil (17.9 g, 46%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.15 (d, 1H, *J* = 12.6 Hz), 6.73 (d, 1H, *J* = 13.2 Hz), 4.21 (q, 2H, *J* = 7.2 Hz), 1.56–1.40 (m, 6H), 1.34–1.24 (m, 9H), 1.04–0.83 (m, 15H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.7, 157.0, 135.4, 60.5, 29.2, 27.4, 14.3, 13.7, 11.0.

A suspension of the (*Z*)-ester (1.17 g, 3.01 mmol, 1.0 eq.) and $LiOH\cdot H_2O$ (151 mg, 3.61 mmol, 1.2 eq) in THF (7.2 mL), MeOH (3.7 mL) and H_2O (7.2 mL) was heated at 60 °C overnight. The mixture was cooled down to rt and THF and MeOH were evaporated. After diluted with water (25 mL), *aq*. HCl (1.0 M) was added until pH = 1 and the mixture was extracted with EA (2 × 25 mL). The combined organic phases were concentrated and the residue was purified by column chromatography on silica gel (PE/EA) affording the desired product **16** as a yellow oil (1076 mg, 99%). R_f = 0.22 (PE: EA = 40 : 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.40 (d, 1H, *J* = 12.6 Hz), 6.78 (d, 1H, *J* = 12.6 Hz), 1.58–1.40 (m, 6H), 1.35–1.24 (m, 6H), 1.04–0.82 (m, 15H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 172.9, 161.9, 134.6, 29.1, 27.3, 13.7, 11.2.

*4.3.19. (S)−N-((S,1Z,6Z)-4-((Tert-butyldiphenylsilyl)oxy)octa-1,6-dien-1-yl)-3,3-dimethyl-2-((Z)-3-(tributylstannyl)acrylamido)butanamide (**17**)*

To a solution of amine **15** (246 mg, 0.50 mmol, 1.0 eq.) and **16** (217 mg, 0.60 mmol, 1.2 eq) in DCM (14 mL) and DMF (3.5 mL) at 0 °C was added diisopropylethylamine (DIPEA) (131 μL, 0.75 mmol, 1.5 eq.) followed by 1-Hydroxy-7-azabenzotriazole (HOAt) (75 mg, 0.55 mmol, 1.1 eq.) and *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uranium hexafluorophosphate (HATU) (247 mg, 0.65 mmol, 1.3 eq). After 30 min the reaction mixture was quenched with a sat. *aq*. NH_4Cl (25 mL), diluted with water (25 mL) and extracted with MTBE (100 mL). The combined organic phases were washed with water (50 mL), concentrated and the residue was purified by column chromatography on silica gel (PE/EA) affording the desired product **17** as a yellow oil (380 mg, 91%). R_f = 0.55 (PE:

EA = 10 : 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.72–7.65 (m, 4H, Ar*H*), 7.48–7.34 (m, 6H, Ar*H*), 7.02 (d, 1H, J = 12.0 Hz, C^2*H*), 6.96 (d, 1H, J = 10.8 Hz, N^5*H*), 6.75 (d, 1H, J = 12.6 Hz, C^1*H*), 6.65 (dd, 1H, J = 10.8, 9.0 Hz, C^6*H*), 6.22 (d, 1H, J = 9.6 Hz, N^3*H*), 5.51 (m, 1H, C^{12}*H*), 5.34 (m, 1H, C^{11}*H*), 4.82 (dt, 1H, J = 8.4, 7.8 Hz, C^7*H*), 4.31 (d, 1H, J = 9.6 Hz, C^4*H*), 3.86 (m, 1H, C^9*H*), 2.31–1.96 (m, 4H, C^8*H*$_2$, C^{10}*H*$_2$), 1.55–1.39 (m, 9H, C^{13}*H*$_3$, Sn(n-C$_4$*H*$_9$)$_3$), 1.31–1.21 (m, 6H, Sn(n-C$_4$*H*$_9$)$_3$), 1.06 (s, 9H, SiPh$_2$C*Me*$_3$), 0.96 (s, 9H, C*Me*$_3$), 0.99–0.80 (m, 15H, Sn(n-C$_4$*H*$_9$)$_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.8, 166.0, 153.7, 136.1, 135.9, 134.1, 129.78, 129.75, 127.7, 127.6, 126.5, 125.8, 121.4, 108.8, 72.3, 60.4, 35.4, 33.8, 32.5, 29.3, 27.4, 27.0, 26.5, 19.3, 13.8, 13.0, 11.6. The data were in agreement with those reported in the literature [15]. HRMS (*m/z*): 837.4409 $[M+H]^+$ ($C_{45}H_{72}N_2O_3SiSn$), required 837.4401.

4.3.20. (S)-6-((S,3E,5Z)-6-iodo-4-methylhexa-3,5-dien-2-yl)-3-methoxy-5,6-dihydro-2H-pyran-2-one (**18**)

R_f = 0.53 (PE: EA = 2 : 1). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 6.69 (d, 1H, J = 8.4 Hz, C^7*H*), 6.22 (d, 1H, J = 8.4 Hz, C^8*H*), 5.64 (dd, 1H, J = 6.6, 2.4 Hz, C^2*H*), 5.45 (d, 1H, J = 10.2 Hz, C^6*H*), 4.22 (ddd, 1H, J = 11.4, 7.8, 3.6 Hz, C^4*H*), 3.66 (s, 3H, OC^1*H*$_3$), 2.86 (m, 1H, C^5*H*), 2.56 (ddd, 1H, J = 17.4, 6.6, 3.6 Hz, C^3*H*$_2$), 2.46 (ddd, 1H, J = 17.4, 11.4, 2.4 Hz, C^3*H*$_2$), 1.89 (d, 3H, J = 1.2 Hz, C^{10}*H*$_3$), 1.17 (d, 3H, J = 6.6 Hz, C^9*H*$_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.6, 145.2, 141.8, 134.5, 132.8, 108.3, 81.8, 77.4, 55.4, 37.2, 26.6, 16.5, 16.2. The Data were in agreement with those reported in the literature [15].

4.3.21. (S,2Z,4Z,6E)-N-((S)-1-(((S,1Z,6Z)-4-((Tert-butyldiphenylsilyl)oxy)octa-1,6-dien-1-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)-8-((S)-5-methoxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)-6-methylnona-2,4,6-trienamide (**19**)

To a solution of stannane **17** (161 mg, 0.193 mmol, 1.0 eq.) and **18** (81 mg, 0.233 mmol, 1.2 eq.) in 1-methyl-2-pyrrolidinone (NMP) (15 mL) at 0 °C was added Cu(I) thiophene-2-carboxylate (CuTc) (55 mg, 0.288 mmol, 1.5 eq.). The reaction was stirred at 0 °C for 45 min and then 18 h at rt. The crude mixture was filtered through a plug of neutral alumina, washed with MTBE: EA 1:1 (75 mL) and the combined filtrates were washed with *aq*. HCl 0.5 M (75 and 2 × 45 mL) and water (2 × 45 mL). The organic solution was concentrated and the residue was purified by column chromatography on silica gel (PE/EA) affording the desired product **19** as a colorless oil (108 mg, 73%). R_f = 0.31 (PE: EA = 2 : 1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.70–7.66 (m, 4H, Ar*H*), 7.46–7.35 (m, 7H, N^{13}H, Ar*H*), 7.25 (m, 1H, C^8*H*), 6.89 (ddd, 1H, J = 11.4, 11.4, 0.6 Hz, C^9*H*), 6.64 (dd, 1H, J = 10.8, 9.0 Hz, C^{14}*H*), 6.31 (d, 1H, J = 9.0 Hz, N^{11}*H*), 6.16 (d, 1H, J = 11.4 Hz, C^7*H*), 5.66 (d, 1H, J = 11.4 Hz, C^2*H*), 5.62 (dd, 1H, J = 6.0, 3.0 Hz, C^{10}*H*), 5.50 (m, 1H, C^{20}*H*), 5.32 (m, 1H, C^{19}*H*), 5.28 (d, 1H, J = 10.2 Hz, C^6*H*), 4.82 (dt, 1H, J = 7.8, 7.8 Hz, C^{15}*H*), 4.29 (d, 1H, J = 9.6 Hz, C^{12}*H*), 4.21 (ddd, 1H, J = 12.0, 7.2, 4.2 Hz, C^4*H*), 3.85 (m, 1H, C^{17}*H*), 3.65 (s, 3H, OC^1*H*$_3$), 2.84 (m, 1H, C^5*H*), 2.46–2.06 (m, 6H, C^3*H*$_2$, C^{16}*H*$_2$, C^{18}*H*$_2$), 1.84 (d, 3H, J = 1.2 Hz, C^{23}*H*$_3$), 1.44 (dd, 3H, J = 6.6, 1.2 Hz, C^{21}*H*$_3$), 1.16 (d, 3H, J = 6.6 Hz, C^{22}*H*$_3$), 1.05 (s, 9H, SiPh$_2$C*Me*$_3$), 0.99 (s, 9H, C*Me*$_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.0, 166.1, 161.6, 145.2, 140.2, 137.3, 135.9, 134.14, 134.11, 129.74, 129.70, 127.62, 127.58, 126.5, 125.9, 124.1, 121.4, 120.8, 109.0, 108.1, 81.8, 72.4, 60.3, 55.4, 37.3, 35.0, 33.9, 32.5, 27.0, 26.6, 26.3, 19.3, 17.2, 16.8, 13.0. The Data were in agreement with those reported in the literature [15].

4.3.22. (S,2Z,4Z,6E)-N-((S)-1-(((S,1Z,6Z)-4-hydroxyocta-1,6-dien-1-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)-8-((S)-5-methoxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)-6-methylnona-2,4,6-trienamide (**20**)

To a solution of **19** (108 mg, 0.141 mmol, 1.0 eq.) in THF (20 mL) at 0 °C, *n*-tetrabutylammonium fluoride (TBAF) (1.0 M in THF, 564 μL, 0.564 mmol, 4.0 eq) was added. The reaction was stirred at rt for 60 min and then quenched with a sat. *aq*. NH_4Cl (5.4 mL), diluted with water (20 mL) and extracted with EA (50 and 20 mL). The combined organic phases were concentrated and the residue was purified by column chromatography on silica gel (PE/EA) to give crude product. The crude product was purified by semi-preparative HPLC (YMC-Pac ODS-A C18 250*20 mm, gradient H_2O: CH_3CN from 30 to 100% CH_3CN, UV detection, flow 9.0 mL/min) to afford the desired product **20** as white solid (49 mg, 66%). R_f = 0.14 (PE: EA = 1 : 1). $[\alpha]_D^{20}$ +61.0 (c = 0.1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.02 (d, 1H, J = 10.2 Hz), 7.26 (m, 1H), 6.88 (dd, 1H, J = 12.0, 11.4 Hz), 6.76 (dd, 1H, J = 10.2, 9.0 Hz), 6.53 (d, 1H, J = 9.6 Hz), 6.16 (d, 1H, J = 11.4 Hz), 5.69 (d, 1H, J = 12.0 Hz), 5.67–5.60 (m, 2H), 5.42 (m, 1H), 5.28 (d, 1H, J = 10.2 Hz), 4.89 (dt, 1H, J = 8.4, 7.8 Hz), 4.36 (d, 1H, J = 9.6 Hz), 4.22 (ddd, 1H, J = 11.4, 7.8, 4.8 Hz), 3.76 (m, 1H), 3.66 (s, 3H), 2.85 (m, 1H), 2.46–2.36 (m, 2H), 2.34–2.14 (m, 4H), 1.84 (d, 3H, J = 1.2 Hz), 1.64 (d, 3H, J = 6.6 Hz), 1.16 (d, 3H, J = 6.6 Hz), 1.03 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.6, 166.5, 161.7, 145.4, 140.3, 137.5, 134.3, 134.2, 127.8, 125.8, 124.3, 123.7, 120.9, 108.9, 108.3, 82.0, 72.1, 60.8, 55.6, 37.5, 35.0, 34.8, 33.2, 26.8, 26.5, 17.3, 16.9, 13.2. HRMS (*m/z*): 529.3277 $[M+H]^+$ ($C_{30}H_{44}N_2O_6$), required 529.3272.

4.3.23. (S,1Z,6Z)-1-((S)-2-((S,2Z,4Z,6E)-8-((S)-5-Methoxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)-6-methylnona-2,4,6-trienamido)-3,3-dimethylbutanamido)octa-1,6-dien-4-yl carbamate (**placabulin**)

To a solution of **20** (37 mg, 0.070 mmol, 1.0 eq) in DCM (5.0 mL) at 0 °C, trichloroacetyl isocyanate (TCAI) (13 μL, 0.109 mmol, 1.6 eq) was added. The reaction was stirred at 0 °C for 30 min and then neutral aluminum oxide (185 mg) was added. The mixture was stirred for 30 min and then was soaked into a pad of aluminum oxide. The product was washed out using a mixture of DCM/MeOH (*v/v* 50:1, 30 mL). The filtrate was evaporated under vacuum and the residue was purified by column chromatography (PE/EA) to give crude product. The crude product was further purified by semi-preparative HPLC (YMC-Pac ODS-A C18 250*20 mm, gradient H_2O: CH_3CN from 20 to 100% CH_3CN, UV detection, flow 9.0 mL/min) affording **placabulin** as a white solid (27 mg, 68%). $[\alpha]_D^{20}$ −64.0 (c = 0.1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.70 (d, 1H, J = 10.8 Hz, N^{13}*H*), 7.31 (dd, 1H, J = 12.0, 11.4 Hz, C^8*H*), 6.91 (ddd, 1H, J = 11.4, 11.4, 0.6 Hz, C^9*H*), 6.82 (m, 1H, C^{14}*H*), 6.53 (d, 1H, J = 9.6 Hz, N^{11}*H*), 6.16 (d, 1H, J = 11.4 Hz, C^7*H*), 5.71 (d, 1H, J = 11.4 Hz, C^2*H*), 5.64 (dd, 1H, J = 7.2, 3.0 Hz, C^{10}*H*), 5.60 (m, 1H, C^{20}*H*), 5.40 (m, 1H, C^{19}*H*), 5.30 (d, 1H, J = 9.6 Hz, C^6*H*), 4.83 (dt, 1H, J = 8.4, 8.4 Hz, C^{15}*H*), 4.46 (m, 1H, C^{17}*H*), 4.44 (d, 1H, J = 9.6 Hz, C^{12}*H*), 4.25 (ddd, 1H, J = 11.4, 7.2, 4.2 Hz, C^4*H*), 3.66 (s, 3H, OC^1*H*$_3$), 2.86 (m, 1H, C^5*H*), 2.49–2.41 (m, 2H, C^3*H*$_2$, C^{16}*H*$_2$), 2.39 (m, 1H, C^3*H*$_2$), 2.38–2.33 (m, 2H, C^{18}*H*$_2$), 2.12 (m, 1H, C^{16}*H*$_2$), 1.82 (d, 3H, J = 0.6 Hz, C^{23}*H*$_3$), 1.63 (d, 3H, J = 1.2 Hz, C^{21}*H*$_3$), 1.16 (d, 3H, J = 7.2 Hz, C^{22}*H*$_3$), 1.04 (s, 9H, C*Me*$_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.2, 166.3, 161.7, 157.6, 145.2, 140.2, 137.5, 134.1, 133.8, 127.1, 124.9, 124.4, 124.2, 120.8, 108.3, 105.8, 81.9, 75.7, 60.7, 55.5, 37.1, 34.8, 31.4, 30.9, 26.7, 26.1, 17.1, 16.4, 13.0. HRMS (*m/z*): 572.3310 $[M+1]^+$ ($C_{41}H_{45}N_3O_7$) required 572.3330. The Data were in agreement with those reported the literature [15].

Supplementary material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Declaration of competing interest

All the authors claim that there are no conflicts to declare.

Acknowledgments

We thank National Natural Science Foundation of China (No. 81773576) for the financial support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.131953.

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