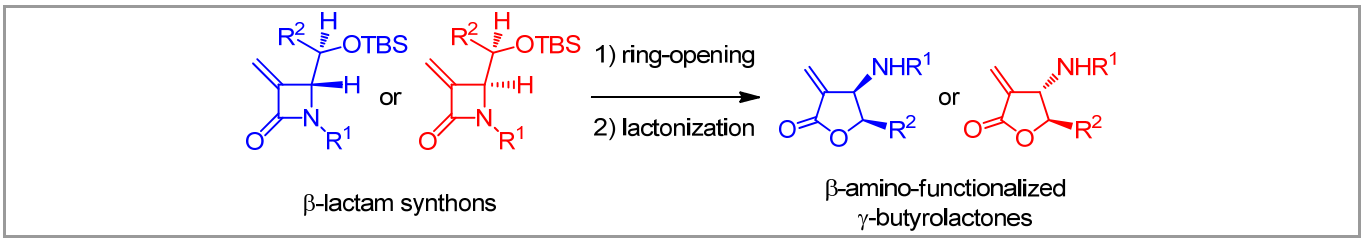
Synthesis of β-Amino-Functionalized α-exo-Methylene-γ-butyrolactones via a β-Lactam Synthon Strategy



Graphics Abstract

Synthesis of β-Amino-functionalized α-*exo*-Methylene–γ-butyrolactones via a β-Lactam Synthon Strategy

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Abstract: A convenient and effective synthetic approach was developed to access a structurally novel class of β-amino-functionalized α-*exo*-methylene–γ-butyrolactones by the use of chiral β-lactam synthons.

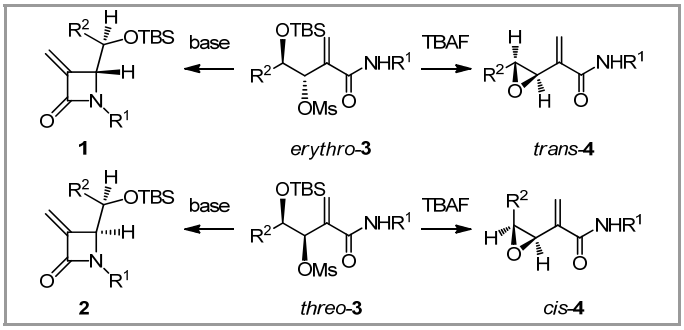
Keywords: α-methylene carbonyl compounds, Michael acceptor, β-lactam synthon, α-*exo*-methylene-β-lactam, β-amino-α-*exo*-methylene-γ-butyrolactone

Introduction

α-Methylene carbonyl compounds are of biological importance because of their high potency that can be attributed to the chemical reactivity to act as a Michael acceptor.[1] In particular, α-*exo*-methylene-γ-butyrolactone skeletal system represents a key structural motif found in many natural sesquiterpene lactones displaying strong cytotoxic, anti-inflammatory, phytotoxic, and antimicrobial properties.[2] Despite its obvious synthetic significance, an effective and versatile methodology for the construction of this type of heterocyclic structure, particularly β-functionalized derivatives, substantially remains underdeveloped compared to unsubstituted γ-butyrolactones.[3] The β-lactam synthon method can offer an efficient and versatile strategy for preparation of a wide variety of chiral carbonyl compounds through highly chemo- and stereoselective transformations accompanied by cleavage of the C(O)-N bond in the strained four-membered ring.[4] It is worth noting that, to our knowledge, no reports have appeared previously describing application of the β-lactam synthon strategy for the synthesis of the α-*exo*-methylene-γ-butyrolactones. In the present publication, we report here a convenient and effective procedure for the synthesis of a structurally novel class of β-amino-functionalized α-*exo*-methylene–γ-butyrolactones by the use of α-*exo*-methylene–β-lactams as a highly effective chiral synthon.[5]

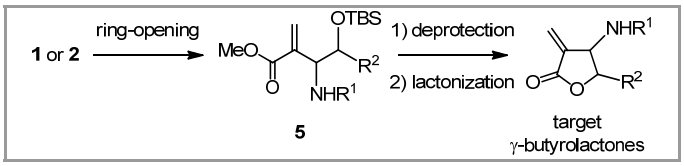
Results and Discussion

The requisite α-*exo*-methylene–β-lactams **1** and **2** were prepared according to the published procedure.[6] As described in the literature, two possible diastereomers of variously substituted mesylates *erythro*- and *threo*-**3**, whose relative stereochemistries were established on the basis of the ^{1}H NMR vicinal coupling constants of the corresponding 3,4-epoxides *trans*- and *cis*-**4**, were separated into analytically pure forms by column chromatography on silica gel, respectively.[7] Thus, the diastereomerically pure samples of **1** and **2** could be obtained from *erythro*- and *threo*-**3** through displacement of the mesylates by deprotonated amide nitrogens, respectively (Scheme 1).



Scheme 1. Preparation and stereochemical assignment of β-lactam synthons

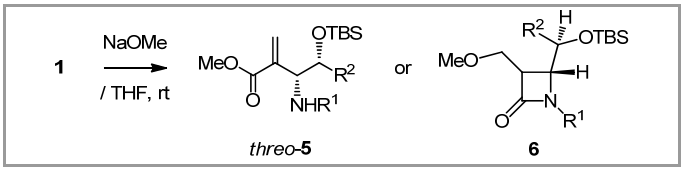
With these starting materials in hand, we set out to synthesize the target γ-butyrolactones employing the β-lactam synthon method. Key to the successful implementation of the plan was preparation of appropriate γ-butyrolactone precursors **5** that may be produced by ring-opening of the β-lactam synthons **1** and **2** (Scheme 2).[8]



Scheme 2. Synthetic strategy for the preparation of γ-butyrolactones

Therefore, we first examined the ring-opening reactions driven by nucleophilic addition of sodium methoxide (Scheme 3).[9] The reaction of **1a**, bearing an aliphatic substituent on the nitrogen, with 3.0 equiv of sodium methoxide in THF at ambient temperature gave only recovered starting material, while the reaction attempted at reflux failed again to give even trace quantities of any products. When the reaction was carried out by refluxing the substrate in methanol, none of the desired product was observed, resulting in the formation of 1,4-adduct **6** in 21% yield (Table 1, entry 1).[10] In contrast, reactions of a series of aromatic derivatives **1b-f** led to exclusive productions of the ring-opened materials *threo*-**5b-f** (en-

tries 2-6), whose *threo* configurations at two stereocenters can be assigned on the basis of clean ^{1}H NMR spectral data and precise mechanistic interpretation for this transformation. The pronounced difference between the reactivity of *N*-alkyl and *N*-aromatic β-lactams containing the strained ring systems can be understood in terms of degree of conjugation within the amido functionality.[11] In comparison to *N*-alkyl systems, the C(O)-N double bond character is substantially less dominated for *N*-aromatic systems by delocalization of the free electron pair on the amide nitrogen via the conjugation with the aromatic units. As a consequence, the *N*-aromatic series of β-lactams are more reactive toward sodium methoxide due to the increased lability of the amide bond.



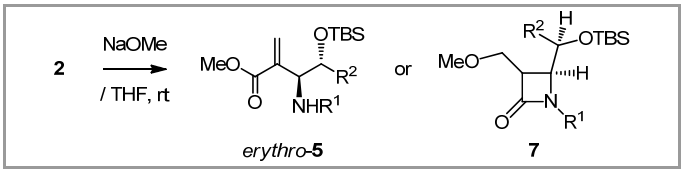
Scheme 3. Synthesis of *threo*-**5**

Table 1 Ring-opening reactions of **1**

Entry	1	R^1	R^2	*threo*-**5** (%)[a]
1	a	*n*-C_5H_{11}	*n*-C_7H_{15}	0[b]
2	b	Ph	*n*-C_7H_{15}	77
3	c	Ph	$(CH_2)_2$Ph	87
4	d	*p*-tolyl	*n*-C_7H_{15}	88
5	e	1-naphthyl	CH_3	76
6	f	1-naphthyl	*n*-C_7H_{15}	49

[a] Isolated yield. [b] The reaction in refluxing THF gave only recovered starting material, while the reaction in refluxing methanol resulted in the predominant formation of **6** (21%).

Another series of β-lactam synthons **2**, which represent diastereomeric counterparts of **1**, behaved similarly regarding the issue of potential reactivity (Scheme 4). As can be seen in Table 2, *N*-alkyl β-lactam **2a** showed its chemical inertness under the given standard conditions as well as the same chemical reactivity in refluxing methanol to provide the corresponding 1,4-adduct **7** (entry 1),[12] whereas *N*-aromatic derivatives **2b-f** underwent the ring-opening reactions, leading to **5b-f**, respectively (entries 2-6). It is important to note that in all these cases, only single diastereomers corresponding to *erythro*-**5** were also obtained through the ring-opening processes as determined by observation of simple ^{1}H NMR spectra of the products. From the examples above it appears that the *N*-aromatic β-lactams **1** and **2** can be separately converted to the γ-butyrolactone precursors *threo*- and *erythro*-**5** with good yields and complete retention of the stereochemistry at C3 and C4, respectively.



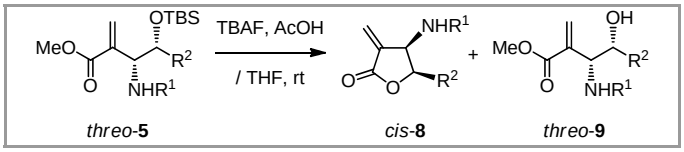
Scheme 4. Synthesis of *erythro*-**5**

Table 2 Ring-opening reactions of **2**

Entry	2	R^1	R^2	*erythro*-**5** (%)[a]
1	a	*n*-C_5H_{11}	*n*-C_7H_{15}	0[b]
2	b	Ph	*n*-C_7H_{15}	62
3	c	Ph	$(CH_2)_2$Ph	60
4	d	*p*-tolyl	*n*-C_7H_{15}	67
5	e	1-naphthyl	CH_3	49
6	f	1-naphthyl	*n*-C_7H_{15}	65

[a] Isolated yield. [b] The reaction in refluxing THF gave only recovered starting material, while the reaction in refluxing methanol resulted in the predominant formation of **7** (34%).

Having these compounds in hand, our next objective was to construct the target γ-butyrolactones through lactonization of γ-hydroxy esters that could be prepared from **5** (Scheme 5).[13] Initially, we attempted removal of the silyl group of *threo*-**5b**, which was carried out by adding 1.2 equiv of tetrabutylammonium fluoride (TBAF) in THF at room temperature. Under these conditions, desilylated intermediate generated in the reaction mixture underwent in situ lactonization to afford *cis*-fused β-amino γ-butyrolactone *cis*-**8b**, but in low yield (32%, entry 1 in Table 3).



Scheme 5. Synthesis of *cis*-**8**

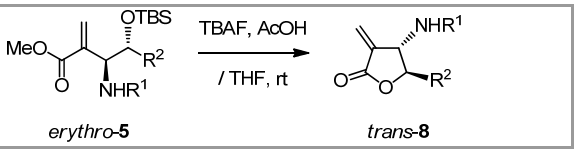
Table 3 Reactions of *threo*-**5**

Entry	*threo*-**5**	TBAF (equiv)	AcOH (equiv)	Time	*cis*-**8** (%)[a]	*threo*-**9** (%)[a]
1	b	1.2	0	11 d	32	0
2	b	3.0	1.5	11 d	69	0
3	c	3.0	1.5	3 d	70	0
4	d	3.0	1.5	2 d	83	0
5	e	3.0	1.5	21 h	50	33
6	f	3.0	1.5	9 d	33	48

[a] Isolated yield.

Considering that slight excess of TBAF would cause the decrease of product yield, we reexamined the reaction with acetic acid and much larger amounts of this reagent. Reaction with 1.5 equiv of acetic acid and 3.0 equiv of TBAF significantly improved the yield (69%) with no production of the γ-hydroxy ester intermediate (entry 2). Likewise, *threo*-**5c** and -**5d** were cyclized under the same conditions to provide predominantly *cis*-**8c** and -**8d** in 70 and 83% isolated yields (entries 3 and 4), respectively. In contrast, however, *threo*-**5e** and -**5f** bearing sterically demanding 1-naphthyl substituents behaved differently in that the formation of γ-hydroxy esters competed with the lactonization process, where the desilylated byproducts *threo*-**9e** and -**9f** were obtained in 33 and 48%, respectively (entries 5 and 6). The observed lower efficiency of the cyclization reactions are mainly due to increased steric hindrance on the lactone rings created by *cis*-fused bulky substituents. In fact, *threo*-**9f** was found to be essentially inert under the conditions used for lactonization, giving only recovered

starting material. This provides unambiguous evidence for the lack of reactivity for this compound on the basis of the steric inhibition.[14]



Scheme 6. Synthesis of *trans*-**6**

Table 4 Reactions of *erythro*-**5**

Entry	*erythro*-**5**	TBAF (equiv)	AcOH (equiv)	Time	*trans*-**8** (%)[a]
1	b	3.0	1.5	7 d	75
2	c	3.0	1.5	8 d	86
3	d	3.0	1.5	4 d	65[b]
4	e	3.0	1.5	21 d	79
5	f	3.0	1.5	5 d	69[c]

[a] Isolated yield. [b] 13% starting material recovered. [c] 15% starting material recovered.

The above rationalization can account for the transformation of *erythro*-**5** into *trans*-fused β-amino γ-butyrolactones *trans*-**8** that would be thermodynamically more favored than the *cis*-isomers (Scheme 6). In almost all cases, marked improvements in the cyclization efficiency were observed for the reactions carried out under identical conditions, affording exclusively the desired products in good to excellent yields (65-86%) without formation of any acyclic byproducts (Table 4). Considering that in every case, there is no difference in relative rates of the desilylation between *threo*- and *erythro*-**5**, the desilylated reactive species generated from *erythro*-**5** might be expected to cyclize rapidly through conformationally less-constrained transition states, thereby accounting for the high efficiencies observed.

Conclusion

We have developed the efficient synthesis of a new class of β-amino-functionalized α-*exo*-methylene–γ-butyrolactones via a β-lactam synthon strategy involving ring cleavage and cyclization. The synthetic approach described allows the attachment of amino groups to α-*exo*-methylene–γ-butyrolactone skeletons at the β-position,[15] which cannot otherwise be achieved through direct lactonization of acyclic intermediates. Therefore, this work has demonstrated the versatility of our synthetic methodology in rapidly accessing a variety of biologically potent analogues.

Experimental section

General

All solvents and reagents were of reagent grade quality from Wako Pure Chemicals and Tokyo Chemical Industry (TCI) used without further purification. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra operating at the frequencies of 300 and 75 MHz, respectively, were recorded on a JEOL JNM-AL300 spectrometer in chloroform-*d* ($CDCl_3$). Chemical shifts are reported in parts per million (ppm) relative to TMS and the solvent used as internal standards, and the coupling constants are reported in hertz (Hz). Fourier transform infrared (FTIR) spectra were recorded on a JASCO FT/IR-550 spectrometer. Elemental analyses were performed by JSL Model JM 10 instruments.

General procedure for the synthesis of γ-butyrolactone precursors 5

All γ-butyrolactone precursors **5** were prepared as described in the following typical procedure. For example, the synthesis of *threo*-**5b** was exemplified as follows.

Preparation of threo-**5b**. To a solution containing sodium methoxide in THF (2.0 mL), which was prepared from methanol (0.0292 g, 0.912 mmol, 3.0 equiv) and sodium hydride (55% dispersion in mineral oil, 0.0398 g, 0.912 mmol, 3.0 equiv), was added a solution of **1b** (0.122 g, 0.304 mmol, 1.0 equiv) in THF (1.0 mL) with stirring under a nitrogen atmosphere at 0 °C. After 20 min, the reaction mixture was quenched with saturated NH_4Cl_{aq} (5.0 mL). The resulting mixture was extracted with ethyl acetate (20 mL), washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flush column chromatography on silica gel (eluent: hexane/ethyl acetate = 30/1) gave *threo*-**5b** (0.102 g, 0.235 mmol, 77%) as colorless oil: IR (NaCl): 3425 (N-H), 2953 (C-H), 2929 (C-H), 2857 (C-H), 1717 cm^{-1} (C=O) 1602 (C=C), 1505 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (m, 2H, Ar*H*), 6.66 (m, 1H, Ar*H*), 6.52 (m, 2H, Ar*H*), 6.31 (d, *J* = 0.9 Hz, 1H, CH_2=C), 5.74 (d, *J* = 0.9 Hz, 1H, CH_2=C), 4.54 (d, *J* = 7.2 Hz, 1H, N*H*), 4.43 (d, *J* = 7.2 Hz, 1H, C*H*), 3.90 (m, 1H, C*H*), 3.83 (s, 3H, OCH_3) 1.84-1.27 (m, 12H, CH_2), 0.92-0.87 (m, 12H, C(CH_3)$_3$, CH_3), 0.05 (s, 3H, CH_3), -0.05 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5 (*C*=O), 146.9 (*C*), 138.5 (*C*), 129.3 (*C*H), 127.1 (*C*H$_2$), 116.8 (*C*H), 112.8 (*C*H), 73.0 (*C*H), 55.0 (*C*H), 51.7 (*C*H$_3$), 35.3 (*C*H$_2$), 31.7 (*C*H$_2$), 29.5 (*C*H$_2$), 29.1 (*C*H$_2$), 25.9 (*C*H$_3$), 25.6 (*C*H$_2$), 22.5 (*C*H$_2$), 18.0 (*C*), 13.9 (*C*H$_3$), -4.5 (*C*H$_3$), -4.6 (*C*H$_3$). Anal. Calcd for $C_{25}H_{43}NO_3Si$: C, 69.23; H, 9.99; N, 3.23. Found: C, 69.10; H, 9.65; N, 3.63.

Characterization data for threo-**5c**. This compound was obtained (0.0467 g, 0.105 mmol, 87%) as colorless oil: IR (NaCl): 3426 (N-H), 3023 (C-H), 2950 (C-H), 2929 (C-H), 2857 (C-H), 1713 cm^{-1} (C=O), 1602 (C=C), 1505 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27-7.11 (m, 7H, Ar*H*), 6.67 (t, *J* = 7.2 Hz, 1H, Ar*H*), 6.52 (d, *J* = 8.2 Hz, 2H, Ar*H*), 6.30 (s, 1H, CH_2=C), 5.74 (s, 1H, CH_2=C), 4.54 (brs, 1H, N*H*), 4.49 (s, 1H, C*H*), 3.96 (dd, *J* = 4.5, 8.4 Hz, 1H, C*H*), 3.81 (s, 3H, OCH_3), 2.75-2.61 (m, 2H, CH_2), 2.10 (m, 1H, CH_2), 1.84 (m, 1H, CH_2), 0.88 (s, 9H, C(CH_3)$_3$), 0.02 (s, 3H, CH_3), -0.12 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5 (*C*=O), 146.8 (*C*), 142.0 (*C*), 138.4 (*C*), 129.3 (*C*H), 128.4 (*C*H), 128.3

(*C*H), 127.3 (*C*H$_2$), 125.8 (*C*H), 117.0 (*C*H), 112.9 (*C*H), 72.6 (*C*H), 55.2 (*C*H), 51.8 (*C*H$_3$), 37.2 (*C*H$_2$), 31.9 (*C*H$_2$), 25.9 (*C*H$_3$), 18.0 (*C*), -4.6 (*C*H$_3$). Anal. Calcd for $C_{26}H_{37}NO_3Si$: C, 71.03; H, 8.48; N, 3.19. Found: C, 70.98; H, 8.19; N, 3.38.

Characterization data for threo-**5d**. This compound was obtained (0.0212 g, 0.0470 mmol, 88%) as colorless oil: IR (NaCl): 3427 (N-H), 3020 (C-H), 2953 (C-H), 2928 (C-H), 2858 (C-H), 1719 cm^{-1} (C=O), 1521 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.95 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.42 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.28 (s, 1H, C*H*$_2$=C), 5.71 (s, 1H, C*H*$_2$=C), 4.38 (m, 2H, C*H* and N*H*), 3.87 (m, 1H, C*H*), 3.81 (s, 3H, OC*H*$_3$), 2.22 (s, 3H, C*H*$_3$), 1.82-1.26 (m, 12H, C*H*$_2$), 0.89 (m, 12H, C(C*H*$_3$)$_3$, C*H*$_3$), 0.02 (s, 3H, C*H*$_3$), -0.09 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6 (*C*=O), 144.6 (*C*), 138.6 (*C*), 129.8 (*C*H), 127.1 (*C*H$_2$), 125.9 (*C*), 112.8 (*C*H), 73.1 (*C*H), 55.1 (*C*H), 51.7 (*C*H$_3$), 35.3 (*C*H$_2$), 31.7 (*C*H$_2$), 29.5 (*C*H$_2$), 29.1 (*C*H$_2$), 25.9 (*C*H$_3$), 25.6 (*C*H$_2$), 22.5 (*C*H$_2$), 20.2 (*C*H$_3$), 18.0 (*C*), 14.0 (*C*H$_3$), -4.5 (*C*H$_3$), -4.6 (*C*H$_3$). Anal. Calcd for $C_{26}H_{45}NO_3Si$: C, 69.75; H, 10.13; N, 3.13. Found: C, 69.86; H, 9.76; N, 3.41.

Characterization data for threo-**5e**. This compound was obtained (0.0422 g, 0.105 mmol, 76%) as colorless oil: IR (NaCl): 3447 (N-H), 2956 (C-H), 2931 (C-H), 2858 (C-H), 1708 cm^{-1} (C=O), 1582 (C=C), 1529 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (m, 1H, Ar*H*), 7.78 (m, 1H, Ar*H*), 7.47-7.44 (m, 2H, Ar*H*), 7.28-7.15 (m, 2H, Ar*H*), 6.31 (d, *J* = 7.2 Hz, 1H, Ar*H*), 6.26 (s, 1H, C*H*$_2$=C), 5.70 (s, 1H, C*H*$_2$=C), 5.46 (d, *J* = 7.2 Hz, 1H, N*H*), 4.46 (d, *J* = 7.2 Hz, 1H, C*H*), 4.18 (dq, *J* = 1.5, 6.0 Hz, 1H, C*H*), 3.83 (s, 3H, OC*H*$_3$), 1.38 (d, *J* = 6.0 Hz, 3H, C*H*$_3$), 0.94 (s, 9H, C(C*H*$_3$)$_3$), 0.09 (s, 3H, C*H*$_3$), -0.03 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6 (*C*=O), 141.8 (*C*), 138.0 (*C*), 134.5 (*C*), 128.9 (*C*H), 126.7 (*C*H), 126.6 (*C*H$_2$), 125.7 (*C*H), 124.7 (*C*H), 123.2 (*C*), 119.6 (*C*H), 116.7 (*C*H), 104.8 (*C*H), 69.3 (*C*H), 58.3 (*C*H), 51.9 (*C*H$_3$), 25.8 (*C*H$_3$), 22.1 (*C*H$_3$), 17.9 (*C*), -4.6 (*C*H$_3$), -4.9 (*C*H$_3$). Anal. Calcd for $C_{23}H_{33}NO_3Si$: C, 69.13; H, 8.32; N, 3.51. Found: C, 68.84; H, 7.92; N, 3.90.

Characterization data for threo-**5f**. This compound was obtained (0.0143 g, 0.0295 mmol, 49%) as colorless oil: IR (NaCl): 3447 (N-H), 3059 (C-H), 2953 (C-H), 2931 (C-H), 2858 (C-H), 1716 cm^{-1} (C=O), 1582 (C=C), 1527 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88-7.77 (m, 2H, Ar*H*), 7.47-7.44 (m, 2H, Ar*H*), 7.28-7.14 (m, 2H, Ar*H*), 6.29 (m, 1H, Ar*H*), 6.27 (s, 1H, C*H*$_2$=C), 5.69 (s, 1H, C*H*$_2$=C), 5.48 (d, *J* = 8.1 Hz, 1H, N*H*), 4.58 (d, *J* = 8.1 Hz, 1H, C*H*), 3.98 (dd, *J* = 4.5, 8.7 Hz, 1H, C*H*), 3.84 (s, 3H, OC*H*$_3$), 1.85 (m, 1H, C*H*$_2$), 1.58 (m, 1H, C*H*$_2$), 1.39-1.20 (m, 10H, C*H*$_2$), 0.94 (s, 9H, C(C*H*$_3$)$_3$), 0.83 (t, *J* = 6.3 Hz, 3H, C*H*$_3$), 0.08 (s, 3H, C*H*$_3$), -0.05 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6 (*C*=O), 141.7 (*C*), 137.8 (*C*), 134.6 (*C*), 128.9 (*C*H), 126.9 (*C*H$_2$), 126.8 (*C*H), 125.7 (*C*H), 124.7 (*C*H), 123.1 (*C*), 119.5 (*C*H), 116.5 (*C*H), 104.6 (*C*H), 73.3 (*C*H), 55.1 (*C*H), 51.8 (*C*H$_3$), 35.7 (*C*H$_2$), 31.7 (*C*H$_2$), 29.6 (*C*H$_2$), 29.1 (*C*H$_2$), 25.9 (*C*H$_3$), 25.6 (*C*H$_2$), 22.5 (*C*H$_2$), 17.9 (*C*), 13.9 (*C*H$_3$), -4.4 (*C*H$_3$), -4.6 (*C*H$_3$). Anal. Calcd for $C_{29}H_{45}NO_3Si$: C, 72.00; H, 9.38; N, 2.90. Found: C, 72.20; H, 9.24; N, 3.26.

Characterization data for erythro-**5b**. This compound was obtained (0.0536 g, 0.124 mmol, 62%) as colorless oil: IR (NaCl): 3397 (N-H), 2953 (C-H), 2929 (C-H), 2856 (C-H), 1717 cm^{-1} (C=O), 1602 (C=C), 1505 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12 (m, 2H, Ar*H*), 6.68 (m, 1H, Ar*H*), 6.53 (m, 2H, Ar*H*), 6.32 (d, *J* = 1.5 Hz, 1H, C*H*$_2$=C), 5.86 (brs, 1H, C*H*$_2$=C), 4.37-4.33 (m, 2H, C*H* and N*H*), 4.05 (m, 1H, C*H*), 3.79 (s, 3H, OC*H*$_3$) 1.58-1.24 (m, 12H, C*H*$_2$), 0.88 (t, *J* = 6.6 Hz, 3H, C*H*$_3$), 0.86 (s, 9H, C(C*H*$_3$)$_3$), 0.08 (s, 3H, C*H*$_3$), 0.03 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3 (*C*=O), 147.5 (*C*), 137.8 (*C*), 129.1 (*C*H), 128.2 (*C*H$_2$), 117.7 (*C*H), 113.9 (*C*H), 72.7 (*C*H), 59.1 (*C*H), 51.7 (*C*H$_3$), 32.1 (*C*H$_2$), 31.7 (*C*H$_2$), 29.5 (*C*H$_2$), 29.1 (*C*H$_2$), 25.7 (*C*H$_3$), 25.5 (*C*H$_2$), 22.5 (*C*H$_2$), 17.9 (*C*), 14.0 (*C*H$_3$), -4.7 (*C*H$_3$), -4.8 (*C*H$_3$). Anal. Calcd for $C_{25}H_{43}NO_3Si$: C, 69.23; H, 9.99; N, 3.23. Found: C, 69.37; H, 9.62; N, 3.63.

Characterization data for erythro-**5c**. This compound was obtained (0.0150 g, 0.0339 mmol, 60%) as colorless oil: IR (NaCl): 3397 (N-H), 3020 (C-H), 2953 (C-H), 2929 (C-H), 2857 (C-H), 1717 cm^{-1} (C=O), 1602 (C=C), 1505 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27-7.11 (m, 7H, Ar*H*), 6.70 (m, 1H, Ar*H*), 6.54 (m, 2H, Ar*H*), 6.33 (d, *J* = 1.2 Hz, 1H, C*H*$_2$=C), 5.87 (d, *J* = 1.2 Hz, 1H, C*H*$_2$=C), 4.39-4.36 (m, 2H, C*H* and N*H*), 4.13 (m, 1H, C*H*), 3.78 (s, 3H, OC*H*$_3$), 2.80 (ddd, *J* = 5.4, 10.8, 13.5 Hz, 1H, C*H*$_2$), 2.58 (ddd, *J* = 5.7, 10.5, 13.5 Hz, 1H, C*H*$_2$), 1.89-1.68 (m, 2H, C*H*$_2$), 0.89 (s, 9H, C(C*H*$_3$)$_3$), 0.11 (s, 3H, C*H*$_3$), 0.02 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2 (*C*=O), 147.5 (*C*), 142.2 (*C*), 137.5 (*C*), 129.1 (*C*H), 128.5 (2*C*H), 128.4 (*C*H$_2$), 125.9 (*C*H), 117.9 (*C*H), 113.9 (*C*H), 72.2 (*C*H), 59.2 (*C*H), 51.8 (*C*H$_3$), 34.1 (*C*H$_2$), 31.9 (*C*H$_2$), 25.7 (*C*H$_3$), 18.0 (*C*), -4.7 (*C*H$_3$), -4.8 (*C*H$_3$). Anal. Calcd for $C_{26}H_{37}NO_3Si$: C, 71.03; H, 8.48; N, 3.19. Found: C, 70.67; H, 8.13; N, 3.58.

Characterization data for erythro-**5d**. This compound was obtained (0.0341 g, 0.0757 mmol, 67%) as colorless oil: IR (NaCl): 3397 (N-H), 3020 (C-H), 2953 (C-H), 2928 (C-H), 2858 (C-H), 1711 cm^{-1} (C=O), 1618 (C=C), 1519 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.92 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.45 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.31 (d, *J* = 1.2 Hz, 1H, C*H*$_2$=C), 5.84 (d, *J* = 1.2 Hz, 1H, C*H*$_2$=C), 4.31-4.26 (m, 2H, C*H* and N*H*), 4.04 (m, 1H, C*H*), 3.78 (s, 3H, OC*H*$_3$), 2.20 (s, 3H, C*H*$_3$), 1.60-1.23 (m, 12H, C*H*$_2$), 0.88 (t, *J* = 6.6. Hz, 3H, C*H*$_3$), 0.86 (s, 9H, C(C*H*$_3$)$_3$), 0.08 (s, 3H, C*H*$_3$), 0.03 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3 (*C*=O), 145.2 (*C*), 137.8 (*C*), 129.6 (*C*H), 128.2 (*C*H$_2$), 126.9 (*C*), 114.0 (*C*H), 72.7 (*C*H), 59.3 (*C*H), 51.7 (*C*H$_3$), 32.1 (*C*H$_2$), 31.7 (*C*H$_2$), 29.5 (*C*H$_2$), 29.2 (*C*H$_2$), 25.7 (*C*H$_3$), 25.5 (*C*H$_2$), 22.5 (*C*H$_2$), 20.3 (*C*H$_3$), 17.9 (*C*), 14.0 (*C*H$_3$), -4.7 (*C*H$_3$), -4.8 (*C*H$_3$). Anal. Calcd for $C_{26}H_{45}NO_3Si$: C, 69.75; H, 10.13; N, 3.13. Found: C, 69.56; H, 9.79; N, 3.53.

Characterization data for erythro-**5e**. This compound was obtained (0.0218 g, 0.0542 mmol, 49%) as colorless oil: IR (NaCl): 3441 (N-H), 3062 (C-H), 2953 (C-H), 2928 (C-H), 2858 (C-H), 1719 cm^{-1} (C=O), 1582 (C=C), 1529 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (m, 1H, Ar*H*), 7.78 (m, 1H, Ar*H*), 7.45-7.43 (m, 2H, Ar*H*), 7.30-7.20 (m, 2H, Ar*H*), 6.44 (dd, *J* = 0.6, 7.2 Hz, 1H, Ar*H*), 6.31 (d, *J* = 1.2 Hz, 1H, CH_2=C), 5.86 (t, *J* = 1.2 Hz, 1H, CH_2=C), 5.31 (d, *J* = 5.1 Hz, 1H, N*H*), 4.49 (t, *J* = 5.1 Hz, 1H, C*H*), 4.36 (dq, *J* = 5.4, 6.3 Hz, 1H, C*H*), 3.81 (s, 3H, OCH_3), 1.23 (d, *J* = 6.3 Hz, 3H, CH_3), 0.88 (s, 9H, C(CH_3)$_3$), 0.11 (s, 3H, CH_3), 0.07 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5 (*C*=O), 142.2 (*C*), 137.4 (*C*), 134.4 (*C*), 128.7 (*C*H), 128.1 (*C*H_2), 126.5 (*C*H), 125.7 (*C*H), 124.8 (*C*H), 124.0 (*C*), 120.0 (*C*H), 117.6 (*C*H), 106.0 (*C*H), 69.3 (*C*H), 59.6 (*C*H), 51.9 (*C*H_3), 25.7 (*C*H_3), 19.6 (*C*H_3), 17.9 (*C*), -4.6 (*C*H_3), -5.0 (*C*H_3). Anal. Calcd for $C_{23}H_{33}NO_3Si$: C, 69.13; H, 8.32; N, 3.51. Found: C, 69.07; H, 8.27; N, 3.79.

Characterization data for erythro-**5f**. This compound was obtained (0.0138 g, 0.0285 mmol, 65%) as colorless oil: IR (NaCl): 3405 (N-H), 2953 (C-H), 2928 (C-H), 2855 (C-H), 1719 cm^{-1} (C=O), 1585 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (m, 1H, Ar*H*), 7.78 (m, 1H, Ar*H*), 7.45 (m, 2H, Ar*H*), 7.27-7.23 (m, 2H, Ar*H*), 6.39 (m, 1H, Ar*H*), 6.34 (s, 1H, CH_2=C), 5.88 (s, 1H, CH_2=C), 5.23 (brs, 1H, N*H*), 4.53 (d, *J* = 3.6 Hz, 1H, C*H*), 4.21 (m, 1H, C*H*), 3.83 (s, 3H, OCH_3), 1.70-1.28 (m, 12H, CH_2), 0.88 (t, *J* = 6.9 Hz, 3H, CH_3), 0.82 (s, 9H, C(CH_3)$_3$), 0.10 (s, 3H, CH_3), 0.00 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3 (*C*=O), 142.4 (*C*), 137.1 (*C*), 134.4 (*C*), 128.7 (*C*H), 128.2 (*C*H_2), 126.5 (*C*H), 125.6 (*C*H), 124.8 (*C*H), 124.2 (*C*), 120.0 (*C*H), 117.8 (*C*H), 106.1 (*C*H), 72.6 (*C*H), 59.2 (*C*H), 51.8 (*C*H_3), 32.0 (2*C*H_2), 31.8 (*C*H_2), 29.6 (*C*H_2), 29.2 (*C*H_2), 25.7 (*C*H_3), 22.5 (*C*H_2), 17.9 (*C*), 14.0 (*C*H_3), -4.7 (*C*H_3), -4.8 (*C*H_3). Anal. Calcd for $C_{29}H_{45}NO_3Si$: C, 72.00; H, 9.38; N, 2.90. Found: C, 72.07; H, 9.15; N, 3.22.

General procedure for the synthesis of β-amino-γ-butyrolactones ***8***

All β-amino-γ-butyrolactones **8** were prepared as described in the following typical procedure. For example, the synthesis of *cis*-**8b** was exemplified as follows.

Preparation of cis-**8b**. To a solution of *threo*-**5b** (0.0250 g, 0.0577 mmol, 1.0 equiv) in THF (0.19 mL) was added acetic acid (0.0050 g, 0.084 mmol, 1.5 equiv) and TBAF (1.0 M, 0.17 mL, 0.17 mmol, 3.0 equiv) with stirring under a nitrogen atmosphere at room temperature. After 11 days, the reaction mixture was concentrated *in vacuo*. Purification of the residue by flush column chromatography on silica gel (eluent: hexane/ethyl acetate = 10/1) gave *cis*-**8b** (0.0114 g, 0.0397 mmol, 69%) as colorless oil: IR (NaCl): 3377 (N-H), 2926 (C-H), 1762 cm^{-1} (C=O), 1603 (C=C), 1507 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23 (m, 2H, Ar*H*), 6.80 (tt, *J* = 0.9, 7.2 Hz, 1H, Ar*H*), 6.67 (m, 2H, Ar*H*), 6.39 (d, *J* = 2.7 Hz, 1H, CH_2=C), 5.83 (d, *J* = 2.7 Hz, 1H, CH_2=C), 4.91 (brs, 1H, C*H*), 4.77 (ddd, *J* = 3.3, 7.5, 9.3 Hz, 1H, C*H*), 3.78 (d, *J* = 6.6 Hz, 1H, N*H*), 1.60-1.23 (m, 12H, CH_2), 0.85 (t, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7 (*C*=O), 146.1 (*C*), 137.3 (*C*), 129.8 (*C*H), 123.7 (*C*H_2), 119.0 (*C*H), 113.1 (*C*H), 81.1 (*C*H), 54.8 (*C*H), 31.6 (*C*H_2), 29.9 (*C*H_2), 29.1 (*C*H_2), 29.0 (*C*H_2), 25.1 (*C*H_2), 22.5 (*C*H_2), 13.9 (*C*H_3). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.19; H, 8.43; N, 5.24.

Characterization data for cis-**8c**. This compound was obtained (0.0100 g, 0.0337 mmol, 70%) as colorless oil: IR (NaCl): 3383 (N-H), 3025 (C-H), 1762 (C=O), 1603 (C=C), 1507 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28-7.10 (m, 7H, Ar*H*), 6.81 (m, 1H, Ar*H*), 6.63-6.60 (m, 2H, Ar*H*), 6.42 (d, *J* = 3.0 Hz, 1H, CH_2=C), 5.86 (d, *J* = 3.0 Hz, 1H, CH_2=C), 4.90 (brs, 1H, C*H*), 4.77 (ddd, *J* = 3.3, 7.5, 11.1 Hz, 1H, C*H*), 3.79 (brs, 1H, N*H*), 2.88 (ddd, *J* = 4.8, 9.0, 13.8 Hz, 1H, CH_2), 2.68 (ddd, *J* = 7.8, 8.7, 13.8 Hz, 1H, CH_2), 1.96-1.70 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6 (*C*=O), 146.0 (*C*), 140.6 (*C*), 137.2 (*C*), 129.8 (*C*H), 128.6 (2*C*H), 126.3 (*C*H), 124.1 (*C*H_2), 119.1 (*C*H), 113.1 (*C*H), 80.1 (*C*H), 54.7 (*C*H), 31.7 (*C*H_2), 31.1 (*C*H_2). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.71; H, 6.56; N, 5.13.

Characterization data for cis-**8d**. This compound was obtained (0.0118 g, 0.0388 mmol, 83%) as colorless oil: IR (NaCl): 3374 (N-H), 2925 (C-H), 2855 (C-H), 1762 (C=O), 1617 (C=C), 1522 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.58 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.37 (d, *J* = 3.0 Hz, 1H, CH_2=C), 5.83 (d, *J* = 3.0 Hz, 1H, CH_2=C), 4.88 (brs, 1H, C*H*), 4.79 (m, 1H, C*H*), 3.67 (brs, 1H, N*H*), 2.26 (s, 3H, CH_3) 1.61-1.23 (m, 12H, CH_2), 0.85 (t, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8 (*C*=O), 143.8 (*C*), 137.4 (*C*), 130.2 (*C*H), 128.3 (*C*), 123.5 (*C*H_2), 113.4 (*C*H), 81.2 (*C*H), 55.1 (*C*H), 31.6 (*C*H_2), 29.9 (*C*H_2), 29.1 (*C*H_2), 29.0 (*C*H_2), 25.1 (*C*H_2), 22.5 (*C*H_2), 20.3 (*C*H_3), 13.9 (*C*H_3). Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.64. Found: C, 75.32; H, 8.69; N, 5.03.

Characterization data for cis-**8e**. This compound was obtained (0.0070 g, 0.027 mmol, 50%) as colorless oil: IR (NaCl): 3397 (N-H), 3053 (C-H), 2981 (C-H), 1761 (C=O), 1581 (C=C), 1528 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85-7.79 (m, 2H, Ar*H*), 7.52-7.49 (m, 2H, Ar*H*), 7.36-7.34 (m, 2H, Ar*H*), 6.46 (m, 1H, Ar*H*), 6.54 (d, *J* = 2.7 Hz, 1H, CH_2=C), 6.01 (d, *J* = 2.7 Hz, 1H, CH_2=C), 5.22-5.08 (m, 2H, C*H*), 4.51 (d, *J* = 7.8 Hz, 1H, N*H*), 1.27 (d, *J* = 6.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.5 (*C*=O), 141.2 (*C*), 137.2 (*C*), 134.5 (*C*), 129.0 (*C*H), 126.4 (*C*H), 126.3 (*C*H), 125.5 (*C*H), 124.9 (*C*H_2), 123.3 (*C*), 119.5 (*C*H), 119.3 (*C*H), 105.1 (*C*H), 77.5 (*C*H), 51.9 (*C*H), 15.5 (*C*H_3). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.04; H, 6.00; N, 5.74.

Characterization data for threo-**9e**. This compound was obtained (0.0052g, 0.018 mmol, 33%) as colorless oil: IR (NaCl): 3436 (N-H), 3061 (C-H), 1762 (C=O), 1582 (C=C), 1522 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (m, 1H, Ar*H*), 7.79 (m, 1H, Ar*H*), 7.48-7.44 (m, 2H,

Ar*H*), 7.32-7.22 (m, 2H, Ar*H*), 6.48 (dd, *J* = 1.5, 7.2 Hz, 1H, Ar*H*), 6.30 (s, 1H, CH_2=C), 5.83 (s, 1H, CH_2=C), 5.38 (brs, 1H, N*H*), 4.38 (d, *J* = 4.2 Hz, 1H, C*H*), 4.20 (dq, *J* = 4.2, 6.0 Hz, 1H, C*H*), 3.80 (s, 3H, OCH_3), 2.54 (brs, 1H, O*H*), 1.36 (d, *J* = 6.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2 (*C*=O), 141.9 (*C*), 138.4 (*C*), 134.5 (*C*), 128.8 (*C*H), 127.6 (*C*H_2), 126.5 (*C*H), 125.9 (*C*H), 125.0 (*C*H), 123.9 (*C*), 120.0 (*C*H), 118.0 (*C*H), 106.0 (*C*H), 68.8 (*C*H), 61.1 (*C*H), 52.1 (*C*H_3), 20.0 (*C*H_3). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.76; H, 6.60; N, 5.02.

Characterization data for cis-**8f**. This compound was obtained (0.0014 g, 4.1 μmol, 33%) as colorless oil: IR (NaCl): 3405 (N-H), 3053 (C-H), 2925 (C-H), 2855 (C-H), 1762 (C=O), 1581 (C=C), 1528 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86-7.78 (m, 2H, Ar*H*), 7.53-7.49 (m, 2H, Ar*H*), 7.36-7.30 (m, 2H, Ar*H*), 6.65 (m, 1H, Ar*H*), 6.49 (d, *J* = 3.0 Hz, 1H, CH_2=C), 5.97 (d, *J* = 3.0 Hz, 1H, CH_2=C), 5.10 (m, 1H, C*H*), 4.96 (m, 1H, C*H*), 4.46 (m, 1H, N*H*), 1.50-1.18 (m, 12H, CH_2), 0.82 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7 (*C*=O), 141.3 (*C*), 137.5 (*C*), 134.5 (*C*), 129.0 (*C*H), 126.4 (*C*H), 126.3 (*C*H), 125.5 (*C*H), 124.0 (*C*H_2), 123.3 (*C*), 119.6 (*C*H), 119.3 (*C*H), 105.1 (*C*H), 81.1 (*C*H), 54.9 (*C*H), 31.6 (*C*H_2), 29.8 (*C*H_2), 29.1 (*C*H_2), 29.0 (*C*H_2), 25.1 (*C*H_2), 22.4 (*C*H_2), 13.9 (*C*H_3). Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.34; H, 7.95; N, 4.51.

Characterization data for threo-**9f**. This compound was obtained (0.0022 g, 6.0 μmol, 48%) as colorless oil: IR (NaCl): 3441 (N-H), 3062 (C-H), 2927 (C-H), 3062 (O-H), 1718 (C=O), 1582 (C=C), 1526 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (m, 1H, Ar*H*), 7.79 (m, 1H, Ar*H*), 7.48-7.44 (m, 2H, Ar*H*), 7.30-7.20 (m, 2H, Ar*H*), 6.42 (m, 1H, Ar*H*), 6.30 (d, *J* = 0.9 Hz, 1H, CH_2=C), 5.80 (s, 1H, CH_2=C), 4.48 (m, 1H, C*H*), 3.95 (m, 1H, C*H*), 3.82 (s, 3H, OCH_3), 1.73-1.26 (m, 12H, CH_2), 0.86 (t, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3 (*C*=O), 141.8 (*C*), 138.5 (*C*), 134.5 (*C*), 128.8 (*C*H), 127.3 (*C*H_2), 126.6 (*C*H), 125.8 (*C*H), 124.9 (*C*H), 123.6 (*C*), 119.9 (*C*H), 117.6 (*C*H), 105.6 (*C*H), 72.5 (*C*H), 58.7 (*C*H), 52.1 (*C*H_3), 34.0 (*C*H_2), 31.7 (*C*H_2), 29.4 (*C*H_2), 29.1 (*C*H_2), 25.8 (*C*H_2), 22.5 (*C*H_2), 14.0 (*C*H_3). Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.47; H, 8.30; N, 4.18.

Characterization data for trans-**8b**. This compound was obtained (0.0140 g, 0.0487 mmol, 75%) as colorless oil: IR (NaCl): 3377 (N-H), 2927 (C-H), 2855 (C-H), 1762 (C=O), 1604 (C=C), 1507 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (m, 2H, Ar*H*), 6.80 (tt, *J* = 0.9, 7.2 Hz, 1H, Ar*H*), 6.66 (m, 2H, Ar*H*), 6.35 (d, *J* = 2.4 Hz, 1H, CH_2=C), 5.86 (d, *J* = 2.4 Hz, 1H, CH_2=C), 4.42 (brs, 1H, C*H*), 4.26 (ddd, *J* = 4.2, 5.1, 8.4 Hz, 1H, C*H*), 3.84 (brs, 1H, N*H*), 1.86-1.20 (m, 12H, CH_2), 0.87 (t, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0 (*C*=O), 146.0 (*C*), 138.2 (*C*), 129.7 (*C*H), 124.9 (*C*H_2), 119.1 (*C*H), 113.6 (*C*H), 83.8 (*C*H), 57.7 (*C*H), 34.5 (*C*H_2), 31.6 (*C*H_2), 29.1 (*C*H_2), 28.9 (*C*H_2), 25.0 (*C*H_2), 22.5 (*C*H_2), 13.9 (*C*H_3). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.33; H, 8.40; N, 5.20.

Characterization data for trans-**8c**. This compound was obtained (0.0086 g, 0.029 mmol, 86%) as colorless oil: IR (NaCl): 3366 (N-H), 3051 (C-H), 2978 (C-H), 1762 (C=O), 1602 (C=C), 1507 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31-7.17 (m, 7H, Ar*H*), 6.80 (m, 1H, Ar*H*), 6.63 (m, 2H, Ar*H*), 6.36 (d, *J* = 2.4 Hz, 1H, CH_2=C), 5.87 (d, *J* = 2.4 Hz, 1H, CH_2=C), 4.46 (brs, 1H, C*H*), 4.22 (ddd, *J* = 3.6, 5.4, 9.0 Hz, 1H, C*H*), 3.74 (brs, 1H, N*H*), 2.92 (ddd, *J* = 5.1, 9.6, 14.1 Hz, 1H, CH_2), 2.77 (ddd, *J* = 7.2, 9.0, 14.1 Hz, 1H, CH_2), 2.24-1.98 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9 (*C*=O), 145.9 (*C*), 140.5 (*C*), 138.1 (*C*), 129.7 (*C*H), 128.6 (*C*H), 128.5 (*C*H), 126.3 (*C*H), 125.0 (*C*H_2), 119.2 (*C*H), 113.6 (*C*H), 82.8 (*C*H), 57.8 (*C*H), 36.2 (*C*H_2), 31.3 (*C*H_2). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.72; H, 6.52; N, 5.05.

Characterization data for trans-**8d**. This compound was obtained (0.0133 g, 0.0437 mmol, 65%) as colorless oil with a fractional recovery of *erythro*-**5d** (0.0041 g, 9.1 μmol, 13%): IR (NaCl): 3330 (N-H), 2925 (C-H), 2855 (C-H), 1730 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.58 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.33 (d, *J* = 2.4 Hz, 1H, CH_2=C), 5.85 (d, *J* = 2.4 Hz, 1H, CH_2=C), 4.38 (m, 1H, C*H*), 4.24 (dt, *J* = 4.2, 8.4 Hz, 1H, C*H*), 3.67 (brs, 1H, N*H*), 2.26 (s, 3H, CH_3) 1.88-1.26 (m, 12H, CH_2), 0.88 (t, *J* = 7.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1 (*C*=O), 143.6 (*C*), 138.3 (*C*), 130.2 (*C*H), 128.3 (*C*), 124.8 (*C*H_2), 113.9 (*C*H), 83.9 (*C*H), 58.0 (*C*H), 34.5 (*C*H_2), 31.6 (*C*H_2), 29.1 (*C*H_2), 29.0 (*C*H_2), 25.0 (*C*H_2), 22.5 (*C*H_2), 20.3 (*C*H_3), 13.9 (*C*H_3). Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.64. Found: C, 75.38; H, 8.85; N, 4.97.

Characterization data for trans-**8e**. This compound was obtained (0.0110 g, 0.0430 mmol, 79%) as colorless oil: IR (NaCl): 3397 (N-H), 3051 (C-H), 2978 (C-H), 1759 (C=O), 1581 (C=C), 1534 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85-7.76 (m, 2H, Ar*H*), 7.50-7.48 (m, 2H, Ar*H*), 7.36-7.34 (m, 2H, Ar*H*), 6.63 (m, 1H, Ar*H*), 6.46 (d, *J* = 1.5 Hz, 1H, CH_2=C), 5.98 (d, *J* = 1.5 Hz, 1H, CH_2=C), 4.56-4.54 (m, 2H, 2C*H*), 4.48 (brs, 1H, N*H*), 1.57 (d, *J* = 6.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9 (*C*=O), 141.2 (*C*), 138.0 (*C*), 134.6 (*C*), 128.9 (*C*H), 126.3 (*C*H), 126.2 (*C*H), 125.9 (*C*H_2), 125.5 (*C*H), 123.7 (*C*) 119.8 (*C*H), 119.4 (*C*H), 105.6 (*C*H), 80.3 (*C*H), 59.0 (*C*H), 20.2 (*C*H_3). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.70; H, 5.81; N, 5.80.

Characterization data for trans-**8f**. This compound was obtained (0.0066 g, 0.020 mmol, 69%) as colorless oil with a fractional recovery of *erythro*-**5f** (0.0021 g, 4.3 μmol, 15%): IR (NaCl): 3396 (N-H), 2927 (C-H), 2855 (C-H), 1757 (C=O), 1582 (C=C), 1534 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86-7.76 (m, 2H, Ar*H*), 7.52-7.47 (m, 2H, Ar*H*), 7.36-7.34 (m, 2H, Ar*H*), 6.66 (m, 1H, Ar*H*), 6.43 (d, *J* = 2.4 Hz, 1H, CH_2=C), 5.95 (d, *J* = 2.4 Hz, 1H, CH_2=C), 4.61 (brs, 1H, C*H*), 4.45-4.39 (m, 2H,

C*H* and N*H*), 1.96-1.24 (m, 12H, CH_2), 0.89-0.85 (m, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1 (*C*=O), 141.2 (CH_2=*C*), 138.2 (*C*), 134.5 (*C*), 128.9 (*C*H), 126.3 (*C*H), 126.2 (CH_2=C), 125.4 (*C*H), 123.7 (*C*), 125.4 (*C*H), 119.8 (*C*H), 119.4 (*C*H), 105.7 (*C*H), 83.8 (*C*H), 57.7 (*C*H), 34.6 (CH_2), 31.6 (*C*H_2), 29.1 (*C*H_2), 29.0 (*C*H_2), 25.0 (*C*H_2), 22.5 (*C*H_2), 13.9 (*C*H_3). Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.14; H, 7.95; N, 4.23.

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(10) The compound **6** was obtained as a single diastereomer whose stereochemistry was not determined. ^{1}H NMR data for **6**: δ 3.80 (q, *J* = 5.1 Hz, 1H, C*H*), 3.68-3.56 (m, 4H, C*H*, C*H*), 3.45 (dt, *J* = 7.8, 13.8 Hz, 1H, CH_2), 3.35 (s, 3H, OCH_3), 3.00-2.92 (m, 2H, CH_2), 1.59-1.27 (m, 18H, CH_2), 0.92-0.86 (m, 6H, CH_3), 0.90 (s, 9H, C(CH_3)$_3$), 0.08 (s, 3H, CH_3), 0.07 (s, 3H, CH_3).

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(13) It should be noted that our initial attempts to generate the target compounds via cyclization of γ-hydroxy esters under basic and/or mild acidic conditions failed due to low stability of the products.

(14) The formation of *cis*-**8e** and -**8f** may be interpreted in terms of intramolecular nucleophilic attacks of alkoxides in situ generated from removal of the TBS groups, which would act as the primary reactive species.

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