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Regioselective electrophilic substitution of 2,3-aziridino-γ-lactones: preliminary studies aimed at the synthesis of α,α-disubstituted α- or β-amino acids

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Abstract

2,3-Aziridino-γ-lactones are versatile synthons for the preparation of polysubstituted α- or β-amino acids. With the intention of preparing α,α-disubstituted α- or β-amino acids, regioselective electrophilic substitution of aziridino-γ-lactones at C2 was realized using two different methods. In the first, the anion was generated at C2 with LDA in the presence of the electrophilic agent. In the second method, the anion was trapped with TMS. Subsequent treatment of the C2 silylated product with a fluoride ion source regenerated the anion, which then reacted in situ with various electrophiles. Intramolecular aziridine opening of the C2 benzyl derivative prepared by the first method allowed access to a novel furan derivative, a direct precursor of an α,α-disubstituted β-amino acid.

1. Introduction

Chiral non-racemic aziridine carboxylic esters are easily prepared compounds which, by virtue of their propensity to nucleophilic attack at C3 by all types of nucleophiles, allow a convenient access to a wide variety of α-amino acids.[1] In order to allow preparation of more complex α-amino acids, and particularly their α-substituted versions,[2] several groups have studied the possibility of generating stabilized anion species from such aziridine esters or their equivalents and reacting these with electrophiles.[3] The first reported attempts in this direction were those of Seebach and co-workers.[4] While treatment of aziridine esters with LDA in THF at −78 °C led only to degradation or self-condensation, replacement of the carboxylate function by a thiol ester (**1**) allowed formation of the C2 anion under the same conditions and subsequent incorporation of substituents at this position (Fig. 1). Conversion of the ester functionality into an oxazoline (**2a**) or thiazoline (**2b**) also allowed Florio and co-workers[5] to generate the C2 lithiated species using *n*-butyllithium at −78 °C, which could be reacted with a variety of electrophiles. Using a *tert*-butyl ester to minimize self-condensation and a 2-methoxy-1-phenylethyl group on the aziridine nitrogen to stabilize the anion (**3**), Husson and co-workers[6] were able to prepare the C2 lithiated derivative with LDA in THF at −78 °C. They obtained C2 substituted aziridines in reasonable yields and with generally excellent retention of configuration in contrast to results with the thiol esters. More recently, Wulff and co-workers[7] described the successful lithiation/electrophilic substitution at C2 of C3-substituted *N*-benzhydryl protected aziridine

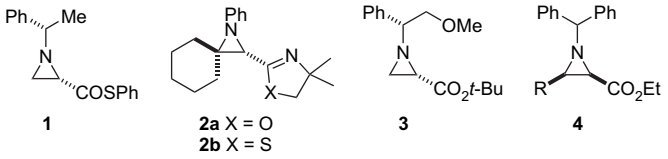

Figure 1.

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2-carboxylates (**4**) also using LDA. Interestingly, the self-condensation product was observed only when no substituent was present at C3 (R=H). Both retention and inversion of configuration at C2 were observed depending on the electrophile.

In our laboratory, 2,3-aziridino-γ-lactones (**5**) have been used as synthetic tools for the preparation of polysubstituted α- or β-amino acids as demonstrated by the synthesis of (−)-polyoxamic acid (**6**),[8] (2*S*,3*S*,4*S*)-3,4-dihydroxyglutamic acid (**7**),[9] and APTO (**8**), the β-amino acid fragment of microsclerodermins C and D (Fig. 2).[10] In contrast to aziridine carboxylic esters, this possibility of preparing either type of amino acid is due to a particular feature of 2,3-aziridino-γ-lactones whereby they are attacked regioselectively at C2 or C3 by soft or hard nucleophiles, respectively.[11]

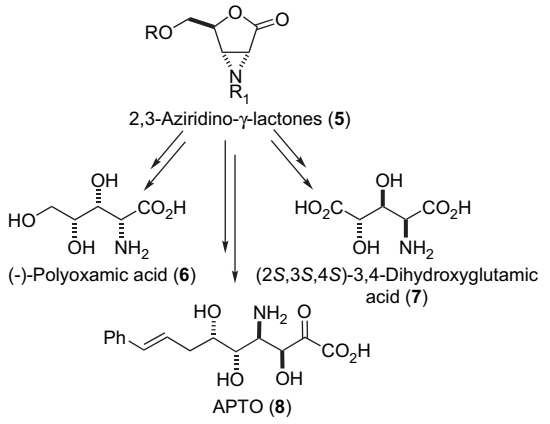


Figure 2.

By analogy with the formation of lithiated aziridine carboxylic esters and their derivatives, we decided to investigate the possibility of preparing C2 lithiated aziridino-γ-lactones and their subsequent reaction with electrophiles. The resulting new α-substituted aziridine-γ-lactones formed (**9**) can be envisaged as synthons for the preparation of α,α-disubstituted α- or β-amino acids such as **10** and **11**, respectively (Fig. 3). In comparison with aziridine *tert*-butyl esters **3** or the C2 oxa- and thiazolines **2**, the lactone function of our synthons was anticipated to be particularly sensitive to strong lithiating bases. On the other hand, the rigid nature of these substrates was expected to guarantee the configurational stability of the anion generated.

We present herein two complementary methodologies for the regioselective electrophilic substitution of 2,3-aziridino-γ-lactones as a first step toward the synthesis of α,α-disubstituted amino acids. Preliminary results concerning intra- and intermolecular nucleophilic ring opening of these substrates are also presented.

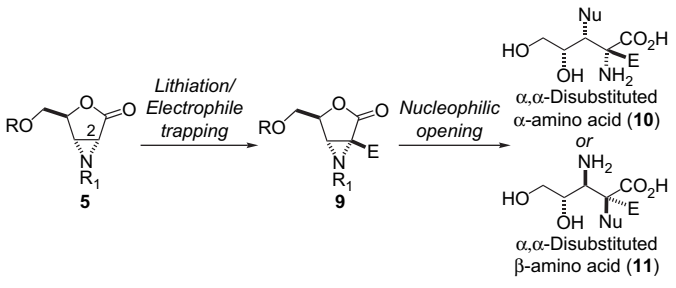
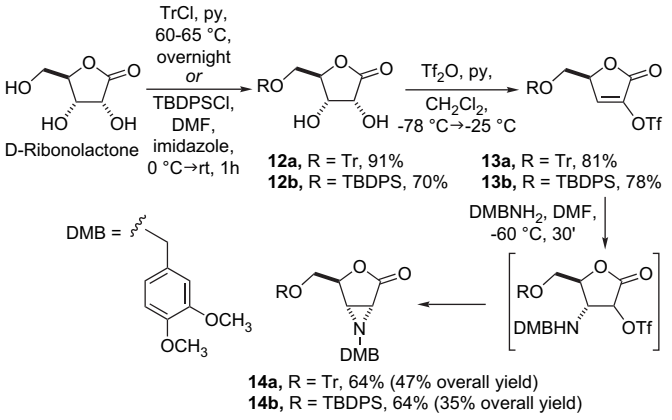


Figure 3.

2. Results and discussion

2.1. Preparation of 2,3-aziridino-γ-lactones

We have previously shown that 2,3-aziridino-γ-lactones of type **5** can be conveniently prepared in three steps starting from D-ribonolactone.[8,12] For the purposes of this study, the primary hydroxyl group of the latter was first selectively protected with a trityl[13] or a TBDPS[14] group (Scheme 1, **12a** and **12b**, respectively). These were treated with triflic anhydride/pyridine at −78 °C to generate the corresponding enol triflates **13a** (81%) and **13b** (78%). The aziridines **14a** and **14b** were then formed in good yields (64%) by way of a Michael-type 1,4-addition of 3,4-dimethoxybenzylamine ($DMBNH_2$) in DMF with concomitant cyclization. As previously demonstrated,[8] the DMB group can be easily replaced by an electron-withdrawing substituent in order to activate aziridine ring opening (vide infra).

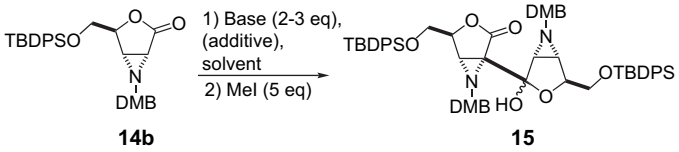


Scheme 1.

2.2. Electrophilic substitution of 2,3-aziridino-γ-lactones

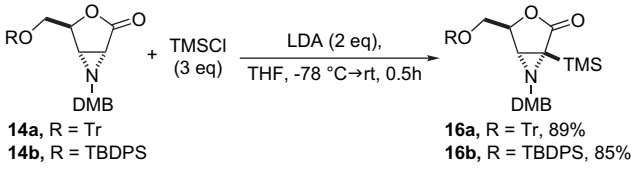
We first investigated formation of aziridine-γ-lactone anions using Husson's[6] reaction conditions for the lithiation of *tert*-butyl aziridine-2-carboxylates (**3**). Thus, treatment of **14b** with 2 equiv of freshly prepared LDA in THF at −78 °C for 1 h followed by addition of methyl iodide and DMPU led exclusively to formation of the self-condensation product **15** (25%) accompanied by degradation products (Scheme 2). Use of a 5:1 mixture of DME and Et_2O as solvent[6] led, in the absence of DMPU, essentially to the same result. Hodgson and co-workers[15] have shown that aziridine anions can be effectively generated using very short exposure to LTMP as base followed by addition of the electrophile. In our hands, treatment of **14b** with 3 equiv of LTMP in THF for 90 s at −78 °C followed by addition of methyl iodide led once more to formation of dimer **15** in 35% yield as the only

isolable product. These results indicate that the C2 anion is indeed formed under these reaction conditions but reacts rapidly with the lactone function before it can be trapped by the electrophile.



Scheme 2.

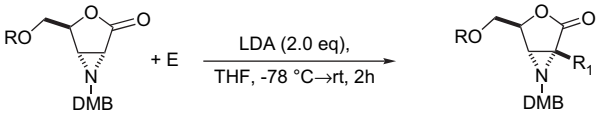
A similar observation was made by Kobayashi and co-workers[16] during the course of their study of the anion derived from an α,β-epoxy-γ-butyrolactone. A solution to this problem was found by generating the anion in the presence of an excess of the electrophilic agent, in their case, TMSCl, thereby trapping the anion before it can react to form the dimer. We were thus pleased to observe that addition of a solution of aziridine **14a** and of excess TMSCl in THF to a solution of LDA in THF at −78 °C led, after 0.5 h at room temperature, to formation of the desired C2-trimethylsilyl aziridine-γ-lactone derivative **16a**, obtained in 89% yield after flash chromatography. Under the same reaction conditions, the 5-*O*-TBDPS aziridine-γ-lactone **14b** furnished the analogous TMS derivative **16b** in 85% yield (Scheme 3).



Scheme 3.

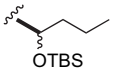
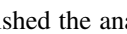
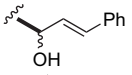
Using this methodology (Table 1), a variety of electrophiles could now be introduced at C2 of aziridines **14a** in generally reasonable to good yields and starting material was recovered in almost all cases. Thus, while use of methyl iodide still gave no C2-alkylated product starting from **14a**, the use of another alkyl halide, benzyl bromide, gave a low but reproducible yield of the expected C2 benzyl derivative **18a** (25%, entry 2). In contrast, benzaldehyde gave a satisfactory yield of the addition product from **14a**, isolated as the more stable *tert*-butyldimethylsilyl derivative **19a** by treatment of the crude product with TBSOTf/Et_3N (51%, entry 3). Use of pivaldehyde as electrophile also gave a good yield of addition product **20a** (66%, entry 4) while enolizable aldehydes such as isobutyraldehyde and butyraldehyde were less satisfactory (**21a**, 30%, and **22a**, 15%, entries 5 and 6) as was *trans*-cinnamaldehyde (**23a**, 28%, entry 7). In contrast to the analogous results of Kobayashi using epoxy-γ-butyrolactone substrates,[16] no appreciable diastereoselectivity was observed with respect to the newly created chiral center in these products. Reaction of ketones with the aziridine anion of **14a** gave more consistent results. Thus, the use of cyclopentanone, cyclohexanone, and 3-pentanone afforded the expected products **24a**, **25a**, and **26a**, respectively, in 44, 56, and 45% yields (entries 8–10). Other electrophiles such as benzenesulfonyl

Table 1
Electrophilic substitution of **14a** and **14b** by electrophiles mediated by LDA



14a: R = Tr
14b: R = TBDPS

17a-29a: R = Tr
17b, 18b, 24b, 26b, 28b: R = TBDPS

Entry	E	Product (R_1)	Yield[a] (%)	
			R=Tr	R=TBDPS
1	MeI	Me	**17a**:0	**17b**:10
2	BnBr	Bn	**18a**:25	**18b**:25
3	PhCHO		**19a**:51[b]	
4	*tert*-BuCHO		**20a**:66	
5	*i*-PrCHO		**21a**:30[b]	
6	*n*-PrCHO		**22a**:15[b]	
7			**23a**:28	
8	Cyclopentanone		**24a**:44	**24b**:33
9	Cyclohexanone		**25a**:56	
10	$Et_2C{=}O$		**26a**:45	**26b**:40
11	$PhSO_2F$	SO_2Ph	**27a**:62	
12	Bu_3SnCl	$SnBu_3$	**28a**:55	**28b**:48
13	I_2	I	**29a**:41	

[a] The yields were calculated based on the recovery of starting material.
[b] Isolated as the silylated derivative (TBSOTf, Et_3N, CH_2Cl_2).

fluoride and tri-*n*-butylstannyl chloride also provided the corresponding C2 substituted aziridine lactones **27a** and **28a** in good yields (62 and 55%, entries 11 and 12) while iodine gave the 2-iodo product **29a** in 41% yield (entry 13). Use of the 5-*O*-TBDPS aziridine-γ-lactone **14b** as starting material in these reactions gave essentially similar results for the electrophiles tested (entries 2, 8, 10, and 12) except in the case of methyl iodide whereby the C2 methylated aziridino-γ-lactone **17b** could finally be isolated, albeit in low yield (10%, entry 1). The poor results with methyl iodide are probably due to its incompatibility with a strong lithiated base such as LDA.[17]

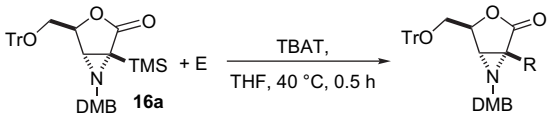
As demonstrated by Kobayashi and co-workers[16] using epoxy-γ-butyrolactones and Aggarwal and co-workers[18] using simple aziridines, treatment of their C2 TMS derivatives with a fluoride ion source at room temperature or at 40 °C, respectively, generates the corresponding anion, which reacts

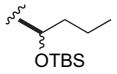
cleanly with diverse electrophiles. Application of this technique to the TMS aziridine-γ-lactones **16a** and **16b**, obtained in very high yields from **14a** and **14b**, respectively would thus present an alternative route to the C2 substituted derivatives described in Table 1.

In initial experiments, a solution of the silylated aziridine **16a** and excess aldehyde (benzaldehyde, propionaldehyde) in THF treated at −40 °C or at −30 °C with 1 equiv of TBAT (tetrabutylammonium triphenyldifluorosilicate)[19] resulted only in recovery of starting material. On the other hand, when the reaction was conducted at room temperature, the product of desilylation **14a** was obtained suggesting that the anion is indeed formed under these conditions but is insufficiently reactive with respect to the aldehyde. Finally, addition of a mixture of silylated aziridine **16a** and benzaldehyde to a solution of TBAT in THF held at 40 °C gave, after 30 min and after in situ silylation of the secondary hydroxyl group, product **19a** in 51% yield (entry 3, Table 2) identical to that obtained by the previous method (entry 3, Table 1). Again, no diastereoselectivity was observed in this reaction in contrast to the results observed by Aggarwal and co-workers.[18]

This methodology was applied to other electrophiles in order to compare its efficiency with that of the one-step procedure shown in Table 1. Except in the case of benzaldehyde (entry 3) the yields of C2 substituted aziridines were consistently lower using the other aldehydes (isobutyraldehyde, butyraldehyde, entries 4 and 5) and ketones (cyclopentanone, cyclohexanone, 3-pentanone, entries 6–8) as electrophiles. Similarly, benzenesulfonyl fluoride and iodine gave lower yields of C2 substituted products **27a** and **29a**, respectively (32 and 16%, entries 9 and 11, compared to 62 and 41% via the one-step procedure). In contrast to the one-step procedure, however, neither methyl iodide, benzyl bromide nor tri-*n*-butylstannyl chloride gave the expected products starting from silylated aziridine **16a** (entries 1, 2, and 10, respectively). This procedure thus appears to be generally less satisfactory than the direct lithiation/electrophilic substitution method.

Table 2
Electrophilic substitution of **16a** by electrophiles mediated by TBAT



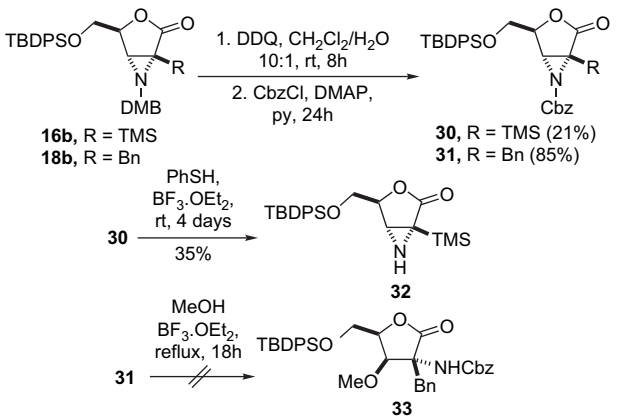
Entry	E	Product (R)	Yield[a] (%)
1	MeI	Me	**17a**:0
2	BnBr	Bn	**18a**:0
3	PhCHO		**19a**:51[b]
4	*i*-PrCHO		**21a**:19[b]
5	*n*-PrCHO		**22a**:10[b]
6	Cyclopentanone		**24a**:21
7	Cyclohexanone		**25a**:43
8	$Et_2C{=}O$		**26a**:30
9	$PhSO_2F$	SO_2Ph	**27a**:32
10	Bu_3SnCl	$SnBu_3$	**28a**:0
11	I_2	I	**29a**:16

[a] The yields were calculated based on the recovery of starting material.
[b] Isolated as the silylated derivative (TBSOTf, Et_3N, CH_2Cl_2).

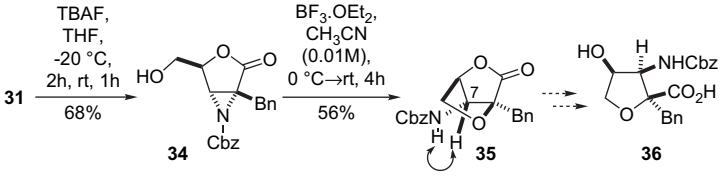
2.3. Intra/intermolecular opening of the C2 substituted aziridino-γ-lactones: preliminary results

To examine the reactivity and the regioselectivity of nucleophilic ring opening of C2 substituted aziridino-γ-lactones, the DMB group was first replaced by a more activating Cbz group (Scheme 4).[8,20] Thus, treatment of the C2 silyl and benzyl aziridino-γ-lactones **16b** and **18b** with DDQ in wet CH_2Cl_2 at room temperature for 8 h followed by reaction of the crude products with CbzCl in pyridine provided the corresponding *N*-Cbz aziridine derivatives **30** and **31**, respectively. Treatment of compound **30** with excess thiophenol (solvent) in the presence of $BF_3{\cdot}Et_2O$, conditions shown previously by us to provide high yields of aziridine ring opened products when the C2 position is unsubstituted (i.e., of type **5**),[11] gave in this case only the product of Cbz cleavage, compound **32**. Alternatively, treatment of compound **31** with methanol and $BF_3{\cdot}Et_2O$ at reflux for 18 h led to degradation products with no observable formation of the desired C3 ring-opened product **33**. This unexpected lack of reactivity of these C2 substituted aziridino-γ-lactones may be attributed to the high steric hindrance provided by the combination of the C2 substituent and the OTBDPS group at C5.

We thus proceeded to remove the latter by treating compound **31** with TBAF in THF, affording compound **34** in 68% yield (Scheme 5). Interestingly, treatment of alcohol **34**



Scheme 4.



Scheme 5.

with $BF_3 \cdot OEt_2$ in CH_3CN at room temperature provided bicyclic lactone **35** in 56% yield, the product of regioselective intramolecular aziridine ring opening at the more substituted carbon (C2) with concomitant inversion of configuration. The regioselectivity of attack was confirmed by a COSY experiment, which indicated a coupling between the hydrogen atom of the amine and H7. The formation of compound **35** opens the way to the preparation of potentially valuable, highly substituted, optically pure tetrahydrofuran derivatives (**36**) after hydrolysis of the lactone.

3. Conclusion

In conclusion, we have demonstrated that regioselective substitution at C2 of 2,3-aziridino-γ-lactones by a variety of electrophiles is possible using two different but complementary methodologies. The more direct method, involving LDA treatment of the aziridine substrate in the presence of the electrophile, generally presented better results than that in which the anion is first trapped by a TMS group and is afterward regenerated by fluoride ion. Attempts at intermolecular aziridine opening have so far failed, most likely for reasons of steric hindrance around both electrophilic sites. However, intramolecular aziridine opening at C2 by the 5-hydroxy group of the 2-benzyl aziridine-γ-lactone **34** was successful, providing a precursor of a tetrahydrofuran derivative having three contiguous stereogenic centers. The latter (**36**), particularly rich in synthetic possibilities, may also be seen as an α,α-disubstituted β-amino acid. The possibility of improving the yields of lithiation/electrophilic trapping of aziridino-γ-lactones by incorporating an *N*-substituent able to chelate the C2 anion is currently being investigated as is the use of less sterically encumbered substrates, which can facilitate intermolecular aziridine opening of the C2 substituted derivatives.

4. Experimental

4.1. General

Melting points, measured in capillary tubes and recorded using a Büchi B-540 melting point apparatus, are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR spectrometer. Optical rotations were determined with a JASCO P-1010 polarimeter. Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on Bruker spectrometers: AC 250 (250 MHz), Aspect 3000 (300 MHz), Avance 300 NMR or 500 NMR (300 and 500 MHz, respectively). Chemical shifts (δ) are reported in parts per million (ppm) with reference to tetramethylsilane (TMS) as internal standard. NMR experiments were carried out in deuterochloroform ($CDCl_3$) or in deuterobenzene (C_6D_6). The following abbreviations are used for the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet for proton spectra. Coupling constants (J) are reported in hertz (Hz). Mass spectra were obtained either with an AEI MS-9 instrument using electron spray (ESI-MS) or with a MALDI-TOF instrument for high resolution mass spectra (HREIMS). Thin-layer chromatography was performed on silica gel 60 plates with a fluorescent indicator and visualized under a UVP Mineralight UVGL-58 lamp (254 nm) and with a 7% solution of phosphomolybdic acid in ethanol. Flash chromatography was performed using silica gel 60 (40–63 μm, 230–400 mesh ASTM) at medium pressure (200 mbar). All solvents were distilled and stored over 4 Å molecular sieves before use. Benzaldehyde, isobutyraldehyde, butyraldehyde, cyclopentanone, and cyclohexanone were dried over $CaSO_4$, distilled and stored over 4 Å molecular sieves before use. Et_3N and pyridine were dried over sodium metal, distilled and stored over 4 Å molecular sieves. All reagents were obtained from commercial suppliers unless otherwise stated. Organic extracts were, in general, dried over magnesium sulfate ($MgSO_4$) or sodium sulfate (Na_2SO_4). Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

*4.2. (3R,4S,5R)-3,4-Dihydroxy-5-(trityloxymethyl)-dihydrofuran-2(3H)-one (**12a**)*

To a solution of D-ribonolactone (2.00 g, 13.50 mmol) in pyridine (100 mL) was added chlorotriphenylmethane (4.54 g, 16.30 mmol) under argon. The reaction mixture was stirred at 60–65 °C overnight. The cooled mixture was then diluted with methanol (10 mL), concentrated under vacuum to 1/3 of volume, diluted again with CH_2Cl_2 (110 mL), and washed successively with water (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and water (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and the solvent was removed in vacuo. Hot EtOAc (35 mL) was added to the residue and the insoluble solids formed were removed by filtration. The filtrate was concentrated and the oil obtained was dissolved in warm heptane (30 mL) and chloroform (5 mL). The solution was stored at 0 °C overnight affording compound **12a** as a white solid (4.79 g, 12.28 mmol) in 91% yield. R_f 0.23 (EtOAc/heptane 1:1); $[\alpha]_D^{20}$ +43.0 (*c* 1.08, CH_2Cl_2) (lit.[13] $[\alpha]_D^{20}$ +50.0 (*c* 3.80, CH_2Cl_2)); mp 172–174 °C (lit.[13] 172–173 °C); IR (film, cm^{-1}): 3428 (OH), 3059, 2922, 1781 (C=O), 1449, 1092; ^1H NMR (300 MHz, $CDCl_3$): δ 3.19 (dd, J=2.3, 11.1 Hz, 1H, H6), 3.67 (dd, J=3.0, 11.1 Hz, 1H, H6′), 4.25 (d, J=5.1 Hz,

1H, H4), 4.52 (m, 1H, H5), 4.88 (d, J=5.5 Hz, 1H, H3), 7.20–7.41 (m, 15H, H arom); ESI-MS m/z 391 $[M+H]^+$.

4.3. (3R,4S,5R)-5-((tert-Butyldiphenylsilyloxy)methyl)-3,4-dihydroxydihydrofuran-2(3H)-one (**12b**)

To a solution of D-ribonolactone (4.00 g, 27.0 mmol) in *N*,*N*-dimethylformamide (27 mL) held at 0 °C under argon, were successively added imidazole (4.04 g, 59.0 mmol) and *tert*-butyldiphenylsilyl chloride (7.6 mL, 30.0 mmol). After 30 min of stirring at 0 °C, the mixture was warmed to room temperature and stirred for an additional 30 min. The reaction solution was diluted with EtOAc (35 mL) and water (35 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2×30 mL). The organic extracts were combined, washed with water (2×30 mL), dried over $MgSO_4$, and evaporated to dryness. The resulting residue was purified by flash chromatography on silica gel (heptane/EtOAc 2:1) to afford the diol **12b** (7.30 g, 19.03 mmol) in 70% yield as a white solid. R_f 0.30 (EtOAc/heptane 7:3); $[\alpha]_D^{21}$ +43 (c 1.35, $CHCl_3$) (lit.[14] $[\alpha]_D^{21}$ +46.3 (c 0.84, $CHCl_3$)); mp 69.5–71 °C (lit.[14] 65–70 °C); IR (film, cm^{-1}): 3362, 1782, 1427, 1178, 1113, 700; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.99 (s, 9H, C(CH_3)$_3$), 3.82 (dd, J=2.1, 11.9 Hz, 1H, H6), 3.91 (dd, J=2.8, 11.9 Hz, 1H, H6′), 4.52 (t, J=2.3 Hz, 1H, H5), 4.55 (d, J=5.5 Hz, 1H, H4), 4.88 (d, J=5.7 Hz, 1H, H3), 7.2–7.6 (m, 10H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.5, 63.4, 69.4, 70.3, 85.6, 128.1, 130.2, 131.8, 132.2, 135.5, 135.6, 176.8 (C=O).

4.4. (S)-2-Oxo-5-(trityloxymethyl)-2,5-dihydrofuran-3-yl trifluoromethanesulfonate (**13a**)

To a solution of diol **12a** (1.20 g, 3.10 mmol) in CH_2Cl_2 were added pyridine (1.2 mL, 15.00 mmol) and trifluoromethanesulfonic anhydride (1.4 mL, 8.00 mmol) at −78 °C under argon. The reaction mixture was stirred for 15 min at −78 °C and then at −25 °C for 3 h. The solution was added to cold ether (100 mL), the salt precipitate was removed by filtration and the filtrate was concentrated in vacuo at 0 °C. The orange solid obtained was purified by column chromatography on silica gel (EtOAc/heptane 1:2) to give the product **13a** as a yellow solid (1.27 g, 2.50 mmol) in 81% yield. R_f 0.73 (EtOAc/heptane 1:1); IR (film, cm^{-1}): 3033, 3020, 2995, 1788 (C=O), 1653 (C=C), 1436, 1138 (SO_2); ^1H NMR (300 MHz, $CDCl_3$): δ 3.46 (dd, J=4.4, 10.5 Hz, 1H, H6), 3.57 (dd, J=4.6, 10.5 Hz, 1H, H6′), 5.10 (dt, J=1.9, 4.5, 4.5 Hz, 1H, H5), 7.30 (m, 16H, H arom and H4); ^{13}C NMR (75 MHz, $CDCl_3$): δ 62.9 (C6), 77.8 (C5), 87.5 (CPh_3), 128.0, 127.6, 128.2, 128.6 (CH arom), 136.3 (C4), 137.9 (C3), 143.1 (Cq, CPh_3), 164.0 (C=O); ESI-MS m/z 527 $[M+Na]^+$.

4.5. (S)-5-((tert-Butyldiphenylsilyloxy)methyl)-2-oxo-2,5-dihydrofuran-3-yl trifluoromethanesulfonate (**13b**)

To a solution of diol **12b** (3.50 g, 9.10 mmol) in CH_2Cl_2 (85 mL) held at −78 °C under argon were successively added pyridine (3.5 mL, 45.51 mmol) and a solution of trifluoromethanesulfonic anhydride (4.20 mL, 24.60 mmol) in CH_2Cl_2 (30 mL). After 15 min of stirring at −78 °C, the reaction mixture was slowly warmed to −25 °C over a period of 3 h. The reaction solution was then poured into cold diethyl ether (110 mL). The precipitate was removed by filtration and the filtrate was evaporated in vacuo at 0 °C. The resulting residue was purified by flash chromatography on silica gel (EtOAc/heptane 1:2) to afford triflate **13b** (3.55 g, 7.1 mmol, 78%) as a yellow oil. R_f 0.80 (EtOAc/heptane 1:1); IR (film, cm^{-1}): 3073, 2934, 2861, 1792, 1656, 1433, 1221, 1137, 1104, 703; ^1H NMR (250 MHz, $CDCl_3$): δ 0.98 (s, 9H, C(CH_3)$_3$), 3.84 (ddd, J=3.8, 4.5, 11.5 Hz, 2H, H6, H6′), 4.98 (dt, J=4.1, 1.8 Hz, 1H, H5), 7.03 (d, J=1.9 Hz, 1H, H4), 7.2–7.6 (m, 10H, H arom); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.7, 26.6, 62.7, 88.1, 121.0, 128.0, 128.3, 130.2, 132.0, 132.2, 135.5, 135.7, 138.0, 163.6 (C=O); HREIMS m/z calcd for $C_{22}H_{23}F_3O_6SSiNa^+$ $[M+Na]^+$: 523.0834, found 523.0823.

4.6. (1R,4S,5S)-6-(3,4-Dimethoxybenzyl)-4-(trityloxymethyl)-3-oxa-6-azabicyclo[3.1.0]-hexan-2-one (**14a**)

To a solution of triflate **13a** (3.55 g, 7.1 mmol) in *N*,*N*-dimethylformamide (35 mL) held at −60 °C under argon was added dropwise 3,4-dimethoxybenzylamine (1.6 mL, 10.7 mmol). The reaction mixture was stirred for 30 min at −60 °C, diluted with EtOAc (40 mL) and water (40 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2×30 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The resulting oily residue was purified by flash chromatography on silica gel (EtOAc/heptane 1:2) to afford the aziridine-γ-lactone **14a** (2.35 g, 4.5 mmol) in 64% yield as a viscous oil, which crystallized on standing. R_f 0.20 (EtOAc/heptane 2:3); $[\alpha]_D^{20}$ +19.0 (c 1.00, $CHCl_3$); mp 62–63 °C; IR (film, cm^{-1}): 3058, 2933, 1777, 1516, 1449, 1265, 1157, 1027, 763, 706; ^1H NMR (250 MHz, $CDCl_3$): δ 2.78 (d, J=4.4 Hz, 1H, H5), 2.80 (d, J=4.4 Hz, 1H, H1), 3.09 (dd, J=3.1, 10.5 Hz, 1H, H7), 3.38 (d, J=13.2 Hz, 1H, N–CHH), 3.39 (dd, J=4.1, 10.5 Hz, 1H, H7), 3.62 (d, 1H, J=13.2 Hz, 1H, N–CHH), 3.79 (2×s, 6H, 2×OCH_3), 4.40 (t, J=3.5 Hz, 1H, H4), 6.62–7.39 (m, 18H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.9 (C1), 43.4 (C5), 54.9 (2×OCH_3), 59.8 (CH_2, N–CH_2), 62.3 (C7), 78.4 (C4), 86.0 (CPh_3), 110.2 (C2′, C5′), 119.0 (C6′), 126.3, 127.0, 127.5 (CH arom), 128.7 (C1′), 142.2 (Cq, CPh_3), 147.5 (C3′), 148.1 (C4′), 171.1 (C=O); ESI-MS m/z 544 [M+Na]. Anal. Calcd for $C_{33}H_{31}NO_5$: C, 75.99; H, 5.99; N, 2.69; O, 15.34. Found: C, 75.79; H, 6.27; N, 2.62; O, 15.49.

4.7. (1R,4S,5S)-4-((tert-Butyldiphenylsilyloxy)methyl)-6-(3,4-dimethoxybenzyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**14b**)

To a solution of triflate **13b** (3.55 g, 7.12 mmol) in *N*,*N*-dimethylformamide (35 mL) held at −60 °C under argon was added dropwise 3,4-dimethoxybenzylamine (1.6 mL, 10.65 mmol).

The reaction mixture was stirred for 30 min at −60 °C, diluted with EtOAc (40 mL) and water (40 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2×30 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The resulting oily residue was purified by flash chromatography on silica gel (heptane/EtOAc 2:1) to afford aziridine-γ-lactone **14b** (2.35 g, 4.53 mmol) in 64% yield as a viscous oil that crystallized on standing. R_f 0.50 (EtOAc/heptane 1:1); $[\alpha]_D^{20}$ +15.0 (*c* 1.08, CH_2Cl_2); mp 46–47 °C; IR (film, cm^{-1}): 3071, 2933, 1781, 1516, 1113, 704; ^1H NMR (250 MHz, $CDCl_3$): δ 0.97 (s, 9H, $C(CH_3)_3$), 2.71 (d, *J*=4.3 Hz, 2H, H1, H5), 3.43 (d, *J*=13.4 Hz, 2H, N–CH_2), 3.78 (dd, *J*=2.9, 11.4 Hz, 1H, H7), 3.93 (s, 6H, 2×OCH_3), 3.93 (dd, *J*=3.9, 11.4 Hz, 1H, H7′), 4.37 (m, 1H, H4), 6.76–7.64 (m, 13H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1, 26.7, 39.9, 44.2, 55.9, 60.9, 63.5, 80.2, 111.1, 120.1, 127.9, 129.7, 130.8, 132.8, 135.5, 149.1, 172.0 (C=O); ESI-MS *m/z* 517 $[M+H-TBDPS]^+$. Anal. Calcd for $C_{30}H_{35}NO_5Si$: C, 69.60; H, 6.81; N, 2.71. Found: C, 69.12; H, 6.87; N, 2.51.

4.8. Selected procedure for the preparation of dimer *15*

In a flame-dried round-bottom flask equipped with a magnetic stirring bar and a septum, diisopropylamine (100 μL, 0.71 mmol) was treated with *n*-BuLi (1.6 M in hexanes, 0.4 mL, 0.65 mmol) in THF (0.5 mL) at −10 °C under argon. After 1 h of stirring, a solution of the aziridine **14b** (168 mg, 0.33 mmol) in THF (3.2 mL) was added to the LDA solution via cannula. The yellow solution was stirred at −78 °C for 1 h, and a solution of methyl iodide (61 μL, 0.97 mmol) and DMPU (118 μL, 0.97 mmol) in THF (0.5 mL) was added. The reaction mixture was then gradually allowed to reach room temperature under constant stirring. After 8 h, the reaction was quenched with saturated aqueous NH_4Cl and washed successively with saturated aqueous $NaHCO_3$ (2×5 mL) and saturated aqueous NaCl (2×5 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The oil obtained was purified by flash chromatography (EtOAc/heptane 1:5) to furnish **15** (84 mg, 0.08 mmol, 25% yield) as a pasty solid. R_f 0.4 (EtOAc/heptane 3:4); IR (film, cm^{-1}): 3495 (OH), 3071, 2999, 2933, 2858, 1757 (C=O lactone), 1516, 1464, 1264, 1112, 1030, 703; ^1H NMR (250 MHz, $CDCl_3$): δ 1.02 (s, 9H, $SiC(CH_3)_3$), 1.10 (s, 9H, $SiC(CH_3)_3$), 2.52 (d, 1H, $J_{10,9}$=3.8 Hz, H10), 2.55 (d, 1H, $J_{9,10}$=3.8 Hz, H9), 3.31 (4H, *J*=13.0 Hz, 2×NCH_2Ar), 3.47 (s, 1H, H5), 3.59–3.89 (m, 10H, 2×OCH_3, H7, H7′, H12, H12′), 4.17 (m, 2H, H4, H11), 6.63–6.93 (m, 6H, H arom DMB), 7.34–7.75 (m, 20H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 (2×$SiC(CH_3)_3$), 26.6, 26.9 (2×$SiC(CH_3)_3$), 43.0 (C10), 46.5 (C5), 48.2 (C9), 49.8 (C1), 55.9 (4×OCH_3), 60.8 (2×NCH_2Ar), 63.9, 64.8 (C7, C12), 74.4, 80.6 (C4, C11), 102.0 (C8), 110.9, 111.1, 111.4, 111.8, 120.0, 120.8 (CH arom DMB), 127.8, 127.9, 130.0, 130.4, 130.8 132.6, 132.8, 133.0, 133.1, 135.5, 135.6 (CH arom, 2×Cq, DMB), 148.2, 148.7, 148.8 (4×Cq, OCH_3), 172.8 (C=O lactone); HREIMS *m/z* calcd for $C_{60}H_{70}N_2O_{10}Si_2Na^+$ $[M+Na]^+$: 1057.4467, found 1057.4512.

4.9. General procedures for the preparation of the substituted aziridino-γ-lactones

4.9.1. General method A

In a flame-dried round-bottom flask equipped with a magnetic stirring bar and a septum, a solution of diisopropylamine (59 mL, 0.42 mmol) was treated with *n*-BuLi (250 μL of a 1.6 M solution in hexanes, 0.40 mmol) in THF (1 mL) at −78 °C under argon. After 30 min of stirring, a solution of the aziridine **14a** (100 mg, 0.19 mmol) and of the electrophile (0.57 mmol) in THF (3 mL) was added to the LDA solution via cannula. The final concentration of the aziridine was 0.032 M. The color of the reaction turned to transparent brown. The reaction mixture was then gradually allowed to reach room temperature under constant stirring. After 2 h, the reaction was quenched with saturated aqueous NH_4Cl and washed successively with saturated aqueous $NaHCO_3$ (2×2 mL) and then with saturated aqueous NaCl (2×2 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed in vacuo. The resulting crude product was purified by column chromatography on silica gel using a gradient of EtOAc/heptane. This method was also used for aziridine **14b** utilizing reagents of same molarity.

4.9.2. General method B

To a solution of TBAT (92 mg, 0.17 mmol) in THF (1 mL) at 40 °C was added a solution of aziridine **14a** (100 mg, 0.17 mmol) and of the electrophile (0.51 mmol) in THF (3 mL) via cannula. After 30 min of stirring, the reaction was quenched with saturated aqueous NH_4Cl and washed successively with saturated aqueous $NaHCO_3$ (2×2 mL) and then saturated aqueous NaCl (2×2 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed in vacuo. The resulting crude product was purified by column chromatography on silica gel using a gradient of EtOAc/heptane.

4.9.3. (1*S*,4*S*,5*R*)-6-(3,4-Dimethoxybenzyl)-1-(trimethylsilyl)-4-(trityloxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (*16a*)

Using general method A and chlorotrimethylsilane (0.73 mL, 5.76 mmol) as the electrophile, compound **16a** (101 mg, 0.17 mmol) was obtained from **14a** in 89% yield as a pasty white oil. R_f 0.40 (EtOAc/heptane 3:2); $[\alpha]_D^{20}$ +17.0 (*c* 0.80, $CHCl_3$); IR (film, cm^{-1}): 3071, 2929, 1757, 1515, 1449, 1264, 1030, 842, 705; ^1H NMR (250 MHz, $CDCl_3$): δ −0.04, 0.16 (s, 9H, $Si(CH_3)_3$), 3.09 (s, 1H, H5), 3.34 (dd, *J*=5.1, 10.3 Hz, 1H, H7), 3.43 (dd, *J*=5.1, 10.3 Hz, 1H, H7′), 3.64 (d, *J*=13.1 Hz, 2H, N–CH_2), 3.87 (2×s, 6H, 2×OCH_3), 4.44 (t, *J*=4.4 Hz, 1H, H4), 6.78–7.47 (m, 18H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ −3.8, 0.0 ($(CH_3)_3$), 38.8 (C1), 49.9 (C5), 51.9 (N–CH_2), 56.4, 56.5 (2×OCH_3), 64.5 (C7), 73.8 (C4), 111.5 (C2′), 112.7 (C5′), 121.6 (C6′), 127.9, 128.5, 129.2 (CH arom), 131.2 (C1′),

143.7 (Cq, C*Ph*$_3$), 148.9 (C3′), 149.4 (C4′), 173.9 (C=O lactone); ESI-MS *m/z* 616 $[M+Na]^+$. Anal. Calcd for $C_{36}H_{39}NO_5Si$: C, 72.82; H, 6.62; N, 2.36. Found: C, 72.74; H, 6.88; N, 2.08.

*4.9.4. (1S,4S,5R)-4-((tert-Butyldiphenylsilyloxy)methyl)-6-(3,4-dimethoxybenzyl)-1-(trimethylsilyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**16b**)*

Using general method A and chlorotrimethylsilane (0.19 mL, 1.44 mmol) as the electrophile, compound **16b** was obtained from **14b** (250 mg, 0.48 mmol) as a colorless oil in 85% (241 mg, 0.40 mmol) after flash chromatography of the crude product (EtOAc/heptane 1:5). R_f 0.5 (EtOAc/heptane 1:2); $[\alpha]_D^{20}$ +25 (*c* 0.9, $CHCl_3$); IR (film, cm^{-1}): 3071, 2957, 2933, 2859, 1758 (C=O lactone), 1515, 1464, 1264, 1138, 1113, 843, 702; ^1H NMR (300 MHz, $CDCl_3$): δ −0.07 (s, 9H, $Si(CH_3)_3$), 1.07 (s, 9H, $OSiC(CH_3)_3$), 3.17 (s, 1H, H5), 3.53 (dd, 2H, *J*=12.3 Hz, NCH_2Ar), 3.68–3.87 (m, 2H, H7, H7′), 3.87 (s, 6H, 2×OCH_3), 4.41 (m, 1H, H4), 6.74–7.66 (m, 13H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ −3.8 ($Si(CH_3)_3$), 19.0 ($OSiC(CH_3)_3$), 26.6 ($OSiC(CH_3)_3$), 37.9 (C1), 48.8 (C5), 51.2 (NCH_2Ar), 55.6, 55.7 (2×OCH_3), 64.4 (C7), 74.0 (C4), 110.8, 111.9 (C2′, C5′), 120.8 (C6′), 127.7, 129.8, 132.3, 132.4, 135.3 (Cq arom), 148.1, 148.6 (C3′, C4′), 172.8 (C=O lactone); HREIMS *m/z* calcd for $C_{33}H_{43}NO_5Si_2Na^+$ $[M+Na]^+$: 612.2578, found 612.2573.

*4.9.5. (1R,4S,5S)-4-((tert-Butyldiphenylsilyloxy)methyl)-6-(3,4-dimethoxybenzyl)-1-methyl-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**17b**)*

Using general method A and methyl iodide (101 μL, 1.63 mmol) as the electrophile, compound **17b** was obtained from **14b** in 10% yield (27 mg, 0.032 mmol) after flash chromatography (EtOAc/heptane 1:5) of the crude product (114 mg). R_f 0.5 (EtOAc/heptane 3:4); $[\alpha]_D^{20}$ +12 (*c* 1.22, $CHCl_3$); IR (film, cm^{-1}): 2933, 2858, 1774 (C=O lactone), 1516, 1464, 1264, 1112, 703; ^1H NMR (250 MHz, $CDCl_3$): δ 1.06 (s, 9H, $SiC(CH_3)_3$), 1.46 (s, 1H, CH_3), 3.06 (1H, H5), 3.43–3.88 (m, 4H, NCH_2Ar, H7, H7′), 3.89 (s, 6H, 2×OCH_3), 4.33 (m, 1H, H4), 6.82–7.65 (m, 13H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6 (CH_3), 19.2 ($SiC(CH_3)_3$), 26.7 ($SiC(CH_3)_3$), 44.7 (C1), 48.2 (C5), 50.4 (NCH_2Ar), 55.9 (OCH_3), 63.9 (C7), 74.4 (C4), 111.1, 111.4 (C2′, C5′), 120.3 (C6′), 127.9, 130.0, 132.2, 132.4, 135.5, 135.7 (Cq arom), 148.3, 149.0 (C3′, C4′), 172.9 (C=O lactone).

*4.9.6. (1R,4S,5S)-1-Benzyl-6-(3,4-dimethoxybenzyl)-4-(trityloxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**18a**)*

Using general method A and benzyl bromide (69 μL, 0.10 mmol) as the electrophile, compound **18a** was obtained from **14a** in 17% yield (20 mg, 0.33 mmol; 25% yield based on recovery of starting material) as a white solid after flash chromatography (EtOAc/heptane 3:7) of the crude product. R_f 0.60 (EtOAc/heptane 1:1); $[\alpha]_D^{20}$ −10.1 (*c* 0.50, $CHCl_3$); mp 155 °C (decomp.); IR (film, cm^{-1}): 2959, 2918, 2871, 2850, 1765, 1752, 1592, 1517, 1450, 1323, 1267, 1230, 1157, 1027, 882, 746, 698; ^1H NMR (300 MHz, $CDCl_3$): δ 2.78 (s, 1H, H5), 3.10 (d, *J*=14.5 Hz, 1H, N−CH_2), 3.19 (d, *J*=14.5 Hz, 1H, N−CH_2), 3.06 (dd, *J*=3.4 Hz, 1H, H7), 3.44 (dd, *J*=3.8, 10.2 Hz, 1H, H7), 3.59 (s, 2H, CH_2Ph), 3.86, 3.88 (2×OCH_3), 4.34 (t, *J*=3.4 Hz, 1H, H4), 6.78–7.75 (m, 23H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.8 (CH_2, Bn), 47.0 (C5), 48.4 (C1), 50.5 (N−CH_2), 55.8, 55.9 (2×OMe), 63.7 (C7), 73.2 (C4), 87.2 (*C*Ph$_3$), 111.0 (C2′), 111.7 (C5′), 120.6 (C6′), 126.5, 127.3, 128.0, 128.6 129.8, 130.4 (CH arom), 136.2 (Cq, Bn), 143.2 (Cq, C*Ph*$_3$), 148.3 (C3′), 148.9 (C4′), 172.3 (C=O); HREIMS *m/z* calcd for $C_{40}H_{37}NNaO_5^+$ $[M+Na]^+$: 634.2569, found 634.2564.

*4.9.7. (1R,4S,5S)-1-Benzyl-4-((tert-butyldiphenylsilyloxy)-methyl)-6-(3,4-dimethoxybenzyl)-3-oxa-6-azabicyclo-[3.1.0]hexan-2-one (**18b**)*

Using general method A and benzyl bromide (69 μL, 0.10 mmol) as the electrophile, compound **18b** was obtained from **14b** in 17% yield (20 mg, 0.033 mmol; 25% yield based on recovery of starting material) as a colorless oil after flash chromatography (EtOAc/heptane 3:7) of the crude product. R_f 0.60 (EtOAc/heptane 1:1); $[\alpha]_D^{20}$ −5.1 (*c* 1.65, $CHCl_3$); IR (film, cm^{-1}): 2931, 2857, 1768 (C=O lactone), 1513, 1461, 1264, 1236, 1106, 1026, 699; ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, 9H, $C(CH_3)_3$), 3.02 (s, 1H, H1), 3.05 (d, *J*=14.1 Hz, 1H, N−CH_2), 3.13 (d, *J*=13.9 Hz, 1H, N−CH_2), 3.57 (s, 2H, CH_2, Bn), 3.70 (br d, *J*=4.7 Hz, 2H, H7), 3.83, 3.86 (2×s, 6H, 2×OCH_3), 4.31 (t, *J*=4.0 Hz, 1H, H4), 6.78–7.00 (m, 18H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5 ($C(CH_3)_3$), 27.2 ($C(CH_3)_3$), 34.4 (CH_2Ph), 47.3 (C5), 48.8 (C1), 50.8 (N−CH_2), 56.1, 56.2 (2×OCH_3), 64.3 (C7), 74.3 (C4), 111.2 (C2′), 112.0 (C4′), 120.9 (C6′), 126.9, 128.2, 128.3, 130.0, 130.3, 135.9 (Cq, Bn, CH arom), 130.6 (C1′), 132.5 and 133.0 (Cq arom, TBDPS), 148.6 (C3′), 149.2 (C4′), 172.5 (C=O lactone); HREIMS *m/z* calcd for $C_{37}H_{41}NNaO_5S^+$ $[M+Na]^+$: 630.2646, found 630.2664.

*4.9.8. (1S,4S,5S)-1-(1-(tert-Butyldimethylsilyloxy)-(phenyl)methyl)-6-(3,4-dimethoxybenzyl)-4-(trityloxymethyl)-3-oxa-6-azabicyclo-[3.1.0]hexan-2-one (**19a**)*

Using general method A and benzaldehyde (59 μL, 0.58 mmol) as the electrophile, a crude product was obtained from **14a** after work-up, which was dried under vacuum and then dissolved in CH_2Cl_2 (3 mL) under argon. Et_3N (61 μL, 0.43 mmol) was added followed by TBSOTf (75 μL, 0.33 mmol) dropwise at 0 °C. The solution was stirred for 2 h, diluted with CH_2Cl_2 (5 mL), and washed with saturated aqueous NaCl (2×10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude product was then purified by column chromatography on silica gel using a gradient of EtOAc/heptane 1:9 affording compound **19a** (75 mg, 0.10 mmol) as a colorless oil in 46% yield (51% yield based on recovery of starting material) and as a 1.4:1 mixture of diastereomers. R_f 0.20 (EtOAc/heptane 2:8); IR (film, cm^{-1}): 3061, 2928, 2855, 1772, 1595, 1515, 1447, 1260, 1060, 1028, 836, 760, 697; ^1H NMR

(300 MHz, $CDCl_3$): δ −0.26, −0.16, −0.06, 0.07 (4×s, 10.2H, 4×CH_3, TBS), 0.73, 0.79 (2×s, 15.3H, 2×C(CH_3)$_3$, TBS), 2.79, 3.00 (2×s, 1.7H, H5), 3.07 (dd, J=4.9, 10.4 Hz, 0.7H, H7, minor diast.), 3.21 (dd, J=6.4, 9.8 Hz, 1.0H, H7, major diast.), 3.28 (dd, J=4.9, 10.0 Hz, 0.7H, H7, minor diast.), 3.42 (d, J=13.4 Hz, 1H, N−CH_2, major diast.), 3.47 (dd, J=5.8, 9.5 Hz, 1.0H, H7′, major diast.), 3.52 (d, J=13.4 Hz, N−CH_2, minor diast.), 3.57 (d, J=13.4 Hz, 1H, N−CH_2, major diast.), 3.71 (d, J=13.4 Hz, N−CH_2, minor diast.), 3.82, 3.85, 3.87, 3.89 (4×s, 10.2H, 4×OCH_3), 3.82, 3.85, 3.87, 3.89 (4×s, 10.2H, 4×OCH_3), 4.25, 4.34 (2×t, J=5.8 Hz, H4), 5.07, 5.2 (2×s, 1.7H, C*H*OTBS), 6.69−7.51 (m, 39.1H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.3, −5.0, −4.7, −4.5 (4×CH_3, TBS), 18.0, 18.2 (*C*(CH_3)$_3$), 25.7 (C(*C*H_3)$_3$), 44.9 (C1), 50.6, 52.4 (N−CH_2), 55.7, 55.8, 55.9 (OCH_3), 64.1, 64.7 (C7), 70.7, 71.1 (*C*HPh), 72.8, 73.0 (C4), 87.2 (*C*Ph_3), 110.8, 111.0 (C2′), 111.9 (C5′), 120.7, 120.8 (C6′), 127.0, 127.3, 127.4, 128.0, 128.6 (CH arom), 130.2 (C1′), 134.4, 139.7, 143.2, 143.3 (Cq, C*Ph*$_3$), 148.3, 148.5 (C3′), 170.6, 170.8 (C═O); HREIMS *m/z* calcd for $C_{46}H_{51}NO_6SiNa^+$ $[M+Na]^+$: 764.3339, found 764.3349.

Using general method B and benzaldehyde (61 mg, 0.58 mmol) as the electrophile, the crude product obtained from **16a** was treated with TBSOTf as above affording compound **19a** (75 mg, 0.10 mmol) in 46% yield (51% yield based on recovery of starting material) and as a 1.4:1 mixture of diastereomers and was identical in all respects to the product prepared by method A.

*4.9.9. (1S,4S,5S)-6-(3,4-Dimethoxybenzyl)-1-(1-hydroxy-2,2-dimethylpropyl)-4-(trityloxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**20a**)*

Using general method A and pivaldehyde (62 μL, 0.57 mmol) as the electrophile, compound **20a** was obtained from **14a** as a colorless oil and as a mixture of diastereoisomers (1:1.7) in 66% yield (57 mg, 0.094 mmol) following flash chromatography of the crude product on silica gel (EtOAc/heptane 2:8). R_f 0.60 (EtOAc/heptane 1:1); IR (film, cm^{-1}): 3516, 3058, 2953, 1767, 1593, 1514, 1490, 1448, 1263, 1235, 1156, 1138, 1056, 1027, 903; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76, 0.88 (2×s, 15.3H, C(CH_3)$_3$), 3.00 (s, 0.6H, H5, minor diast.), 3.20 (dd, J=7.4, 9.8 Hz, 0.8H, H7, minor diast.), 3.28 (s, 1.0H, H5, major diast.), 3.37 (dd, 0.9H, J=5.7, 10.0 Hz, H7, major diast.), 3.45 (dd, J=3.6, 10.2 Hz, H7, major diast.), 3.47 (d, J=14.9 Hz, 1H, N−CH_2, major diast.), 3.52 (d, J=5.09 Hz, C*H*(CH_3)$_3$), 3.53 (d, J=13.4 Hz, N−CH_2, minor diast.), 3.62 (dd, J=6.4, 9.80 Hz, minor diast.), 3.68 (d, J=13.4 Hz, N−CH_2), 3.87 (s, 10.2H, OCH_3), 4.41 (t, J=5.6 Hz, 1.0H, H4, major diast.), 4.52 (t, J=6.8 Hz, 0.6H, H4, minor diast.), 6.72−7.61 (m, 30.6H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.7 (*C*(CH_3)$_3$), 26.3, 26.6 (C(*C*H_3)$_3$), 35.3, 35.9 (C1), 46.1, 47.7 (C5), 49.7, 50.3 (N−CH_2), 55.7, 55.9, 56.0, 56.2 (4×OCH_3), 63.7 (C7), 70.2 (*C*(CH_3)$_3$), 73.1, 73.3 (C4), 87.4, 87.5 (*C*Ph_3), 111.2, 111.4 (C2′), 111.7 (C5′), 120.4, 120.6 (C6′), 127.4, 127.7, 127.8, 128.0, 128.3, 128.5, 128.6, 128.8, 128.9, 129.2 (CH arom), 142.9, 143.0 (Cq, C*Ph*$_3$), 130.1 (C1), 148.5, 148.6 (C4′), 149.0, 149.1 (C3′), 170.8, 172.2 (C═O); HREIMS *m/z* calcd for $C_{38}H_{41}NNaO_6^+$ $[M+Na]^+$: 630.2832, found 630.2864.

*4.9.10. (1S,4S,5S)-1-(1-(tert-Butyldimethylsilyloxy)-2-methylpropyl)-6-(3,4-dimethoxybenzyl)-4-(trityloxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**21a**)*

Using general method A and isobutyraldehyde (53 μL, 0.58 mmol) as the electrophile, a crude product was obtained from **14a** after work-up, which was dried under vacuum and then dissolved in CH_2Cl_2 (3 mL) under argon. Et_3N (53 μL, 0.38 mmol) was added followed by dropwise addition of TBSOTf (66 μL, 0.29 mmol) at 0 °C. The solution was stirred for 2 h, diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous NaCl (2×10 mL). The organic layer was dried over $MgSO_4$, filtered and removed in vacuo. The crude product was then purified by column chromatography on silica gel using a gradient of EtOAc/heptane 1:9 affording compound **21a** (27 mg, 0.038 mmol) as a colorless oil in 22% yield (30% yield based on recovery of starting material) and as 1.7:1 mixture of diastereoisomers. R_f 0.60 (EtOAc/heptane 1:9); IR (film, cm^{-1}): 3058, 2953, 2927, 2854, 1769, 1737, 1514, 1448, 1236, 1056, 1029, 834, 771, 703; ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.16, −0.07, −0.02, 0.01 (4×s, 9.6H, CH_3, TBS), 0.78, 0.82, 0.83 (2×C(CH_3)$_3$, 14.4H, TBS), 0.67, 0.90 (2×d, J=6.7 Hz, 9.6H, 2×CH(CH_3)$_2$), 1.88, 2.09 (m, 2.6H, 2×C*H*(CH_3)$_2$, 1.6H), 3.10, 3.14 (2×s, 1.6H, H5), 3.21, 3.22 (m, J=6.4, 10.1 Hz, 1.6H, H7, major or minor diast.), 3.36, 3.81 (2×d, J=14.0 Hz, 2.0H, N−CH_2, major diast.), 3.42, 3.89 (2×d, J=14.0 Hz, 1.2H, N−CH_2, minor diast.), 3.46, 3.51 (2×dd, J=6.7, 10.1 Hz, 0.6H, H7′, major or minor diast.), 3.75, 4.02 (2×d, J=4.3 Hz, 1.6H, C*H*OTBS, major or minor diast.), 3.87, 3.88 (4×OCH_3, 10.9H, major or minor diast.), 4.33 (2×t, J=6.4, 6.1 Hz, 1.6H, H4, major or minor diast.), 6.78−7.50 (m, 28.8H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.6, −4.5, −4.0, −3.6 (4×CH_3, TBS), 16.9, 18.3, 19.6, 20.7 (CH(*C*H_3)$_2$), 17.3, 18.1 (*C*(CH_3)$_3$), 25.9 (C(*C*H_3)$_3$), 29.7, 31.3 (*C*H(CH_3)$_2$), 45.9, 46.4 (C1), 49.9, 50.8 (C5), 50.1, 51.3 (N−CH_2), 55.9 (OCH_3), 64.3, 64.9 (C7), 73.1 (C4), 72.5, 73.3 (*C*HOTBS), 87.3 (*C*Ph_3), 111.0, 111.1 (C2′), 111.4 (C5′), 120.3, 120.4 (C6′), 127.3, 128.0, 128.1, 128.5, 128.8, 128.9 (CH arom), 130.4, 130.5 (C1′), 143.2 (Cq, C*Ph*$_3$), 148.4 (C4′), 149.0 (C3′), 170.8, 171.6 (C═O); HREIMS *m/z* calcd for $C_{43}H_{53}NO_6SiNa^+$ $[M+Na]^+$: 730.3534, found 730.3540.

Using general method B and isobutyraldehyde (58 μL, 51 mmol) as the electrophile, the crude product obtained from **16a** was treated with TBSOTf as above, affording compound **21a** (16 mg, 0.020 mmol) in 12% yield (19% yield based on recovery of starting material) and as 1.7:1 mixture of diastereoisomers and was identical in all respects to the product prepared by method A.

*4.9.11. (1S,4S,5S)-1-(1-(tert-Butyldimethylsilyloxy)butyl)-6-(3,4-dimethoxybenzyl)-4-(trityloxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**22a**)*

Using general method A and *n*-butyraldehyde (51 μL, 0.58 mmol) as the electrophile, a crude product was obtained from **14a** after work-up, which was dried under vacuum and

then dissolved in CH_2Cl_2 (3 mL) under argon. Et_3N (53 μL, 0.38 mmol) was added followed by dropwise addition of TBSOTf (66 μL, 0.29 mmol) at 0 °C. The solution was stirred for 2 h, diluted with CH_2Cl_2 (5 mL), and washed with saturated aqueous NaCl (2×10 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude product was then purified by column chromatography on silica using a gradient of EtOAc/heptane 1:9 affording compound **22a** (14 mg, 0.038 mmol) as a colorless oil in 10% yield (15% yield based on recovery of starting material) and as a 1:1 mixture of diastereomers. R_f 0.80 (EtOAc/heptane 1:1); IR (film, cm^{-1}): 2954, 2928, 2855, 1770, 1593, 1514, 1448, 1259, 1137, 1029, 834, 773, 704; ^1H NMR (300 MHz, $CDCl_3$): δ 0.77 (s, 6H, 2×CH_3, TBS), 0.84 (m, 6H, 2×$(CH_2)_2CH_3$), 0.88 (s, 18H, 2×$C(CH_3)_3$, TBS), 1.21–1.44 (m, 8H, 2×$-(CH_2)_2CH_3$), 3.02 (s, 1H, H1), 3.22 (dd, J=7.6, 9.8 Hz, 1H, H7), 3.62 (dd, J=6.1, 9.8 Hz, 1H), 3.30 (s, 1H, H1), 3.38 (dd, J=5.8, 10.1 Hz, 1H, H7), 3.43 (d, J=5.2 Hz, 1H, C*H*OTBS), 3.44 (m, 1H, H7), 3.48 (d, J=13.7 Hz, 1H, $N-CH_2$), 3.53 (d, J=5.2 Hz, 1H, C*H*OTBS), 3.54 (d, J=13.4 Hz, 1H, $N-CH_2$), 3.68 (d, J=13.4 Hz, 1H, $N-CH_2$), 3.79 (d, J=13.7 Hz, 1H, $N-CH_2$), 3.87 (2×s, 12H, 4×OCH_3), 4.41 (t, J=5.2 Hz, 1H, H4), 4.52 (t, J=6.7 Hz, 1H, H4), 6.53–7.52 (m, 26H, CH arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.8, −4.5, −4.2 ($SiC(CH_3)_3(CH_3)_2$), 14.1, 14.2 ($OTBSCH(CH_2)_2CH_3$), 18.0 ($SiC(CH_3)_3(CH_3)_2$), 18.7, 18.9 ($CHOTBSCH_2CH_2CH_3$), 25.7, 25.8, 25.9 ($SiC(CH_3)_3(CH_3)_2$, TBS), 29.3, 29.7 ($CHOTBSCH_2CH_2CH_3$), 36.3, 36.5 (*C*HOTBS$(CH_2)_2CH_3$), 45.9, 46.5 (C1), 50.4, 50.5 (C5), 51.1, 51.6 ($N-CH_2$), 55.8, 56.0 (OCH_3), 64.6, 64.9 (C7), 68.0, 69.7 (C8), 73.0, 73.3 (C4), 87.3, 87.4 (CPh_3), 111.0, 111.1 (C2′), 111.7, 111.8 (C5′), 120.6, 120.7 (C6′), 127.3, 127.7, 128.0, 128.6, 128.9 (CH arom), 130.3, 130.4 (C1′), 143.2, 143.3 (Cq, CPh_3), 148.4, 148.5 (C4′), 149.0, 149.1 (C3′), 170.5, 171.4 (C=O); HREIMS *m/z* calcd for $C_{43}H_{53}NO_6SiNa^+$ $[M+Na]^+$: 730.3540, found 730.3555.

Using general method B and *n*-butyraldehyde (45 μL, 51 mmol) as the electrophile, the crude product obtained from **16a** was treated with TBSOTf as above affording compound **22a** (9 mg, 0.012 mmol) in 6% yield (10% yield based on recovery of starting material) and as a 1:1 mixture of diastereomers and was identical in all respects to the product prepared by method A.

*4.9.12. (1S,4S,5S)-6-(3,4-Dimethoxybenzyl)-1-((E)-1-hydroxy-3-phenylallyl)-4-(trityloxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**23a**)*

Using general method A and *trans*-cinnamaldehyde (72 μL, 0.57 mmol) as the electrophile, compound **23a** was obtained from **14a** as a yellow oil in 28% yield (30 mg, 0.046 mmol) after flash chromatography (EtOAc/heptane 3:7) of the crude product. Only one diastereoisomer of the 1:1 mixture was isolated for characterization (15 mg, 0.023 mmol). R_f 0.55 (EtOAc/heptane 1:1); IR (film, cm^{-1}): 3410, 2955, 2932, 1730, 1674, 1516, 1448, 1264, 1237, 1138, 1026, 747, 764, 632; ^1H NMR (300 MHz, $CDCl_3$): δ 3.28 (s, 1H, H5), 3.36 (dd, J=5.5, 9.5 Hz, 1H, H7), 3.44 (dd, J=5.5, 9.4 Hz, 1H, H7′), 3.54 (d, J=8.3 Hz, C*H*OH, 1H, H8), 3.44 (d, J=13.6 Hz, 1H, $N-CH_2$), 3.79 (d, J=13.6 Hz, 1H, $N-CH_2$), 3.88 (s, 6H, 2×OCH_3), 4.41 (t, J=5.46 Hz, 1H, H4), 6.79–7.00 (m, J=18.8 Hz, 4H, H9, H10, H arom), 7.14–7.47 (m, 15H, H arom); HREIMS *m/z* calcd for $C_{42}H_{39}NNaO_6^+$ $[M+Na]^+$: 676.2675, found 676.2701.

*4.9.13. (1S,4S,5S)-6-(3,4-Dimethoxybenzyl)-1-(1-hydroxycyclopentyl)-4-(trityloxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**24a**)*

Using general method A and cyclopentanone (51 μL, 0.57 mmol) as the electrophile, compound **24a** (32 mg, 0.053 mmol) was obtained from **14a** as a colorless oil in 31% yield (44% yield based on recovery of starting material) after flash chromatography (EtOAc/heptane 3:7) of the crude product. R_f 0.55 (EtOAc/heptane 1:1); $[\alpha]_D^{20}$ +16.5 (*c* 0.30, $CHCl_3$); IR (film, cm^{-1}): 3528, 2932, 2868, 1762, 1593, 1514, 1448, 1262, 1027, 761, 704; ^1H NMR (300 MHz, $CDCl_3$): δ 1.58 (m, 4H, $COH(-CH_2CH_2-)_2$), 1.80 (m, 4H, $COH(-CH_2CH_2-)_2$), 3.21 (s, 1H, H5), 3.40 (dd, J=4.5, 10.4 Hz, 1H, H7), 3.47 (dd, J=5.1, 10.5 Hz, 1H, H7′), 3.57 (d, J=13.2 Hz, 1H, $N-CH_2$), 3.72 (d, J=13.2 Hz, 1H, $N-CH_2$), 3.89 (s, 6H, 2×OCH_3), 4.39 (t, J=4.9 Hz, 1H, H4), 6.8–7.55 (m, 18H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.9 ($-CH_2-CH_2-$), 24.3 ($-CH_2CH_2-$), 36.6 ($-CH_2COHCH_2-$), 37.2 ($-CH_2COHCH_2-$), 47.1 (C1), 50.6 ($N-CH_2$), 52.2 (C5), 55.9 (2×OMe), 63.9 (C7), 72.9 ($-CH_2COHCH_2-$), 78.5 (C4), 87.5 (CPh_3), 111.1 (C4′), 112.0 (C5′), 120.9 (C6′), 127.3, 128.0, 128.7 (CH arom), 130.0 (Cq arom), 143.1 (Cq, CPh_3), 148.6 (C3′), 149.0 (C4′), 171.1 (C=O); HREIMS *m/z* calcd for $C_{38}H_{39}O_6NNa^+$ $[M+Na]^+$: 628.2675, found 628.2702.

Using general method B and cyclopentanone (45 μL, 0.51 mmol) as the electrophile, compound **24a** (15 mg, 0.025 mmol) was obtained from **16a** in 14% yield (21% yield based on recovery of starting material) after flash chromatography (EtOAc/heptane 3:7) of the crude product and was identical in all respects to the compound prepared by method A.

*4.9.14. (1S,4S,5S)-4-((tert-Butyldiphenylsilyloxy)methyl)-6-(3,4-dimethoxybenzyl)-1-(1-hydroxycyclopentyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**24b**)*

Using general method A and cyclopentanone (52 mL, 0.58 mmol) as the electrophile, compound **24b** (38 mg, 0.063 mmol) was obtained from **14b** as a colorless oil in 33% yield after flash chromatography (EtOAc/heptane 3:7) of the crude product: R_f 0.60 (EtOAc/heptane 1:1); $[\alpha]_D^{20}$ +10.1 (*c* 1.30, $CHCl_3$); IR (film, cm^{-1}): 3513, 2930, 1764, 1590, 1514, 1462, 1263, 1104, 1027, 821, 700; ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, $C(CH_3)_3$, 9H), 1.41–1.94 (m, 8H, $-(CH_2)_4-$), 2.34 (br s, OH, 1H), 3.26 (s, 1H, H5), 3.55 (d, J=13.1 Hz, 1H, $N-CH_2$), 3.68 (d, J=13.1 Hz, 1H, $N-CH_2$), 3.75–3.86 (m, J=5.46 Hz, 2H, H7, H7′), 3.85 (s, 6H, 2×OMe), 4.35 (t, J=5.09 Hz, 1H, H4), 6.73–7.78 (m, 13H, H arom); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.2 ($C(CH_3)_3$), 23.9 ($-CH_2CH_2-$), 24.3 ($-CH_2CH_2-$), 26.8 ($C(CH_3)_3$), 36.6 ($-CH_2COHCH_2-$), 37.1 ($-CH_2COHCH_2-$), 46.9 (C1), 50.6 ($N-CH_2$), 52.2 (C5), 55.9 (2×OMe), 64.4 (C7), 73.8

(−CH_2*C*OHCH_2−), 78.6 (C4), 111.0 (C4′), 111.9 (C5′), 120.8 (C6′), 127.8, 129.9 (CH arom), 132.5 (C1′), 132.6 (Cq arom), 135.6 (CH arom), 148.5 (C3′), 149.0 (C4′), 171.1 (C=O); HREIMS *m/z* calcd for $C_{35}H_{43}NO_6SiNa^+$ $[M+Na]^+$: 624.2757, found 624.2749.

*4.9.15. (1S,4S,5S)-6-(3,4-Dimethoxybenzyl)-1-(1-hydroxycyclohexyl)-4-(trityloxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**25a**)*

Using general method A and cyclohexanone (60 μL, 0.58 mmol) as the electrophile, compound **25a** (54 mg, 0.087 mmol) was obtained from **14a** as a white solid in 45% yield (56% yield based on recovery of starting material) after flash chromatography (EtOAc/heptane 3:7) of the crude product. R_f 0.55 (EtOAc/heptane 1:1); $[\alpha]_D^{20}$ +19.1 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}): 3483, 2932, 2863, 1748, 1513, 1446, 1259, 1029, 762, 707, 631; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.8−1.71 (m, −(CH_2)$_5$−, 10H), 3.19 (s, 1H, H5), 3.37 (d, *J*=5.2 Hz, 2H, H7, H7′), 3.54 (d, *J*=13.2 Hz, 1H, N−CH_2), 3.65 (d, *J*=13.2 Hz, 1H, N−CH_2), 3.87 (s, 6H, 2×OCH_3), 4.35 (t, *J*=5.0 Hz, 1H, H4), 6.77−7.40 (m, 18H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 25.4, 32.8, 33.3 (COH(*C*H_2)$_5$−), 46.4 (C1), 50.6 (N−CH_2), 54.2 (C5), 55.9 (2×OCH_3), 64.0 (C7), 68.1 (*C*OH(CH_2)$_5$−), 72.7 (C4), 87.7 (*C*Ph_3), 111.1 (C2′), 112.0 (C3′), 121.0 (C6′), 127.3, 128.0, 128.7 (CH arom), 129.9 (C1′), 143.1 (Cq, C*Ph*$_3$), 148.6 (C3′), 149.0 (C4′), 170.6 (C=O); HREIMS *m/z* calcd for $C_{39}H_{41}NO_6Na^+$ $[M+Na]^+$: 642.2832, found 642.2842.

Using general method B and cyclohexanone (52 μL, 0.50 mmol) as the electrophile, compound **25a** (32 mg, 0.026 mmol) was obtained from **16a** in 30% yield (43% yield based on recovery of starting material) after flash chromatography (EtOAc/heptane 3:7) of the crude product and was identical in all respects to the product prepared by method A.

*4.9.16. (1S,4S,5S)-6-(3,4-Dimethoxybenzyl)-1-(3-hydroxypentan-3-yl)-4-(trityloxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**26a**)*

Using general method A and 3-pentanone (60 mL, 0.58 mmol) as the electrophile, compound **26a** (76 mg, 0.13 mmol) was obtained from **14a** as a colorless oil in 33% yield (45% yield based on recovery of starting material) after flash chromatography (EtOAc/heptane 3:7) of the crude product. R_f 0.60 (EtOAc/heptane 1:1); $[\alpha]_D^{20}$ −12.6 (*c* 2.00, $CHCl_3$); IR (film, cm^{-1}): 3511, 2928, 2876, 1765, 1681, 1593, 1514, 1448, 1263, 1236, 1155, 1137, 1057, 1027, 763, 746, 704; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.73, 0.83 (2×t, *J*=7.8 Hz, 6H, COH(CH_2C*H*$_3$)$_2$), 1.58 (m, 4H, COH(C*H*$_2$$CH_3$)$_2$), 3.23 (s, 1H, H5), 3.29 (dd, *J*=6.6, 9.8 Hz, 1H, H7), 3.51 (dd, *J*=5.7, 9.8 Hz, 1H, H7′), 3.53 (d, *J*=13.1 Hz, 1H, N−CH_2), 3.82 (d, *J*=13.1 Hz, 1H, N−CH_2), 3.91 (s, 6H, 2×OMe), 4.4 (t, *J*=6.3 Hz, 1H, H4), 6.81−7.60 (m, 18H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.5, 7.8 (COH(CH_2C*H*$_3$)$_2$), 29.1, 29.3 (COH(*C*$H_2$$CH_3$)$_2$), 45.9 (C1), 49.8 (N−$CH_2$), 52.4 (C5), 56.0 (2×OMe), 63.7 (C7), 70.6 (*C*OH($CH_2$$CH_3$)$_2$), 72.5 (C4), 87.5 (*C*$Ph_3$), 111.2 (C2′), 111.5 (C5′), 120.5 (C6′), 127.4, 128.0, 128.6 (CH arom), 129.9 (C1′), 143.1 (Cq, C*Ph*$_3$), 148.7 (C3′), 149.1 (C4′), 170.1 (C=O); HREIMS *m/z* calcd for $C_{38}H_{41}NO_6Na^+$ $[M+Na]^+$: 630.2832, found 630.2794.

Using general method B and 3-pentanone (54 mL, 0.51 mmol) as the electrophile, compound **26a** (23 mg, 0.038 mmol) was obtained from **16a** as a colorless oil in 22% yield (30% yield based on recovery of starting material) after flash chromatography (EtOAc/heptane 3:7) of the crude product and was identical in all respects to the product prepared by method A.

*4.9.17. (1S,4S,5S)-4-((tert-Butyldiphenylsilyloxy)methyl)-6-(3,4-dimethoxybenzyl)-1-(3-hydroxypentan-3-yl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**26b**)*

Using general method A and 3-pentanone (61 μL, 0.58 mmol) as the electrophile, compound **26b** (41 mg, 0.068 mmol) was obtained from **14b** as a colorless oil in 35% yield (40% yield based on recovery of starting material) after flash chromatography (EtOAc/heptane 3:7) of the crude product. R_f 0.60 (EtOAc/heptane 1:1); $[\alpha]_D^{20}$ −15.9 (*c* 0.50, $CHCl_3$); IR (film, cm^{-1}): 3493, 2932, 2857, 1766, 1681, 1589, 1514, 1462, 1427, 1265, 1427, 1265, 1237, 1135, 1105, 1057, 1026, 822, 700; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.79, 0.84 (2×t, *J*=7.5 Hz, 4H, COH(CH_2C*H*$_3$)$_2$), 1.05 (s, 9H, C(C*H*$_3$)$_3$), 1.68, 1.82 (m, 4H, COH(C*H*$_2$$CH_3$)$_2$), 3.27 (s, 1H, H5), 3.46 (d, *J*=13.8 Hz, 1H, N−CH_2), 3.74 (dd, *J*=6.8, 10.9 Hz, H7), 3.86 (m, 1H, N−CH_2), 3.88 (dd, *J*=7.5 Hz, 1H, H7′), 6.87−7.66 (m, 13H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.6 (COH(CH_2C*H*$_3$)$_2$), 19.1 (*C*(CH_3)$_3$), 26.8 (C(*C*H_3)$_3$), 29.3 (COH(*C*$H_2$$CH_3$)$_2$), 45.5 (C1), 49.8 (N−$CH_2$), 52.6 (C5), 55.9 (2×$OCH_3$), 63.9 (C7), 70.6 (*C*OH($CH_2$$CH_3$)$_2$), 73.6 (C4), 111.1 (C4′), 111.4 (C5′), 120.4 (C6′), 127.7, 127.9, 129.8, 130.0 (CH arom), 132.3 (C1′), 135.5 (Cq arom), 148.5 (C3′), 149.1 (C4′), 170.0 (C=O); HREIMS *m/z* calcd for $C_{35}H_{45}NO_6SiNa^+$ $[M+Na]^+$: 626.2908, found 626.2908.

*4.9.18. (1S,4S,5R)-6-(3,4-Dimethoxybenzyl)-1-(phenylsulfonyl)-4-(trityloxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**27a**)*

Using general method A and benzenesulfonyl fluoride (69 μL, 0.58 mmol) as the electrophile, compound **27a** (63 mg, 0.095 mmol) was obtained from **14a** as a white solid in 50% yield (62% yield based on recovery of starting material) after flash chromatography (EtOAc/heptane 3:7) of the crude product. R_f 0.45 (EtOAc/heptane 1:1); IR (film, cm^{-1}): 3060, 2927, 1778, 1593, 1515, 1448, 1330, 1266, 1239, 1155, 1063, 1027, 750, 704, 632; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.23 (s, 1H, H5), 3.45 (dd, *J*=4.0, 10.9 Hz, H7), 3.62 (dd, *J*=4.3, 10.9 Hz, 1H, H7′), 3.85 (s, 6H, 2×OMe), 4.34 (t, *J*=4.3 Hz, 1H, H4), 6.45−7.75 (m, 23H, H arom); HREIMS *m/z* calcd for $C_{39}H_{35}NO_7SNa^+$ $[M+Na]^+$: 684.2032, found 684.2041.

Using general method B and benzenesulfonyl fluoride (61 μL, 0.51 mmol) as the electrophile, compound **27a** (17 mg, 0.026 mmol) was obtained from **16a** in 15% yield (32% yield based on recovery of starting material) after flash chromatography (EtOAc/heptane 3:7) of the crude product and was identical in all aspects to the product prepared by method A.

*4.9.19. (1S,4S,5R)-6-(3,4-Dimethoxybenzyl)-1-(tri-n-butylstannyl)-4-(trityloxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**28a**)*

Using general method A and *n*-Bu_3SnCl (157 μM, 0.58 mmol) as the electrophile, the crude product obtained from **14a** was first purified by passage through a small column comprising 10% w/w of finely ground KF and 90% w/w of silica gel, developed with CH_2Cl_2 to remove organotin impurities and then with EtOAc to elute the product.[21] Flash chromatography of the latter (EtOAc/heptane 1:9) afforded compound **28a** (75 mg, 0.093 mmol) as a colorless oil in 55% yield. R_f 0.60 (EtOAc/heptane 1:4); $[\alpha]_D^{20}$ +22.6 (*c* 1.50, $CHCl_3$); IR (film, cm^{-1}): 2953, 2922, 1754, 1592, 1513, 1448, 1263, 1154, 1074, 1029, 761, 703, 631; ^1H NMR (300 MHz, $CDCl_3$): δ 0.80–0.91 (m, 9H, 3×$(CH_2)_2CH_3$), 0.93–1.54 (m, 18H, 3×$(CH_2)_2CH_3$), 2.80 (s, 1H, H5), 3.11 (dd, *J*=6.8, 9.8 Hz, 1H, H7), 3.28 (d, *J*=13.4 Hz, 1H, N–CH_2), 3.37 (dd, *J*=6.8, 9.8 Hz, 1H, H7′), 3.76 (d, 1H, N–CH_2), 3.90 (m, 6H, 2×OCH_3), 4.56 (dd, *J*=5.09, 6.41 Hz, 1H, H4), 6.74–7.78 (m, 18H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.4, 11.0, 13.5 (3×$(CH_2)_3CH_3$), 27.2, 28.7, 28.8, 28.9, 29.6 (3×$(CH_2)_3CH_3$), 40.5 (C1), 48.4 (N–CH_2), 51.4 (C5), 55.8, 55.9 (2×OCH_3), 63.7 (C7), 79.3 (C4), 87.1 (CPh_3), 110.8 (C2′), 111.1 (C5′), 119.6 (C6′), 127.3, 127.9, 128.6 (CH arom), 130.6 (C1′), 143.4 (Cq, CPh_3), 148.4 (C3′), 149.2 (C4′), 176.9 (C=O); HREIMS *m/z* calcd for $C_{45}H_{57}NO_5SnNa^+$ $[M+Na]^+$: 834.3156, found 834.3149.

*4.9.20. (1S,4S,5R)-4-((tert-Butyldiphenylsilyloxy)methyl)-6-(3,4-dimethoxybenzyl)-1-(tri-n-butylstannyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**28b**)*

Using general method A and *n*-Bu_3SnCl (157 μL, 0.58 mmol) as the electrophile, the crude product obtained from **14b** was first purified by passage through a small column comprising 10% w/w of finely ground KF and 90% w/w of silica gel, developed with CH_2Cl_2 to remove organotin impurities and then with EtOAc to elute the product. Flash chromatography of the latter (EtOAc/heptane 1:9) afforded compound **28b** (61 mg, 0.075 mmol) as a colorless oil in 45% yield (48% yield based on recovery of starting material). R_f 0.65 (EtOAc/heptane 1:4); $[\alpha]_D^{20}$ +26.4 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}): 2953, 2929, 2854, 1756, 1515, 1463, 1427, 1337, 1264, 1236, 1111, 1030, 823; ^1H NMR (300 MHz, $CDCl_3$): δ 0.75–0.91 (m, 9H, 3×$(CH_2)_2CH_3$), 0.93–1.60 (m, 18H, 3×$(CH_2)_2CH_3$), 1.05 (s, 9H, $C(CH_3)_3$), 2.88 (s, 1H, H5), 3.27 (d, *J*=13.4 Hz, 1H, N–CH_2), 3.56 (dd, *J*=7.7, 10.6 Hz, 1H, H7), 3.76 (d, 1H, N–CH_2), 3.81 (dd, *J*=4.9, 10.6 Hz, 1H, H7′), 3.88 (2×s, 6H, 2×OCH_3), 4.50 (dd, *J*=4.9, 7.7 Hz, 1H, H4), 6.74–7.72 (m, 18H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.4, 11.0, 13.5 (3×$(CH_2)_3CH_3$), 19.2 ($C(CH_3)_3$), 26.8 ($C(CH_3)_3$), 27.2, 27.6, 28.7, 28.8, 29.0 (3×$(CH_2)_3CH_3$), 40.3 (C1), 48.2 (N–CH_2), 51.4 (C5), 55.9 (2×OCH_3), 63.7 (C7), 80.0 (C4), 110.8 (C2′), 111.1 (C5′), 119.6 (C6′), 127.8, 127.8, 129.9 (CH arom), 130.6 (C1′), 132.6, 132.8 (Cq arom), 148.3 (C3′), 149.1 (C4′), 176.9 (C=O); HREIMS *m/z* calcd for $C_{42}H_{61}NO_5SiSnNa^+$ $[M+Na]^+$: 830.3239, found 830.3260.

*4.9.21. (1S,4S,5R)-6-(3,4-Dimethoxybenzyl)-1-iodo-4-(trityloxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**29a**)*

Using general method A and iodine (145 mg, 0.57 mmol) as the electrophile, compound **29a** (32 mg, 0.049 mmol) was obtained from **14a** as a white solid in 25% yield (41% based on recovery of starting material) after flash chromatography (EtOAc/heptane 3:7) of the crude product. R_f 0.65 (EtOAc/heptane 1:1); $[\alpha]_D^{20}$ −0.2 (*c* 0.50, $CHCl_3$); mp=157–159 °C; IR (film, cm^{-1}): 2931, 1774, 1681, 1593, 1514, 1447, 1418, 1331, 1263, 1155, 1023, 999, 761, 703, 631; ^1H NMR (300 MHz, $CDCl_3$): δ 2.90 (s, 1H, H5), 3.19 (dd, *J*=2.4, 11.0 Hz, 1H, H7), 3.67 (dd, *J*=2.47, *J*=11.5 Hz, 1H, H7′), 3.67 (d, *J*=13.8 Hz, 1H, N–CH_2), 3.72 (d, *J*=14.0 Hz, 1H, N–CH_2), 3.86, 3.88 (2×s, 6H, 2×OCH_3), 4.43 (t, *J*=2.5 Hz, 1H, H4), 6.77–7.56 (m, 18H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.7 (C1), 49.8 (N–CH_2), 53.3 (C5), 55.9, 56.0 (2×OMe), 62.8 (C7), 87.3 (CPh_3), 111.1 (C2′), 111.5 (C5′), 120.3 (C6′), 127.3, 128.0, 128.7 (CH arom), 143.0 (Cq, CPh_3), 148.6 (C3′), 149.1 (C4′), 192.5 (C=O); HREIMS *m/z* calcd for $C_{33}H_{30}INO_5Na^+$ $[M+Na]^+$: 670.1061, found 670.1077.

Using general method B and iodine (129 mg, 0.51 mmol) as the electrophile, compound **29a** (11 mg, 0.017 mmol) was obtained from **16a** as a white solid in 10% yield (16% based on recovery of starting material) after flash chromatography (EtOAc/heptane 3:7) of the crude product and was identical in all respects to the product prepared by method A.

*4.9.22. (1S,4S,5R)-6-Benzyloxycarbonyl-4-((tert-butyldiphenylsilyloxy)methyl)-1-(trimethylsilyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**30**)*

To a solution of **16b** (188 mg, 0.32 mmol) in CH_2Cl_2 (3.2 mL) and H_2O (0.32 mL) was added DDQ (73 mg, 0.32 mmol) at room temperature. After 8 h of stirring, pyridine (0.38 mL, 3.7 mmol), benzyl chloroformate (91 mL, 0.64 mmol), and DMAP (8 mg, 0.06 mmol) were added. After 15 h, the mixture was diluted in CH_2Cl_2 (3 mL) and an aqueous solution of HCl 10% (5 mL) was added. The organic phase was washed successively with water (2×5 mL) and with a saturated aqueous solution $NaHCO_3$ (5 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by flash chromatography (EtOAc/heptane 1:5) to afford **30** (38 mg, 0.07 mmol, 21%) as a colorless oil. R_f 0.7 (EtOAc/heptane 2:3); $[\alpha]_D^{20}$ +25 (*c* 0.9, $CHCl_3$); IR (film, cm^{-1}): 3071, 2958, 2858, 1777 (C=O lactone), 1730 (C=O carbamate), 1264, 1196, 844, 700; ^1H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 9H, $Si(CH_3)_3$), 1.03 (s, 9H, $OSiC(CH_3)_3$), 3.46 (s, 1H, H5), 3.68, 3.76 (2H, $J_{7,7}$=11.3 Hz, $J_{7,4}$=3.6 Hz, H7, H7′), 4.69 (m, 1H, H4), 5.09 (2H, *J*=12.2 Hz, CH_2Ph), 7.15–7.62 (m, 15H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ −3.5 ($Si(CH_3)_3$), 19.3 ($OSiC(CH_3)_3$), 26.9 (2×$SiC(CH_3)_3$), 39.5 (C1), 46.7 (C5), 64.1 (C7), 68.9 (CH_2Ar), 75.3 (C4), 127.9, 128.1, 128.5, 128.6, 130.1, 132.4, 135.0, 135.1, 135.5 (Cq arom), 158.9 (C=O carbamate), 171.7 (C=O lactone); HREIMS

m/z calcd for $C_{32}H_{39}NO_5Si_2Na^+$ $[M+Na]^+$: 596.2265, found 596.2228.

*4.9.23. (1R,4S,5S)-1-Benzyl-6-benzyloxycarbonyl-4-((tert-butyldiphenylsilyloxy)methyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**31**)*

A solution of aziridine **18b** (860 mg, 1.65 mmol) and DDQ (449 mg, 1.98 mmol) in a 10:1 mixture of CH_2Cl_2 (60 mL) and water (6 mL) was stirred for 24 h at room temperature. Pyridine (269 μL, 3.30 mmol), benzyl chloroformate (469 μL, 3.30 mmol), and DMAP (40 mg, 0.33 mmol) were then successively added. The reaction mixture was stirred for 2 h at room temperature and CH_2Cl_2 (10 mL) was added followed by aqueous 10% v/v HCl (20 mL). The aqueous layer was separated and the organic layer was washed successively with aqueous 10% v/v of HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and water (30 mL). The organic phase was dried over $MgSO_4$ and evaporated to dryness under vacuum. The resulting residue was purified by column chromatography on silica gel (EtOAc/heptane 2:8) affording compound **31** (829 mg, 2.57 mmol) in 85% yield as a colorless oil. R_f 0.55 (EtOAc/heptane 3:7); $[\alpha]_D^{20}$ −35.6 (*c* 0.70, $CHCl_3$); IR (film, cm^{-1}): 3031, 2928, 2856, 1786 (C═O lactone), 1728 (C═O carbamate), 1426, 1379, 1227, 1103, 1055, 697; ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (s, 9H, $C(CH_3)_3$), 3.19 (d, J=14.7 Hz, 1H, CH_2Ph), 3.24 (s, 1H, H5), 3.45 (d, J=14.7 Hz, 1H, CH_2Ph), 3.72 (dd, J=2.3, 11.9 Hz, 1H, H7), 3.87 (dd, J=4.0, 11.3 Hz, 1H, H7′), 4.69 (t, J=2.6 Hz, 1H, H4), 5.13 (d, J=13.0 Hz, 1H, CH_2 carbamate), 5.19 (d, J=13.0 Hz, 1H, CH_2 carbamate), 7.10−7.71 (m, 20H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 ($C(CH_3)_3$), 26.8 ($C(CH_3)_3$), 31.8 (C5), 45.6 (CH_2Ph), 48.3 (C1), 63.6 (C7), 68.9 (CH_2 carbamate), 74.8 (C4), 127.0, 127.5, 127.8, 128.4, 130.0, 130.1, 131.8, 132.6, 134.6, 134.8, 135.4 (Cq, CH arom), 135.6 (Cq, Bn), 158.1 (C═O carbamate), 170.2 (C═O lactone); HREIMS *m/z* calcd for $C_{36}H_{37}NO_5SiNa^+$ $[M+Na]^+$: 614.2339, found 614.2366.

*4.9.24. (1S,4S,5R)-4-((tert-Butyldiphenylsilyloxy)methyl)-1-(trimethylsilyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**32**)*

To a solution of **30** (78 mg, 0.14 mmol) in thiophenol (0.6 mL) was added boron trifluoride etherate (17 μL, 0.14 mmol) at 0 °C under argon. The reaction mixture was then gradually allowed to reach room temperature under constant stirring. After 4 days, the solution was diluted with EtOAc (5 mL) and neutralized with a 10% aqueous $NaHCO_3$ solution. After separation of the phases, the aqueous phase was extracted with EtOAc (2×5 mL). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude oil obtained was purified by flash chromatography (EtOAc/heptane 6:1) to give **32** (21 mg, 0.05 mmol, 35%) as a colorless oil. R_f 0.3 (EtOAc/heptane 1:2); IR (film, cm^{-1}): 3266 (NH), 3071, 2956, 2930, 2857, 1762 (C═O lactone), 1250, 1114, 844, 701; ^1H NMR (300 MHz, $CDCl_3$): δ 0.11 (s, 9H, $Si(CH_3)_3$, 1.07 (s, 9H, $OSi(CH_3)_3$), 3.13 (s, 1H, H5), 3.64, 3.83 (2H, J=10.9, 6.4, 4.1 Hz, H7, H7′), 4.48 (dd, 1H, J=6.3, 4.1 Hz, H4), 7.36−7.67 (m, 10H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ −3.1 ($Si(CH_3)_3$), 19.3 ($OSiC(CH_3)_3$), 26.9 ($SiC(CH_3)_3$), 31.5 (C1), 43.3 (C5), 64.3 (C7), 78.7 (C4), 127.9, 130.0, 132.6, 135.5 (Cq arom), 171.9 (C═O lactone); HREIMS *m/z* calcd for $C_{24}H_{33}NO_3Si_2Na^+$ $[M+Na]^+$: 462.1897, found 462.1904.

*4.9.25. (1R,4S,5S)-1-Benzyl-6-benzyloxycarbonyl-4-(hydroxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one (**34**)*

Aziridine **31** (240 mg, 0.406 mmol) was dissolved in anhydrous THF (5 mL) and a solution of TBAF in THF (1 M, 608 μL, 0.608 mmol) was added at −20 °C under argon. The reaction mixture was stirred for 2 h and then allowed to warm to room temperature over 1 h. The mixture was washed successively with saturated aqueous $NaHCO_3$ (2×20 mL) and saturated aqueous NaCl (2×20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude product was then purified by chromatography on silica gel (EtOAc/heptane 7:3) affording compound **34** in 68% yield (95 mg, 0.179 mmol) as a white solid. R_f 0.30 (EtOAc/heptane 1:1); $[\alpha]_D^{20}$ −72.9 (*c* 0.50, $CHCl_3$); mp 115−117 °C; IR (film, cm^{-1}): 3448, 3062, 3032, 2961, 1789 (C═O lactone), 1718 (C═O carbamate), 1494, 1408, 1268, 1224, 1165, 1073, 693; ^1H NMR (300 MHz, $CDCl_3$): δ 3.32 (s, 1H, H5), 3.24 (d, J=14.7 Hz, 1H, CH_2Ph), 3.40 (d, J=14.7 Hz, 1H, CH_2Ph), 3.67 (dd, J=2.4, 12.5 Hz, 1H, H7), 3.90 (dd, J=3.0, 12.6 Hz, 1H, H7′), 4.69 (t, J=2.8 Hz, 1H, H4), 5.13 (d, J=12.2 Hz, 1H, CH_2 carbamate), 5.20 (d, 1H, J=12.1 Hz, CH_2 carbamate), 7.17−7.48 Hz (m, 10H, H arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.1 (CH_2, Bn), 45.5 (C5), 48.7 (C1), 62.1 (CH_2OH), 69.0 (CH_2 carbamate), 75.5 (C4), 127.1, 128.3, 128.6, 130.0 (CH arom), 134.3 (Cq, Bn), 134.7 (Cq carbamate), 158.4 (C═O carbamate), 170.8 (C═O lactone); HREIMS *m/z* calcd for $C_{20}H_{19}NNaO_5^+$ $[M+Na]^+$: 376.1161, found 376.1143.

*4.9.26. (1R,4S,7R)-1-Benzyl-7-benzyloxycarbonylamino-2,5-dioxabicyclo[2.2.1]heptan-6-one (**35**)*

To a solution of compound **34** (50 mg, 0.141 mmol) in CH_3CN (14.1 mL, 0.01 M) at 0 °C under argon was added $BF_3{\cdot}OEt_2$ (20 μL, 0.156 mmol). The reaction mixture was warmed to room temperature and stirred for 4 h. The mixture was washed successively with saturated aqueous $NaHCO_3$ (2×10 mL) and saturated aqueous NaCl (2×10 mL), the organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude product was purified by chromatography on silica gel (EtOAc/heptane 2:8) affording the bicyclic lactone **35** in 56% yield (27 mg, 0.057 mmol) as a colorless oil. R_f 0.60 (EtOAc/heptane 1:1); $[\alpha]_D^{20}$ −47.8 (*c* 0.55, $CHCl_3$); IR (film, cm^{-1}): 3379 (fine band, NH), 2959, 2924, 1799 (C═O lactone), 1722 (C═O carbamate), 1515, 1244, 1142, 1023, 980, 895, 744, 696; ^1H NMR (300 MHz, C_6D_6): δ 2.97 (d, J=15.0 Hz, 1H, CH_2Ph), 3.04 (br d, J=8.2 Hz, 1H, H5), 3.15 (d, J=9.2 Hz, 1H, H5′), 3.34 (d, J=15.0 Hz, 1H, 1H, CH_2Ph), 3.83 (sl, 1H, H7), 4.09 (s, 1H, H4), 4.59 (br s, 1H, NH), 5.06 (s, 2H, CH_2 carbamate), 7.10−7.44 (m, 10H, H arom); ^{13}C NMR (75 MHz, C_6D_6): δ 31.6 (CH_2, Bn), 60.3 (C7), 67.4 (CH_2 carbamate), 68.2 (C5), 80.1 (C4), 83.3 (C1), 127.8, 128.0, 128.2, 128.3, 128.7, 130.8, 134.5 (Cq Bn), 136.4 (Cq carbamate), 155.4

(C=O carbamate), 171.5 (C=O lactone); HREIMS *m/z* calcd for $C_{20}H_{19}NNaO_5^+$ $[M+Na]^+$: 376.1161, found 376.1135.

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