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Progress toward the Total Synthesis of 9 β -Hydroxyvertine: Construction of an Advanced Quinolizidine Intermediate

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ABSTRACT

Progress toward the total synthesis of 9 β -hydroxyvertine **2** is described. Our approach involves a Petasis borono-Mannich reaction to assemble a key intermediate **A**, securing the correct configuration at H-9 and H-10 in the final targeted molecule. Subsequent formation of the quinolizidine framework **B** allowed the synthesis of an advanced intermediate containing all but the lactone moiety of **2**. Our unsuccessful attempts at introducing this lactone feature are also described.

Keywords: 9 β -hydroxyvertine, Petasis borono-Mannich reaction, quinolizidine, biphenyl, rotamers

1. Introduction

Since the discovery of seven alkaloids from the extracts of *Decodon verticillatus* (family Lythraceae) by Ferris in 1962 many other Lythraceae alkaloids have been isolated, especially from *Heimia salicifolia*, a wild flowering plant in the *Lythraceae* family.¹⁻⁴ This plant has been used in traditional medicine as an antipyretic, an emetic, a laxative, a diuretic and as an anti-inflammatory agent.^{1,3,4} Several Lythraceae alkaloids were found to exhibit remarkable biological activities, including vertine **1** (Figure 1), first isolated by Ferris² and more recently in 2008 by Khan and coworkers,⁵ from the leaves of *H. salicifolia*, who demonstrated it had anti-inflammatory and antimalarial activities. The latter author also established the configuration of vertine at the three stereogenic centres and the chiral axis (as shown in Figure 1) by X-ray diffraction analysis.⁵ This alkaloid, and others in this family, comprise a quinolizidine ring skeleton with an axially chiral biphenyl substituent at C-4 which forms part of a 12-membered ring lactone system. The related alkaloid, 9 β -hydroxyvertine **2**, having a β -hydroxy group at the C-9 position, was also isolated in this study, however no information concerning its biological activity was reported. Other members of this alkaloid family include decinine (10-*epi*-13,14-dihydrovertine), lythrine (10-*epi*-vertine) and lyfoline **3**.^{2,6} A 2018 study reported the isolation on 13 new related alkaloids along with vertine, lythrine and lyfoline **3** (Figure 1) and three related biphenyl ether quinolizidine lactone alkaloids.⁷

Figure 1. Structures of vertine (**1**), 9 β -hydroxyvertine (**2**) and lyfoline.

Because of their challenging ring structures and interesting biological properties, Lythraceae alkaloids have become attractive synthetic target molecules. Vertine **1** was first synthesised by Kündig and co-workers in 2010, as the racemate and then in 2012 as the (+)-enantiomer using the ring closing metathesis (RCM) and the Suzuki–Miyaura coupling reactions as key steps to establish the macrocyclic ring (by formation of the C-13–C-14 (*Z*)-olefinic bond) and the biaryl axis (forming the C-1'–C-1'' bond), respectively.^{8,9} In 2015, She and co-workers reported the synthesis of the related alkaloid dihydrolyfoline (13,14-dihydro-**3**), using a hydrolase-catalyzed Mannich reaction to form the quinolizidine ring and a biogenetic, enzymatic oxidative intramolecular coupling reaction of phenols to construct the macrocyclic ring and the biphenyl axis.¹⁰ Much earlier approach to these types of

structures, using non-enzymatic oxidative coupling methods, proved unsuccessful.^{11,12} However, Yang and coworkers reported the successful synthesis of decinine using a VOF₃-mediated intramolecular oxidative coupling reaction of aryl ethers.¹³ To date the total synthesis of 9 β -hydroxyvertine **2** has not been reported. Therefore, this challenging new quinolizidine core structure led us to investigate its synthesis.

2. Results and discussion

Our retrosynthetic analysis of **2** is shown in Scheme 1a. We envisioned that **2** could be synthesized by a sequence that included an intramolecular lactonization procedure from the dienylic acid **4**. For example, via the intramolecular bromolactonization reaction of acid **4** followed by reductive removal of the bromine substituent from bromo lactone **C** (Scheme 1a).¹⁴ Alternatively, **2** could conceivably be obtained by a regioselective hydration (via hydroboration or oxymercuration) of the olefinic moiety of the quinolizidine **4** followed by a lactonization reaction of the possible C-2 secondary alcohol products **D** or **E** via a Yamaguchi¹⁵ (with retention at C-2) or via a Mitsunobu¹⁶ reaction (with inversion at C-2), respectively (Scheme 1b). Such an approach to this lactone ring system has not been reported, however an inspection of molecular models suggested it should be feasible with the desired, of the two interconverting biaryl rotamers (or atropisomers) predicted to cyclize more rapidly. This is also consistent with the findings of Kündig *et al.* using related compounds in their synthesis of vertine.⁹ Indeed, such biaryls having only two relatively small *ortho*-substituents are expected to have a relatively low barrier to rotation and thus best considered as rotamers rather than atropisomers,¹⁷ Compound **4** could be obtained from the *O*-mesylation-cyclisation reaction¹⁸ of alcohol **5** (Scheme 1a) followed by the RCM reaction and subsequent functional group interconversion reactions of the cyano substituent, respectively. We envisioned a Petasis borono-Mannich (PBM) reaction¹⁸ of chiral substrates **6** and **7** and β -styrenylboronic acid as a key step in our synthetic plan to construct the *anti*-amino alcohol moiety in compound **5**. The chiral α -hydroxyaldehyde **6** could be prepared from commercially available pent-4-en-1-ol. The chiral primary amine **7** could be derived from the biaryl product from the Suzuki–Miyaura cross-coupling reaction of aryl halide **8** and boronate ester **9**.

Scheme 1. Retrosynthetic analysis for the synthesis of compound **2**.

First, we investigated the synthesis of the chiral amine **7** (Scheme 2). The synthesis began with the preparation of the boronate ester **9** from 6-bromoveratraldehyde (prepared by bromination of commercially available veratraldehyde¹⁹) following Castle's procedure²⁰ using Pd(OAc)₂, bis(pinacolato)diboron and KOAc.

Scheme 2. Synthesis of chiral amine **7**.

Figure 2. ORTEP plot of **12** which crystalized as the (*aR*) configured isomer (CCDC 1898245)

This reaction unexpectedly provided a separable mixture (3.3:1.2:1) of dehalogenated starting material, the homocoupling product of the aryl bromide and the desired product **9**. Next, we examined Miyaura's reaction conditions²¹ using $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ as a catalyst which afford the desired boronate ester **9** in 93% yield. Employing the Suzuki–Miyaura cross-coupling reaction conditions of Chausset-Boissarie⁹ on the aryl iodide analogue of aryl bromide **8**²² with **9** gave biphenyl aldehyde **10** in only 24% yield, using 10 mol% $\text{Pd}(\text{Ph}_3\text{P})_4$ at 95 °C for 48 h. Increasing the catalyst loading to 15 mol % gave **10** in 88% yield while using bromide **8** and 15 mol% $\text{Pd}(\text{Ph}_3\text{P})_4$ at 95 °C for 48 h gave **10** in the highest yield of 94%.. The resulting aldehyde **10** was treated with (*R*)-*N*-*tert*-butanesulfinamide in the presence of KHSO_4 ²³ to provide the corresponding *N*-sulfinyl imine **11** as a 52:48 mixture of biphenyl axis rotamers. A diastereoselective Zn-mediated allylation reaction of imine **11** with allyl bromide, Zn powder and $\text{Zn}(\text{OTf})_2$ ²⁴ provided chiral homoallylic *N*-sulfinyl amine **12** in 87% yield as a single diastereomer and as a 62:38 mixture of rotamers. Allyl bromide/Zn, in the absence of $\text{Zn}(\text{OTf})_2$, or the use of allylmagnesium bromide, gave much less satisfactory yields of **12**, 74% and 10%, respectively. A single crystal X-ray structural analysis confirmed the structure and configuration at the C-1'' position of compound **12** (Scheme 2), which crystallized as a single diastereomer with the (*aR*)-configuration at the axis. The ^1H NMR spectrum of these crystals, when dissolved in CDCl_3 , showed that this single diastereomeric form in the solid state rapidly (less than 5 min) converted to the original 62:38 mixture of rotamers in solution at ambient temperature. Clearly indicating that these were rotamers rather than atropisomers¹⁷ and these were rapidly interconvertible at room temperature. Heating this mixture in hexadeuterated-DMSO resulted in little change in the rotamer ratio from ^1H NMR analysis. Deprotection of the *N*-sulfinyl group of **12** with TMSCl in MeOH at ambient temperature produced the desired chiral homoallylic amine **7** in 95% yield as a 64:36 mixture of rotamers (Scheme 2).

The equivalent of the chiral α -hydroxyaldehyde **6** was synthesized as the cyclic hemiacetal dimer **15a** in three steps from commercially available pent-4-en-1-ol (Scheme 3). *p*-Methoxybenzylation of pent-4-en-1-ol with PMBCl and DIPEA gave the PMB ether **13**.²⁵ A cross-metathesis reaction²⁶ of **13** with phenyl vinyl sulfone and Grubbs' second generation catalyst provided (*E*)-vinyl sulfone **14**, which underwent subsequent Sharpless asymmetric dihydroxylation (ADH)^{27,28} with AD-mix- β , resulting in the cyclic hemiacetal dimer **15a** of the desired α -hydroxyaldehyde, which was used without further purification. MS analysis of the crude reaction mixture indicated 100% consumption of **14** and ¹H NMR analysis showed resonances consistent with structure **15a** as a mixture of diastereomers.

Scheme 3. Synthesis of the chiral α -hydroxyaldehyde hemiacetal dimer **15a**.

With our two chiral substrates in hand, the next task was constructing the key intermediate **16a** via the PBM reaction as shown in Scheme 4. The aldehyde dimer **15a** was treated with the chiral amine **7** and β -styrenylboronic acid in EtOH which provided a chromatographically separable mixture of two diastereomers, the desired *anti*-1,2-amino alcohol **16a** (37%) and the unexpected *syn*-1,2-amino alcohol **16b** (35%). These were both formed as 60:40 mixtures of rotamers. The configurations of the products **16a** and **16b** were confirmed by treatment of the individual diastereomers with triphosgene to give their respective oxazolidinone derivatives, **17a** (63:37 mixture of rotamers) and **17b** (53:47 mixture of rotamers) (Scheme 4). NOESY spectrum analysis of **17a** showed a key correlation between H-4''' and H-5''' which indicated the relative *syn* stereochemical relationship of these protons in the oxazolidinone **17a**. In comparison, NOESY spectrum analysis of **17b** showed no correlation between H-4''' and H-5''' indicating their *trans*-relative configuration. These results support the assigned *anti* and *syn* stereochemistry of **16a** and **16b**, respectively.

Scheme 4. Synthesis of 1,2-amino alcohols **16a** and **16b** and oxazolidinones **17a** and **17b**.

To further confirm the identity of compounds **16a** and **16b**, we investigated the PBM reaction of amine **7** with the enantiomeric α -hydroxyaldehyde dimer **15b**, which was prepared by an ADH reaction of vinyl sulfone **14** with AD-mix- α (Scheme 5). This reaction provided the *anti*-1,2-amino alcohol product **16c** in 68% yield as a single diastereomer and as a 56:44 mixture of rotamers. The ^1H NMR spectrum of **16c** showed clear differences in chemical shifts and splitting patterns when compared to those of **16a** and **16b**. The relative *anti* configuration of the product **16c** was verified by formation of the *cis*-oxazolidinone **17c** (67:33 mixture of rotamers) and NOE experiments (Scheme 5). This experiment helped confirm our structural assignments to **16a** and **16b** and ruled out the possibility that the α -hydroxyaldehyde **6**, formed *in situ* from **15a**, had undergone epimerization (racemization) to *ent*-**6** before participating in the PBM reaction.

Scheme 5. Synthesis of 1,2-amino alcohol **16c** and oxazolidinones **17c**.

To investigate the PMB reaction further the sterically less demanding homoallylic amine **20** was prepared according to Scheme 6. In this synthesis, the allylation of the less sterically hindered *N*-sulfinyl imine **18** occurred efficiently with allylmagnesium bromide in the absence of a Lewis acid giving **19** in 82% yield. Deprotection of the *N*-sulfinyl group of **19** then produced the desired chiral homoallylic amine **20** in 88% yield. In contrast to amine **7**, the PMB reaction between the chiral amine **20**, the aldehyde dimer **15a** and β -styrenylboronic acid in EtOH gave the *anti*-1,2-amino alcohol **21** in 44% yield as a single diastereomer.

Scheme 6. Synthesis of 1,2-amino alcohol **21**.

Thus the reaction of the aldehyde dimer **15a** with the chiral amine **7** represents one of the few examples of the PBM reaction where poor *anti*-diastereoselectivity has been observed.^{18,28} Our proposed reactive intermediates for the formation of the products **16a**, **16b** and **16c** are shown in Scheme 7. Intermediates **F** and **H** are expected as 1,3-allylic strain between the α -imine substituents and the imine substituents (α -H and imine H “inside”) is minimized.²⁸ However, in the case of the (*R*)-aldehyde **6** (derived from **15a**), when R^1 is large (R^1 = biphenyl substituent) then we would expect to observe poor diastereoselectivity due to steric interference between R^1 and R^3 in intermediate **F**. Therefore reaction *via* the alternative intermediate **G** can compete giving rise to the *syn*-product **16b**. When the (*S*)-aldehyde (*ent*-**6**) derived from **15b** was used then high *anti*-diastereoselectivity was observed. In this case the R^3 group is delivered *anti* to the bulky R^1 group via the expected reactive conformation **H** to give exclusively *anti*-**16c**.

While in principle, compound **21** could be converted to **16a** via a Suzuki–Miyaura cross-coupling reaction with boronate **9**, this was not attempted because of the relative poor yield (44%) of **21** which was similar to the yield of **16a** (37% yield) from the PMB reaction of **7** and **15a** (Scheme 4). Of note was the attempted removal of the PMB ether protecting group of **21** with DDQ, which while successful in the case of **16a** (Scheme 8), resulted in a complex mixture of products from ¹H NMR analysis of the crude reaction mixture. We speculate that the bromodimethoxy-substituted aromatic

ring of **21** may have undergone oxidation to a reactive *para*-quinone intermediate resulting in the formation of undesired products.

Scheme 7. Proposed reactive intermediates for the formation of products **16a**, **b** and **20**.

We next examined the synthesis of the quinolizidine framework **24** as shown in Scheme 8. All products having a biphenyl moiety in Scheme 8, and in later schemes, were formed as mixtures of rotamers. The ratio of these rotamers is provided in the experimental section. The deprotection of the PMB group of the desired alcohol **16a** with DDQ²⁹ in CH₂Cl₂/H₂O provided the corresponding diol **22**. The use of CAN³⁰ in this deprotection reaction resulted in a complex mixture of products. The diol **22** was subsequently subjected to the *O*-mesylation-cyclization reaction conditions¹⁸ using 1 equiv of MsCl to give piperidine **23** in 54% yield and recovered **22** in 31% yield. The RCM reaction of diene **23** with Grubbs' second generation catalyst in the presence of Ti(*i*-PrO)₄ as a Lewis acid, which was expected to prevent deactivation of the Ru catalyst by coordination to the N-atom,^{31,32} provided the quinolizidine **24** in 40% yield. Due to the low yield of **24** and the incomplete *O*-mesylation-cyclization of diol **22**, we decided to modify the original route from alcohol **16a**. The secondary hydroxy group in compound **16a** was protected as a TBS ether which would potentially allow us to increase the amounts of Et₃N and MsCl, and hence enhance the yield, in the *N*-cyclization reaction sequence. Unfortunately, the smooth removal of the PMB group from the resulting TBS ether of **16a**

was unsuccessful. The use of DDQ resulted in a complex mixture, while the use of CAN unexpectedly provided the amine **7** resulting from oxidative cleavage of the styrenyl side chain.

Scheme 8. Synthesis of quinolizidine **24**.

To overcome the above issues, we decided to modify the original route from the preparation of the α -hydroxyaldehyde dimer by protecting the primary hydroxy group of **27** as its TBS ether. Silylation of commercially available pent-4-en-1-ol with TBSCl provided TBS ether **25**. Treatment of **25** under the same cross-metathesis and ADH conditions as depicted in Scheme 3 produced the aldehyde dimer **27** (Scheme 9).

Scheme 9. Synthesis of alcohol **28a and **28b**.**

The PBM reaction of **27**, amine **7** and β -styrenylboronic acid provided a mixture of diastereomeric 1,2-amino alcohols **28a** (43%) and **28b** (35%), which were obtained as pure isomers after separation by column chromatography. The synthesis of quinolizidines **32a** and **32b** is illustrated in Scheme 10. The cyclizations of **28a** and **28b** to their respective piperidine derivatives required protection of their secondary hydroxy groups and then selective deprotection of their primary hydroxy groups. After the secondary hydroxy groups of **28a,b** were protected as their TBS ethers, the primary TBS ethers of **29a,b** were selectively deprotected with HF $\cdot$ pyridine³³ in THF to provide the corresponding primary alcohol products **30a** and **30b**. The *O*-mesylation-cyclization reaction of **30a,b** produced the corresponding piperidines, **31a** and **31b** in 88 and 86% yields, respectively. The RCM reaction of **31b** was initially performed following the literature method,³² with the use of Ti(*i*-PrO)₄ as a Lewis acid in CH₂Cl₂, to give the quinolizidine **32b** in only 26% yield. While, changing the solvent to DCE, in the absence of Ti(*i*-PrO)₄ at 80 °C, significantly improved the yield of **32b** to 67%. We then applied the optimized RCM reaction conditions to the desired compound **31a** resulting in the corresponding quinolizidine **32a** in 70% yield. The 2D NOESY analysis of **32a** showed no correlation between the resonances for H-1'' and H-9a'' which confirmed the relative *anti* stereochemical relationship of these protons in the quinolizidine ring. While the 2D NOESY spectrum of **32b** showed a correlation between the resonances for H-1'' and H-9a'', consistent with their *syn* relative configuration.

Scheme 10. Synthesis of quinolizidines **32a** and **32b**.

With our key intermediates **32a** and **32b** in hand, we focused our investigation towards completion of the total synthesis of **2** (Scheme 11). Therefore, the cyano groups of the quinolizidines **32a,b** were reduced by treatment with DIBAL-H to give their corresponding aldehydes **33a** and **33b**. The ROESY spectrum of compound **33b** showed a clear correlation between the resonance for H-6'' and H-9a'', consistent with their 1,3-diaxial relationship and the overall stereochemical assignments made to this compound and earlier related ones. These were subsequently subjected to Still–Gennari modified Horner-Wadsworth-Emmons (HWE) reactions^{9,34} to afford the methyl esters **34a** and **34b**, respectively, with complete Z-selectivities, as confirmed by the magnitude of $J_{2,3}$ (12.8 Hz)⁹ which was consistent with the expected (Z)-alkene. Hydrolysis of methyl esters **34a,b** with LiOH•H₂O³⁵ provided, after acidification, the corresponding carboxylic acids in >99% conversion as confirmed by LRESIMS analysis of the crude reaction mixture. Attempted bromolactonization of these carboxylic acids using NBS in the presence of a catalytic amount of (PhSe)₂^{14,36} unexpectedly generated decarboxylated products, the (Z)-bromoalkenes **35a** and **35b** (in 18% and 14% yields over the two steps, respectively, bromo-alkene vicinal couplings of 8.0 Hz³⁷). The synthesis of (Z)- β -bromostyrenes from the bromination of (*E*)-cinnamic acids followed by treatment with base is well documented.³⁷ In the case of **34a,b**, the highly electron rich biphenyl substituent clearly favours bromination of the α,β -unsaturated carboxylic acid moiety over that of the alkene group in the quinolizidine ring. The amino group of this ring may assist in the decarboxylative-elimination process leading to the (Z)- β -bromostyrene products. Other halolactonization conditions (e.g. I₂, NaHCO₃, MeCN at rt or 60 °C)^{38,39} were also unsuccessful and resulted in recovered unreacted carboxylic acids.

Scheme 11. Synthesis of methyl esters **35a,b** and attempted bromolactonization.

At this point, and with only limited amounts of advanced materials in hand, we envisioned an alternative strategy involving regioselective hydroboration of the alkene group of the quinolizidine **34a** (Scheme 12). Unfortunately, the reaction was not successful and only starting material was recovered even in the presence of 8 equiv of $\text{BH}_3\cdot\text{SMe}_2$. We suspected that a Lewis acid-base complex was formed between BH_3 and the *N*-atom of **34a** resulting in deactivation of the alkene,

electronically by the withdrawal of electron density towards the cationic N atom, and sterically by increased steric hindrance.

Scheme 12. Attempted hydroboration of **34a**.

We also considered another possible synthetic strategy to approach the alcohol **36** *via* selective hydration of **32a** followed by reduction of the cyano group to an aldehyde and subsequent Z-selective HWE reaction to provide intermediate **36**. To test this possibility, we investigated the oxymercuration reaction⁴⁰ of **32a** by reacting with $\text{Hg}(\text{NO}_3)_2$ in THF at rt, this reaction was surprisingly slow and required 5 d for full consumption of **32a** (by TLC analysis). The reaction mixture was then treated with NaBH_4 and NaOH solution (Scheme 13). Separation of the reaction products over silica gel gave the product **37**, as a single diastereomer, but in only 6% yield. The alcohol **24**, the desilylated product of **32a**, was isolated in 15% yield. An analysis of the COSY NMR spectrum of **37** indicated that the reaction provided the product with the desired regiochemistry but the configuration at H-8 could not be unequivocally determined by NOESY NMR. Performing the reaction with other mercury salts, such as $\text{Hg}(\text{OAc})_2$ and $\text{Hg}(\text{OTFA})_2$, resulted in recovered unreacted starting material.

Scheme 13. Oxymercuration of **32a**.

3. Conclusions

During the course of this study, we have achieved the synthesis of the advanced quinolizidine intermediate **34a** containing most of the structural characteristics of 9 β -hydroxyvertine **2**, including three stereogenic centres. This approach highlights the value of the PBM reaction, coupled with RCM

and the tandem chemoselective *O*-mesylation, *N*-cyclization strategy to prepare highly functionalized quinolizidines. While these methods will be of general utility to synthetic chemists, this study revealed a rare example of a poorly diastereoselective PBM reaction due to the use of a highly hindered and chiral amine component, the presence of which overrides the intrinsic bias for high *anti*-diastereoselectivity in these reactions. Future efforts will be directed towards alternative strategies for completing the synthesis of **2**.

4. Experimental section

4.1 General information

All air and moisture sensitive reactions were conducted under an atmosphere of dry argon or nitrogen using oven-fried or flame-dried glassware in anhydrous solvents. Flash column chromatography was performed on 230-400 mesh silica gel. Reaction products were detected on thin layer chromatography by UV light or by staining with ceric ammonium molybdate solution. ¹H NMR (500 MHz) and ¹³C NMR (125 MHz) spectra were recorded on Varian Unity Inova or Bruker AVANCE 500 MHz spectrometer in deuteriochloroform (CDCl₃) solution. Chemical shifts are reported in ppm (δ) relative to a residual solvent peak (CDCl₃ = 7.26 ppm for ¹H and 77.16 ppm for ¹³C) or tetramethylsilane (TMS). Coupling constants (*J*) are reported in Hertz (Hz). NMR assignments are based on COSY, HSQC, HMBC, and in some cases NOESY, NMR experiments. IR spectra were determined on neat samples on SHIMADZU MIRacle 10 IRAffinity 1 FT-IR spectrometer. Optical rotations were recorded on a JASCO 2000 series polarimeter. Low resolution mass spectra (LRMS) and high resolution mass spectra (HRMS) were recorded on a single quadrupole mass spectrometer and a quadrupole time-of-flight mass spectrometer, respectively, using an electrospray ionization (ESI) source in either the positive or negative modes. Melting points were obtained using a Gallenkamp MF-370 capillary tube melting point apparatus. PS refers to petroleum spirit, bp 40-60 °C.

4.2 Synthesis of 4-(Benzyloxy)-3-bromobenzonitrile (**8**)²²

To a solution of 4-hydroxy-3-bromobenzonitrile (2.43 g, 12.3 mmol, 1.0 equiv) in acetone (25 mL) was added potassium carbonate (5.09 g, 36.8 mmol, 3.0 equiv) and benzyl bromide (2.31 g, 1.6 mL, 13.5 mmol, 1.07 equiv) and the mixture was stirred at reflux for 20 h. After cooling to room temperature, the solvent was filtered and evaporated and redissolved in EtOAc (10 mL) followed by washing with water (2 x 10 mL). The combined organic layer was dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by recrystallization from CH₂Cl₂ to afford the title compound **8** as a pale yellow solid (3.34 g, 95%). The spectroscopic data of this compound matched with those in the literature.¹⁸ *R*_f = 0.27 (EtOAc:PS = 15:85). mp: 98-100 °C. IR (neat): ν_{max} 3062, 2224, 1595, 1492, 1452, 1381, 1258, 998, 812, 737, 695 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.84 (d, *J* = 2.1 Hz, 1H, H-

2), 7.54 (dd, $J = 8.6, 2.1$ Hz, 1H, H-6), 7.47 – 7.32 (m, 5H, ArH), 6.97 (d, $J = 8.6$ Hz, 1H, H-5), 5.22 (s, 2H, PhCH₂O). ¹³C NMR (125 MHz, CDCl₃): δ 158.6 (C-4), 136.9 (C-2), 135.3 (ArC), 133.1 (C-6), 128.9 (2 x ArCH), 128.5 ArCH, 127.1 (2 x ArCH), 117.8 (C $\equiv$ N), 113.5 (C-5), 113.0 (C-3), 105.6 (C-1), 71.1 (PhCH₂O).

4.3 Synthesis of 4,5-Dimethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (**9**)²⁰

To a solution of bis(pinacolato)diboron (1.68 g, 6.6 mmol, 1.1 equiv) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.417 g, 0.18 mmol, 0.03 equiv) in anhydrous THF (19 mL) was added potassium acetate (1.77 g, 18.0 mmol, 3.0 equiv) and 2-bromo-4,5-dimethoxy-benzaldehyde¹⁹ (1.47 g, 6.0 mmol, 1.0 equiv) and the mixture was stirred and heated at 55 °C for 18 h. After cooling to room temperature, the reaction mixture was poured into ice water and extracted with EtOAc (2 x 30 mL). The combined organic layer was washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by column chromatography (20:80 EtOAc/hexanes) to afford the title compound **9** as a white solid (1.62 g, 93%). The spectroscopic data of this compound matched with those in the literature.²⁴ $R_f = 0.47$ (EtOAc:hexanes = 30:70). mp: 98-100 °C. IR (neat): $\nu_{\max}$ 3015, 2980, 1680, 1583, 1517, 1299, 1153, 1035, 877, 734 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 10.59 (s, 1H, CHO), 7.55 (s, 1H, H-6), 7.35 (s, 1H, H-3), 4.01 (s, 3H, OCH₃), 3.96 (s, 3H, OCH₃), 1.38 (s, 12H, 4 x CH₃). ¹³C NMR (125 MHz, CDCl₃): δ 193.7 (C=O), 152.9 (C-4), 151.4 (C-4), 136.5 (C-1 and C-2), 117.4 (C-3), 108.8 (C-6), 84.4 (OC(CH₃)₂), 56.2 (OCH₃), 56.1 (OCH₃), 25.0 (4 x CH₃).

4.4 Synthesis of 6-(Benzyloxy)-2'-formyl-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**10**)

To a solution of aldehyde **8** (0.144 g, 0.5 mmol, 1.0 equiv) in degassed anhydrous 1,2-dimethoxyethane (5 mL) was added boronate ester **9** (0.219 g, 0.75 mmol, 1.5 equiv), cesium fluoride (0.228 g, 1.5 mmol, 3.0 equiv) and Pd(PPh₃)₄ (0.087 g, 0.075 mmol, 0.15 equiv) and the mixture was stirred and heated at reflux for 48 h. After cooling to room temperature, the reaction mixture was filtered through a short pad of celite and the residue was washed with EtOAc. The organic layer was dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by column chromatography (10:20:70 EtOAc/CH₂Cl₂/hexanes) to afford the title compound **10** as a white solid (0.175 g, 94%). $R_f = 0.18$ (EtOAc:hexanes = 20:80). mp: 132-134 °C. IR (neat): $\nu_{\max}$ 3008, 2936, 2225, 1677, 1595, 1511, 1346, 1251, 1154, 989, 728 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 9.66 (s, 1H, CHO), 7.68 (dd, $J = 8.6, 2.1$ Hz, 1H, H-4), 7.58 (d, $J = 2.1$ Hz, 1H, H-2), 7.51 (s, 1H, H-3'), 7.35 – 7.24 (m, 3H, ArH), 7.19 (d, $J = 7.1$ Hz, 2H, ArH), 7.10 (d, $J = 8.6$ Hz, 1H, H-5), 6.75 (s, 1H, H-6'), 5.16 – 5.06 (m, 2H, PhCH₂O), 3.98 (s, 6H, OCH₃), 3.94 (s, 6H, OCH₃). ¹³C NMR (125 MHz, CDCl₃): δ 190.4 (C=O), 159.4 (C-6), 153.8 (C-5'), 149.3 (C-4'), 135.4 (C-2), 135.4 (ArC), 134.4 (C-1'), 134.3 (C-4), 128.9 (C-1 and 2 x ArCH), 128.5 (ArCH), 127.4 (C-2'), 127.1 (2 x ArCH), 118.7 (C $\equiv$ N), 113.1 (C-6'), 113.1

(C-5), 108.8 (C-3'), 104.8 (C-3), 70.9 (PhCH₂O), 56.4 (OCH₃), 56.3 (OCH₃). HRMS (ESI): m/z calcd for C₂₃H₁₉NO₄Na [M + Na]⁺: 396.1212, found: 396.1197.

4.5 Synthesis of (*R*)-*N*-((2'-(Benzyloxy)-5'-cyano-4,5-dimethoxy-[1,1'-biphenyl]-2-yl)methylene)-2-methylpropane-2-sulfinamide (**11**)

To a solution of carbonitrile **10** (0.471 g, 1.26 mmol) in CH₂Cl₂ (3 mL) was added potassium hydrogen sulfate (1.722 g, 12.6 mmol, 10.0 equiv) and (*R*)-(+)-2-methyl-2-propanesulfinamide (0.234 g, 1.89 mmol, 1.5 equiv) and the mixture was stirred at room temperature for 24 h. The reaction mixture was filtered through a short pad of celite and concentrated *in vacuo*. The crude product was purified by column chromatography (25:75 EtOAc/hexanes) to afford the title compound **11** as a white powder (0.537 g, 89%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 52:48 ratio. R_f = 0.42 (EtOAc:hexanes = 30:70). IR (neat): $\nu_{\max}$ 2962, 2222, 1601, 1582, 1510, 1453, 1212, 1156, 1075, 697 cm⁻¹. $[\alpha]_D^{25}$ - 41 (c 0.25, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 8.27 (s, 1H, N=CH), 7.69 – 7.59 (m, 2H, H-3 and H-4'), 7.51 (s, 1H, H-6'), 7.33 – 7.23 (m, 3H, ArH), 7.19 (d, J = 7.3 Hz, 1.04H, ArH), 7.15* (d, J = 7.1 Hz, 0.96H, ArH), 7.08 (d, J = 8.6 Hz, 0.52H, H-3'), 7.04* (d, J = 8.7 Hz, 0.48H, H-3'), 6.75 (s, 1H, H-6), 5.16 – 5.07 (m, 2H, PhCH₂O), 4.00* (s, 1.44H, OCH₃), 3.98 (s, 1.56H, OCH₃), 3.94* (s, 1.44H, OCH₃), 3.92 (s, 1.56H, OCH₃), 1.21 (s, 4.68H, CH₃), 1.11* (s, 4.32H, CH₃). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 161.0 (N=CH), 159.31 (C-2'), 159.28* (C-2'), 152.3 (C-5), 149.2 (C-4), 149.1* (C-4), 135.8* (ArC), 135.6 (C-6'), 135.5 (ArC), 135.2* (C-6'), 134.2 (C-4'), 134.1* (C-4'), 132.8 (C-1), 130.0* (C-1'), 129.4 (C-1'), 128.8 (1 x ArCH), 128.7* (0.9 x ArCH), 128.3 (0.6 x ArCH), 128.0* (0.4 x ArCH), 127.0 (1 x ArCH), 126.4* (0.9 x ArCH), 125.4 (C-2), 118.9 (C≡N), 113.3 (C-3'), 113.19* (C-6), 113.16 (C-6), 109.9* (C-3), 109.2 (C-3), 104.8 (C-5'), 104.7* (C-5'), 70.8 (PhCH₂O), 70.5* (PhCH₂O), 57.8 ((CH₃)₃C), 57.5* ((CH₃)₃C), 56.3*(OCH₃), 56.1 (OCH₃), 22.7 ((CH₃)₃C), 22.5* ((CH₃)₃C). HRMS (ESI): m/z calcd for C₂₇H₂₈N₂O₄NaS [M+Na]⁺: 499.1667, found: 499.1674.

4.6 Synthesis of (*R*)-*N*-((*S*)-1-(2'-(Benzyloxy)-5'-cyano-4,5-dimethoxy-[1,1'-biphenyl]-2-yl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide (**12**)

To a solution of the *N*-sulfinyl imine **11** (0.726 g, 1.52 mmol, 1.0 equiv) in anhydrous THF (5.0 mL) was added zinc powder (0.299 g, 4.57 mmol, 3.0 equiv), zinc trifluoromethanesulfonate (1.70 g, 4.57 mmol, 3.0 equiv) and allyl bromide (0.576 g, 0.42 mL, 4.87 mmol, 3.2 equiv) and the mixture was stirred at room temperature for 8 h. After the reaction had completed, the mixture was quenched with sat. aqueous NH₄Cl solution and extracted with EtOAc (2 x 10 mL). The organic layer was washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by column chromatography (50:50 EtOAc/hexanes) to afford the title compound **12** as a pale yellow

crystalline solid (0.684 g, 87%). ^1H NMR analysis revealed the presence of two biphenyl axis rotamers in a 62:38 ratio. $R_f = 0.21$ (EtOAc:hexanes = 60:40). mp: 156-158 °C. IR (neat): ν_{max} 3271, 2936, 2225, 1662, 1512, 1495, 1155, 1030, 747 cm^{-1} . $[\alpha]_D^{25} = -89$ (c 0.20, CHCl_3). ^1H NMR (500 MHz, the asterisk* denotes the signal of the the minor rotamer, CDCl_3): δ 7.64 – 7.57 (m, 1.38H, H-4' and H-6' (minor)), 7.42 (s, 0.62H, H-6'), 7.31 – 7.15 (m, 5H, ArH), 7.03 (s, 1H, H-3'), 7.01 (s, 0.62 H, H-3), 6.93* (s, 0.38 H, H-3), 6.66 (s, 0.62H, H-6), 6.63* (s, 0.38H, H-6), 5.61 – 5.45 (m, 1H, H-3''), 5.34 (d, $J = 13.1$ Hz, 0.62H, $\text{PhCH}_A\text{H}_B\text{O}$), 5.19 (d, $J = 13.0$ Hz, 0.62H, $\text{PhCH}_A\text{H}_B\text{O}$), 5.15 – 4.96 (m, 2.76H, H-4'' and PhCH_2O (minor)), 4.23 (dd, $J = 8.6, 5.3$ Hz, 0.62H, H-1''), 4.21* – 4.17* (m, 0.38H, H-1''), 3.90 (s, 3H, OCH_3), 3.88 (s, 1.86H, OCH_3), 3.85 (s, 1.14H, OCH_3), 3.54* (s, 0.38H, NH), 3.48 (s, 0.62H, NH), 2.49* (m, 0.38H, H-2''), 2.43 – 2.20 (m, 1.62H, H-2''), 1.17* (s, 3.42H, CH_3), 1.07 (s, 5.58H, CH_3). ^{13}C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl_3): δ 159.5* (C-2'), 159.4 (C-2'), 149.1* (C-4), 149.0 (C-4), 148.0 (C-5), 147.97* (C-5), 136.5 (ArC), 135.8* (ArC), 135.7* (C-6'), 135.4 (C-6'), 134.7* (C-3''), 134.2 (C-3''), 133.8* (C-4'), 133.7 (C-4'), 132.9 (C-2), 132.1* (C-2), 131.1* (C-1'), 131.0 (C-1'), 128.8 (0.76 x ArCH), 128.7* (C-1), 128.5 (1.24 x ArCH), 128.3 (C-1), 128.26* (0.38 x ArCH), 127.7 (0.62 x ArCH), 126.8* (0.76 x ArCH), 126.5 (1.24 x ArCH), 119.5 (C-4''), 119.2 ($\text{C}\equiv\text{N}$), 119.0* ($\text{C}\equiv\text{N}$), 118.8* (C-4''), 113.3 (C-3'), 112.9*(C-6), 112.8* (C-3'), 112.79 (C-6), 109.7 (C-3), 104.8* (C-5'), 103.7 (C-5'), 70.4* (PhCH_2O), 70.3 (PhCH_2O), 56.1 (OCH_3), 56.0* (OCH_3), 55.99* (OCH_3), 55.95 (OCH_3), 55.7* ($\text{C}(\text{CH}_3)_3$), 55.4 ($\text{C}(\text{CH}_3)_3$), 53.6* (C-1''), 53.0 (C-1''), 43.5 (C-2''), 42.6* (C-2''), 22.7* ($\text{C}(\text{CH}_3)_3$), 22.8 ($\text{C}(\text{CH}_3)_3$). HRMS (ESI): m/z calcd for $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_4\text{NaS}$ $[\text{M}+\text{Na}]^+$: 541.2137, found: 541.2135.

4.7 Synthesis of (S)-2'-(1-Aminobut-3-en-1-yl)-6-(benzyloxy)-4',5'-dimethoxy [1,1'-biphenyl]-3-carbonitrile (7)

To a solution of sulfonamide **12** (0.220 g, 0.42 mmol, 1.0 equiv) in MeOH (2.5 mL) was added TMSCl (0.092 g, 0.85 mmol, 2.0 equiv) and the solution was stirred at room temperature for 30 min. The solution was then evaporated to dryness *in vacuo* and the residue was washed with Et₂O (5 mL) and redissolved in CH_2Cl_2 (2 mL). The solution was washed with sat. aqueous NaHCO_3 solution. The organic layer was dried (MgSO_4) and concentrated *in vacuo* to afford the title compound **7** as a pale yellow oil (0.167 g, 95%) which was used in the next step without further purification. ^1H NMR analysis revealed the presence of two biphenyl axis rotamers in a 64:36 ratio. $R_f = 0.21$ (MeOH: CH_2Cl_2 = 5:95). IR (neat): ν_{max} 3420, 3365, 3072, 2917, 2224, 1599, 1490, 1247, 1154, 734, 695 cm^{-1} . ^1H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl_3): δ 7.64 – 7.59 (m, 1H, H-4), 7.49* (s, 0.36H, H-2), 7.46 (s, 0.64H, H-2), 7.30 (d, $J = 7.2$ Hz, 3H, ArH), 7.18 (d, $J = 7.0$ Hz, 2H, ArH), 7.12 – 7.02 (m, 2H, H-5 and H-3'), 6.62* (s, 0.36H, H-6'), 6.57 (s, 0.64H, H-6'), 5.61 – 5.42 (m, 1H, H-3''), 5.17 – 5.07 (m, 2H, PhCH_2O), 5.02 – 4.90 (m, 2H, H-4''), 3.96 (s, 3H, OCH_3), 3.87 (s, 1.92H, OCH_3), 3.84 (s, 1.08H, OCH_3), 3.78 – 3.70 (m, 1H, H-1''), 2.34* – 2.26* (m, 0.36H, H-2''), 2.25 – 2.16 (m, 1.64H, H-2''), 1.45 (br s, 2H, NH_2). ^{13}C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl_3): δ 159.5* (C-2'), 159.4 (C-2'), 149.1* (C-4), 149.0 (C-4), 148.0 (C-5), 147.97* (C-5), 136.5 (ArC), 135.8* (ArC), 135.7* (C-6'), 135.4 (C-6'), 134.7* (C-3''), 134.2 (C-3''), 133.8* (C-4'), 133.7 (C-4'), 132.9 (C-2), 132.1* (C-2), 131.1* (C-1'), 131.0 (C-1'), 128.8 (0.76 x ArCH), 128.7* (C-1), 128.5 (1.24 x ArCH), 128.3 (C-1), 128.26* (0.38 x ArCH), 127.7 (0.62 x ArCH), 126.8* (0.76 x ArCH), 126.5 (1.24 x ArCH), 119.5 (C-4''), 119.2 ($\text{C}\equiv\text{N}$), 119.0* ($\text{C}\equiv\text{N}$), 118.8* (C-4''), 113.3 (C-3'), 112.9*(C-6), 112.8* (C-3'), 112.79 (C-6), 109.7 (C-3), 104.8* (C-5'), 103.7 (C-5'), 70.4* (PhCH_2O), 70.3 (PhCH_2O), 56.1 (OCH_3), 56.0* (OCH_3), 55.99* (OCH_3), 55.95 (OCH_3), 55.7* ($\text{C}(\text{CH}_3)_3$), 55.4 ($\text{C}(\text{CH}_3)_3$), 53.6* (C-1''), 53.0 (C-1''), 43.5 (C-2''), 42.6* (C-2''), 22.7* ($\text{C}(\text{CH}_3)_3$), 22.8 ($\text{C}(\text{CH}_3)_3$).

denotes the signal of the minor rotamer, CDCl₃): δ 159.7* (C-6), 159.2 (C-6), 149.3 (C-4'), 149.2* (C-4'), 147.6 (C-5'), 147.4* (C-5'), 136.9 (C-2'), 136.5* (C-2'), 135.8* (C-2), 135.7 (ArC), 135.6 (C-2), 135.3 (C-3''), 135.2* (C-3''), 133.5* (C-4), 133.3 (C-4), 132.3 (C-1), 131.9* (C-1), 128.9 (1.28 x ArCH), 128.8* (0.72 x ArCH), 128.5 (0.64 x ArCH), 128.2* (0.36 x ArCH), 127.1* (C-1'), 127.0 (1.28 x ArCH), 126.9 (C-1'), 126.7* (0.72 x ArCH), 119.2 (C $\equiv$ N), 117.6 (C-4''), 117.4* (C-4''), 113.0* (C-5), 112.9 (C-5 and C-6' (minor)), 112.6 (C-6'), 108.8* (C-3'), 108.6 (C-3'), 104.5 (C-3), 104.2* (C-3), 70.6 (PhCH₂O), 70.4* (PhCH₂O), 56.2 (OCH₃), 56.1* (OCH₃), 56.09* (OCH₃), 56.07 (OCH₃), 51.8 (C-1''), 51.2* (C-1''), 43.7 (C-2''), 43.2* (C-2''). HRMS (ESI): m/z calcd for C₂₆H₂₇N₂O₃ [M + H]⁺: 415.2012, found: 415.2019.

4.8 Synthesis of 1-Methoxy-4-((pent-4-en-1-yloxy)methyl)benzene (**13**)²⁵

To a solution of 4-penten-1-ol (1.03 g, 12.0 mmol, 1.0 equiv) was added DIPEA (2.019 g, 2.7 mL, 15.6 mmol, 1.3 equiv) and PMBCl (2.05 g, 1.8 mL, 13.1 mmol, 1.1 equiv) and stirred at 150 °C for 2 h. After the reaction had completed, EtOAc (60 mL) was added and washed with 10% NaHSO₄ (60 mL). The aqueous layer was washed with EtOAc (2 x 60 mL). The combined organic layer was dried and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 5:95 EtOAc/hexanes to afford the title compound **13** as a colorless oil (2.378 g, 96%). The spectroscopic data of this compound matched with those in the literature.²¹ R_f = 0.40 (EtOAc:hexanes = 5:95). IR (neat): $\nu_{\max}$ 3078, 2937, 2854, 1613, 1511, 1245, 1097, 1035, 819 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.26 (d, J = 8.5 Hz, 2H, ArH), 6.88 (d, J = 8.5 Hz, 2H, ArH), 5.81 (ddt, J = 17.0, 10.1, 6.7 Hz, 1H, H-4), 5.01 (dd, J = 17.0, 1.8 Hz, 1H, H-5_A), 4.95 (d, J = 10.1 Hz, 1H, H-5_B), 4.43 (s, 2H, PMPCCH₂O), 3.80 (s, 3H, OCH₃), 3.45 (t, J = 6.5 Hz, 2H, H-1), 2.18 – 2.09 (m, 2H, H-3), 1.75 – 1.65 (m, 2H, H-2). ¹³C NMR (125 MHz, CDCl₃): δ 159.2 (ArC), 138.4 (C-4), 130.8 (ArC), 129.3 (2 x ArCH), 114.8 (C-5), 113.8 (2 x ArCH), 72.6 (PMPCH₂O), 69.5 (C-1), 55.3 (OCH₃), 30.5 (C-3), 29.1 (C-2).

4.9 General Method for Olefin Cross Metathesis

4.9.1 Synthesis of (E)-1-Methoxy-4-(((5-(phenylsulfonyl)pent-4-en-1-yl)oxy)methyl)benzene (**14**)

To a solution of alkene **13** (0.516 g, 2.5 mmol, 1.0 equiv) in degassed anhydrous CH₂Cl₂ (9 mL) was added phenyl vinyl sulfone (1.26 g, 7.5 mmol, 3.0 equiv) and Grubbs' II ruthenium catalyst (0.106 g, 0.125 mmol, 0.05 equiv) and the mixture was stirred and heated at reflux for 18 h. The reaction mixture was cooled to room temperature and the solvent was evaporated. The crude product was purified by column chromatography on silica gel eluting with 10:25:65 Et₂O/CH₂Cl₂/hexanes to afford the title compound **14** as a colorless oil (0.654 g, 76%). R_f = 0.62 (EtOAc:hexanes = 40:60). IR (neat): $\nu_{\max}$ 3060, 2861, 1612, 1511, 1447, 1305, 1245, 1144, 1032, 816, 752 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.86 (d, J = 7.7 Hz, 2H, ArH), 7.61 (t, J = 7.5 Hz, 1H, ArH), 7.53 (t, J = 7.7 Hz, 2H,

ArH), 7.22 (d, $J = 8.6$ Hz, 2H, ArH), 6.99 (dt, $J = 15.0, 6.8$ Hz, 1H, H-4), 6.87 (d, $J = 8.6$ Hz, 2H, ArH), 6.30 (d, $J = 15.0$ Hz, 1H, H-5), 4.38 (s, 2H, PMPCH₂O), 3.80 (s, 3H, OCH₃), 3.43 (t, $J = 6.1$ Hz, 2H, H-1), 2.39 – 2.27 (m, 2H, H-3), 1.75 (p, $J = 6.6$ Hz, 2H, H-2). ¹³C NMR (125 MHz, CDCl₃): δ 159.4 (ArC), 146.7 (C-4), 140.9 (ArC), 133.3 (ArCH), 130.9 (C-5), 130.4 (ArC), 129.4 (2 x ArCH), 129.3 (2 x ArCH), 127.7 (2 x ArCH), 114.0 (2 x ArCH), 72.8 (PMPCH₂O), 68.7 (C-1), 55.4 (OCH₃), 28.5 (C-3), 28.0 (C-2). HRMS (ESI): m/z calcd for C₁₉H₂₂O₄NaS [M + Na]⁺: 369.1131, found: 369.1135.

4.10 General Method for Sharpless Asymmetric Dihydroxylation (ADH)

4.10.1 Synthesis of (3R,6R)-3,6-Bis(3-((4-methoxybenzyl)oxy)propyl)-1,4-dioxane-2,5-diol (**15a**).

To a solution of phenylvinylsulfone (0.173 g, 0.5 mmol, 1.0 equiv) in 1:1 *t*-BuOH/water (5 mL) was added methanesulfonamide (0.105 g, 1.1 mmol, 2.2 equiv) and AD-mix- β (3.50 g) and the mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with sat. aqueous NaSO₃ solution and extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine, dried (MgSO₄) and concentrated *in vacuo* to afford a crude Sharpless ADH product as a brown oil which was used without further purification. HRMS (ESI): m/z calcd for C₁₃H₁₉O₄ [M + H]⁺: 239.1283, found: 239.1286.

4.11 General Method for the PBM Reaction with α -Hydroxylaldehyde Dimer

4.11.1 Synthesis of 6-(Benzyloxy)-2'-((S)-1-(((3S,4R,E)-4-hydroxy-7-((4-methoxybenzyl)oxy)-1-phenylhept-1-en-3-yl)amino)but-3-en-1-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**16a**) and 6-(benzyloxy)-2'-((S)-1-(((3R,4R,E)-4-hydroxy-7-((4-methoxybenzyl)oxy)-1-phenylhept-1-en-3-yl)amino)but-3-en-1-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**16b**)

To a solution of the above crude Sharpless ADH product **15a** in EtOH (0.5 mL) was added amine **7** (0.215 g, 0.52 mmol, 1.0 equiv) and β -styrenylboronic acid (0.115 g, 0.78 mmol, 1.5 equiv) and the mixture was stirred at room temperature for 72 h. The solution was evaporated and the residue was dissolved in EtOAc (5 mL) and then washed with sat. aqueous NaHCO₃ solution (2 x 5 mL). The combined organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 1:99 MeOH/CH₂Cl₂ to afford the title compound **16a** as a pale yellow oil (0.1437 g, 37%) and **16b** as a pale yellow oil (0.134 g, 35%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 60:40 ratio for both products. **16a**: $R_f = 0.22$ (MeOH:CH₂Cl₂ = 4:96). IR (neat): $\nu_{\max}$ 3427, 3064, 2935, 2224, 1600, 1512, 1490, 1179, 1033, 817, 737, 695 cm⁻¹. $[\alpha]_D^{25} + 43$ (*c* 1.2, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.52 – 7.44 (m, 1H, H-4), 7.39 (d, $J = 2.2$ Hz, 0.6H, H-2), 7.36* (d, $J = 2.2$ Hz, 0.4H, H-2), 7.32 – 7.11 (m, 10H, ArH), 7.09 – 7.03 (m, 1H, ArH),

7.02 (s, 0.6H, H-3'), 7.00* (s, 0.4H, H-3'), 6.93* (d, $J = 8.7$ Hz, 0.4H, H-5), 6.84 – 6.77 (m, 2.6H, H-5 and ArH), 6.61 (s, 0.6H, H-6'), 6.55* (s, 0.4H, H-6'), 6.26* (d, $J = 16.0$ Hz, 0.4H, H-1'''), 6.03 (d, $J = 16.0$ Hz, 0.6H, H-1'''), 5.93 – 5.81 (m, 1H, H-2'''), 5.68 – 5.53 (m, 1H, H-3''), 5.10 – 4.90 (m, 2.6H, H-4'' and PhCH₂O (minor) and PhCH_AH_BO (major)), 4.87 (d, $J = 12.4$ Hz, 0.4H, PhCH_AH_BO (major)), 4.42 – 4.35 (m, 2H, PMPCCH₂O), 3.91* (s, 1.2H, OCH₃), 3.89 (s, 1.8H, OCH₃), 3.83* (s, 1.2H, OCH₃), 3.82 (s, 1.8H, OCH₃), 3.77* (s, 1.2H, OCH₃), 3.75 (s, 1.8H, OCH₃), 3.62 (t, $J = 6.8$ Hz, 0.6H, H-1''), 3.55* (dd, $J = 8.3, 4.8$ Hz, 0.4H, H-1''), 3.48 – 3.28 (m, 2.4H, H-7'' and H-4''' (minor)), 3.28 – 3.22 (m, 0.6H, H-4'''), 3.01* (dd, $J = 8.8, 3.0$ Hz, 0.4H, H-3'''), 2.96 (dd, $J = 9.4, 3.1$ Hz, 0.6H, H-3'''), 2.45 – 2.30 (m, 1.6H, H-2''), 2.30* – 2.20* (m, 0.4H, H-2'''), 1.77 – 1.56 (m, 1.2H, H-6'''), 1.51* – 1.42* (m, 0.8H, H-6'''), 1.42* – 1.32* (m, 0.8H, H-5'''), 1.16 – 1.06 (m, 1.2H, H-5'''). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 159.6* (C-6), 159.3 (ArC), 159.19* (ArC), 159.16 (C-6), 149.4 (C-4'), 149.2* (C-4'), 147.58* (C-5'), 147.56 (C-5'), 136.8 (ArC), 136.7* (ArC), 135.9 (C-2'), 135.9* (C-2), 135.7* (C-2'), 135.5 (C-2), 135.2* (C-3''), 135.1 (ArC), 135.0 (C-3''), 134.3* (ArC), 133.42* (C-4), 133.40 (C-4), 133.0* (C-1'''), 132.7 (C-1'''), 132.0* (C-1), 131.5 (C-1), 130.7* (ArC), 130.6 (ArC), 129.4 (1.2 x ArCH), 129.36* (0.8 x ArCH), 128.73* (0.8 x ArCH), 128.70 (1.2 x ArCH), 128.66* (0.8 x ArCH), 128.6 (1.2 x ArCH), 128.22* (0.4 x ArCH), 128.16 (0.6 x ArCH), 128.15* (C-1'), 128.0 (0.6 x ArCH), 127.9 (C-1'), 127.7 (C-2'''), 127.69* (C-2'''), 127.3 (0.6 x ArCH), 126.8* (0.8 x ArCH), 126.6 (1.2 x ArCH), 126.5 (ArCH), 119.0 (C $\equiv$ N), 118.9* (C $\equiv$ N), 117.8 (C-4''), 117.2* (C-4''), 113.9 (1.2 x ArCH), 113.8* (0.8 x ArCH), 113.3 (C-5), 112.9* (C-5), 112.84* (C-6'), 112.80 (C-6'), 109.2* (C-3'), 108.9 (C-3'), 104.3* (C-3), 104.1 (C-3), 72.7 (PMPCH₂O), 72.6* (PMPCH₂O), 71.7* (C-4'''), 71.1 (C-4'''), 71.1 (C-1'''), 70.4 (PhCH₂O), 70.2 (C-7'''), 70.15* (PhCH₂O), 63.2* (C-3'''), 62.0 (C-3'''), 56.2 (OCH₃), 56.1* (OCH₃), 56.0* (OCH₃), 55.4* (OCH₃), 55.4 (OCH₃ and C-1''*), 54.9 (C-1''), 41.3* (C-2''), 41.2 (C-2''), 30.6* (C-5'''), 30.5 (C-5'''), 27.2 (C-6'''), 26.8 (C-6'''). HRMS (ESI): m/z calcd for C₄₇H₅₁N₂O₆ [M + H]⁺: 739.3747; found: 739.3749. **16b**: $R_f = 0.31$ (MeOH:CH₂Cl₂ = 4:96). IR (neat): $\nu_{\max}$ 3409, 2923, 2856, 2225, 1600, 1512, 1491, 1246, 1178, 1032, 817, 694 cm⁻¹. [α]_D²⁵ - 43 (c 2.4, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.54 – 7.44 (m, 1.6H, H-4 and H-2), 7.40* (s, 0.4H, H-2), 7.35 – 7.00 (m, 13H, ArH and H-3'), 6.94* (d, $J = 8.6$ Hz, 0.4H, H-5), 6.91 (d, $J = 8.6$ Hz, 0.6H, H-5), 6.79 – 6.76 (m, 2H, ArH), 6.63* (s, 0.4H, H-6'), 6.57 (s, 0.6H, H-6'), 5.88* (d, $J = 16.0$ Hz, 0.4H, H-1'''), 5.84 (d, $J = 16.0$ Hz, 0.6H, H-1'''), 5.67 (dd, $J = 16.0, 8.7$ Hz, 0.6H, H-2'''), 5.64* – 5.55* (m, 0.4H, H-2'''), 5.55 – 5.45 (m, 1H, H-3''), 5.14 – 4.97 (m, 4H, PhCH₂O and H-4''), 4.37 (s, 1.2H, PMPCCH₂O), 4.33* (s, 1.8H, PMPCCH₂O), 3.95 (s, 1.2H, OCH₃), 3.93 (s, 1.8H, OCH₃), 3.87 (s, 1.8H, OCH₃), 3.80 (s, 1.2H, OCH₃), 3.76 (s, 3H, OCH₃), 3.63* (dd, $J = 9.2, 4.1$ Hz, 0.4H, H-1''), 3.51 (d, $J = 7.4$ Hz, 0.8H, H-1''), 3.43 – 3.20 (m, 2.6H, H-4''' and H-7'''), 3.21* – 3.13* (m, 0.4H, H-4'''), 2.60* (t, $J = 8.0$ Hz, 0.4H, H-3'''), 2.51 (t, $J = 8.6$ Hz, 0.6H, H-3'''), 2.47 – 2.25 (m, 1.6H, H-2''), 2.19* – 2.10* (m, 0.4H, H-2''), 1.79* – 1.68* (m, 0.4H, H-6'''), 1.65 – 1.45 (m, 2H, H-6''' and H-5'''_A), 1.42* – 1.33* (m, 0.4H, H-5'''_A), 1.31 – 1.21 (m, 0.6H, H-5'''_B), 1.09* – 1.00* (m, 0.4H, H-

5'''_B). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 159.8 (C-6), 159.1 (ArC), 149.4 (C-4'), 149.37* (C-4'), 147.7 (C-5'), 147.4* (C-5'), 136.8* (ArC), 136.4 (ArC), 135.9 (C-3''), 135.7* (C-2'), 135.6* (C-3''), 135.5 (C-2'), 135.2 (C-2), 135.1* (C-2), 134.7 (ArC), 134.4* (ArC), 133.5 (C-4), 133.3* (C-4), 132.7 (C-1'''), 132.2 (C-1), 131.6* (C-1'''), 131.4* (C-1), 130.7* (ArC), 130.6 (ArC), 129.4 (C-2'''), 129.3 (1.2 x ArCH), 129.26* (0.8x ArCH), 128.8* (0.8 x ArCH), 128.7 (2.4 x ArCH), 128.6* (0.8 x ArCH), 128.57* (C-2'''), 128.3 (ArCH), 127.8 (C-2), 127.7 (0.6 x ArCH), 127.7* (0.4 x ArCH), 126.9 (1.2 x ArCH), 126.5* (0.8 x ArCH), 126.4 (1.2 x ArCH), 126.2* (0.8 x ArCH), 119.0 (C≡N), 118.7* (C-4''), 118.0 (C-4''), 113.8 (1.2 x ArCH), 113.77* (0.8 x ArCH), 113.0 (C-5), 112.9* (C-5), 112.9 (C-6'), 112.7* (C-6'), 109.5 (C-3'), 109.4* (C-3'), 104.3 (C-3), 103.9* (C-3), 73.2* (C-4'''), 73.15 (C-4'''), 72.5 (PMPCH₂O), 72.4* (PMPCH₂O), 70.5 (PhCH₂O), 70.2* (PhCH₂O), 70.0 (C-7'''), 69.97* (C-7'''), 63.3 (C-3'''), 62.4* (C-3'''), 56.1 (OCH₃), 56.0* (OCH₃), 55.4 (OCH₃), 54.0* (C-1''), 53.8 (C-1''), 43.4* (C-2''), 42.1 (C-2''), 30.4 (C-5'''), 30.3* (C-5'''), 26.1 (C-6'''), 26.0* (C-6'''). HRMS (ESI): *m/z* calcd for C₄₇H₅₁N₂O₆ [M + H]⁺: 739.3747; found: 739.3741.

4.12 General Method for Synthesis of Oxazolidinone

4.12.1 Synthesis of 6-(Benzyloxy)-4',5'-dimethoxy-2'-((S)-1-((4S,5R)-5-(3-((4-methoxybenzyl)oxy)propyl)-2-oxo-4-((E)-styryl)oxazolidin-3-yl)but-3-en-1-yl)-[1,1'-biphenyl]-3-carbonitrile (**17a**)

To a solution of **16a** (29.6 mg, 0.04 mmol, 1.0 equiv) and triethylamine (16.2 mg, 22.3 μL, 0.16 mmol, 4.0 equiv) in anhydrous CH₂Cl₂ (0.7 mL) was added triphosgene (5.9 mg, 0.02 mmol, 0.5 equiv) at 0 °C under a nitrogen atmosphere. After being stirred for 15 min, the reaction mixture was allowed to warm to room temperature and stirred for 18 h, and then concentrated *in vacuo* to give the crude product. Purification by column chromatography on silica gel eluting with 30:70 EtOAc/PS gave **17a** as a light brown solid (33.4 mg, 68%). *R_f* = 0.34 (EtOAc:hexanes = 40:60). IR (neat): ν_{max} 3067, 2932, 2223, 1738, 1600, 1512, 1493, 1180, 816, 694 cm⁻¹. [*α*]_D²⁵ + 71 (*c* 0.51, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.55 (s, 0.63H, H-2), 7.49* (dd, *J* = 8.6, 2.1 Hz, 0.37H, H-4), 7.46 (s, 1H, H-3'), 7.41 (dd, *J* = 8.6, 2.1 Hz, 0.63H, H-4), 7.38* (s, 0.37H, H-2), 7.36 – 7.04 (m, 11.26H, ArH), 7.01* (d, *J* = 8.7 Hz, 0.37H, H-5), 6.97* – 6.92* (m, 0.74H, ArH), 6.86 (d, *J* = 8.7 Hz, 0.63H, H-5), 6.83 – 6.77 (m, 2H, ArH), 6.67* (s, 0.37H, H-6'), 6.56 (s, 0.63H, H-6'), 5.99* (d, *J* = 15.8 Hz, 0.37H, H-2'''), 5.83 (d, *J* = 15.8 Hz, 0.63H, H-2'''), 5.77* – 5.68* (m, 0.37H, H-3''), 5.68 – 5.52 (m, 1.26H, H-3'' and H-1'''), 5.41* (dd, *J* = 15.8, 8.3 Hz, 0.37H, H-1'''), 5.19 – 4.96 (m, 4H, H-4'' and PhCH₂O), 4.49* – 4.44* (m, 0.37H, H-1''), 4.37 (s, 1H, PMPCH₂O), 4.34* (s, 1H, PMPCH₂O), 4.18 (dd, *J* = 11.1, 4.5 Hz, 0.63H, H-1'), 3.98 – 3.92 (m, 0.63H, H-5'''), 3.86 (s, 1.89H OCH₃), 3.82 (s, 3.78H OCH₃), 3.77 (s, 1.11H OCH₃), 3.76 (s, 1.11H OCH₃), 3.72* – 3.64* (m, 0.74H, H-4''' and H-5'''), 3.52 (t, *J* = 8.2 Hz, 0.63H, H-4'''), 3.45 – 3.28 (m,

2.63H, H-2''_A and H-3'''), 3.20* – 3.11* (m, 0.37H, H-2''_A), 2.68* (dt, $J = 13.0, 6.0$ Hz, 0.37H, H-2''_B), 2.43 – 2.35 (m, 0.63H, H-2''_B), 1.74 – 1.46 (m, 2.74H, H-2'''' and H-1'''), 1.33 – 1.31 (m, 1.26H, H-1'''). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 159.6* (C-6), 159.4 (C-6), 159.3* (ArC), 159.2 (ArC), 156.8* (C-2'''), 156.6 (C-2'''), 149.1 (C-4'), 148.8* (C-4'), 148.3 (C-5'), 147.9* (C-5'), 135.8* (ArC), 135.6 (C-3'''), 135.5 (ArC), 135.4 (C-2), 135.3* (C-2), 135.26 (ArC), 134.8* (C-3'''), 134.6 (C-2'''), 133.8* (C-2'''), 133.7* (C-4), 133.6 (C-4), 132.2 (C-2'), 131.8 (C-1), 131.1* (C-2'), 130.7,* (C-1) 130.5 (ArC), 130.49* (ArC), 129.4 (1.26 x ArCH), 129.3* (0.74 x ArCH), 128.9* (0.74 x ArCH), 128.8 (1.26 x ArCH), 128.77* (0.74 x ArCH), 128.7 (2.52x ArCH), 128.67* (0.74 x ArCH), 128.6* (0.37 x ArCH), 128.5 (0.63 x ArCH), 128.3 (ArCH), 128.0 (C-1'), 127.1* (0.74 x ArCH), 126.9 (1.26 x ArCH), 126.8* (C-1'''), 126.6 (1.26 x ArCH), 126.5* (0.74 x ArCH), 125.9 (C-1'''), 119.1 (C $\equiv$ N), 118.9* (C $\equiv$ N), 118.4* (C-7'''), 117.6 (C-7'''), 113.9 (2 x ArCH), 113.4 (C-5), 113.2* (C-5 and C-6'), 112.9* (C-6'), 111.4 (C-3'), 111.2* (C-3'), 104.5 (C-3), 104.4* (C-3), 79.0 (C-5'''), 78.8* (C-5'''), 72.6 (PMPCH₂O), 70.8 (PhCH₂O), 70.4* (PhCH₂O), 69.2* (C-3'''), 69.1 (C-3'''), 65.1 (C-4'''), 64.3* (C-4'''), 56.1 (OCH₃), 56.0 (OCH₃), 55.4 (OCH₃), 54.5 (C-1''), 53.8* (C-1''), 36.3* (C-2''), 35.5 (C-2''), 30.6* (C-1'''), 29.8 (C-1'''), 25.4 (C-2'''). HRMS (ESI): m/z calcd for C₄₈H₄₈N₂O₇Na [M + Na]⁺: 787.3359; found: 787.3380.

4.12.2 6-(Benzyloxy)-4',5'-dimethoxy-2'-((S)-1-((4R,5R)-5-(3-((4-methoxybenzyl)oxy)propyl)-2-oxo-4-((E)-styryl)oxazolidin-3-yl)but-3-en-1-yl)-[1,1'-biphenyl]-3-carbonitrile (**17b**)

Oxazolidinone **17b** was prepared from compound **16b** (17.9 mg, 0.024 mmol) according to the General Method for Synthesis of Oxazolidinone. Purification by column chromatography on silica gel eluting with 30:70 EtOAc/hexanes gave the title compound **18** as a pale yellow oil (7.3 mg, 40%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 53:47 ratio. $R_f = 0.34$ (EtOAc:hexanes = 40:60). IR (neat): $\nu_{\max}$ 2924, 2225, 1740, 1600, 1513, 1491, 1248, 1179, 750, 695 cm⁻¹. $[\alpha]_D^{25} + 40$ (c 0.29, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.68* (dd, $J = 8.6, 2.2$ Hz, 0.47H, H-4), 7.63 (dd, $J = 8.6, 2.2$ Hz, 0.53H, H-4), 7.41 – 7.20 (m, 8H, ArH), 7.19 – 7.03 (m, 3H, H-5 and ArH), 6.92* (s, 0.47H, H-3'), 6.90 (s, 0.53H, H-3'), 6.81 – 6.75 (m, 2.53H, H-6' and ArH), 6.69* (s, 0.47H, H-6'), 6.23* (d, $J = 15.8$ Hz, 0.47H, H-2'''), 6.14 (d, $J = 15.8$ Hz, 0.53H, H-2'''), 6.07* (dd, $J = 15.8, 9.7$ Hz, 0.47H, H-1'''), 6.00 (dd, $J = 15.8, 9.7$ Hz, 0.53H, H-1'''), 5.68 – 5.53 (m, 1H, H-3''), 5.22 (d, $J = 12.0$ Hz, 0.53H, PhCH_AH_BO), 5.12 (d, $J = 12.0$ Hz, 0.53H, PhCH_AH_BO), 5.10 – 4.85 (m, 3.94H, H-1'', H-4'' and PhCH₂O (minor)), 4.35* (s, 1H, PMPCH₂O), 4.30 (s, 1H, PMPCH₂O), 4.18* – 4.13* (m, 0.47H, H-5'''), 3.91 (s, 3H, OCH₃), 3.85 – 3.78 (m, 0.53H, H-4'''), 3.77 (s, 4.59H, OCH₃), 3.74 (s, 1.41H, OCH₃), 3.67* (t, $J = 8.9$ Hz, 0.47H, H-4'''), 3.44 – 3.34 (m, 1.59H, H-3'''' and H-5'''), 3.32* – 3.20* (m, 0.94H, H-3'''), 2.83 – 2.46 (m, 2H, H-2''), 1.77* – 1.66* (m, 0.47H, H-2''''_A), 1.61 – 1.45 (m, 2H, H-1''''_A, H-2''''_B and H-2'''), 1.45* – 1.35* (m, 0.47H H-1''''_B), 1.35 – 1.21 (m, 1.06H, H-1'''). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 159.8* (C-6), 159.2* (ArC), 159.15

(ArC), 159.0 (C-6), 156.6 (C-2'''), 156.5* (C-2'''), 148.3 (C-4'), 148.2 (C-5'), 148.17* (C-4'), 148.1* (C-5'), 136.2* (ArC), 135.8 (ArC), 135.5 (ArC), 135.4* (ArC), 135.0* (C-3''), 134.8* (C-2), 134.7* (C-2'''), 134.3 (C-3''), 134.29 (C-2), 134.2 (C-2'''), 134.15* (C-4), 133.9 (C-4), 131.2 (C-1), 130.9* (C-1), 130.7 (C-2'), 130.6 (ArC), 129.9* (C-2'), 129.3 (1.06 x ArCH), 129.2* (0.94 x ArCH), 129.15 (1.06 x ArCH), 129.1* (0.94 x ArCH), 128.8* (0.47 x ArCH), 128.76 (0.53 x ArCH), 128.7* (0.94 x ArCH), 128.66 (1.06 x ArCH), 128.24* (0.47 x ArCH), 128.2 (0.53 x ArCH), 128.0 (C-1'), 127.2 (1.06 x ArCH), 126.7 (1.06 x ArCH), 126.6* (0.94 x ArCH), 126.3* (0.94 x ArCH), 125.8* (C-1'''), 124.7 (C-1'''), 119.2 (C≡N), 119.0* (C≡N), 118.2* (C-4''), 117.5 (C-4''), 113.8 (2 x ArCH), 113.76 (C-6'), 113.5* (C-5), 113.1 (C-5), 111.1* (C-3'), 111.0 (C-3'), 104.5* (C-3), 104.3 (C-3), 77.5 (C-5'''), 77.2* (C-2'''), 72.4 (PMPCH₂O), 70.7 (PhCH₂O), 69.8* (PhCH₂O), 69.2* (C-3'''), 68.8 (C-3'''), 61.3* (C-4'''), 60.1 (C-4'''), 56.2* (OCH₃), 56.1 (OCH₃), 56.0* (OCH₃), 55.95 (OCH₃), 55.4* (OCH₃), 55.37 (OCH₃), 54.1* (C-1''), 53.8 (C-1''), 38.3* (C-2''), 37.3 (C-2''), 27.9* (C-1'''), 27.7 (C-1'''), 26.1* (C-2'''), 26.06 (C-2'''). HRMS (ESI): *m/z* calcd for C₄₈H₄₈N₂O₇Na [M + Na]⁺: 787.3359; found: 787.3398.

4.13 Synthesis of 6-(Benzyloxy)-2'-((*S*)-1-(((3*R*,4*S*,*E*)-4-hydroxy-7-((4-methoxybenzyl)oxy)-1-phenylhept-1-en-3-yl)amino)but-3-en-1-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**16c**)

Compound **14** (68.0 mg, 0.196 mmol) was treated according to the General Method for Sharpless Asymmetric Dihydroxylation (ADH), however AD-mix- α was used instead of AD-mix- β . The crude ADH product (**15b**) was obtained as a brown oil which was used without further purification. Alcohol **16c** was prepared from the above crude Sharpless ADH product (**15b**), amine **7** (31.1 mg, 0.075 mmol, 1.0 equiv) and β -styrenylboronic acid (16.7 mg, 0.1125 mmol, 1.5 equiv) according to the PBM Reaction with α -Hydroxylaldehyde Dimer. The crude product was purified by column chromatography on silica gel eluting with 0.5:99.5 MeOH/CH₂Cl₂ to afford the title compound **16c** as a pale yellow oil (37.6 mg, 68%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 56:44 ratio. *R*_f = 0.28 (MeOH:CH₂Cl₂ = 4:96). IR (neat): $\nu_{\max}$ 3425, 3065, 2933, 2223, 1600, 1512, 1246, 1095, 749, 695 cm⁻¹. [α]_D²⁵ - 68 (*c* 0.06, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.51 (s, 1H, H-4 and H-2), 7.47* (s, 0.44H, H-4), 7.45 (s, 0.56H, H-2), 7.39 – 7.09 (m, 13H, ArH and H-3'), 6.93 (d, *J* = 8.7 Hz, 0.56H, H-5), 6.88* (d, *J* = 8.7 Hz, 0.44H, H-5), 6.85 (d, *J* = 8.6 Hz, 2H, ArH), 6.67* (s, 0.44H, H-6'), 6.61 (s, 0.56H, H-6'), 6.03 (t, *J* = 16.0 Hz, 1H, H-1'''), 5.91 (dd, *J* = 16.0, 8.3 Hz, 0.56H, H-2'''), 5.76* (dd, *J* = 16.0, 7.5 Hz, 1H, H-2'''), 5.73 – 5.53 (m, 1H, H-3''), 5.15* (d, *J* = 12.4 Hz, 0.88H, H-4''), 5.12 – 4.98 (m, 3.12H, H-4'' and PhCH₂O), 4.43 (s, 1.22H, PMPCH₂O), 4.40* (s, 0.88H, PMPCH₂O), 3.99* (s, 1.32H, OCH₃), 3.98 (s, 1.68H, OCH₃), 3.90 (s, 1.68H, OCH₃), 3.84* (s, 1.32H, OCH₃), 3.81 (s, 3H, OCH₃), 3.66* (dd, *J* = 8.9, 4.4 Hz, 0.44H, H-1''), 3.56 (dd, *J* = 10.0, 3.0 Hz, 0.56H, H-1''), 3.52* – 3.48* (m, 0.44H, H-4'''), 3.48* – 3.42* (m, 0.88H, H-7'''), 3.41 – 3.35 (m, 1.68H, H-4''' and H-7'''),

2.92* (dd, $J = 7.7, 4.0$ Hz, 0.44H, H-3'''), 2.87 (dd, $J = 8.3, 4.0$ Hz, 0.56H, H-3'''), 2.48 – 2.28 (m, 1.56H, H-2''), 2.25* – 2.15* (m, 0.44H, H-2''), 1.83 – 1.47 (m, 2.44H, H-6''' and H-5'''_A (minor)), 1.39 – 1.27 (m, 1.12H, H-5'''), 1.27 – 1.17 (m, 0.44H H-5'''_B (minor)). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 159.7 (C-6), 159.2* (C-6 and ArC), 159.1* (ArC), 149.3 (C-4'), 149.2* (C-4'), 147.5 (C-5'), 147.3* (C-5'), 137.0* (ArC), 136.5 (ArC), 136.0 (C-3''), 135.8* (C-2'), 135.6 (C-2'), 135.5* (C-3''), 135.3* (C-2), 135.2 (C-2), 135.0 (ArC), 134.8* (ArC), 133.4 (C-4), 133.3* (C-4), 132.5 (C-1'''), 132.1 (C-1), 131.5* (C-1'''), 131.4* (C-1), 130.5* (ArC), 129.4 (1.12 x ArCH), 129.3* (0.88 x ArCH), 128.9* (C-2'''), 128.8* (0.88 x ArCH), 128.7 (1.12 x ArCH), 128.66 (1.12 x ArCH), 128.6* (0.88 x ArCH), 128.2 (0.56 x ArCH), 128.15* (0.44x ArCH), 128.1 (C-2'''), 127.9 (C-1'), 127.6 (0.56 x ArCH), 127.58* (C-1), 127.5* (0.44 x ArCH), 126.8 (1.12 x ArCH), 126.42* (0.88 x ArCH), 126.39 (1.12 x ArCH), 126.2* (0.88 x ArCH), 119.1* (C $\equiv$ N), 118.9 (C $\equiv$ N), 118.4* (C-4''), 117.8 (C-4''), 113.83 (1.12 x ArCH), 113.81* (0.88 x ArCH), 113.0 (C-5), 112.97* (C-5), 112.8 (C-6'), 112.7* (C-6'), 109.6 (C-3'), 109.4* (C-3'), 104.2 (C-3), 103.8* (C-3), 73.9 (C-4'''), 72.6 (PMPCH₂O), 70.4 (PhCH₂O), 70.1* (PhCH₂O), 70.0* (C-7'''), 69.99 (C-7'''), 62.2 (C-3'''), 61.6* (C-3'''), 56.1 (OCH₃), 56.05 (OCH₃), 56.0 (OCH₃), 55.4 (OCH₃), 54.8* (C-1''), 54.5 (C-1''), 43.4* (C-2''), 42.2 (C-2''), 30.3 (C-5'''), 26.6 (C-6'''). HRMS (ESI): m/z calcd for C₄₇H₅₁N₂O₆ [M + H]⁺: 739.3747; found: 739.3777.

4.14 Synthesis of (*R*)-*N*-(2-Bromo-4,5-dimethoxybenzylidene)-2-methylpropane-2-sulfinamide (**18**)

To a solution of 4-hydroxy-3-bromobenzonitrile (0.259 g, 1.06 mmol, 1.0 equiv.) in CH₂Cl₂ (2 mL) was added potassium hydrogen sulfate (1.45 g, 10.6 mmol, 10.0 equiv.) and (*R*)-(+)-2-methyl-2-propanesulfinamide (0.192 g, 1.58 mmol, 1.5 equiv.) and the mixture was stirred at room temperature for 24 h. The reaction mixture was filtered through a short pad of celite and concentrated in vacuo. Purification by column chromatography on silica gel eluting with 15:85 EtOAc/hexane gave the title compound as a white solid (7.3 mg, 40%). $R_f = 0.5$ (EtOAc:hexane = 50:50). mp: 156-158 °C. $[\alpha]_D^{25} - 64.5$ (c 0.35, CHCl₃). IR (neat): $\nu_{\max}$ 2958, 2841, 1577, 1507, 1440, 1390, 1255, 1213, 1166, 1024, 759 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 8.86 (s, 1H, N=CH), 7.55 (s, 1H, H-6), 7.07 (s, 1H, H-3), 3.95 (s, 3H, OCH₃), 3.93 (s, 3H, OCH₃), 1.28 (s, 9H, C(CH₃)₃). ¹³C NMR (125 MHz, CDCl₃): δ 161.5 (N=CH), 153.0 (C-4), 148.7 (C-5), 125.4 (C-1), 119.0 (C-2), 115.4 (C-3), 110.5 (C-6), 57.8 (C(CH₃)₃), 56.4 (OCH₃), 56.1 (OCH₃), 22.7 (C(CH₃)₃). HRMS (ESI): m/z calculated for C₁₃H₁₈NO₃NaSBr [M + Na]⁺: 370.0088; found: 370.0093.

4.15 Synthesis of (*R*)-*N*-((*S*)-1-(2-Bromo-4,5-dimethoxyphenyl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide (**19**)

To a solution of *N*-sulfinyl imine **18** (102 mg, 0.293 mmol) in anhydrous CH₂Cl₂ (1.5 mL) at -78 °C was added dropwise allylmagnesium bromide (1.0 M in Et₂O, 0.33 mL, 0.323 mmol, 1.1

equiv.). After stirring at -78 °C for 4 h, the reaction was quenched at -78 °C with sat. aqueous NaHCO₃ solution. The aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried (MgSO₄), filtered and the solvent was concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 50:50 EtOAc/hexane to afford the title compound as a pale yellow oil (93.2 mg, 82%). R_f = 0.2 (EtOAc:hexane = 50:50). $[\alpha]_D^{25}$ - 75.7 (c 0.18, CHCl₃). IR (neat): $\nu_{\max}$ 3224, 2957, 2929, 1603, 1505, 1459, 1384, 1254, 1202, 1158, 1051, 1026, 925, 869, 795 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.01 (s, 1H, H-3), 6.93 (s, 1H, H-6), 5.87 – 5.70 (m, 1H, H-3'), 5.25 – 5.16 (m, 2H, H-4'), 4.94 – 4.84 (m, 1H, H-1'), 3.87 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 3.69 (s, 1H, NH), 2.70 – 2.58 (m, 1H, H-2'A), 2.44 – 2.34 (m, 1H, H-2'B), 1.23 (s, 9H, C(CH₃)₃). ¹³C NMR (125 MHz, CDCl₃): δ 148.8 (C-4), 148.5 (C-5), 134.1 (C-3'), 132.6 (C-1), 119.5 (C-4'), 115.5 (C-3), 113.6 (C-2), 111.1 (C-6), 56.2 (OCH₃), 56.0 (OCH₃), 55.8 (C(CH₃)₃), 55.5 (C-1'), 41.9 (C-2'), 22.7 (C(CH₃)₃). HRMS (ESI): m/z calculated for C₁₆H₂₅NO₃SBr [M + H]⁺: 390.0739; found: 390.0737.

4.16 Synthesis of (S)-1-(2-Bromo-4,5-dimethoxyphenyl)but-3-en-1-amine (**20**)

To a solution of sulfinamide **19** (83.3 mg, 0.213 mmol, 1.0 equiv) in MeOH (2 mL) was added TMSCl (46.4 mg, 54.2 μ L, 0.426 mmol, 2.0 equiv) and the solution was stirred at room temperature for 30 min. The solution was then evaporated to dryness in vacuo and the residue was washed with Et₂O (5 mL) and redissolved in CH₂Cl₂ (2 mL). The solution was washed with sat. aqueous NaHCO₃ solution. The organic layer was dried (MgSO₄) and concentrated in vacuo to afford the title compound as a light brown oil (53.7 mg, 88%) which was used in the next step without further purification. The spectroscopic data of this compound matched with those in the literature for the racemate.⁴¹ R_f = 0.3 (MeOH:CH₂Cl₂ = 5:95). $[\alpha]_D^{25}$ - 26.0 (c 0.21, CHCl₃). IR (neat): $\nu_{\max}$ 3363, 2932, 1602, 1498, 1438, 1380, 1255, 1209, 1152, 1028, 791 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.11 (s, 1H, H-6), 6.99 (s, 1H, H-3), 5.86 – 5.74 (m, 1H, H-3'), 5.16 (d, J = 17.2 Hz, 1H, H-4'A), 5.12 (d, J = 10.2 Hz, 1H, H-4'B), 4.38 (dd, J = 8.6, 4.5 Hz, 1H, H-1'), 3.89 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 2.54 – 2.47 (m, 1H, H-2'A), 2.28 – 2.19 (m, 1H, H-2'B), 1.77 (s, 2H, NH₂). ¹³C NMR (125 MHz, CDCl₃): δ 148.7 (C-4), 148.3 (C-5), 136.2 (C-1), 135.2 (C-3'), 118.0 (C-4'), 115.4 (C-3), 112.8 (C-2), 110.1 (C-6), 56.2 (OCH₃), 56.1 (OCH₃), 53.3 (C-1'), 42.5 (C-2'). ESIMS m/z 269 (49%) [M(⁷⁹Br) - NH₂]⁺, 271 (51%) [M(⁸¹Br) - NH₂]⁺.

4.17 Synthesis of (3S,4R,E)-3-(((S)-1-(2-Bromo-4,5-dimethoxyphenyl)but-3-en-1-yl)amino)-7-((4-methoxybenzyl)oxy)-1-phenylhept-1-en-4-ol (**21**)

To a solution of the crude Sharpless ADH product **15a** in EtOH (0.4 mL) was added amine **20** (48.7 mg, 0.170 mmol, 1.0 equiv.) and β -styrenylboronic acid (37.8 mg, 0.255 mmol, 1.5 equiv.) and the solution was stirred at room temperature for 2 d. The reaction mixture was evaporated and

dissolved in EtOAc (5 mL) and then washed with sat. aqueous NaHCO₃ solution (2 x 5 mL). The combined organic layer was dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 2:10:30:58 MeOH/EtOAc/CH₂Cl₂/hexane to afford the title compound as a pale yellow oil (45.6 mg, 44%). *R*_f = 0.2 (EtOAc:hexane = 50:50). $[\alpha]_D^{25} + 18.0$ (c 0.35, CHCl₃). IR (neat): $\nu_{\max}$ 3406, 2932, 1612, 1511, 1438, 1381, 1247, 1030, 970, 820, 751 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.27 – 7.19 (m, 7H, ArH), 6.93 (s, 1H, H-6), 6.90 (s, 1H, H-3), 6.82 (d, *J* = 8.1 Hz, 2H, ArH), 6.37 (d, *J* = 16.0 Hz, 1H, H-1''), 6.06 (dd, *J* = 16.0, 8.8 Hz, 1H, H-2''), 5.82 – 5.73 (m, 1H, H-3'), 5.14 – 5.04 (m, 2H, H-4'), 4.40 (s, 2H, PMPCH₂O), 4.26 (t, *J* = 6.7 Hz, 1H, H-1'), 3.87 (s, 1H, OH), 3.81 (s, 3H, OCH₃), 3.80 – 3.78 (m, 1H, H-4''), 3.77 (s, 3H, OCH₃), 3.47 – 3.40 (m, 2H, H-7''), 3.08 (d, *J* = 8.8 Hz, 1H, H-3''), 2.48 – 2.39 (m, 1H, H-2'A), 2.38 – 2.29 (m, 1H, H-2'B), 1.76 (dt, *J* = 14.0, 6.9 Hz, 1H, H-5'A), 1.65 (dt, *J* = 14.0, 7.1 Hz, 1H, H-5'B), 1.43 (q, *J* = 7.1 Hz, 2H, H-6''). ¹³C NMR (125 MHz, CDCl₃): δ 159.2 (ArC), 148.7 (C-4), 148.4 (C-5), 136.8 (ArC), 134.9 (C-3'), 134.6 (C-1), 132.8 (C-1''), 130.5 (ArC), 129.4 (2 x ArCH), 128.5 (2 x ArCH), 127.6 (ArCH), 127.6 (C-2''), 126.4 (2 x ArCH), 118.0 (C-4'), 115.4 (C-3), 113.9 (C-2), 113.8 (2 x ArCH), 110.5 (C-6), 72.6 (PMPCH₂O), 71.1 (C-4''), 70.1 (C-7''), 63.2 (C-3''), 58.0 (C-1'), 56.2 (2 x OCH₃), 55.4 (OCH₃), 41.5 (C-2'), 30.5 (C-6''), 26.6 (C-5''). HRMS (ESI): *m/z* calculated for C₃₃H₄₁NO₅Br [M + H]⁺: 610.2168; found: 610.2192.

4.18 Synthesis of 6-(Benzyloxy)-4',5'-dimethoxy-2'-((S)-1-((4R,5S)-5-(3-((4-methoxybenzyl)oxy)propyl)-2-oxo-4-((E)-styryl)oxazolidin-3-yl)but-3-en-1-yl)-[1,1'-biphenyl]-3-carbonitrile (21)

Oxazolidinone **21** was prepared from compound **20** (31.4 mg, 0.088 mmol) according to the General Method for Synthesis of Oxazolidinone. Purification by column chromatography on silica gel eluting with 30:70 EtOAc/hexanes gave the title compound **21** as a pale yellow oil (25.2 mg, 37%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 67:33 ratio. *R*_f = 0.24 (EtOAc:hexanes = 40:60). IR (neat): $\nu_{\max}$ 2962, 2225, 1737, 1600, 1513, 1492, 1258, 1080, 1012, 793, 694 cm⁻¹. $[\alpha]_D^{25} - 13$ (c 0.21, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.52 (d, *J* = 2.2 Hz, 0.65H, H-2), 7.49 (dd, *J* = 8.6, 2.2 Hz, 1H, H-4), 7.44 (s, 0.65H, H-3'), 7.42* (s, 0.35H, H-3'), 7.36* (s, 0.35H, H-2), 7.36 – 7.07 (m, 11.65H, ArH), 7.03* – 6.98* (m, 0.7H, H-5 and ArH), 6.89 (d, *J* = 8.6 Hz, 0.65H, H-5), 6.78 (d, *J* = 8.6 Hz, 2H, ArH), 6.62* (s, 0.35H, H-6'), 6.55 (s, 0.65H, H-6'), 5.87* (d, *J* = 15.9 Hz, 0.35H, H-2'''), 5.76 (d, *J* = 15.9 Hz, 0.65H, H-2'''), 5.69 (dd, *J* = 15.8, 9.2 Hz, 0.65H, H-1'''), 5.65 – 5.51 (m, 1.35H, H-3'' and H-1'''), 5.16 – 4.95 (m, 4H, H-4'' and PhCH₂O), 4.38 – 4.31 (m, 2.65H, H-5''' and PMPCH₂O), 4.22* (dd, *J* = 9.6, 6.2 Hz, 0.35H, H-1''), 4.16 – 4.11 (m, 1H, H-1'' and H-5'''), 3.98 – 3.88 (m, 2.05H, H-4''' and OCH₃), 3.85 (s, 1.95H, OCH₃), 3.84 (s, 1.95H, OCH₃), 3.81* (s, 1.05H, OCH₃), 3.78* (s, 1.05H, OCH₃), 3.76 (s, 1.95H, OCH₃), 3.46 – 3.29 (m, 2.65H, H-2''_A and H-3'''), 3.26* – 3.18* (m, 0.35H,

H-2''_A), 2.71* – 2.61* (m, 0.35H, H-2''_B), 2.41 – 2.34 (m, 0.65H, H-2''_B), 1.81 – 1.37 (m, 4H, H-1'''' and H-2'''''). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 159.5 (C-6), 159.3* (ArC), 159.2 (ArC), 157.0* (C-2'''), 156.7 (C-2'''), 149.2 (C-4'), 148.3 (C-5'), 147.9* (C-5'), 135.6* (C-3''), 135.58 (C-3''), 135.5* (ArC), 135.48 (ArC), 135.44 (ArC), 135.4 (C-2), 135.0 (C-2'''''), 134.9* (C-2'''''), 133.6 (C-4), 132.2 (C-1), 132.17 (C-2'), 131.4* (C-2'), 131.3* (C-1), 130.6 (ArC), 130.5* (ArC), 129.3 (2 x ArCH), 128.9* (0.7 x ArCH), 128.89 (1.3 x ArCH), 128.8* (0.7 x ArCH), 128.7 (1.3 x ArCH), 128.6 (ArCH), 128.3 (ArCH), 127.8 (C-1'), 127.2* (0.7 x ArCH), 126.8 (1.3 x ArCH), 126.6 (1.3 x ArCH), 126.5* (0.7 x ArCH), 124.1* (C-1'''''), 123.6 (C-1'''''), 119.1 (C≡N), 118.8* (C≡N), 118.3* (C-4''), 117.7 (C-4''), 113.8 (2 x ArCH), 113.4* (C-5), 113.37 (C-5), 112.9* (C-6'), 112.8 (C-6'), 111.2 (C-3'), 111.1* (C-3'), 104.4 (C-3), 77.4 (C-5'''), 72.6* (PMPCH₂O), 72.5 (PMPCH₂O), 70.8 (PhCH₂O), 70.7* (PhCH₂O), 69.2* (C-3'''), 69.15 (C-3'''), 62.4 (C-4'''), 62.1* (C-4'''), 56.1 (OCH₃), 56.06 (OCH₃), 56.0* (OCH₃), 55.98* (OCH₃), 55.4 (OCH₃), 54.6, (C-1''), 54.57* (C-1''), 37.2* (C-2''), 35.8 (C-2''), 28.0 (C-1'''), 27.8* (C-1'''), 26.2* (C-2'''), 26.1 (C-2'''). HRMS (ESI): *m/z* calcd for C₄₈H₄₈N₂O₇Na [M + Na]⁺: 787.3359; found: 787.3398.

4.19 Synthesis of 6-(Benzyloxy)-2'-((*S*)-1-(((3*S*,4*R*,*E*)-4,7-dihydroxy-1-phenylhept-1-en-3-yl)amino)but-3-en-1-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**22**)

To a solution of 1,2-amino alcohol **16a** (20.0 mg, 0.027 mmol, 1.0 equiv) in 20:1 CH₂Cl₂/water (0.28 mL) was added DDQ (12.3 mg, 0.054 mmol, 2.0 equiv) and the mixture was stirred at room temperature for 6 h. The reaction mixture was quenched with sat. aqueous NaHCO₃ solution. The aqueous layer was extracted with DCM (2 x 3 mL). The combined organic layer was washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 2:98 MeOH/CH₂Cl₂ to afford the title compound **22** as a light brown oil (7.6 mg, 46%). *R_f* = 0.22 (MeOH:CH₂Cl₂ = 5:95). IR (neat): ν_{max} 3333, 2926, 2224, 1600, 1515, 1120, 733, 695 cm⁻¹. [α]_D²⁵ + 45 (*c* 0.58, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.57 (dd, *J* = 8.6, 2.2 Hz, 0.51H, H-4), 7.51* (dd, *J* = 8.6, 2.2 Hz, 0.49H, H-4), 7.41 (d, *J* = 2.2 Hz, 0.51H, H-2), 7.40* (d, *J* = 2.2 Hz, 0.49H, H-2), 7.34 – 7.07 (m, 10H, ArH), 7.02* (s, 0.49H, H-3'), 7.00* (d, *J* = 8.7 Hz, 0.49H, H-5), 6.94 (s, 0.51H, H-3'), 6.91 (d, *J* = 8.6 Hz, 0.51H, H-5), 6.63* (s, 0.49H, H-6'), 6.59 (s, 0.51H, H-6'), 6.26 (d, *J* = 15.9 Hz, 0.51H, H-1'''), 6.13* (s, 0.49H, H-1'''), 5.97* (dd, *J* = 16.0, 8.7 Hz, 0.49H, H-2'''), 5.86 (dd, *J* = 15.9, 9.2 Hz, 0.51H, H-2'''), 5.70 – 5.51 (m, 1H, H-3''), 5.15 – 4.89 (m, 4H, H-4'' and PhCH₂O), 3.90 (s, 3H, OCH₃), 3.86* (s, 1.47H, OCH₃), 3.85 (s, 1.53H, OCH₃), 3.66 – 3.46 (m, 3H, H-1'' and H-7'''), 3.35* (s, 0.49H, H-4'''), 3.24 (d, *J* = 9.2 Hz, 0.51H, H-4'''), 3.06* (s, 0.49H, H-3'''), 2.96 (dd, *J* = 8.7, 3.0 Hz, 0.51H, H-3'''), 2.44 – 2.19* (m, 2H, H-2''), 1.68* – 1.59* (m, 0.98H, H-6'''), 1.58 – 1.47 (m, 1.02H, H-6'''), 1.42 – 1.29 (m, 1.02H, H-5'''), 1.15 – 0.97* (m, 0.98H, H-5'''). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 159.7* (C-6), 159.0 (C-6), 149.33 (C-4'), 149.3* (C-4'), 147.7* (C-5'), 147.69 (C-5'), 136.4 (ArC), 135.7 (ArC), 135.65 (C-3''), 135.5 (C-

2'), 135.4* (C-2), 135.1 (C-2), 134.5* (C-3''), 133.5 (C-4 and C-1'''), 133.2* (C-1'''), 131.8* (C-1), 131.5 (C-1), 128.7 (2.04 x ArCH), 128.6* (1.96 x ArCH), 128.2 (ArCH), 128.19* (C-1'), 128.1 (C-1'), 128.0* (0.49 x ArCH), 127.8 (0.51 x ArCH), 126.8* (C-2''' and 1.96 x ArCH), 126.5 (2.04 x ArCH), 126.4 (C-2'''), 119.1* (C≡N), 118.9 (C≡N), 118.0* (C-4''), 117.2 (C-4''), 113.4* (C-5), 113.0 (C-5), 112.7 (C-6'), 112.6* (C-6'), 108.8* (C-3'), 108.5 (C-3'), 104.4* (C-3), 104.1 (C-3), 70.9* (C-4'''), 70.8 (C-4'''), 70.4 (PhCH₂O), 70.3 (PhCH₂O), 62.9 (C-7'''), 62.8* (C-7''' and C-3'''), 62.3 (C-3'''), 56.1* (OCH₃), 56.0 (OCH₃), 55.1* (C-1''), 55.0 (C-1''), 41.0 (C-2''), 30.7* (C-5'''), 30.6 (C-5'''), 30.3* (C-6'''), 30.2 (C-6'''). HRMS (ESI): *m/z* calcd for C₃₉H₄₃N₂O₅ [M + H]⁺: 619.3172; found: 619.3174.

4.16 General Method for Mesylation-Cyclization

4.16.1 Synthesis of 6-(Benzyloxy)-2'-((S)-1-((2S,3R)-3-hydroxy-2-((E)-styryl)piperidin-1-yl)but-3-en-1-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**23**)

To a solution of diol **22** (45.3 mg, 0.073 mmol, 1.0 equiv) in anhydrous CH₂Cl₂ (0.73 mL) at 0 °C was added triethylamine (7.4 mg, 10.2 μL, 0.073 mmol, 1.0 equiv) and then dropwise methanesulfonyl chloride (7.4 mg, 10.2 μL, 0.073 mmol, 1.0 equiv). The reaction mixture was stirred for 5 min then warmed up to 45 °C and stirred for 18 h. After the reaction had completed, the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 2:98 MeOH/CH₂Cl₂ to afford the title compound **23** as a light green oil (23.8 mg, 54%) and recovered diol **22** as a pale yellow oil (13.8 mg, 31%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 67:33 ratio. *R_f* = 0.27 (MeOH:CH₂Cl₂ = 3:97). IR (neat): ν_{max} 3351, 2930, 2224, 1600, 1514, 1258, 1122, 1024, 746, 695 cm⁻¹. [α]_D²⁵ + 18 (*c* 0.14, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.65 (dd, *J* = 8.6, 2.2 Hz, 1H, H-4), 7.54 (d, *J* = 2.2 Hz, 1H, H-2), 7.45 – 7.10 (m, 8H, ArH), 7.04* (d, *J* = 8.5 Hz, 0.33H, H-5), 6.96* (s, 0.33H, H-3''), 6.91 – 6.88 (m, 2H, ArH), 6.87 (s, 0.67H, H-3''), 6.81 (d, *J* = 8.6 Hz, 0.67H, H-5), 6.65* (s, 0.33H, H-6'), 6.61 (s, 0.67H, H-6'), 6.58 (d, *J* = 15.8 Hz, 1H, H-2'''), 5.65* – 5.50* (m, 0.33H, H-3''), 5.30 (ddt, *J* = 16.9, 10.0, 6.8 Hz, 0.67H, H-3''), 5.13* (d, *J* = 12.4 Hz, 0.33H, PhCH_AH_BO (minor)), 5.07* (d, *J* = 12.4 Hz, 0.33H, PhCH_AH_BO (minor)), 5.00* – 4.92* (m, 0.33H, H-4''_A), 4.85 (dd, *J* = 17.1, 2.0 Hz, 1H, H-4''_B (minor) and H-4''_A), 4.75 (dd, *J* = 15.8, 9.3 Hz, 1H, H-1'''), 4.69 (d, *J* = 12.5 Hz, 0.67H, PhCH_AH_BO), 4.59 (d, *J* = 11.6 Hz, 1.34H, H-4''_B and PhCH_AH_BO), 3.93* (s, 0.99H, OCH₃), 3.93 (s, 2.01H, OCH₃), 3.89 – 3.85* (m, 0.33H, H-1''), 3.84 (s, 2.01H, OCH₃), 3.82* (s, 0.99H, OCH₃), 3.75 (dd, *J* = 11.0, 3.9 Hz, 0.67H, H-1''), 3.17 – 3.10 (m, 1H, H-3'''), 3.08* – 2.98* (m, 0.33H, H-2'''), 2.84 (t, *J* = 8.4 Hz, 0.67H, H-2'''), 2.64 (d, *J* = 11.3 Hz, 0.67H, H-6'''_A), 2.58* – 2.49* (m, 0.66H, H-2''), 2.48 – 2.40 (m, 1.34H, H-2''), 2.40* – 2.33* (m, 0.33H, H-6'''_A), 2.13 (t, *J* = 9.6 Hz, 0.67H, H-6'''_B), 2.08* – 1.96* (m, 0.99H, H-4''' and H-6'''_B), 1.63* – 1.53* (m, 0.66H, H-5'''), 1.32 – 1.16 (m, 2.68H, H-4''' and H-5'''). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 160.2* (C-6), 159.1 (C-6), 147.9* (C-4'), 147.6 (C-

4'), 147.4 (C-5'), 147.2* (C-5'), 137.3 (C-2), 136.5 (ArC), 136.1* (ArC), 136.0 (C-3''), 135.8 (ArC), 135.6* (C-3''), 135.0* (C-2'''), 134.8 (C-2'''), 133.2* (C-4), 132.8 (C-4), 132.7* (C-1), 132.4 (C-1), 131.5* (C-2'), 131.2 (C-2'), 130.9 (C-1'), 130.1* (C-1'), 129.0* (0.66 x ArCH), 128.7* (0.66 x ArCH), 128.6 (1.34 x ArCH), 128.5 (1.34 x ArCH), 128.2* (0.33 x ArCH), 128.1* (0.33 x ArCH), 128.07 (0.67 x ArCH), 127.9 (0.67 x ArCH), 126.8 (1.34 x ArCH), 126.6* (0.66 x ArCH), 126.5* (0.66 x ArCH), 126.47 (1.34 x ArCH), 119.3 (C≡N), 119.1* (C≡N), 117.3* (C-4''), 116.3 (C-4''), 113.9* (C-6'), 113.8 (C-6'), 113.0 (C-5), 112.8* (C-5), 111.9 (C-3'), 111.8* (C-3'), 103.8* (C-3), 103.5 (C-3), 70.9 (C-3'''), 70.5* (C-2'''), 70.4 (C-2'''), 70.1* (PhCH₂O), 70.0 (PhCH₂O), 60.2* (C-1''), 60.1 (C-1''), 56.2 (OCH₃), 56.0* (OCH₃), 44.5* (C-6'''), 44.1 (C-6'''), 31.6 (C-4'''), 30.4* (C-4'''), 27.5 (C-2''), 23.4 (C-5'''), 22.3* (C-5'''). HRMS (ESI): *m/z* calcd for C₃₉H₄₁N₂O₄ [M + H]⁺: 601.3066; found: 601.3086.

4.17 General Method for Ring-Closing Metathesis

4.17.1 Synthesis of 6-(Benzyloxy)-2'-((1*R*,6*S*,9*aS*)-1-hydroxy-1,3,4,6,7,9*a*-hexahydro-2*H*-quinolizin-6-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**24**)

To a solution of carbonitrile **23** (15.8 mg, 0.026 mmol, 1.0 equiv) in N₂ purged anhydrous CH₂Cl₂ (0.26 mL) was added Ti(O*i*Pr)₄ (7.5 mg, 0.026 mmol, 1.0 equiv) and Grubbs' II ruthenium catalyst (4.1 mg, 0.0053 mmol, 0.18 equiv) and the mixture was stirred and heated at 50 °C for 8 h. The reaction mixture was then cooled to room temperature and the solvent was evaporated. The crude product was purified by column chromatography on silica gel eluting with 3:97 MeOH/CH₂Cl₂ to afford the title compound **24** as a light brown oil (5.2 mg, 40%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 75:25 ratio. *R*_f = 0.22 (MeOH:CH₂Cl₂ = 5:95). IR (neat): *ν*_{max} 3351, 2928, 2224, 1600, 1514, 1490, 1253, 1035, 731, 696 cm⁻¹. [*α*]_D²⁵ - 71 (*c* 0.27, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.59 (d, *J* = 9.0 Hz, 1H, H-4), 7.54 (d, *J* = 2.2 Hz, 1H, H-2), 7.35 – 7.13 (m, 5H, ArH), 7.13 – 7.07 (m, 1.25H, H-5 and H-3'), 6.98 (d, *J* = 8.6 Hz, 0.75H, H-5), 6.69* (s, 0.25H, H-6'), 6.58 (s, 0.75H, H-6'), 6.20 – 6.11 (m, 1H, H-9''), 6.02* (d, *J* = 9.1 Hz, 0.25H, H-8''), 5.92 (d, *J* = 10.1 Hz, 0.75H, H-8''), 5.18* (d, *J* = 12.4 Hz, 0.25H, PhCH_AH_BO (minor)), 5.13 – 5.01 (m, 1.75H PhCH_AH_BO (minor) and PhCH₂O), 4.02* (d, *J* = 6.1 Hz, 0.25H, H-6''), 3.88 (s, 2.25H, OCH₃), 3.86* (s, 0.75H, OCH₃), 3.84 (s, 2.25H, OCH₃), 3.82 – 3.79 (m, 0.75H, H-6''), 3.79* (s, 0.75H, OCH₃), 3.29 (br s, 1H, H-1''), 2.76 – 2.58 (m, 2H, H-7''_A (minor), H-7''_A and H-9a''), 2.32* – 2.25* (m, 0.25H, H-7''_B (minor)), 2.22 – 1.77 (m, 4.75H, H-2'', H-3''_A, H-2'' and H-7''_B), 1.53 – 1.09 (m, 2H, H-3''_B, H-2'' (minor)). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 159.6* (C-6), 159.4 (C-6), 149.0 (C-4'), 147.6 (C-5'), 135.8 (ArC), 135.7 (C-2), 133.3 (C-4), 133.1 (C-1), 132.54* (C-1), 132.5 (C-1'), 131.9* (C-1'), 128.8 (2 x ArCH), 128.6 (C-2'), 128.3 (ArCH), 127.0 (2 x ArCH), 126.4 (C-9''), 126.2* (C-8''), 125.8 (C-8''), 119.3 (C≡N), 113.2* (C-5 and C-6), 112.9 (C-5), 112.8 (C-6), 110.4* (C-3'), 110.2 (C-3'), 104.5 (C-3), 71.7 (C-1''), 71.2* (C-1''), 70.8 (PhCH₂O), 70.3* (PhCH₂O), 61.2 (C-9a''), 56.1 (C-6''),

56.0 (2 x OCH₃), 54.6* (C-6''), 51.1 (C-4''), 50.3* (C-4''), 34.5 (C-2''), 31.9 (C-7''), 23.6 (C-3''), 22.8 (C-3''). HRMS (ESI): m/z calcd for C₃₁H₃₃N₂O₄ [M + H]⁺: 497.2440; found: 497.2454.

tert-Butyldimethyl(*pent-4-en-1-yloxy*)silane (**25**).³⁴ To a solution of 4-penten-1-ol (2.15 g, 25.0 mmol, 1.0 equiv) in CH₂Cl₂ (25 mL) was added imidazole (2.04 g, 30.0 mmol, 1.2 equiv) followed by TBSCl (4.52 g, 30.0 mmol, 1.2 equiv) and the reaction mixture was stirred at room temperature for 3 h. After the reaction had completed, water (30 mL) was added and the mixture was extracted with EtOAc (2 x 30 mL). The organic layer was dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 1:99 Et₂O/hexanes to afford the title compound **25** as a colorless oil (4.91 g, 98%). The spectroscopic data of this compound matched with those in the literature.³⁴ ¹H NMR (500 MHz, CDCl₃): δ 5.82 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H, H-4), 5.02 (d, J = 17.0 Hz, 1H, H-5_A), 4.95 (d, J = 10.2 Hz, 1H, H-5_B), 3.62 (t, J = 6.5 Hz, 2H, H-1), 2.10 (q, J = 7.3 Hz, 2H, H-3), 1.61 (p, J = 6.9 Hz, 2H, H-2), 0.90 (s, 9H, (CH₃)₃CSi), 0.05 (s, 6H, 2 x CH₃Si).

4.18 Synthesis of (*E*)-*tert*-Butyldimethyl((5-(phenylsulfonyl)*pent-4-en-1-yl*)oxy)silane (**26**)

Sulfone **26** was prepared from compound **25** (0.401 g, 2.0 mmol) according to the General Method for Olefin Cross Metathesis. Purification by column chromatography on silica gel eluting with 10:10:80 Et₂O/CH₂Cl₂/hexanes gave the title compound **26** as a colorless oil (0.432 g, 63%). R_f = 0.16 (Et₂O:CH₂Cl₂:hexanes = 10:10:80). IR (neat): $\nu_{\max}$ 2929, 2858, 1643, 1473, 1256, 1099, 911 833, 774 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.88 (d, J = 7.1 Hz, 2H, ArH), 7.61 (t, J = 7.6 Hz, 1H, ArH), 7.53 (t, J = 7.8 Hz, 2H, ArH), 7.01 (dt, J = 15.0, 6.9 Hz, 1H, H-4), 6.33 (d, J = 15.0 Hz, 1H, H-5), 3.60 (t, J = 6.0 Hz, 2H, H-1), 2.33 (q, J = 8.3, 7.7 Hz, 2H, H-3), 1.71 – 1.62 (m, 2H, H-2), 0.87 (s, 9H, (CH₃)₃CSi), 0.01 (s, 6H, 2 x CH₃Si). ¹³C NMR (125 MHz, CDCl₃): δ 147.0 (C-4), 140.9 (ArC), 133.3 (ArCH), 130.8 (C-5), 129.4 (2 x ArCH), 127.7 (2 x ArCH), 61.9 (C-1), 30.8 (C-2), 28.2 (C-3), 26.0 ((CH₃)₃CSi), 18.4 ((CH₃)₃CSi), -5.2 (2 x CH₃Si). HRMS (ESI): m/z calcd for C₁₇H₂₉O₃SSi [M + H]⁺: 341.1607; found: 341.1622.

4.19 Synthesis of 6-(Benzyloxy)-2'-((*S*)-1-(((3*S*,4*R*,*E*)-7-((*tert*-butyldimethyl silyl)oxy)-4-hydroxy-1-phenylhept-1-en-3-yl)amino)but-3-en-1-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**28a**) and 6-(benzyloxy)-2'-((*S*)-1-(((3*R*,4*R*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-1-phenylhept-1-en-3-yl)amino)but-3-en-1-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**28b**)

Aldehyde **27** was prepared from compound **26** (68.0 mg, 0.196 mmol) according to the General Method for Sharpless Asymmetric Dihydroxylation (ADH). The crude ADH product was used without further purification. Alcohol **28a** and **28b** were prepared from the above crude Sharpless ADH product **27**, amine **7** (1.0350 g, 2.5 mmol, 1.0 equiv) and (*E*)-2-phenylvinylboronic acid (0.7400 g, 5.0 mmol, 2.0 equiv) according to the PBM Reaction with α -Hydroxylaldehyde Dimer. The crude

product was purified by column chromatography on silica gel eluting with 0:100 to 2:98 MeOH/CH₂Cl₂ to afford the title compound **28a** (0.7813 g, 43%), as a pale yellow oil and compound **28b** (0.6328 g, 35%), as a pale yellow oil. ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 57:43 ratio for compound **28a** and in a 59:41 ratio for compound **28b**. **28a**: *R_f* = 0.20 (EtOAc:hexanes = 30:70). IR (neat): $\nu_{\max}$ 3491, 3023, 2926, 2226, 1600, 1515, 1248, 1034, 967, 834, 749, 693 cm⁻¹. $[\alpha]_D^{25}$ - 74 (*c* 2.3, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.50* (d, *J* = 8.7 Hz, 0.43H, H-4), 7.44 (d, *J* = 8.7 Hz, 0.57H, H-4), 7.40 (s, 0.57H, H-2), 7.37* (s, 0.43H, H-2), 7.34 – 7.03 (m, 11H, H-3' and ArH), 6.94 (d, *J* = 8.7 Hz, 0.57H, H-5), 6.83* (d, *J* = 8.7 Hz, 0.43H, H-5), 6.61 (s, 0.57H, H-6'), 6.56* (s, 0.43H, H-6'), 6.28* (d, *J* = 16.0 Hz, 0.43H, H-1'''), 6.12 (d, *J* = 15.9 Hz, 0.57H, H-1'''), 5.93 – 5.81 (m, 1H, H-2'''), 5.70 – 5.48 (m, 1H, H-3''), 5.12 – 4.89 (m, 4H, H-4'' and PhCH₂O), 3.92* (s, 1.29H, OCH₃), 3.90* (s, 1.29H, OCH₃), 3.84 (s, 3.42H, OCH₃), 3.65* (t, *J* = 5.8 Hz, 0.86H, H-7'''), 3.62 – 3.56 (m, 1H, H-1''), 3.53 (t, *J* = 6.3 Hz, 1.14H, H-7'''), 3.45 – 3.37 (m, 1H, H-4'''), 3.08 – 3.00 (m, 1H, H-3'''), 2.42 – 2.33 (m, 1.57H, H-2'' and H-2''_A (minor)), 2.32* – 2.23* (m, 0.43H, H-2''_B (minor)), 1.67 – 1.51 (m, 1.14H, H-6'''), 1.50 – 1.35 (m, 2H, H-5''' and H-6'''), 1.23* – 1.10* (m, 0.86H, H-5'''), 0.85 (s, 9H, (CH₃)₃CSi), 0.02* (s, 2.58H, CH₃Si), 0.02 (s, 3.42H, CH₃Si). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 159.6 (C-6), 159.0* (C-6), 149.3* (C-4'), 149.2 (C-4'), 147.6* (C-5'), 147.5 (C-5'), 136.8* (ArC), 136.7 (ArC), 135.8 (C-3'' and ArC), 135.7* (ArC), 135.5* (C-2), 135.2 (C-2), 134.9* (C-3''), 134.2 (C-2'), 133.4* (C-4), 133.3 (C-4), 133.0* (C-1'''), 132.5 (C-1'''), 131.9* (C-1), 131.7 (C-1), 128.7 (1.14 x ArCH), 128.7* (0.86 x ArCH), 128.6 (1.14 x ArCH), 128.6* (0.86 x ArCH), 128.2 (1.14 x ArCH), 128.2* (0.86 x ArCH), 128.0* (C-1'), 127.9 (C-1'), 127.7* (C-2'''), 127.6 (C-2'''), 126.8* (0.86 x ArCH), 126.5* (0.86 x ArCH), 126.5 (2.28 x ArCH), 118.9* (C≡N), 118.9 (C≡N), 117.8* (C-4''), 117.2 (C-4''), 113.3 (C-5), 112.9 (C-5), 112.8 (C-6'), 112.7* (C-6'), 109.3* (C-3'), 109.2 (C-3'), 104.2 (C-3), 71.8 (C-4'''), 71.4* (C-4'''), 70.4 (PhCH₂O), 70.3* (PhCH₂O), 63.5* (C-7'''), 63.4 (C-7'''), 63.3 (C-3'''), 62.2* (C-3'''), 56.1 (OCH₃), 56.1* (OCH₃), 56.0* (OCH₃), 55.4 (C-1''), 55.1* (C-1''), 41.2* (C-2''), 41.0 (C-2''), 30.6 (C-5'''), 30.5* (C-5'''), 29.9 (C-6'''), 29.7* (C-6'''), 26.0 ((CH₃)₃CSi), 18.4 ((CH₃)₃CSi), 18.4* ((CH₃)₃CSi), -5.2 (CH₃Si), -5.2* (CH₃Si). HRMS (ESI): *m/z* calcd for C₄₅H₅₇N₂O₅Si [M + H]⁺: 733.4037; found: 733.4058.

28b: *R_f* = 0.39 (MeOH:CH₂Cl₂ = 5:95). IR (neat): $\nu_{\max}$ 3510, 2930, 2225, 1600, 1510, 1251, 1095, 695 cm⁻¹. $[\alpha]_D^{25}$ + 20 (*c* 0.18, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.50 (d, *J* = 2.0 Hz, 0.59H, H-2), 7.49* (dd, *J* = 8.6, 1.9 Hz, 0.41H, H-4), 7.46 (dd, *J* = 8.6, 2.1 Hz, 0.59H, H-4), 7.40* (d, *J* = 2.1 Hz, 0.41H, H-2), 7.34 – 7.19 (m, 8.36H, ArH), 7.17* (d, *J* = 7.4 Hz, 0.82H, ArH), 7.13 – 7.09 (m, 1.82H, H-3' and ArH), 7.04* (d, *J* = 7.5 Hz, 0.82H, ArH), 6.92 (t, *J* = 8.6 Hz, 1H, H-5), 6.63* (s, 0.41H, H-6'), 6.57 (s, 0.59H, H-6'), 5.91* (d, *J* = 16.0 Hz, 0.41H, H-1'''), 5.86 (d, *J* = 15.9 Hz, 0.59H, H-1'''), 5.67 (dd, *J* = 15.9, 8.6 Hz, 0.59H, H-2'''), 5.59* (dd, *J* = 16.0, 7.7 Hz, 0.41H, H-2'''), 5.63 – 5.45 (m, 1H, H-3''), 5.16* – 5.08* (m, 0.41H, H-

4''), 5.08 – 4.96 (m, 2.59H, H-4'' and PhCH₂O), 3.96* (s, 1.23H, OCH₃), 3.94 (s, 1.77H, OCH₃), 3.87 (s, 1.77H, OCH₃), 3.80* (s, 1.23H, OCH₃), 3.63* (dd, *J* = 9.3, 4.3 Hz, 0.41H, H-1''), 3.60 – 3.39 (m, 2.59H, H-1'' and H-7'''), 3.24 (td, *J* = 8.5, 2.4 Hz, 0.59H, H-4'''), 3.17* (td, *J* = 8.0, 2.5 Hz, 0.41H, H-4'''), 2.61* (t, *J* = 8.0 Hz, 0.41H, H-3'''), 2.53 (t, *J* = 8.5 Hz, 0.59H, H-3'''), 2.46 – 2.23 (m, 1.41H, H-2'' (minor) and H-2''_A), 2.14 (dt, *J* = 14.5, 9.6 Hz, 0.59H, H-2''_B), 1.71 – 1.33 (m, 2H, H-6'''), 1.24 – 0.98 (m, 2H, H-5'''), 0.81 (s, 9H, (CH₃)₃CSi), -0.02* (s, 1.23H, CH₃Si), -0.02 (s, 1.77H, CH₃Si), -0.03 (s, 1.77H, CH₃Si), -0.03* (s, 1.23H, CH₃Si). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 159.8 (C-6), 159.2* (C-6), 149.5 (C-4'), 149.4* (C-4'), 147.7 (C-5'), 147.4* (C-5'), 136.9 (ArC), 136.4 (ArC), 136.0* (C-3''), 135.7* (C-2'), 135.6* (C-2), 135.6 (C-2'), 135.3 (C-3''), 135.2 (C-2), 134.8 (ArC), 134.5* (ArC), 133.4 (C-4), 133.3* (C-4), 132.7 (C-1'''), 132.3 (C-1), 131.6* (C-1'''), 131.5 (C-1), 129.6* (C-2'''), 128.8* (0.82 x ArCH), 128.76 (C-2'''), 128.7 (1.18 x ArCH), 128.68 (1.18 x ArCH), 128.6* (0.82 x ArCH), 128.3 (ArCH), 127.9 (C-2), 127.7 (0.59 x ArCH), 127.68* (C-2), 127.6* (0.41 x ArCH), 126.9 (1.18 x ArCH), 126.5* (0.82 x ArCH), 126.4 (1.18 x ArCH), 126.2* (0.82 x ArCH), 119.0* (C≡N), 118.9 (C≡N), 118.6* (C-4''), 117.9 (C-4''), 113.1 (C-5), 113.0* (C-5), 112.9 (C-6'), 112.7* (C-6'), 109.6 (C-3'), 109.5* (C-3'), 104.4 (C-3), 103.9 (C-3), 73.5* (C-4'''), 73.4 (C-4'''), 70.5 (PhCH₂O), 70.2 (PhCH₂O), 63.4 (C-3'''), 63.3 (C-7'''), 63.2* (C-7'''), 62.5* (C-3'''), 56.1 (OCH₃), 56.08 (OCH₃), 54.1* (C-1''), 53.9 (C-1''), 43.5* (C-2''), 42.2 (C-2''), 30.2 (C-5'''), 30.1* (C-5'''), 29.2 (C-6'''), 29.1* (C-6'''), 26.0 ((CH₃)₃CSi), 18.4 ((CH₃)₃CSi), -5.2 (2 x CH₃Si). HRMS (ESI): *m/z* calcd for C₄₅H₅₇N₂O₅Si [M + H]⁺: 733.4037; found: 733.4042.

4.20 General Method for the Silylation of a Secondary Alcohol

4.20.1 Synthesis of 6-(Benzyloxy)-2'-((*S*)-1-(((3*S*,4*R*,*E*)-4,7-bis((*tert*-butyldimethylsilyl)oxy)-1-phenylhept-1-en-3-yl)amino)but-3-en-1-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**29a**)

To a solution of 1,2-amino alcohol **28a** (0.446 g, 0.608 mmol, 1.0 equiv) in anhydrous CH₂Cl₂ (1.5 mL) was added imidazole (0.331 g, 4.866 mmol, 8.0 equiv) followed by TBSCl (0.550 g, 3.649 mmol, 6.0 equiv) and the reaction mixture was stirred at 50 °C for 20 h. The reaction was quenched with sat. aqueous NH₄Cl solution and extracted with CH₂Cl₂ (2 x 2 mL). The organic layer was washed with water, brine, dried (MgSO₄), and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 15:85 EtOAc/hexanes to afford the title compound **29a** as a pale yellow oil (0.453 g, 88%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 58:42 ratio. *R_f* = 0.28 (EtOAc:hexanes = 20:80). IR (neat): ν_{max} 2928, 2225, 1600, 1514, 1037, 834, 693 cm⁻¹. [α]_D²⁵ + 11 (*c* 1.7, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.38* (dd, *J* = 8.7, 2.1 Hz, 0.42H, H-4), 7.36* (d, *J* = 2.1 Hz, 0.42H, H-2), 7.34 – 7.00 (m, 12.16H, H-2, H-4, H-3' and ArH), 6.84 (d, *J* = 8.6 Hz, 0.58H, H-5), 6.53* (s, 0.42H, H-6'), 6.45 (s, 0.58H, H-6'), 6.43* (d, *J* = 8.7 Hz, 0.42H, H-5), 6.18 (d, *J* = 16.0 Hz, 0.58H, H-1'''), 6.06* (d, *J* = 16.0 Hz, 0.42H, H-1'''), 5.76* (dd, *J* = 16.0, 9.1 Hz, 0.42H, H-2'''),

5.62 (dd, $J = 16.0, 8.7$ Hz, 0.58H, H-2''), 5.60 – 5.50 (m, 1H, H-3''), 5.08 – 4.90 (m, 2.32H, H-4'' and PhCH₂O), 4.89* – 4.76* (m, 1.68H, H-4'' and PhCH₂O), 3.95 (s, 1.74H, OCH₃), 3.91* (s, 1.26H, OCH₃), 3.79* (s, 1.26H, OCH₃), 3.75 (s, 1.74H, OCH₃), 3.70* – 3.66* (m, 0.42H, H-4'''), 3.66 – 3.61 (m, 0.58H, H-4'''), 3.59 – 3.47 (m, 2.58H, H-1'' and H-7'''), 3.43* (dd, $J = 7.7, 5.2$ Hz, 0.42H, H-1''), 3.18 (dd, $J = 8.7, 3.3$ Hz, 0.58H, H-3'''), 3.07* (dd, $J = 9.2, 3.4$ Hz, 0.42H, H-3'''), 2.42 – 2.23 (m, 2H, H-2''), 1.77 (br s, 1H, NH), 1.68 – 1.32 (m, 4H, H-5''' and H-6'''), 0.87 (s, 5.22H, (CH₃)₃CSi), 0.85* (s, 3.78H, (CH₃)₃CSi), 0.85 (s, 5.22H, (CH₃)₃CSi), 0.79* (s, 3.78H, (CH₃)₃CSi), 0.05* (s, 2.52H, CH₃Si), 0.04 (s, 3.48H, CH₃Si), 0.00* (s, 3.48H, CH₃Si), -0.01* (s, 2.52H, CH₃Si). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 159.6 (C-6), 159.0* (C-6), 148.9* (C-4'), 148.8 (C-4'), 147.3 (C-5'), 147.2* (C-5'), 137.5* (ArC), 137.0 (ArC), 136.2 (ArC), 136.1* (ArC), 136.1 (C-3''), 135.9 (C-2'), 135.7* (C-2), 135.4* (C-3''), 135.37* (C-2'), 135.2 (C-2), 133.1 (C-4), 132.9* (C-4), 132.0 (C-1), 131.9* (C-1'''), 131.1 (C-1'''), 130.6 (C-2'''), 129.0* (C-2'''), 128.7 (1.16 x ArCH), 128.66 (1.16 x ArCH), 128.5 * (0.84 x ArCH), 128.45 * (0.84 x ArCH), 128.1 (0.58 x ArCH), 128.0 * (0.42 x ArCH), 127.4 (C-1), 127.3 (ArCH), 126.7 (1.16 x ArCH), 126.5* (0.84 x ArCH), 126.45 (1.16 x ArCH), 126.4* (0.84x ArCH), 119.2* (C $\equiv$ N), 119.0 (C $\equiv$ N), 117.3* (C-4''), 117.2 (C-4''), 113.2* (C-5), 112.8 (C-5), 112.7 (C-6'), 112.4* (C-6'), 110.5 (C-3'), 110.2* (C-3'), 104.0 (C-3), 103.6* (C-3), 76.2 (C-4'''), 75.8* (C-4'''), 70.3 (PhCH₂O), 70.0* (PhCH₂O), 65.0 (C-3''), 63.3 (C-7'''), 63.28* (C-7'''), 61.6* (C-3''), 56.7 (C-1''), 56.1 (OCH₃), 56.0 (OCH₃), 55.97* (OCH₃), 55.9* (OCH₃), 55.2* (C-1''), 41.4 (C-2''), 41.2* (C-2''), 31.1* (C-6'''), 29.5 (C-6'''), 29.3 (C-5'''), 28.8* (C-5'''), 26.1 ((CH₃)₃CSi), 26.0 ((CH₃)₃CSi), 18.4 ((CH₃)₃CSi), 18.2 ((CH₃)₃CSi), -3.9* (CH₃Si), -4.08 (CH₃Si), -4.1 (CH₃Si), -4.3* (CH₃Si), -5.16 (CH₃Si), -5.2* (CH₃Si). HRMS (ESI): m/z calcd for C₅₁H₇₁N₂O₅Si [M + H]⁺: 847.4902; found: 847.4904.

4.20.2 Synthesis of 6-(Benzyloxy)-2'-((S)-1-(((3R,4R,E)-4,7-bis((tert-butyldimethylsilyl)oxy)-1-phenylhept-1-en-3-yl)amino)but-3-en-1-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**29b**)

TBS ether **29b** was prepared from compound **28b** (105.0 mg, 0.143 mmol) according to the General Method for the Silylation of a Secondary Alcohol. Purification by column chromatography on silica gel eluting with 10:90 EtOAc/hexanes gave the title compound **29b** as a pale yellow oil (89.4 mg, 85%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 55:45 ratio. $R_f = 0.56$ (EtOAc:hexanes = 30:70). IR (neat): $\nu_{\max}$ 2926, 2856, 2225, 1600, 1513, 1490, 1361, 1155, 1035, 834, 744, 693 cm⁻¹. $[\alpha]_D^{25} - 36$ (c 0.18, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.43 – 7.09 (m, 11.1H, H-2, H-4 and ArH), 7.00* (d, $J = 7.5$ Hz, 0.9H, ArH), 6.84 (d, $J = 8.5$ Hz, 0.55H, H-5), 6.66* (d, $J = 8.7$ Hz, 0.45H, H-5), 6.63* (s, 0.45H, H-6'), 6.55 (s, 0.55H, H-6'), 5.96 (d, $J = 16.1$ Hz, 0.55H, H-1'''), 5.93 – 5.85 (m, 1H, H-1''' and H-2'''), 5.71* (dd, $J = 16.0, 7.1$ Hz, 0.45H, H-2'''), 5.72* – 5.64* (m, 0.45H, H-3''), 5.63 – 5.50 (m, 0.55H, H-3''), 5.13* (d, $J = 16.1$ Hz, 0.9H, H-4''), 5.10 – 4.95 (m, 2.2H, H-4'' and PhCH₂O), 4.87* (s, 0.90H, PhCH₂O), 3.96* (s, 1.35H, OCH₃), 3.95 (s, 2.65H OCH₃), 3.85 (s, 2.65H OCH₃), 3.77* (s, 1.35H

OCH₃), 3.61* (dd, $J = 9.5, 3.7$ Hz, 0.45H, H-1''), 3.58 – 3.42 (m, 3.55H, H-1'', H-4''' and H-7'''), 2.86 – 2.77 (m, 1H, H-3'''), 2.43 – 2.22 (m, 1.45H, H-2'' (minor) and H-2''_A), 2.12 (dt, $J = 13.9, 9.2$ Hz, 0.55H, H-2''_B), 1.84 (br s, 1H, NH), 1.76 – 1.67 (m, 1.1H, H-5'''), 1.53* – 1.45* (m, 0.9H, H-5'''), 1.43 – 1.27 (m, 2H, H-6'''), 0.89 – 0.85 (m, 13.95H, (CH₃)₃CSi), 0.82* (s, 4.05H, (CH₃)₃CSi), 0.01 (s, 6.3H, CH₃Si), -0.01 (s, 1.65H, CH₃Si), -0.05* (s, 1.35H, CH₃Si), -0.08* (s, 1.35H, CH₃Si), -0.16* (s, 1.35H, CH₃Si). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 159.7 (C-6), 159.1* (C-6), 149.2* (C-4'), 149.1 (C-4'), 147.3 (C-5'), 147.1* (C-5'), 137.5* (ArC), 136.9 (ArC), 136.3 (C-3''), 136.1* (C-2), 135.8 (C-2), 135.7 (ArC), 135.7* (C-3''), 135.4* (C-2'), 135.2 (C-2'), 133.2 (C-4), 133.0* (C-4), 132.7* (C-2'''), 132.1 (C-1), 131.4* (C-1), 131.3 (C-2'''), 130.9 (C-1'''), 130.2* (C-1'''), 128.7* (0.9 x ArCH), 128.7 (1.1 x ArCH), 128.7 (1.1 x ArCH), 128.5* (0.9 x ArCH), 128.1 (0.55 x ArCH), 128.0* (0.45 x ArCH), 127.9 (C-1'), 127.4* (C-1'), 127.3 (0.55 x ArCH), 127.1* (0.45 x ArCH), 126.8 (1.1 x ArCH), 126.2 (2 x ArCH), 126.0* (0.9 x ArCH), 119.2* (C $\equiv$ N), 118.9 (C $\equiv$ N), 118.1* (C-4''), 117.4 (C-4''), 113.1* (C-6'), 112.9* (C-5), 112.8 (C-6'), 112.7 (C-5), 109.8 (C-3'), 109.6* (C-3'), 104.2 (C-3), 103.5* (C-3), 76.4* (C-4'''), 76.2 (C-4'''), 70.4 (PhCH₂O), 69.9* (PhCH₂O), 63.3 (C-7'''), 63.2* (C-7'''), 60.0 (C-3'''), 59.2* (C-3'''), 56.1* (OCH₃), 56.0 (OCH₃), 54.1 (C-1''), 54.0* (C-1''), 44.0* (C-2''), 42.4 (C-2''), 30.2* (C-5'''), 30.2 (C-5'''), 29.0* (C-6'''), 28.9 (C-6'''), 26.1 ((CH₃)₃CSi), 26.1* ((CH₃)₃CSi), 26.0* ((CH₃)₃CSi), 18.4 ((CH₃)₃CSi), 18.2* ((CH₃)₃CSi), 18.2* ((CH₃)₃CSi), -4.1* (CH₃Si), -4.1* (CH₃Si), -4.5 (CH₃Si), -5.2 (CH₃Si). HRMS (ESI): m/z calcd for C₅₁H₇₁N₂O₅Si₂ [M + H]⁺: 847.4902; found: 847.4935.

4.21 General Method for the Selective Deprotection of a Primary TBS Ether

4.21.1 Synthesis of 6-(Benzyloxy)-2'-((S)-1-(((3R,4R,E)-4-((tert-butyldimethylsilyl)oxy)-7-hydroxy-1-phenylhept-1-en-3-yl)amino)but-3-en-1-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**30a**)

A solution of bis-silyl ether **29a** (72.40 g, 0.085 mmol, 1.0 equiv) in anhydrous THF (0.85 mL) in a plastic vial was cooled at 0 °C. HF·py solution, which was prepared from 2.00 g of 70% HF·pyridine, 4 mL of pyridine and 16 mL of THF, (1.46 mL, 1.025 mmol, 12.0 equiv) was added in one portion and the mixture was stirred at 0 °C for 4 h and then quenched by careful addition of sat. aqueous NaHCO₃ solution. The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 0:100 to 4:96 MeOH/CH₂Cl₂ to afford the title compound **30a** as a pale yellow oil (49.4 mg, 79%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 60:40 ratio. $R_f = 0.37$ (MeOH:CH₂Cl₂ = 3:97). IR (neat): $\nu_{\max}$ 3519, 2929, 2224, 1600, 1515, 1250, 1035, 694 cm⁻¹. $[\alpha]_D^{25} + 36$ (c 0.74, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.44* (dd, $J = 8.6, 2.1$ Hz, 0.4H, H-4), 7.38* (d, $J = 2.1$ Hz, 0.4H, H-2), 7.35 (d, $J = 2.1$ Hz, 0.6H, H-2), 7.34 – 7.03 (m, 11.6H, H-4, H-3' and ArH), 6.89 (d, $J = 8.6$ Hz, 0.6H, H-5), 6.55* (s, 0.4H, H-6'), 6.51* (d, $J = 9.1$ Hz, 0.4H, H-5),

6.49 (s, 0.6H, H-6'), 6.22 (d, $J = 16.0$ Hz, 0.6H, H-1'''), 6.09* (d, $J = 16.0$ Hz, 0.4H, H-1'''), 5.71* (dd, $J = 16.0$, 9.1 Hz, 0.4H, H-2'''), 5.64 (dd, $J = 16.0$, 8.6 Hz, 0.6H, H-2'''), 5.60 – 5.48 (m, 1H, H-3''), 5.09 – 5.00 (m, 1.2H, PhCH₂O), 5.00 – 4.79 (m, 2.8H, H-4'' and PhCH₂O), 3.95 (s, 1.8H, OCH₃), 3.92* (s, 1.2H, OCH₃), 3.81* (s, 1.2H, OCH₃), 3.77 (s, 1.8H, OCH₃), 3.65 – 3.52 (m, 3.4H, H-1'', H-4''' and H-7'''), 3.45 (t, $J = 6.5$ Hz, 0.6H, H-1''), 3.22 (dd, $J = 8.8$, 3.4 Hz, 0.6H, H-3'''), 3.11* (dd, $J = 9.1$, 4.2 Hz, 0.4H, H-3'''), 2.46 – 2.25 (m, 2H, H-2''), 1.83 (s, 2H, OH and NH), 1.71 – 1.39 (m, 4H, H-5''' and H-6'''), 0.88 (s, 5.4H, (CH₃)₃CSi), 0.80* (s, 3.6H, (CH₃)₃CSi), 0.06 (s, 1.8H, CH₃Si), 0.04* (s, 1.2H, CH₃Si), 0.01 (s, 1.8H, CH₃Si), -0.01* (s, 1.2H, CH₃Si). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 159.6 (C-6), 159.0* (C-6), 149.0* (C-4'), 148.9 (C-4'), 147.3 (C-5'), 137.3* (ArC), 136.9 (ArC), 136.1* (ArC), 136.0 (C-3''), 135.8 (ArC), 135.7* (C-3''), 135.67 (C-2'), 135.5 (C-2), 135.2* (C-2), 135.1* (C-2'), 133.1 (C-4), 132.9* (C-4), 132.1* (C-1'''), 132.0 (C-1), 131.9* (C-1), 131.3 (C-1'''), 130.4 (C-2'''), 129.3 (C-2'''), 128.7* (0.8 x ArCH), 128.69 (1.2 x ArCH), 128.6 (1.2 x ArCH), 128.5* (0.8 x ArCH), 128.1 (0.6 x ArCH), 128.09* (0.4 x ArCH), 127.6 (C-1'), 127.5* (C-1'), 127.4 (ArCH), 126.7 (1.2 x ArCH), 126.5* (1.6 x ArCH), 126.4 (1.2 x ArCH), 119.2 (C $\equiv$ N), 119.16* (C $\equiv$ N), 117.4* (C-4''), 117.3 (C-4''), 113.2* (C-5), 112.9 (C-5), 112.7* (C-6'), 112.4 (C-6'), 110.4 (C-3'), 110.3* (C-3'), 103.8 (C-3), 103.7* (C-3), 75.9 (C-4'''), 75.4* (C-4'''), 70.3 (PhCH₂O), 70.1* (PhCH₂O), 64.7 (C-3'''), 63.1 (C-7'''), 62.9* (C-7'''), 61.9* (C-3'''), 56.6 (C-1''), 56.1 (OCH₃), 56.03 (OCH₃), 56.0* (OCH₃), 55.96* (OCH₃), 55.4* (C-1''), 41.1 (C-2''), 40.8* (C-2''), 30.8* (C-6'''), 29.4 (C-6'''), 29.2 (C-5'''), 28.4* (C-5'''), 26.1 ((CH₃)₃CSi), 26.0* ((CH₃)₃CSi), 18.2 ((CH₃)₃CSi), 18.18* ((CH₃)₃CSi), -4.0* (CH₃Si), -4.1 (CH₃Si), -4.2* (CH₃Si). HRMS (ESI): m/z calcd for C₄₅H₅₇N₂O₅Si [M + H]⁺: 733.4037; found: 733.4057.

4.21.2 Synthesis of 6-(Benzyloxy)-2'-((S)-1-(((3S,4R,E)-4-((tert-butyldimethylsilyl)oxy)-7-hydroxy-1-phenylhept-1-en-3-yl)amino)but-3-en-1-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**30b**)

Diol **30b** was prepared from compound **29b** (55.9 mg, 0.066 mmol) according to General Method for the Selective Deprotection of a Primary TBS Ether. The crude product was purified by column chromatography on silica gel eluting with 0:100 to 1:99 MeOH/CH₂Cl₂ to afford the title compound **30b** as a pale yellow oil (37.1 mg, 77%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 54:46 ratio. $R_f = 0.37$ (MeOH:CH₂Cl₂ = 3:97). IR (neat): $\nu_{\max}$ 3519, 2930, 2224, 1599, 1513, 1490, 1248, 1153, 1035, 734, 745, 694 cm⁻¹. $[\alpha]_D^{25} - 64$ (c 0.51, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.42 – 7.38 (m, 1.46H, H-2 and H-4), 7.36 (dd, $J = 8.6$, 2.1 Hz, 0.54H, H-4), 7.34 – 7.19 (m, 8.16H, ArH), 7.18 – 7.11 (m, 1.92H, H-3' and ArH), 7.02* (d, $J = 6.9$ Hz, 0.92H, ArH), 6.86 (d, $J = 8.6$ Hz, 0.54H, H-5), 6.71* (d, $J = 9.2$ Hz, 0.46H, H-5), 6.65* (s, 0.46H, H-6'), 6.57 (s, 0.54H, H-6'), 5.95 (d, $J = 16.1$ Hz, 0.54H, H-1'''), 5.92 – 5.85 (m, 1H, H-1''' and H-2'''), 5.72* (dd, $J = 16.0$, 7.1 Hz, 0.46H, H-2'''), 5.72 – 5.49 (m, 1H, H-3''), 5.18* – 5.09* (m, 0.92H, H-4''), 5.08 – 5.02 (m, 1.08H, PhCH₂O), 5.02 – 4.96 (m, 1.08H, H-4''), 4.95* – 4.86* (m, 0.92H, PhCH₂O), 3.98* (s, 1.38H, OCH₃), 3.97 (s, 1.62H, OCH₃), 3.86 (s,

1.62H, OCH₃), 3.79* (s, 1.38H, OCH₃), 3.62 – 3.54 (m, 2H, H-1'' (minor), H-4''' (minor) and H-7'''), 3.53 – 3.42 (m, 2H, H-1'', H-4''' and H-7''' (minor)), 2.84 (dd, *J* = 7.3, 3.8 Hz, 0.54H, H-3'''), 2.81* (dd, *J* = 6.9, 2.9 Hz, 0.46H, H-3'''), 2.45 – 2.25 (m, 1.54H, H-2'' and H-2''_A), 2.17* (dt, *J* = 14.0, 9.3 Hz, 0.46H, H-2''_B), 1.55 – 1.18 (m, 4H, H-5''' and H-6'''), 0.87 (s, 4.86H, (CH₃)₃CSi), 0.83* (s, 4.14H, (CH₃)₃CSi), -0.00 (s, 1.62H, CH₃Si), -0.04* (s, 1.38H, CH₃Si), -0.08 (s, 1.62H, CH₃Si), -0.16* (s, 1.38H, CH₃Si). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 159.7 (C-6), 159.1* (C-6), 149.2 (C-4'), 149.15* (C-4'), 147.5 (C-5'), 147.2* (C-5'), 137.4* (ArC), 136.9 (ArC), 136.3 (C-3''), 136.1* (C-2'), 135.8 (C-2'), 135.7 (ArC), 135.67* (ArC), 135.6 (C-3'), 135.4* (C-2), 135.3 (C-2), 133.3 (C-5), 133.1* (C-5), 132.4* (C-2'''), 132.2 (C-1), 131.3* (C-1), 131.1 (C-4'''), 131.0* (C-4'''), 130.2 (C-2'''), 128.8* (0.92 x ArCH), 128.7 (1.08 x ArCH), 128.69 (1.08 x ArCH), 128.5* (0.92 x ArCH), 128.2 (0.54 x ArCH), 128.1* (0.46 x ArCH), 128.0 (C-1'), 127.8* (C-1'), 127.4 (0.54 x ArCH), 127.2* (0.46 x ArCH), 126.8 (1.08 x ArCH), 126.4* (0.92 x ArCH), 126.3 (1.08 x ArCH), 126.1* (0.92 x ArCH), 119.2* (C≡N), 119.0 (C≡N), 118.2* (C-4''), 117.5 (C-4''), 113.1* (C-6'), 112.8 (C-6'), 112.79 (C-5), 110.2* (C-3'), 110.1 (C-3'), 104.2 (C-3), 103.6* (C-3), 76.2* (C-4'''), 75.9 (C-4'''), 70.4 (PhCH₂O), 69.9* (PhCH₂O), 63.2 (C-7'''), 63.1* (C-7'''), 60.3 (C-3'''), 59.1* (C-3'''), 56.3* (OCH₃), 56.2 (OCH₃), 56.1 (OCH₃), 56.05* (OCH₃), 54.4 (C-1''), 54.1* (C-1''), 43.8* (C-2''), 42.3 (C-2''), 30.4* (C-6'''), 30.2 (C-6'''), 28.9* (C-5'''), 28.8 (C-5'''), 26.03 ((CH₃)₃CSi), 26.0* ((CH₃)₃CSi), 18.2 ((CH₃)₃CSi), 18.16* ((CH₃)₃CSi), -4.08 (CH₃Si), -4.1* (CH₃Si), -4.48* (CH₃Si), -4.5 (CH₃Si). HRMS (ESI): *m/z* calcd for C₄₅H₅₇N₂O₅Si [M + H]⁺: 733.4037; found: 733.4037.

4.22 Synthesis of 6-(Benzyloxy)-2'-((*S*)-1-((2*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-((*E*)-styryl)piperidin-1-yl)but-3-en-1-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**31a**)

Piperidine **31a** was prepared from compound **30a** (0.655 g, 0.89 mmol) according to General Method for Mesylation-Cyclization. Purification by column chromatography on silica gel eluting with 15:85 EtOAc/hexanes gave the title compound **31a** as a pale yellow oil (0.573 g, 90%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 88:12 ratio. *R_f* = 0.29 (EtOAc:hexanes = 20:80). IR (neat): ν_{max} 2925, 2852, 2223, 1599, 1516, 1491, 1094, 835, 747, 694 cm⁻¹. [*α*]_D²⁵ - 29 (*c* 2.4, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.68 (dd, *J* = 8.5, 2.2 Hz, 1H, H-4), 7.55 (d, *J* = 2.2 Hz, 1H, H-2), 7.43 – 7.10 (m, 8H, ArH), 7.09* (s, 0.12H, H-5), 6.96* (s, 0.12H, H-3'), 6.85 (s, 0.88H, H-3'), 6.83 – 6.78 (m, 2H, ArH), 6.81 (d, *J* = 8.7 Hz, 0.88H, H-5), 6.66* (s, 0.12H, H-6'), 6.61 (s, 0.88H, H-6'), 6.44 (d, *J* = 15.9 Hz, 1H, H-2'''), 5.66* – 5.53* (m, 0.12H, H-3''), 5.32 – 5.21 (m, 0.88H, H-3''), 5.16* (d, *J* = 12.4 Hz, 0.12H, PhCH_AH_BO), 5.08* (d, *J* = 12.4 Hz, 0.12H, PhCH_AH_BO), 4.92* (t, *J* = 17.0, 13.6 Hz, 0.12H, H-4''_A), 4.85 (d, *J* = 17.0 Hz, 0.88H, H-4''_A), 4.73* (dd, *J* = 15.9, 9.4 Hz, 0.12H, H-4''_B), 4.57 (d, *J* = 12.4 Hz, 0.88H, PhCH₂O), 4.53 (d, *J* = 10.2 Hz, 0.88H, H-4''_B), 4.45 (d, *J* = 12.4 Hz, 0.88H, PhCH₂O), 4.48 – 4.41 (m, 1H, H-1'''), 3.92* (s, 0.36H, OCH₃), 3.91 (s, 2.64H, OCH₃), 3.84 (s, 2.64H,

OCH₃), 3.80* (s, 0.36H, OCH₃), 3.78 (dd, $J = 11.5, 3.4$ Hz, 1H, H-1''), 3.15 – 3.06 (m, 1.76H, H-3'''), 2.95* – 2.88* (m, 0.24H, H-3'''), 2.77 (t, $J = 8.7$ Hz, 1H, H-2'''), 2.63 – 2.56 (m, 1H, H-6'''_A), 2.56 – 2.49 (m, 1H, H-2''_A), 2.48 – 2.38 (m, 1H, H-2''_B), 2.06 – 2.00 (m, 1H, H-6'''_B), 1.95 – 1.90 (m, 1H, H-4'''_A), 1.54 – 1.49 (m, 1H, H-5'''_A), 1.27 – 1.19 (m, 2H, H-4'''_B and H-5'''_B), 0.75 (s, 9H, (CH₃)₃CSi), 0.01 (s, 2.64H, CH₃Si), -0.09* (s, 0.36H, CH₃Si), -0.10 (s, 2.64H, CH₃Si), -0.20* (s, 0.36H, CH₃Si). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 160.6* (C-6), 159.1 (C-6), 147.6* (C-4'), 147.4 (C-4'), 147.3 (C-5'), 147.1* (C-5'), 137.8 (C-2), 137.4 (ArC), 136.8* (ArC), 136.2 (C-3''), 136.1* (ArC), 135.9 (ArC), 133.5 9 (C-2'''), 133.3* 9 (C-2'''), 132.5 (C-1), 132.4 (C-4), 131.7* (C-1'), 131.4 (C-1'), 131.3 (C-2'), 130.9 (C-1'''), 130.4* (C-2'), 128.9* (0.24 x ArCH), 128.7* (0.24 x ArCH), 128.4 (3.52 x ArCH), 128.1* (0.12 x ArCH), 127.8 (0.88 x ArCH), 127.5* (0.12 x ArCH), 127.4 (0.88 x ArCH), 126.8 (1.76 x ArCH), 126.5 (2 x ArCH), 126.3* (0.24 x ArCH), 119.4 (C $\equiv$ N), 119.1* (C $\equiv$ N), 116.8* (C-4''), 116.1 (C-4''), 114.2* (C-6'), 113.8 (C-6'), 113.1 (C-5), 112.6* (C-5), 112.5* (C-3'), 112.2 (C-3'), 104.0* (C-3), 103.5 (C-3), 72.4 (C-3'''), 72.3* (C-3'''), 71.3* (C-2'''), 71.1 (C-2'''), 70.1* (PhCH₂O), 69.9 (PhCH₂O), 59.6 (C-1''), 56.2 (OCH₃), 56.0 (OCH₃), 44.6* (C-6'''), 44.3* (C-6'''), 34.8 (C-4'''), 34.4* (C-4'''), 27.0* (C-2''), 26.1 (C-2''), 25.9 ((CH₃)₃CSi), 24.1 (C-5'''), 23.4* (C-5'''), 18.1* ((CH₃)₃CSi), 18.0 ((CH₃)₃CSi), -4.3 (CH₃Si), -4.4 (CH₃Si). HRMS (ESI): m/z calcd for C₄₅H₅₅N₂O₄Si [M + H]⁺: 715.3931; found: 715.3958.

4.23 Synthesis of 6-(Benzyloxy)-2'-((S)-1-((2R,3R)-3-((tert-butyldimethylsilyl)oxy)-2-((E)-styryl)piperidin-1-yl)but-3-en-1-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**31b**)

Piperidine **31b** was prepared from compound **30b** (0.489 g, 0.667 mmol) according to General Method for Mesylation-Cyclization. Purification by column chromatography on silica gel eluting with 10:90 EtOAc/hexanes gave the title compound **31b** as a pale yellow oil (0.410 g, 86%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 51:49 ratio. $R_f = 0.50$ (EtOAc:hexanes = 30:70). IR (neat): $\nu_{\max}$ 2925, 2857, 2218, 1599, 1508, 1489, 1251, 1023, 834, 773 cm⁻¹. $[\alpha]_D^{25} - 46$ (c 0.23, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.54 – 7.41 (m, 2H, H-2 and H-4), 7.35 – 7.09 (m, 9.51H, H-3' and ArH), 7.02 (s, 0.51H, H-3'), 6.97* (d, $J = 7.2$ Hz, 0.98H, ArH), 6.92* (d, $J = 8.5$ Hz, 0.49H, H-5), 6.70* (s, 0.49H, H-6'), 6.64 (d, $J = 8.5$ Hz, 0.51H, H-5), 6.56 (s, 0.51H, H-6'), 6.29* (dd, $J = 16.0, 8.4$ Hz, 0.49H, H-1'''), 6.19 – 6.03 (m, 1.51H, H-1''' and H-2'''), 5.82 – 5.70 (m, 0.51H, H-3''), 5.70* – 5.60* (m, 0.49H, H-3''), 5.13 – 4.94 (m, 2H, H-4'' and PhCH₂O), 4.82* (d, $J = 12.2$ Hz, 0.49H, PhCH_AH_BO), 4.79 – 4.62 (m, 1.51H, H-4'' and PhCH_AH_BO), 3.93* (s, 1.47H, OCH₃), 3.84 (s, 3.06H, OCH₃), 3.81* – 3.76* (m, 0.49H, H-1''), 3.72* (s, 1.47H, OCH₃), 3.72 – 3.67 (m, 0.51H, H-1''), 3.67 – 3.60 (m, 1H, H-3'''), 3.20 – 3.17 (m, 0.51H, H-2'''), 3.17* – 3.11* (m, 0.49H, H-2'''), 2.81* – 2.73* (m, 0.49H, H-6'''_A), 2.62 – 2.36 (m, 3.51H, H-2'', H-6''' (major) and H-6'''_B), 1.74 – 1.31 (m, 4H, H-5''' and H-6'''), 0.80 (s, 4.59H, (CH₃)₃CSi), 0.75* (s, 4.41H, (CH₃)₃CSi), -0.03* (s, 1.47H, CH₃Si), -0.08 (s, 1.53H, CH₃Si), -0.11 (s, 1.53H, CH₃Si), -0.18* (s, 1.47H, CH₃Si). ¹³C NMR (125 MHz, the asterisk* denotes the

signal of the minor rotamer, CDCl₃): δ 159.3* (C-6), 159.2 (C-6), 148.7* (C-4'), 148.0 (C-4'), 147.1* (C-5'), 146.8 (C-5'), 138.2 (ArC), 137.6* (ArC), 136.4* (C-3''), 136.1 (ArC), 136.0 (C-3''), 135.7 (C-2), 134.2* (C-2'), 134.0 (C-2'''), 133.7 (C-2'), 133.3* (C-2'''), 133.0* (C-4), 132.8 (C-4), 132.6 (C-1), 130.9* (C-1), 128.7* (0.98 x ArCH), 128.68 (2.04 x ArCH), 128.3* (0.98 x ArCH), 128.1 (0.51 x ArCH), 128.0* (0.49 x ArCH), 127.3 (C-1'), 127.2 (0.51 x ArCH), 127.0* (0.49 x ArCH), 126.8* (0.98 x ArCH), 126.7 (C-1'''), 126.3* (0.98 x ArCH), 126.26 (1.02 x ArCH), 126.2 (1.02 x ArCH), 124.8 (C-1'''), 119.3* (C $\equiv$ N), 118.9 (C $\equiv$ N), 117.3* (C-4''), 116.0 (C-4''), 113.8 (C-6'), 113.6* (C-6'), 113.0* (C-5), 112.8 (C-5), 111.3 (C-3'), 110.8* (C-3'), 104.2 (C-3), 103.2* (C-3), 71.8 (C-3'''), 71.6* (C-3'''), 70.4 (PhCH₂O), 69.8* (PhCH₂O), 65.3 (C-2'''), 62.9* (C-2'''), 61.4 (C-1''), 59.9* (C-1''), 56.1* (OCH₃), 56.0* (OCH₃), 55.9 (OCH₃), 43.3* (C-6'''), 42.2 (C-6'''), 39.7 (C-2''), 36.4* (C-2''), 30.4* (C-4'''), 29.7 (C-4'''), 26.0 ((CH₃)₃CSi), 24.5 (C-5'''), 23.9* (C-5'''), 18.2 ((CH₃)₃CSi), -4.4* (CH₃Si), -4.48 (CH₃Si), -4.5 (CH₃Si), -4.7* (CH₃Si). HRMS (ESI): m/z calculated for C₄₅H₅₅N₂O₄Si [M + H]⁺: 715.3944; found: 715.3940.

4.24 Synthesis of 6-(Benzyloxy)-2'-((1*R*,6*S*,9*aS*)-1-((*tert*-butyldimethylsilyl)oxy)-1,3,4,6,7,9*a*-hexahydro-2*H*-quinolizin-6-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**32a**)

Quinolizidine **32a** was prepared from compound **31a** (71.5 mg, 0.1 mmol) according to General Method for Ring-Closing Metathesis, using Grubbs' II Ru catalyst (8.5 mg, 0.001 mmol, 0.1 equiv). Purification by column chromatography on silica gel eluting with 20:80 EtOAc/hexanes gave the title compound **32a** as a light brown oil (43.0 mg, 70%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 76:24 ratio. R_f = 0.22 (EtOAc:hexanes = 30:70). IR (neat): $\nu_{\max}$ 2923, 2853, 2229, 1600, 1515, 1463, 1252, 836, 775, 696 cm⁻¹. [α]_D²⁵ + 7.7 (*c* 2.2, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.61* (d, J = 8.9 Hz, 0.24H, H-4), 7.58 (dd, J = 8.5, 2.2 Hz, 0.76H, H-4), 7.53 (d, J = 2.2 Hz, 0.76H, H-2), 7.34 – 7.25 (m, 4.24H, H-2 and ArH), 7.22* (d, J = 7.3 Hz, 0.48H, ArH), 7.17 (d, J = 6.1 Hz, 1.52H, ArH), 7.14* (s, 0.24H, H-3'), 7.11 (s, 0.76H, H-3'), 7.08* (d, J = 8.6 Hz, 0.24H, H-5), 6.97 (d, J = 8.6 Hz, 0.76H, H-5), 6.70* (s, 0.24H, H-6'), 6.57 (s, 0.76H, H-6'), 6.11 (d, J = 10.0 Hz, 1H, H-9''), 5.96* (d, J = 9.7 Hz, 0.24H, H-8''), 5.86 (d, J = 10.0 Hz, 0.76H, H-8''), 5.17* (d, J = 12.2 Hz, 0.24H, PhCH_AH_BO (minor)), 5.12 – 5.01 (m, 1.76H, PhCH_AH_BO (minor) and PhCH₂O), 4.03* (d, J = 6.1 Hz, 0.24H, H-6''), 3.88 (s, 2.28H, OCH₃), 3.85* (s, 0.72H, OCH₃), 3.83 (s, 2.28H, OCH₃), 3.82 – 3.78 (m, 0.76H, H-6''), 3.78* (s, 0.72H, OCH₃), 3.34 – 3.20 (m, 1H, H-1''), 2.80 – 2.55 (m, 2H, H-7''_A (minor), H-7''_A and H-9a''), 2.27* (d, J = 17.1 Hz, 0.24H, H-7''_B (minor)), 2.10 – 1.91 (m, 1.76H, H-4''_A and H-7''_B), 1.85 (dd, J = 12.8, 3.8 Hz, 1H, H-2''_A), 1.78 (td, J = 11.8, 3.0 Hz, 1H, H-4''_B), 1.50 – 1.29 (m, 2H, H-3''), 1.20 – 1.08 (m, 1H, H-2''_B), 0.88 (s, 9H, (CH₃)₃CSi), 0.05 (s, 2.28H, CH₃Si), 0.03 (s, 2.28H, CH₃Si), 0.01* (s, 0.72H, CH₃Si), 0.00* (s, 0.72H, CH₃Si). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 159.5* (C-6), 159.4 (C-6), 148.9 (C-4'), 147.5 (C-5'), 146.9* (C-5'), 135.9* (C-2), 135.89* (ArC), 135.8 (ArC), 135.7 (C-2), 133.2 (C-4), 133.17 (C-1), 132.6 (C-2'),

132.3* (C-1), 131.8* (C-2'), 128.8* (0.48 x ArCH), 128.77 (1.52 x ArCH), 128.6 (C-1'), 128.5* (C-1'), 128.3 (0.76 x ArCH), 128.2* (0.24 x ArCH), 127.6* (C-9''), 127.4 (C-9''), 127.0 (1.52 x ArCH), 126.6* (0.48 x ArCH), 125.3 (C-8''), 124.8* (C-8''), 119.2 (C≡N), 119.1* (C≡N), 113.2* (C-5), 113.1* (C-6'), 112.9 (C-5), 112.7 (C-6'), 110.6* (C-3'), 110.4 (C-3'), 104.5 (C-3), 104.0* (C-3), 72.6 (C-1''), 72.4* (C-1''), 70.8 (PhCH₂O), 70.3* (PhCH₂O), 61.7* (C-9a''), 61.3 (C-9a''), 56.3 (C-6''), 56.0 (OCH₃), 55.95* (OCH₃), 55.9 (OCH₃), 54.8* (C-6''), 51.4 (C-4''), 50.7* (C-4''), 35.1* (C-2''), 34.9 (C-2''), 32.7* (C-7''), 32.0 (C-7''), 26.0 ((CH₃)₃CSi), 23.7 (C-3''), 23.3* (C-3''), 18.2 ((CH₃)₃CSi), -3.8 (CH₃Si), -3.9* (CH₃Si), -4.5* (CH₃Si), -4.6 (CH₃Si). HRMS (ESI): *m/z* calcd for C₃₇H₄₇N₂O₄Si [M + H]⁺: 611.3305; found: 611.3324.

4.25 Synthesis of 6-(Benzyloxy)-2'-((1*R*,6*S*,9*aR*)-1-((*tert*-butyldimethylsilyl)oxy)-1,3,4,6,7,9*a*-hexahydro-2*H*-quinolizin-6-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**32b**)

Quinolizidine **32b** was prepared from compound **31b** (190.2 mg, 0.2660 mmol) according to General Method for Ring-Closing Metathesis, using Grubbs' II Ru catalyst (33.9 mg, 0.0399 mmol, 0.15 equiv). The crude product was purified by column chromatography on silica gel eluting with 2:98 MeOH/CH₂Cl₂ to afford the title compound **32b** as a light brown oil (109.2 mg, 67%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 56:44 ratio. *R_f* = 0.27 (EtOAc:hexanes = 20:80). IR (neat): *v*_{max} 2925, 2853, 2224, 1601, 1516, 1252, 1034, 834, 772, 735, 695 cm⁻¹. [*α*]_D²⁵ + 33 (*c* 0.17, CHCl₃) ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.59* (d, *J* = 8.6 Hz, 0.44H, H-4), 7.56 (d, *J* = 8.6 Hz, 0.56H, H-4), 7.42* (s, 0.44H, H-2), 7.38 (s, 0.56H, H-2), 7.32 – 7.15 (m, 6H, H-3 and ArH), 7.02* (d, *J* = 8.6 Hz, 0.44H, H-5), 6.99 (d, *J* = 8.6 Hz, 0.56H, H-5), 6.57 (s, 0.56H, H-6'), 6.55 (s, 0.44H, H-6'), 5.69 – 5.59 (m, 1H, H-8''), 5.39 (d, *J* = 10.2 Hz, 0.56H, H-9''), 5.35* (d, *J* = 10.3 Hz, 0.44H, H-9''), 5.18 – 5.05 (m, 2H, PhCH₂O), 3.91 (s, 1.68H, OCH₃), 3.90* (s, 1.32H, OCH₃), 3.84 (s, 1.68H, OCH₃), 3.83* (s, 1.32H, OCH₃), 3.79 – 3.71 (m, 1H, H-1''), 3.18 (s, 0.56H, H-6''), 3.04* (s, 0.44H, H-6''), 2.74 – 2.57 (m, 3H, H-4'' and H-9a''), 2.35* – 2.16* (m, 0.88H, H-7''), 2.04 – 1.89 (m, 1.12H, H-7''), 1.85 – 1.58 (m, 2H, H-2'' and H-3''), 1.49* – 1.36* (m, 0.88H, H-2''), 1.35 – 1.21 (m, 1.22H, H-3''), 0.91 (s, 9H, (CH₃)₃CSi), 0.03* (s, 1.32H, CH₃Si), 0.02 (s, 1.68H, CH₃Si), 0.01 (s, 3H, CH₃Si). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 159.8* (C-6), 159.3 (C-6), 149.5* (C-4'), 149.4 (C-4'), 147.3* (C-5'), 147.1 (C-5'), 136.0* (ArC), 135.96 (ArC), 135.9 (C-2), 135.2* (C-2), 133.3* (C-4), 133.1 (C-4), 132.4 (C-2'), 132.2 (C-1), 128.8 (C-9'' and 1.12 x ArCH), 128.7* (0.88 x ArCH), 128.2 (0.56 x ArCH), 128.1* (0.44 x ArCH), 127.6 (C-1'), 126.8* (0.88 x ArCH), 126.7 (1.12 x ArCH), 125.3 (C-8''), 124.9* (C-8''), 119.4 (C≡N), 119.3* (C≡N), 113.0 (C-5), 112.8* (C-5), 112.3 (C-6'), 110.1 (C-3'), 109.7* (C-3'), 104.0* (C-3), 103.9 (C-3), 70.4 (PhCH₂O), 70.3* (PhCH₂O), 69.8 (C-1''), 69.76* (C-1''), 65.9 (C-9a''), 59.7 (C-6''), 59.4* (C-6''), 56.1 (OCH₃), 56.0 (OCH₃), 55.9* (OCH₃), 55.8* (OCH₃), 52.2 (C-4''), 35.9 (C-7''), 33.4* (C-2''), 33.0 (C-2''), 25.94 ((CH₃)₃CSi), 25.9* ((CH₃)₃CSi), 21.8 (C-3''), 21.5* (C-3''), 18.32 ((CH₃)₃CSi), 18.3 ((CH₃)₃CSi), -

4.2* (CH₃Si), -4.5 (CH₃Si). HRMS (ESI): *m/z* calcd for C₃₇H₄₇N₂O₄Si [M + H]⁺: 611.3305; found: 611.3311.

4.26 General Method for Reduction of a Nitrile

4.26.1 Synthesis of 6-(Benzyloxy)-2'-((1*R*,6*S*,9*aS*)-1-((*tert*-butyldimethylsilyl)oxy)-1,3,4,6,7,9*a*-hexahydro-2*H*-quinolizin-6-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbaldehyde (**33a**)

To a solution of carbonitrile **32a** (91.6 mg, 0.15 mmol, 1.0 equiv) in toluene (0.54 mL) at -78 °C was added DIBAL-H (0.3 mL, 0.30 mmol, 1.0 M in toluene, 2.0 equiv). After stirring for 1 h, the reaction was quenched with water at -78 °C and allowed to reach room temperature and stirred for another 30 min. The reaction mixture was extracted with EtOAc (3 x 2 mL). The combined organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 25:75 EtOAc/CH₂Cl₂ to afford the title compound **33a** as a pale yellow oil (77.9 mg, 83%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 77:23 ratio. *R_f* = 0.37 (EtOAc:hexanes = 40:60). IR (neat): *v*_{max} 2933, 2852, 1692, 1599, 1515, 1251, 1115, 835, 773 cm⁻¹. [*α*]_D²⁵ + 8.6 (*c* 0.34, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 9.93 (s, 0.77H, CHO), 9.90* (s, 0.23H, CHO), 7.86* (dd, *J* = 8.5, 2.2 Hz, 0.23H, H-4), 7.82 (dd, *J* = 8.5, 2.2 Hz, 0.77H, H-4), 7.79 (d, *J* = 2.2 Hz, 0.77H, H-2), 7.57* (d, *J* = 2.2 Hz, 0.23H, H-2), 7.36 – 7.16 (m, 5.23H, H-5 and ArH), 7.15* (s, 0.23H, H-3'), 7.11 (s, 0.77H, H-3'), 7.04 (d, *J* = 8.5 Hz, 0.77H, H-5), 6.75* (s, 0.23H, H-6'), 6.64 (s, 0.77H, H-6'), 6.10 (d, *J* = 9.8 Hz, 1H, H-9''), 5.98 – 5.93* (m, 0.23H, H-8''), 5.89 – 5.84 (m, 0.77H, H-8''), 5.22* (d, *J* = 12.3 Hz, 0.23H, PhCH_AH_BO (minor)), 5.17 – 5.03 (m, 1.77H, PhCH₂O and PhCH_AH_BO (minor)), 4.12* – 4.07* (m, 0.23H, H-6''), 3.88 (s, 2.31H, OCH₃), 3.86* (s, 0.69H, OCH₃), 3.83 (s, 3.08H, H-6'' and OCH₃), 3.78* (s, 0.69H, OCH₃), 3.31 – 3.18 (m, 1H, H-1''), 2.78 – 2.55 (m, 2H, H-7''_A (minor), H-7''_A, H-9a''), 2.35* – 2.24* (m, 0.23H, H-7''_B (minor)), 2.16 – 1.91 (m, 1.77H, H-4''_A and H-7''_B), 1.88 – 1.72 (m, 2H, H-2''_A and H-4''_B), 1.42 – 1.29 (m, 2H, H-3''), 1.21 – 1.07 (m, 1H, H-2''_B), 0.88 (s, 6.93H, (CH₃)₃CSi), 0.87* (s, 2.07H, (CH₃)₃CSi), 0.05 (s, 2.31H, CH₃Si), 0.03* (s, 0.69H, CH₃Si), 0.02 (s, 2.31H, CH₃Si), -0.00* (s, 0.69H, CH₃Si). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 191.0 (C=O), 190.8* (C=O), 161.1* (C-6), 161.06 (C-6), 148.7 (C-4'), 147.5 (C-5'), 146.9* (C-5'), 136.2* (ArC), 136.1 (ArC), 134.0* (C-2), 133.3 (C-2), 132.6 (C-1), 132.5 (C-2'), 132.3* (C-1), 131.7 (C-4), 131.3* (C-4), 130.1 (C-3), 129.6 (C-1'), 129.5* (C-1'), 128.8 (1.54 x ArCH), 128.7* (0.46 x ArCH), 128.2 (C-1), 127.6* (C-9''), 127.4 (C-9''), 126.9 (1.54 x ArCH), 126.6* (0.46 x ArCH), 125.4 (C-8''), 124.9* (C-8''), 113.3* (C-6'), 112.9 (C-6'), 112.6* (C-5), 112.3 (C-5), 110.6* (C-3'), 110.3 (C-3'), 72.6 (C-1''), 72.4* (C-1''), 70.8 (PhCH₂O), 70.3 (PhCH₂O), 61.7* (C-9a''), 61.4 (C-9a''), 56.2 (C-6''), 56.0 (OCH₃), 55.9 (OCH₃), 54.7* (C-6''), 51.3 (C-4''), 50.7* (C-4''), 35.1* (C-2''), 34.9 (C-2''), 32.8* (C-7''), 32.1 (C-7''), 26.0

((CH₃)₃CSi), 23.7 (C-3''), 23.3* (C-3''), 18.2 ((CH₃)₃CSi), -3.8 (CH₃Si), -3.9* (CH₃Si), -4.5 (CH₃Si). HRMS (ESI): *m/z* calcd for C₃₇H₄₈NO₅Si [M + H]⁺: 614.3302; found: 614.3313.

4.26.2 Synthesis of 6-(Benzyloxy)-2'-((1*R*,6*S*,9*aR*)-1-((*tert*-butyldimethylsilyl)oxy)-1,3,4,6,7,9*a*-hexahydro-2*H*-quinolizin-6-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbaldehyde (**33b**)

Aldehyde **33b** was prepared from compound **32b** (46.0 mg, 0.075 mmol) according to the General Method for Reduction of a Nitrile. The crude product was purified by column chromatography on silica gel eluting with 15:85 EtOAc/CH₂Cl₂ to afford the title compound **33b** as a pale yellow oil (24.8 mg, 54 %). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 53:47 ratio. *R_f* = 0.33 (EtOAc:hexanes = 30:70). IR (neat): *v*_{max} 2927, 2854, 1691, 1597, 1251, 1116, 835, 773 cm⁻¹. [*α*]_D²⁵ + 9.4 (*c* 0.55, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 9.94 (s, 0.53H, CHO), 9.93* (s, 0.47H, CHO), 7.87 (dd, *J* = 8.7, 2.1 Hz, 0.53H, H-4), 7.85* (dd, *J* = 8.6, 2.1 Hz, 0.47H, H-4), 7.71* (d, *J* = 2.1 Hz, 0.47H, H-2), 7.68 (d, *J* = 2.1 Hz, 0.53H, H-2), 7.35 – 7.21 (m, 6H, H-3' and ArH), 7.12* (d, *J* = 8.6 Hz, 0.47H, H-5), 7.09 (d, *J* = 8.7 Hz, 0.53H, H-5), 6.66 (s, 0.53H, H-6'), 6.63* (s, 0.47H, H-6'), 5.66 (br s, 1H, H-8''), 5.40* (d, *J* = 10.5 Hz, 0.47H, H-9''), 5.36 (d, *J* = 10.5 Hz, 0.53H, H-9''), 5.26 – 5.12 (m, 2H, PhCH₂O), 3.95 (s, 1.59H, OCH₃), 3.94* (s, 1.41H, OCH₃), 3.87 (s, 3H, OCH₃), 3.77 (br s, 1H, H-1''), 3.25 (br s, 0.53H, H-6''), 3.12* (br s, 0.47H, H-6''), 2.77 – 2.67 (m, 2.53H, H-4'' and H-9a''), 2.64 (br s, 0.47H, H-9a''), 2.36* – 2.16* (m, 0.94H, H-7''), 2.06 – 1.96 (m, 1.06H, H-7''), 1.94 – 1.40 (m, 4H, H-2'' and H-3''), 0.94 (s, 9H, (CH₃)₃CSi), 0.05 (s, 2.82H, CH₃Si), 0.04 (s, 3.18H, CH₃Si). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 191.05 (C=O), 191.0* (C=O), 161.4 (C-6), 161.0* (C-6), 149.3* (C-4'), 149.3 (C-4'), 147.2* (C-5'), 147.0 (C-5'), 136.6* (C-2'), 136.3 (ArC), 136.2* (ArC), 135.5 (C-2'), 133.8 (C-2), 133.2* (C-2), 131.8 (C-1), 131.6* (C-1), 131.5* (C-4), 131.2 (C-4), 129.7* (C-3), 129.7 (C-3), 129.1* (C-1'), 128.7 (1.06 x ArCH), 128.6* (0.94 x ArCH), 128.5 (C-1'), 128.1 (0.53 x ArCH), 128.0* (0.47 x ArCH), 126.8* (0.94 x ArCH), 126.7 (1.06 x ArCH), 125.4 (C-8''), 125.0* (C-8''), 112.5* (C-5), 112.5 (C-6'), 112.3 (C-5), 110.0 (C-3'), 109.6* (C-3'), 70.3 (PhCH₂O), 70.3* (PhCH₂O), 69.8 (C-1''), 69.8* (C-1''), 66.0 (C-9a''), 65.9* (C-9a''), 59.7 (C-6''), 59.4* (C-6''), 56.0 (OCH₃), 56.0 (OCH₃), 55.9* (OCH₃), 55.8* (OCH₃), 52.3 (C-4''), 35.8 (C-7''), 33.4* (C-2''), 33.1 (C-2''), 25.9 ((CH₃)₃CSi), 21.8 (C-3''), 21.5* (C-3''), 18.3 ((CH₃)₃CSi), -4.2 (CH₃Si), -4.5 (CH₃Si). HRMS (ESI): *m/z* calcd for C₃₇H₄₈NO₅Si [M + H]⁺: 614.3302; found: 614.3306.

4.27 General Method for the Still–Gennari Modified Horner–Wadsworth–Emmons Reaction

4.27.1 Synthesis of Methyl (Z)-3-(6-(benzyloxy)-2'-((1*R*,6*S*,9*aS*)-1-((*tert*-butyldimethylsilyl)oxy)-1,3,4,6,7,9*a*-hexahydro-2*H*-quinolizin-6-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-yl)acrylate (**34a**)

To a solution of 18-crown-6 (66.5 mg, 0.2515 mmol, 5.0 equiv) in anhydrous THF (1.0 mL) at -78 °C was added KHMDS (0.15 mL, 0.0755 mmol, 0.5 M in toluene, 1.5 equiv) and the mixture was stirred for 10 min. Bis(2,2,2-trifluoro-ethyl)(methoxycarbonylmethyl)phosphonate (24.0 mg, 0.0755 mmol, 1.5 equiv) was added and the reaction mixture was stirred for 10 min. A solution of aldehyde **33a** (30.9 mg, 0.0503 mmol, 1.0 equiv) in THF (0.11 mL) was added slowly and stirring was continued for 2 h. The reaction was quenched with sat. aqueous NH₄Cl solution and extracted with EtOAc (3 x 5 mL). The combined organic layer was brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 30:70 EtOAc/hexanes to afford the title compound **34a** as a pale yellow oil (20.9 mg, 60%). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 71:29 ratio. *R*_f = 0.25 (EtOAc:hexanes = 30:70). IR (neat): ν_{max} 2927, 1723, 1626, 1598, 1515, 1495, 1462, 1250, 1192, 1169, 1114, 1042, 835, 773, 696 cm⁻¹. [α]_D²⁵ + 30 (c 0.19, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.78* (dd, *J* = 8.7, 2.3 Hz, 0.29H, H-4'), 7.72 (dd, *J* = 8.5, 2.3 Hz, 0.71H, H-4'), 7.54 (d, *J* = 2.3 Hz, 0.71H, H-2'), 7.42* (d, *J* = 2.3 Hz, 0.29H, H-2'), 7.34 – 7.16 (m, 5H, ArH), 7.15* (s, 0.29H, H-3''), 7.10 (s, 0.71H, H-3''), 7.01* (d, *J* = 8.7 Hz, 0.29H, H-5'), 6.93 – 6.81 (m, 1.71H, H-3 and H-5'), 6.79* (s, 0.29H, H-6''), 6.68 (s, 0.71H, H-6''), 6.10 (d, *J* = 9.8 Hz, 1H, H-9''), 5.96* (d, *J* = 10.1 Hz, 0.29H, H-8''), 5.89 – 5.82 (m, 0.71H, H-8''), 5.86 (d, *J* = 12.6 Hz, 1H, H-2), 5.15* (d, *J* = 12.3 Hz, 0.29H, PhCH_AH_BO (minor)), 5.03 (dd, *J* = 13.7, 7.1 Hz, 1.71H, PhCH_AH_BO (minor) and PhCH₂O), 4.26* (d, *J* = 6.8 Hz, 0.29H, H-6'''), 3.96 (d, *J* = 7.1 Hz, 0.71H, H-6'''), 3.88 (s, 2.73H, OCH₃), 3.85* (s, 0.87H, OCH₃), 3.83 (s, 2.73H, OCH₃), 3.77* (s, 0.87H, OCH₃), 3.71 (s, 3H, OCH₃), 3.32 – 3.22 (m, 1H, H-1'''), 2.78* (d, *J* = 18.3 Hz, 0.29H, H-7'''_A (minor)), 2.74 – 2.60 (m, 1.71H, H-7'''_A and H-9a'''), 2.31* (d, *J* = 17.4 Hz, 0.29H, H-7'''_B (minor)), 2.18 – 1.93 (m, 1.71H, H-4'''_A and H-7'''_B), 1.87 – 1.72 (m, 2H, H-2'''_A and H-4'''_B), 1.47 – 1.30 (m, 2H, H-3'''), 1.19 – 1.11 (m, 1H, H-2'''_B), 0.88 (s, 6.39H, (CH₃)₃CSi), 0.87* (s, 2.61H, (CH₃)₃CSi), 0.05 (s, 2.13H, CH₃Si), 0.03* (s, 0.87H, CH₃Si), 0.02 (s, 2.13H, CH₃Si), 0.00* (s, 0.87H, CH₃Si). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 166.7 (C-1), 166.6* (C-1), 157.0* (C-6'), 156.9 (C-6'), 148.3 (C-4'), 147.3 (C-5''), 146.7* (C-5''), 143.5* (C-3), 143.4 (C-3), 137.0* (ArC), 136.95 (ArC), 135.0* (C-2'), 134.7 (C-2'), 132.5 (C-2''), 132.1* (C-2''), 131.2 (C-1'), 131.2* (C-4'), 131.0 (C-4'), 130.7 (C-1''), 130.6* (C-1'), 130.0* (C-1''), 128.7* (0.58 x ArCH), 128.6 (1.42 x ArCH), 127.9 (0.71 x ArCH), 127.8* (0.29 x ArCH), 127.7* (C-9'''), 127.6 (C-3'), 127.4 (C-9'''), 127.1* (C-3'), 126.9 (1.42x ArCH), 126.5* (0.58 x ArCH), 125.7 (C-8'''), 125.2* (C-8'''), 117.3 (C-2), 113.7* (C-5'), 113.2 (C-5'), 112.0* (C-6''), 112.0 (C-6''), 110.6* (C-3''), 110.3 (C-3''), 72.7 (C-1'''), 72.5* (C-1'''), 70.6 (PhCH₂O), 69.9* (PhCH₂O), 61.7* (C-9a'''), 61.4 (C-9a'''), 56.1 (C-6'''), 55.9 (OCH₃), 55.89* (OCH₃), 54.5* (C-6'''), 51.4 (OCH₃), 51.3 (C-4'''), 50.6* (C-4'''), 35.1* (C-2'''), 35.0 (C-2'''), 32.8* (C-7'''), 32.1 (C-7'''), 26.0 ((CH₃)₃CSi), 23.7 (C-3'''), 23.3 (C-3'''), 18.2 ((CH₃)₃CSi), -3.8 (CH₃Si), -3.9* (CH₃Si), -4.5 (CH₃Si). HRMS (ESI): *m/z* calcd for C₄₀H₅₂NO₆Si [M + H]⁺: 670.3564; found: 670.3581.

4.27.2 Synthesis of Methyl (Z)-3-(6-(benzyloxy)-2'-((1R,6S,9aR)-1-((tert-butyldimethylsilyl)oxy)-1,3,4,6,7,9a-hexahydro-2H-quinolizin-6-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-yl)acrylate (**34b**)

Ester **34b** was prepared from compound **33b** (24.4 mg, 0.0397 mmol) according to the General Method for the Still–Gennari Modified Horner–Wadsworth–Emmons Reaction. Purification by column chromatography on silica gel eluting with 20:80 EtOAc/hexanes afforded the title compound **34b** as a pale yellow oil (14.7 mg, 56 %). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 48:52 ratio. *R_f* = 0.23 (EtOAc:hexanes = 20:80). IR (neat): $\nu_{\max}$ 2933, 2852, 1721, 1599, 1514, 1498, 1250, 1172, 831, 773 cm⁻¹. $[\alpha]_D^{25} + 14$ (c 0.92, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.83 (td, *J* = 8.3, 2.3 Hz, 1H, H-4'), 7.38 (d, *J* = 2.4 Hz, 0.52H, H-2'), 7.35* (d, *J* = 2.4 Hz, 0.48H, H-2'), 7.32 – 7.16 (m, 6H, ArH and H-3''), 6.94 (d, *J* = 8.7 Hz, 0.52H, H-5'), 6.92* (d, *J* = 8.7 Hz, 0.48H, H-5'), 6.84* (d, *J* = 12.8 Hz, 0.48H, H-3), 6.83 (d, *J* = 12.8 Hz, 0.52H, H-3), 6.65* (s, 0.48H, H-6''), 6.62 (s, 0.52H, H-6''), 5.84* (d, *J* = 12.8 Hz, 0.48H, H-2), 5.84 (d, *J* = 12.8 Hz, 0.52H, H-2), 5.65 – 5.57 (m, 1H, H-8''), 5.33 (t, *J* = 12.0 Hz, 1H, H-9''), 5.16 – 5.02 (m, 2H, PhCH₂O), 3.90* (s, 1.44H, OCH₃), 3.89* (s, 1.44H, OCH₃), 3.84 (s, 1.56H, OCH₃), 3.83 (s, 1.56H, OCH₃), 3.74 (s, 1H, H-1'''), 3.71 (s, 3H, OCH₃), 3.32* – 3.28* (m, 0.48H, H-6'''), 3.20 – 3.15 (s, 0.52H, H-6'''), 2.74 – 2.61 (m, 3H, H-4''' and H-9a'''), 2.26 – 1.95 (m, 2H, H-7'''), 1.88 – 1.55 (m, 2H, H-2'''_A (major), H-3'''_A (major) and H-3'''_A (minor)), 1.50 – 1.36 (m, 0.96H, H-2''' (minor)), 1.36 – 1.20 (m, 1H, H-2'''_B (major), H-3'''_B (minor)), 0.91 (s, 9.52H, H-3'''_B (major) and (CH₃)₃CSi), 0.01 (s, 6H CH₃Si). ¹³C NMR (125 MHz, CDCl₃): δ 166.7 (C-1), 157.3* (C-6'), 156.7 (C-6'), 148.9 (C-4''), 148.8* (C-4''), 146.8 (C-5), 146.7* (C-5), 143.5 (C-3), 143.46* (C-3), 136.9* (ArC), 136.87 (ArC), 136.5 (C-2''), 135.5* (C-2''), 134.9 (C-2'), 134.4* (C-2'), 130.9 (C-4'), 130.6* (C-4'), 130.4 (C-1'), 130.2* (C-1'), 129.8* (C-1''), 129.3 (C-1''), 128.8 (C-9'''), 128.6* (C-9'''), 128.5* (0.96 x ArCH), 128.3 (1.04 x ArCH), 127.6* (0.48 x ArCH), 127.57 (0.52 x ArCH), 127.0* (C-3'), 126.9 (C-3'), 126.7* (0.96 x ArCH), 126.6 (1.04 x ArCH), 125.4* (C-8'''), 124.9 (C-8'''), 116.9 (C-2), 116.8* (C-2), 112.53* (C-6''), 112.5 (C-6''), 112.0 (C-5'), 111.8* (C-5'), 109.7 (C-3''), 109.4 (C-3''), 70.0 (PhCH₂O), 69.9* (PhCH₂O), 69.7* (C-1'''), 69.69 (C-1'''), 65.9* (C-9a'''), 65.7 (C-9a'''), 59.4 (C-6'''), 59.1* (C-6'''), 55.83 (OCH₃), 55.8* (OCH₃), 55.7* (OCH₃), 55.6 (OCH₃), 52.2 (C-4'''), 51.3 (OCH₃), 35.7 (C-7'''), 34.5* (C-7'''), 33.3 (C-2'''), 33.1* (C-2'''), 25.8 ((CH₃)₃CSi), 25.78* ((CH₃)₃CSi), 21.6* (C-3'''), 21.3 (C-3'''), 18.2* ((CH₃)₃CSi), 18.2 ((CH₃)₃CSi), -4.3 (CH₃Si), -4.7 (CH₃Si). HRMS (ESI): *m/z* calcd for C₄₀H₅₂NO₆Si [M + H]⁺: 670.3564; found: 670.3595.

4.28 Synthesis of (1R,6S,9aS)-6-(2'-(Benzyloxy)-5'-((Z)-2-bromovinyl)-4,5-dimethoxy-[1,1'-biphenyl]-2-yl)-1-((tert-butyldimethylsilyl)oxy)-1,3,4,6,7,9a-hexahydro-2H-quinolizine (**35a**)

To a solution of the crude acid **34a** (10.6 mg, 16.1 μ mol, 1.0 equiv) in MeCN (81 μ L) was added diphenyl diselenide (0.3 mg, 0.81 μ mol, 0.05 equiv) and the mixture was cooled to at -30 °C. Next, *N*-bromosuccinimide (3.5 mg, 19.4 μ mol, 1.2 equiv) was added and the reaction mixture was

stirred for 2 h. The mixture was dilute with EtOAc (0.8 mL) and washed with water (2 x 2 mL). The organic layer was brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 20:80 EtOAc/hexanes to afford the title compound **35a** as a pale yellow oil (2.0 mg, 18 %). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 39:61 ratio. *R_f* = 0.35 (EtOAc:hexanes = 30:70). IR (neat): $\nu_{\max}$ 3037, 2927, 2854, 1660, 1513, 1492, 1462, 1250, 1113, 1092, 1016, 834, 774, 734, 696 cm⁻¹. $[\alpha]_D^{25}$ - 12.3 (*c* 0.10, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.64 (d, *J* = 2.4 Hz, 0.69H, H-6''), 7.57 (dd, *J* = 8.6, 2.4 Hz, 0.69H, H-4''), 7.55* (dd, *J* = 8.6, 2.4 Hz, 0.31H, H-4''), 7.52* (d, *J* = 2.3 Hz, 0.31H, H-6''), 7.33 – 7.16 (m, 5H, ArH), 7.15* (s, 0.31H, H-3'), 7.11 (s, 0.69H, H-3'), 7.04* (d, *J* = 8.6 Hz, 0.31H, H-3''), 7.02 (d, *J* = 8.0 Hz, 0.69H, H-1'''), 6.99* (d, *J* = 8.0 Hz, 0.31H, H-1'''), 6.91* (d, *J* = 8.6 Hz, 0.31H, H-3''), 6.81* (s, 0.31H, H-6'), 6.66 (s, 0.69H, H-6'), 6.34 (d, *J* = 8.0 Hz, 0.69H, H-2'''), 6.32* (d, *J* = 8.0 Hz, 0.31H, H-2'''), 6.14 – 6.07 (m, 1H, H-9), 5.99* – 5.93* (m, 0.31H, H-8), 5.90 – 5.86 (m, 0.69H, H-8), 5.15* (d, *J* = 12.4 Hz, 0.31H PhCH_AH_BO (minor)), 5.08 – 4.98 (m, 1.69H, PhCH_AH_BO (minor) and PhCH₂O), 4.32* (dd, *J* = 6.9, 2.7 Hz, 0.31H, H-6), 3.97 (d, *J* = 6.9 Hz, 0.69H, H-6), 3.87 (s, 2.07H, OCH₃), 3.85* (s, 0.93H, OCH₃), 3.83 (s, 2.07H, OCH₃), 3.78* (s, 0.93H, OCH₃), 3.31 – 3.24 (m, 1H, H-1), 2.81 – 2.68 (m, 1H, H-7_A and H-7_A (minor)), 2.65 (d, *J* = 7.8 Hz, 1H, H-9a), 2.37* – 2.30* (m, 0.31H, H-7_B (minor)), 2.19 – 2.12 (m, 1H, H-4_A), 2.11 – 2.04 (m, 0.69H, H-7_B), 1.86 – 1.79 (m, 2H, H-2_A and H-4_B), 1.40 – 1.35 (m, 2H, H-3), 1.18 – 1.12 (m, 1H, H-2_B), 0.88 (d, *J* = 1.2 Hz, 6.21H, (CH₃)₃CSi), 0.87* (s, 2.79H, (CH₃)₃CSi), 0.05 (s, 2.07H, CH₃Si), 0.03* (s, 0.93H, CH₃Si), 0.02 (s, 3H, CH₃Si). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 155.9* (C-2''), 155.8 (C-2''), 148.3* (C-4'), 148.2 (C-4'), 147.2 (C-5'), 136.9 (ArC), 136.5* (ArC), 132.9* (C-6''), 132.7 (C-6''), 132.4 (C-2'), 131.9* (C-2'), 131.6 (C-1'''), 131.4* (C-1'''), 130.6 (C-1' and C-1''), 129.6* (C-4''), 129.5 (C-4''), 128.5* (C-5'' and 0.62 x ArCH), 128.45 (1.38 x ArCH), 127.8* (0.31 x ArCH), 127.7 (0.69 x ArCH), 127.3 (C-9), 126.8 (1.38x ArCH), 126.4* (0.62 x ArCH), 125.5 (C-8), 125.0* (C-8), 113.5* (C-6'), 112.8 (C-6'), 112.2* (C-3''), 112.1 (C-3''), 110.4* (C-3'), 110.1 (C-3'), 104.8 (C-2'''), 72.6 (C-1), 72.2* (C-1), 70.5 (PhCH₂O), 69.7* (PhCH₂O), 61.6* (C-9a), 61.3 (C-9a), 56.0 (C-6), 55.8 (OCH₃), 54.3* (C-6), 51.3 (C-4), 50.4* (C-4), 35.0* (C-2), 34.8 (C-2), 32.8* (C-7), 32.0 (C-7), 25.9 ((CH₃)₃CSi), 23.6 (C-3), 18.1 ((CH₃)₃CSi), -4.0 (CH₃Si), -4.7 (CH₃Si). HRMS (ESI): *m/z* calcd for C₃₈H₄₉NO₄SiBr [M + H]⁺: 690.2614; found: 690.2648.

4.29 Synthesis of (1*R*,6*S*,9*aR*)-6-(2'-(Benzyloxy)-5'-((*Z*)-2-bromovinyl)-4,5-dimethoxy-[1,1'-biphenyl]-2-yl)-1-((*tert*-butyldimethylsilyl)oxy)-1,3,4,6,7,9*a*-hexahydro-2*H*-quinolizine (**35b**)

To a solution of the crude acid **34b** (5.0 mg, 7.6 μ mol, 1.0 equiv) in MeCN (38 μ L) was added diphenyl diselenide (0.1 mg, 0.38 μ mol, 0.05 equiv) and the mixture was cooled to at -30 °C. Next, *N*-bromosuccinimide (1.5 mg, 8.36 μ mol, 1.1 equiv) was added and the reaction mixture was stirred for 5 h. The mixture was dilute with EtOAc (2 mL) and washed with water (2 x 5 mL). The

organic layer was brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 10:90 EtOAc/hexanes to afford the title compound **35b** as a pale yellow oil (1.0 mg, 14 %). ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 48:52 ratio. *R_f* = 0.34 (EtOAc:hexanes = 15:75). IR (neat): ν_{max} 3029, 2925, 2852, 1645, 1600, 1515, 1493, 1460, 1251, 1119, 1022, 871, 736, 696 cm⁻¹. [α]_D²⁵ + 19 (*c* 0.05, CHCl₃). ¹H NMR (500 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 7.66 (d, *J* = 8.5 Hz, 1H, H-4''), 7.49 (s, 1H, H-6''), 7.32 – 7.16 (m, 6H, , H-3' and ArH), 7.00* (d, *J* = 8.1 Hz, 0.48H, H-1'''), 6.99 (d, *J* = 8.1 Hz, 0.52H, H-1'''), 6.96 (d, *J* = 8.7 Hz, 0.52H, H-3''), 6.94* (d, *J* = 8.7 Hz, 0.48H, H-3''), 6.64* (s, 0.48H, H-6'), 6.63 (s, 0.52H, H-6'), 6.31 (d, *J* = 8.1 Hz, 1H, H-2'''), 5.62 (d, *J* = 8.5 Hz, 1H, H-8), 5.34 (t, *J* = 11.5 Hz, 1H, H-9), 5.12 – 5.01 (m, 2H, PhCH₂O), 3.91* (s, 1.44H, OCH₃), 3.89* (s, 1.44H, OCH₃), 3.83 (s, 3.12H, OCH₃), 3.77 – 3.72 (m, 1H, H-1), 3.35 – 3.30 (m, 0.52H, H-6), 3.24* – 3.18* (m, 0.48H, H-6), 2.77 – 2.60 (m, 3H, H-4 and H-9a), 2.31 – 1.98 (m, 2H, H-7), 1.88 – 1.28 (m, 4H, H-2 and H-3), 0.91 (s, 9H, (CH₃)₃CSi), 0.01 (s, 6H, CH₃Si). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): δ 156.3* (C-2''), 155.7 (C-2''), 148.9 (C-4'), 148.8* (C-4'), 146.8* (C-5'), 146.7 (C-5'), 137.0 (ArC), 136.97* (ArC), 136.4* (C-2'), 135.5 (C-2'), 132.9 (C-6''), 132.6* (C-6''), 131.6 (C-3'''), 131.59* (C-3'''), 130.7 (C-1''), 130.5* (C-1''), 129.9* (C-1'), 129.5 (C-1'), 129.3 (C-4''), 129.1* (C-4''), 128.8 (C-9), 128.5 (1.04 x ArCH), 128.3* (0.96 x ArCH), 127.6* (0.48 x ArCH), 127.56 (0.52 x ArCH), 127.3 (C-5''), 127.28* (C-5''), 126.6* (0.96 x ArCH), 126.58 (1.04 x ArCH), 125.4* (C-8), 124.9 (C-8), 112.5 (C-6'), 112.2 (C-3''), 112.1* (C-3''), 109.7* (C-3'), 109.4 (C-3'), 104.5 (C-2'''), 104.4* (C-2'''), 70.0 (PhCH₂O), 69.96* (PhCH₂O), 69.7 (C-1), 65.9 (C-9a), 65.8* (C-9a), 59.3 (C-6), 59.1* (C-6), 55.9 (OCH₃), 55.8 (OCH₃), 55.7* (OCH₃), 55.65* (OCH₃), 33.3* (C-2), 33.1 (C-2), 25.8 ((CH₃)₃CSi), 21.6* (C-3), 21.3 (C-3), 18.2 ((CH₃)₃CSi), -4.3 (CH₃Si), -4.7* (CH₃Si) (The methylene carbons C-4 and C-7 were not detected.). HRMS (ESI): *m/z* calcd for C₃₈H₄₉NO₄SiBr [M + H]⁺: 690.2614; found: 690.2642.

4.30 Synthesis of 6-(Benzyloxy)-2'-((4*S*,9*R*,9*aS*)-9-((*tert*-butyldimethylsilyl)oxy)-2-hydroxyoctahydro-2*H*-quinolizin-4-yl)-4',5'-dimethoxy-[1,1'-biphenyl]-3-carbonitrile (**37**)

To a solution of the crude acid **32a** (30.5 mg, 0.05 mmol) in THF (100 μ L) was added Hg(NO₃)₂ (35.9 mg, 0.11 mmol, 2.2 equiv) and water (100 μ L). The mixture was stirred for 5 days at room temperature; NaBH₄ solution (0.5 M in 3 M NaOH, 110 μ L) was added. The mixture was dilute with EtOAc (0.5 mL), the solid mercury was allowed to settle, and the organic layer was separated, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with 40:60 EtOAc/hexanes to afford the title compound **39** as a pale yellow oil (1.0 mg, 6%) and desilylated product **24** (3.8 mg, 15%) as a pale yellow oil. ¹H NMR analysis revealed the presence of two biphenyl axis rotamers in a 49:51 ratio. *R_f* = 0.51 (EtOAc:hexanes = 50:50). IR (neat): ν_{max} 3400, 3061, 2921, 2851, 2224, 1601, 1512, 1492, 1461, 1250, 1119, 1069, 831, 737, 693 cm⁻¹. ¹H NMR (500 MHz, the asterisk* denotes the signal of the

minor rotamer, CDCl₃): 7.61 (d, *J* = 8.5 Hz, 1H, H-4), 7.39 (s, 1.49H, H-2 and H-3'(minor)), 7.32 – 7.25 (m, 3.51H, H-3' (major) and ArH), 7.22* (d, *J* = 8.2 Hz, 1H, ArH), 7.17 (d, *J* = 7.9 Hz, 1H, ArH), 7.04 (dd, *J* = 8.5, 3.3 Hz, 1H, H-5), 6.54 (s, 1H, H-6'), 5.16 – 5.09 (m, 1.49H, PhCH₂O (minor) and PhCH_AH_BO), 5.07 (d, *J* = 12.3 Hz, 0.51H, PhCH_AH_BO), 4.07* (s, 0.49H, H-8''), 3.98 (s, 0.51H, H-8''), 3.90* (s, 1.47H, OCH₃), 3.89* (s, 1.47H, OCH₃), 3.84 (s, 3.06H, OCH₃), 3.55 – 3.49 (m, 1H, H-1''), 3.16 – 3.10 (m, 1H, H-6''), 2.66* (d, *J* = 10.9 Hz, 0.49H, H-4''_A), 2.59 (d, *J* = 11.7 Hz, 0.51H, H-4''_A), 2.37 – 2.27 (m, 1H, H-9a''), 2.02 – 1.92 (m, 1H, H-9''_A), 1.75 – 1.51 (m, *J* = 39.2, 13.4 Hz, 4.49H, H-2''_A, H-3''_A, H-4''_B (minor) and H-7''), 1.40 – 1.25 (m, 4.51H, H-2''_B, H-3''_B, H-4''_B and H-9''_B), 0.94 (s, 9H, (CH₃)₃CSi), 0.03* (s, 2.94H, CH₃Si), 0.02 (s, 3.06H, CH₃Si). ¹³C NMR (125 MHz, the asterisk* denotes the signal of the minor rotamer, CDCl₃): 159.9* (C-6), 159.3 (C-6), 149.5 (C-4'), 147.2* (C-5'), 147.0 (C-5'), 136.0 (ArC), 135.7* (C-2), 135.3 (C-2), 133.5 (C-4), 133.4* (C-4), 132.3 (ArC), 131.9 (ArC), 128.8 (1.02 x ArCH), 128.7* (0.98 x ArCH), 128.3* (ArCH), 128.1 (1.02 x ArCH), 127.1* (ArCH), 126.9 (1.02 x ArCH), 119.4 (C≡N), 113.0* (C-5), 112.9 (C-5), 112.4 (C-6'), 112.2* (C-6'), 109.9* (C-3'), 109.4 (C-3'), 104.2 (C-3), 103.9* (C-3), 70.5* (PhCH₂O), 70.4 (PhCH₂O), 69.9 (C-1''), 65.3* (C-8''), 65.0 (C-8''), 59.5* (C-9a''), 59.0 (C-9a''), 58.4* (C-6''), 58.1 (C-6''), 56.1 (OCH₃), 55.8* (OCH₃), 53.3 (C-4''), 52.6* (C-4''), 42.8 (C-7''), 41.2* (C-7''), 36.3* (C-9''), 35.9 (C-9''), 33.3 (C-2''), 33.1* (C-2''), 26.0 ((CH₃)₃CSi), 20.5 (C-3''), 18.3 ((CH₃)₃CSi), -4.1 (CH₃Si), -4.8* (CH₃Si). HRMS (ESI): *m/z* calcd for C₃₇H₄₉N₂O₅Si [M + H]⁺: 629.3405; found: 629.3411.

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