Ring Enlargement of Carbohydrate-Derived 1,2-Oxazines to Enantiopure 5-Bromo-1,2-oxazepines and Subsequent Palladium-Catalyzed Reactions

Ahmed Al-Harrasi,[a,b] Sebastian Fischer,[a] Reinhold Zimmer,[a] Hans-Ulrich Reissig*[a]

[a] Institut für Chemie und Biochemie, Freie Universität Berlin, Takustr. 3, 14195 Berlin, Germany
Fax +49(30)83855367; E-mail: hans.reissig@chemie.fu-berlin.de

[b] Department of Chemistry, College of Science, Sultan Qaboos University, Alkhod 123, Sultanate of Oman

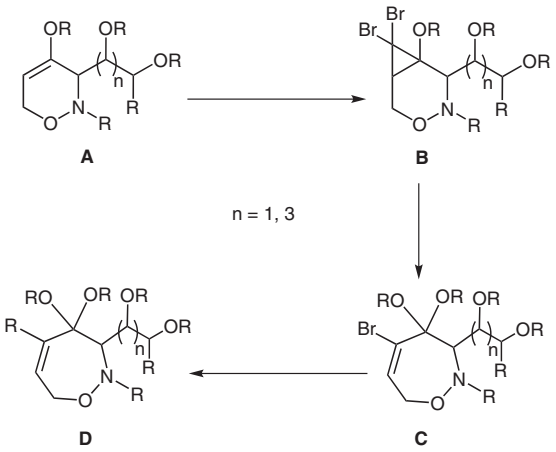
Received 14 August 2009

Abstract: Dibromocarbene addition to D-glyceraldehyde-derived 1,2-oxazines *syn*-**1** and *anti*-**1** provided dibromocyclopropane intermediates *syn*-**3** and *anti*-**3**, which smoothly reacted with methanol under ring enlargement to furnish 5-bromo-1,2-oxazepine derivatives *syn*-**4** and *anti*-**4**. Related 1,2-oxazines such as arabinose-derived compounds furnished the 1,2-oxazepine derivatives *syn*-**4e** and *anti*-**4f** with fair efficacy. The alkenyl bromide moiety of 1,2-oxazepine derivatives *syn*-**4** and *anti*-**4** was then exploited for the introduction of new substituents via palladium-catalyzed C–C bond forming processes (Sonogashira, Suzuki, Stille, and Heck reactions). These transformations led to a series of new highly substituted 1,2-oxazepine derivatives *syn*-**5** or *anti*-**5**–**11** being of considerable interest for further synthetic elaborations.

Key words: 1,2-oxazines, carbene additions, cyclopropanes, ring enlargement, 1,2-oxazepines, palladium catalysis, alkynes

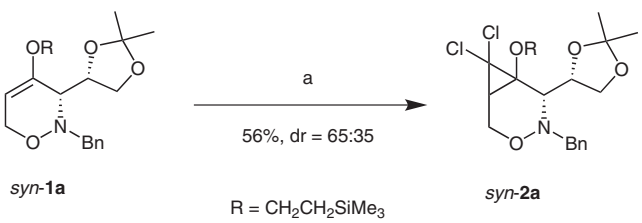
Over the years, we have systematically explored the chemistry of alkoxyallenes for the construction of nitrogen-containing heterocycles including pyrrolidine alkaloids, substituted imidazole derivatives, and functionalized pyridines.[1] The stereocontrolled [3+3] cyclization of lithiated alkoxyallenes and carbohydrate-derived nitrones is a particularly interesting example demonstrating the synthetic utility of these fascinating C_3 building blocks.[2] It furnishes novel enantiopure 3,6-dihydro-2*H*-1,2-oxazines of type **A**, which are remarkably versatile precursors for the synthesis of a multitude of biologically active target compounds. Reductive, acid-induced and Lewis acid promoted transformations lead to aminopolyols, hydroxylated pyrrolidines and azetidine derivatives,[3] or carbohydrate[4] and sugar amino acid mimetics.[5]

The full extent of the synthetic utility of 3,6-dihydro-2*H*-1,2-oxazines **A** has yet to be explored. Moreover, the electron-rich enol ether moiety of **A** was not fully exploited for the introduction of additional substituents or functional groups. Herein, we present full details[6] involving dibromocarbene cycloadditions[7] to this activated double bond of **A** to furnish the ring-enlarged 5-bromo-1,2-oxazepine derivatives of type **C** via the intermediate dibromocyclopropanes **B**. The palladium-catalyzed reactions of **C** provided new highly substituted 1,2-oxazepines **D** of remarkable diversity (Scheme 1). The oxazepine moiety has been found in many pharmaceutically important compounds[8] and 1,2-oxazepines[9] in particular are versatile compounds, from which many interesting product classes, for example, amino substituted polyols (heptanose derivatives) or stereodefined piperidines, can be prepared. Moreover, several 1,2-oxazepine derivatives are known to be potential opioid analgesics.[9b]



Scheme 1 Transformation of carbohydrate-derived 3,6-dihydro-2*H*-1,2-oxazines **A** into 1,2-oxazepine derivatives **C** and **D** via dibromocyclopropanes **B**.

We started this investigation with the cycloaddition of in situ generated dichlorocarbene. Treatment of D-glyceraldehyde-derived 1,2-oxazine *syn*-**1a** dissolved in chloroform with 50% aqueous solution of sodium hydroxide in the presence of a phase-transfer catalyst[10] afforded the corresponding dichlorocyclopropane derivative *syn*-**2a** in 56% yield (Scheme 2). Not unexpectedly, a diastereomeric mixture was obtained (ratio 65:35), since the highly re-

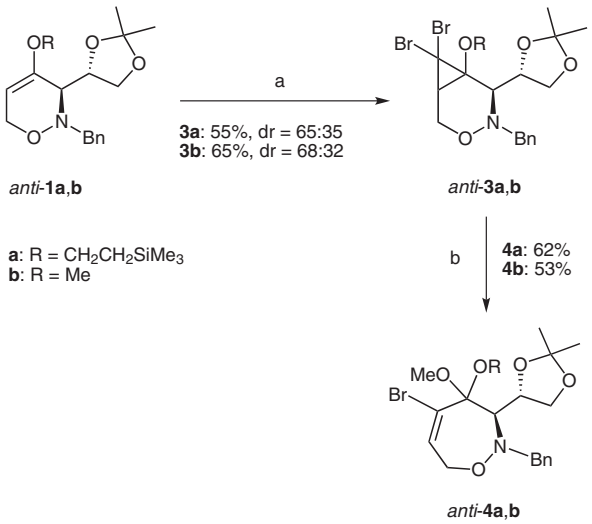


Scheme 2 Conversion of D-glyceraldehyde-derived 1,2-oxazine *syn*-**1a** into dichlorocarbene adduct *syn*-**2a**. *Reagents and conditions*: a) $CHCl_3$, 50% aq NaOH, Et_3BnNCl, r.t., 2 d.

SYNTHESIS 2010, No. 2, pp 0304–0314
Advanced online publication: 20.11.2009
DOI: 10.1055/s-0029-1217126; Art ID: T16109SS

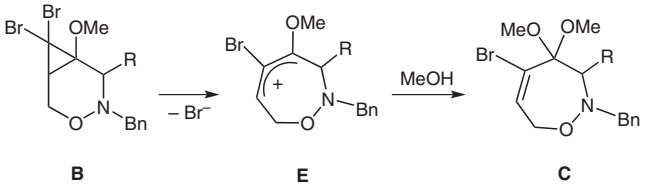
active dichlorocarbene only moderately differentiates the diastereotopic faces of the 1,2-oxazine ring.

When the reaction was carried out under identical conditions, but by replacing chloroform with bromoform, no product was isolated. Instead, the starting material had undergone fast decomposition. This problem could be avoided by employing a large excess of potassium fluoride as an additive. Similar observations have been recorded in literature for related reactions.[10] Under these conditions, the addition of dibromocarbene to the *anti*-configured 1,2-oxazine derivatives *anti*-**1a**,**b** took place smoothly and *gem*-dibromocyclopropane derivatives *anti*-**3a**,**b** were isolated in 55% and 65% yield, respectively. Again the diastereoselectivity was only moderate (Scheme 3). The separation of the two diastereomers, though it is possible in all cases, was not attempted except for characterization purposes. Subsequent solvolysis of dibromocyclopropane derivatives in refluxing methanol with potassium carbonate[10] furnished the ring-enlarged 5-bromo-1,2-oxazepine derivatives *anti*-**4a/b** in reasonable yields (Scheme 3).



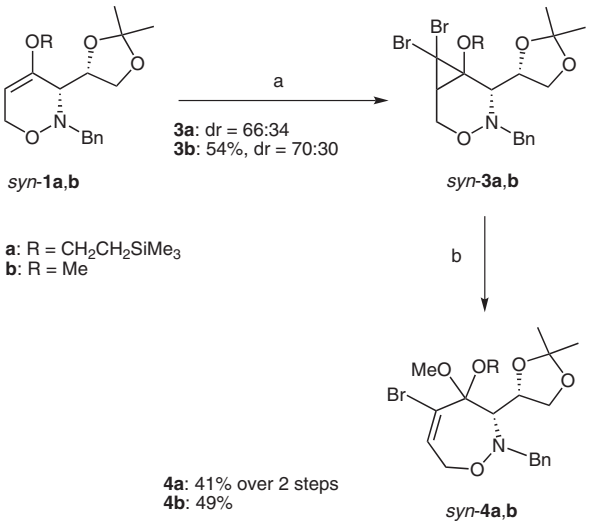
Scheme 3 Synthesis of dibromocarbene adducts *anti*-**3a**,**b** and 5-bromo-1,2-oxazepine derivatives *anti*-**4a**,**b**. *Reagents and conditions*: a) $CHBr_3$, 50% aq NaOH, KF, Et_3BnNCl, r.t., 2 d; b) K_2CO_3, MeOH, reflux, 20 h.

There are many reports in literature dealing with the ring opening of dihalocyclopropanes[7] and it is well established that a stereospecific opening of the cyclopropane ring is concerted with the departure of the leaving group.[7e] The mechanism for our examples is depicted in Scheme 4. The cyclopropyl cation resulting from the loss of halogen from **B** simultaneously rearranges in such a way, that the developing allyl cation **E** is immediately stabilized by the methoxy group. Trapping by a nucleophilic solvent like methanol will then provide the 7-membered heterocycle **C**. The presence of an alkoxy group (methoxy or trimethylsilylethoxy) is essential in stabilizing the transition state of this electrocyclic reaction.[7g] The ring enlargement of our compounds **3** under these conditions is apparently accompanied with significant decomposition products which account for the moderate yields of the resulting 1,2-oxazepines. However, no side products could be isolated.



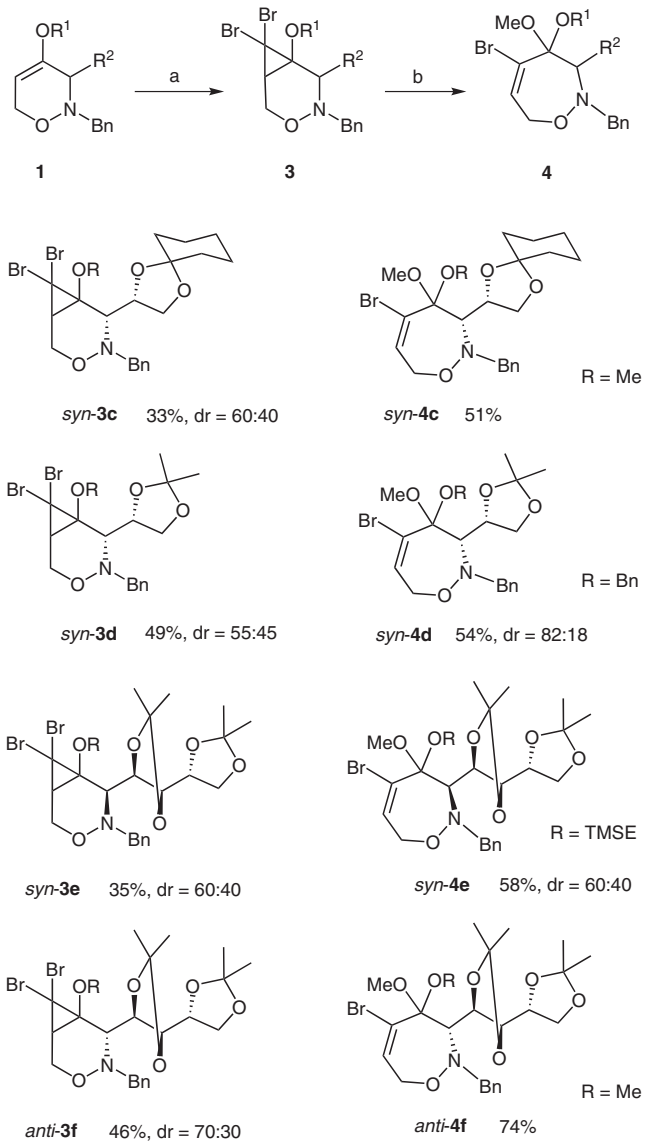
Scheme 4 Mechanism of the ring opening of compounds **3** leading to 5-bromo-1,2-oxazepines **4**.

Encouraged by these results and to further examine the general applicability of this method, the ring enlargement reactions of other 1,2-oxazine derivatives were carried out. When the corresponding *syn*-1,2-oxazines *syn*-**1a**,**b** were treated with bromoform and 50% aqueous sodium hydroxide and potassium fluoride in the presence of a catalytic amount of benzyltriethylammonium chloride for two days, diastereomeric mixtures of the dibromo derivatives *syn*-**3a**,**b** were isolated. No separation of the diastereomers was attempted and the mixtures were then refluxed in methanol in the presence of anhydrous potassium carbonate for 20 hours. The expected 5-bromo-1,2-oxazepine derivative *syn*-**4a** was isolated after column chromatography in 41% yield over two steps, whilst *syn*-**4b** was obtained in 49% (Scheme 5). Thus, 1,2-oxazines *syn*-**1** and *anti*-**1**, being available in a stereodivergent manner from the D-glyceraldehyde derived nitrone,[2a,c] could be converted into the two diastereomeric ring-enlarged homologues *syn*- and *anti*-**4** in a straightforward fashion.



Scheme 5 Synthesis of 5-bromo-1,2-oxazepines *syn*-**4a**,**b**. *Reagents and conditions*: a) $CHBr_3$, 50% aq NaOH, KF, Et_3BnNCl, r.t., 2 d; b) K_2CO_3, MeOH, reflux, 20 h.

To further screen the scope of this route to new enantiopure and highly functionalized 1,2-oxazepine derivatives we investigated the dibromocarbene additions to 1,2-oxazines either bearing other alkoxy groups or different



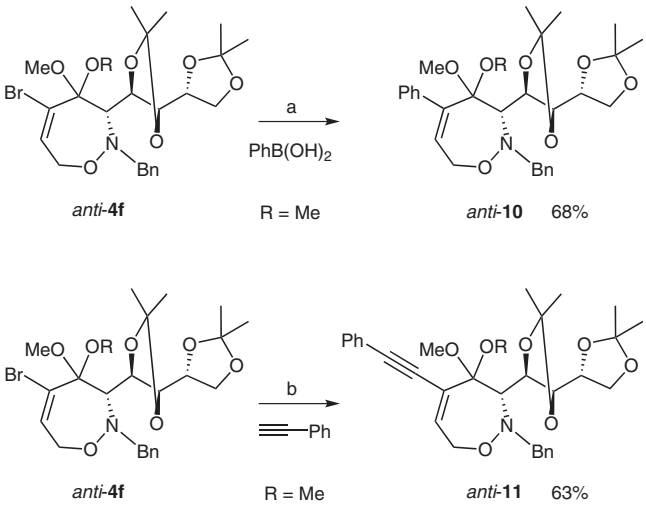
Scheme 6 Synthesis of various 5-bromo-1,2-oxazepines *anti*- and *syn*-**4**. *Reagents and conditions*: a) $CHBr_3$, 50% aq NaOH, KF, Et_3BnNCl, r.t., 2 d; b) K_2CO_3, MeOH, reflux, 20 h.

chiral side chains at C-3 (Scheme 6). Thus, the *O*-cyclohexylidene derivative *syn*-**4c** was available as desired via dibromocyclopropane *syn*-**3c**. The related benzyloxy substituted compound *syn*-**3d** smoothly underwent ring enlargement to the expected 5-bromo-1,2-oxazepine derivative *syn*-**4d** with one diastereomer clearly predominating in this case. Finally, two D-arabinose-derived 1,2-oxazines were subjected to the two-step sequence. The *syn*-configured precursor provided cyclopropane derivative *syn*-**3e** only in low yield, but the transformation to the 5-bromo-1,2-oxazepine *syn*-**4e** proceeded quite efficiently (58%). The related *anti*-configured intermediate *anti*-**3f** was obtained in 46% yield and converted into the ring-enlarged heterocycle *anti*-**4f** in a remarkably good yield of 74%. These examples clearly demonstrate that the developed two-step method for the preparation of enantiopure 5-bromo-1,2-oxazepine derivatives apparently has a fairly broad scope. Although the yield are often only moderate the simplicity and flexibility of the method certainly compensates this limitation.

The prepared enantiopure 5-bromo-1,2-oxazepines *syn*- and *anti*-**4** should allow smooth access to many interesting product classes, for example, amino substituted polyols (heptanose derivatives) or stereodefined piperidines. The presence of a bromoalkenyl moiety, however, makes these intermediates also ideal precursors for palladium-catalyzed coupling reactions. First, 1,2-oxazepine derivative *syn*-**4b** was selected to examine Sonogashira cross-coupling reactions[11] and subjected to the standard protocol with phenylacetylene using 5 mol% $Pd(OAc)_2$, Ph_3P, CuI, and diisopropylamine as base (Table 1). This procedure proved to be successful and hence phenylacetylene was cross-coupled to bromo derivative *syn*-**4b** to afford the disubstituted alkyne *syn*-**5** in 95% yield.

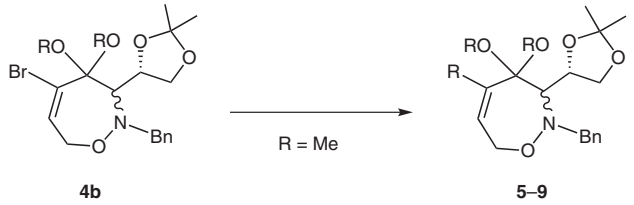
Table 1 summarizes additional transformations employing *anti*-**4b** as precursor, demonstrating that Sonogashira[11] or Suzuki reaction[12] provide compounds such as *anti*-**5**, *anti*-**6**, and *anti*-**7**, respectively, in excellent yields. Gratifyingly, Stille[13] and Heck couplings[14] to 1,2-oxazepine *anti*-**4b** also took place smoothly furnishing 1,3-dienes *anti*-**8** and *anti*-**9** with very good efficacy. These compounds should be interesting partners for Diels–Alder reactions, which may lead to novel enantiopure skeletons incorporating a 1,2-oxazepine ring. Thus, structurally highly diverse compounds should be accessible by this route.

Arabinose-derived 5-bromo-1,2-oxazine *anti*-**4f** also underwent smooth palladium-catalyzed transformations as demonstrated by the synthesis of Suzuki-coupling product *anti*-**10** and the phenylalkynyl substituted compound *anti*-**11** obtained by Sonogashira reaction (Scheme 7). Without any optimization the yields for these couplings were in the range of 65%. All these examples demonstrate that the scope of the chain-elongation of carbohydrate derivatives



Scheme 7 Cross-coupling reactions of D-arabinose-derived 5-bromo-1,2-oxazepine *anti*-**4f** leading to substituted 1,2-oxazepines *anti*-**10**,**11**. *Reagents and conditions*: a) $Pd(OAc)_2$ (5 mol%), Ph_3P (0.2 equiv), K_2CO_3 (1.5 equiv), DMF, 70 °C, 12 h; b) $Pd(OAc)_2$ (5 mol%), Ph_3P (0.2 equiv), CuI (5 mol%), *i*-Pr_2NH, DMF, r.t., 10 h.

Table 1 Cross-Coupling Reactions of *syn*-**4b** and *anti*-**4b** Leading to Substituted 1,2-Oxazepines **5**–**9**[a]



1,2-Oxazepine	Reagent	Conditions	Product	Yield
syn-**4b**	Ph	a	*syn*-**5**	95%
anti-**4b**	Ph	a	*anti*-**5**	95%
anti-**4b**	OMe	a	*anti*-**6**	72%
anti-**4b**	$PhB(OH)_2$	b	*anti*-**7**	80%
anti-**4b**	$SnBu_3$	c	*anti*-**8**	94%
anti-**4b**	CO_2Me	d	*anti*-**9**	82%

[a] Reaction conditions: a) $Pd(OAc)_2$ (5 mol%), Ph_3P (0.2 equiv), CuI (5 mol%), *i*-Pr_2NH, DMF, r.t., 10 h; b) $Pd(OAc)_2$ (5 mol%), Ph_3P (0.2 equiv), K_2CO_3 (1.5 equiv), DMF, 70 °C, 10 h; c) $Pd(OAc)_2$ (10 mol%), Ph_3P (0.2 equiv), DMF, 65 °C, 3 h; d) $Pd(OAc)_2$ (5 mol%), LiCl (3 equiv), Et_3N (1 equiv), DMF, 70 °C, 10 h.

following the sequence nitrone, 1,2-oxazine derivative, 5-bromo-1,2-oxazepine, and coupling product is obviously very broad and it will hence allow the modification of carbohydrates into libraries of interesting compounds in a most flexible fashion.

In summary, starting from easily available 3,6-dihydro-2*H*-1,2-oxazines **1** we have developed a convenient route to enantiopure 1,2-oxazepine derivatives. First experiments show that palladium-catalyzed couplings smoothly occur leading to building blocks, which should be highly suitable for diversity orientated synthesis.[15]

Reactions were generally performed under argon in flame-dried flasks, and the components were added by syringe. Products were purified by flash chromatography on silica gel (230–400 mesh, Merck). Unless otherwise stated, yields refer to analytically pure samples. ^1H NMR [$CHCl_3$ (δ = 7.26 ppm), TMS (δ = 0.00 ppm) as internal standard] and ^{13}C NMR spectra [$CDCl_3$ (δ = 77.0 ppm) as internal standard] were recorded on Bruker AC 250, DRX 500, or AV 700 or Joel Eclipse 500 instruments in $CDCl_3$ solutions. Integrals are in accordance with assignments; coupling constants are given in Hz. Missing signals of minor diastereomers are overlapped by those of major diastereomers, or they could not be unambiguously identified due to low intensity. IR spectra were recorded on Nicolet 5 SXC FTIR spectrometer. MS and HRMS analyses were

performed with Finnigan MAT 711 (EI, 80 eV, 8 kV), MAT 95 (EI, 70 eV), and MAT CH7A (EI, 80 eV, 3 kV) instruments. The elemental analyses were determined using 'Elemental-Analyzers' (Perkin-Elmer or Carlo Erba). Melting points were measured with a Reichert apparatus and are uncorrected. Optical rotations ($[\alpha]_D$) were determined with a Perkin-Elmer 141 or Perkin-Elmer 241 polarimeter at the temperatures given. All other chemicals are commercially available and were used without further purification.

(5*S*,4′*S*)-4-Benzyl-7,7-dichloro-5-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-6-[2-(trimethylsilyl)ethoxy]-3-oxa-4-azabicyclo[4.1.0]-heptane (*syn*-2a)

Aqueous solution of NaOH (50%, 3 mL) was added to a vigorously stirred solution of 1,2-oxazine *syn*-**1a** (300 mg, 0.780 mmol) in $CHCl_3$ (3 mL) containing $BnEt_3NCl$ (4.0 mg). The reaction mixture was stirred at r.t. overnight, then diluted with H_2O (5 mL), and extracted with CH_2Cl_2 (3 × 5 mL) to give 273 mg of the crude product. This was purified by column chromatography (silica gel, hexane–EtOAc, 16:1) to yield colorless crystals of *syn*-**2a** 140 mg (56%) as a mixture of diastereomers (65:35); mp 59–61 °C.

IR (KBr): 3085–3030 (=CH), 2895–2870 (C–H), 1060 cm^{-1} (C–O).

Major Diastereomer

^1H NMR (500 MHz, $CDCl_3$): δ = 0.05 [s, 9 H, $Si(CH_3)_3$], 0.90–1.20 (m, 2 H, CH_2Si), 1.36, 1.44 (2 s, 3 H each, CH_3), 2.08 (dd, *J* = 3.3, 9.0 Hz, 1 H, 1-H), 3.42–3.98 (m, 1 H, 5-H), 3.47 (dt, *J* = 7.2, 9.2 Hz, 1 H, OCH_2), 3.60 (d, *J* = 15.1 Hz, 1 H, C*H*$_2$Ph), 3.76 (dt, *J* = 6.2, 9.2 Hz, 1 H, OCH_2), 3.87 (dd, *J* = 3.3, 12.2 Hz, 1 H, 2-H), 4.17 (dd, *J* = 9.0, 12.2 Hz, 1 H, 2-H), 4.24 (dd, *J* = 6.0, 8.7 Hz, 1 H, 5′-H), 4.33 (dd, *J* = 7.0, 8.7 Hz, 1 H, 5′-H), 4.45–4.48 (m, 1 H, 4′-H), 4.55 (d, *J* = 15.1 Hz, 1 H, C*H*$_2$Ph), 7.29–7.35 (m, 5 H, C_6H_5).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = –1.3 [q, $Si(CH_3)_3$], 18.3 (t, CH_2Si), 26.2, 26.7 (2 q, CH_3), 33.1 (d, C-1), 38.3 (s, C-7), 59.9 (t, *C*H_2Ph), 63.4 (d, C-4′), 64.4 (t, C-2), 64.9 (t, OCH_2), 65.0 (d, C-5), 66.2 (t, C-5′), 68.8 (s, C-6), 74.2 (d, C-4′), 109.1 (s, C-2′), 126.7, 128.0, 128.1, 138.7 (3 d, s, C_6H_5).

Minor Diastereomer (Additional Signals)

^1H NMR (500 MHz, $CDCl_3$): δ = 0.06 [s, 9 H, $Si(CH_3)_3$], 1.39, 1.46 (2 s, 3 H each, CH_3), 1.83 (br d, *J* = 5.2 Hz, 1 H, 1-H), 3.53 (d, *J* = 8.8 Hz, 1 H), 3.61–3.67, 3.81–3.86 (2 m, 1 H, 3 H), 4.08 (dd, *J* = 5.4, 6.6 Hz, 1 H, 5′-H), 3.90 (d, *J* = 13.9 Hz, 1 H, C*H*$_2$Ph), 4.35, 4.49–4.54 (m_c, m, 1 H, 2 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = –1.4 [q, $Si(CH_3)_3$], 18.2 (t, CH_2Si), 25.6, 26.4 (2 q, CH_3), 29.4 (d, C-1), 67.0 (d, C-5), 69.3 (s, C-6), 109.2 (s, C-2′), 126.6, 128.03, 128.13, 139.1 (3 d, s, C_6H_5).

MS (EI, 80 eV, 100 °C): *m*/*z* (%) = 474 (M^+, <1), 457 (M^+ – Me, <1), 400 (M^+ – Me_3Si, <1), 372 (M^+ – $C_5H_9O_2$, 12), 101 ($C_5H_9O_2^+$, 24), 91 ($C_7H_7^+$, 100), 73 ($C_3H_9Si^+$, 75).

Anal. Calcd for $C_{22}H_{33}Cl_2NO_4Si$ (474.5): C, 55.69; H, 7.01; N, 2.95. Found: C, 55.18; H, 6.81; N, 2.76.

(1*S*,5*R*,6*R*,4′*S*)- and (1*R*,5*R*,6*S*,4′*S*)-4-Benzyl-7,7-dibromo-5-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-6-methoxy-3-oxa-4-azabicyclo[4.1.0]heptane (*anti*-3b)

A solution of NaOH (270 mg) and KF (1.90 g) in H_2O (2 mL) was added to a vigorously stirred solution of 1,2-oxazine *anti*-**1b** (230 mg, 0.751 mmol) in $CHBr_3$ (1.2 mL) containing $BnEt_3NCl$ (2.5 mg). The biphasic mixture was stirred for 2 d at r.t., then diluted with H_2O (2 mL), and extracted with Et_2O (3 × 5 mL). The combined Et_2O extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The excess of $CHBr_3$ was removed under high vacuum. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 4:1) to give the dibromo-substituted 1,2-oxazine derivative *anti*-**3b** (232 mg, 64%, dr = 68:32). The diastereomers could be separated by HPLC (hexane–EtOAc, 8:1).

***anti*-3b (Major Diastereomer)**

Colorless crystals; $[\alpha]_D^{22}$ +22.0 (*c* 1.0, $CHCl_3$).

IR (KBr): 3090–3050 (=C–H), 2990–2940 (C–H), 1060 cm^{-1} (C–O–C).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.36, 1.43 (2 s, 3 H each, CH_3), 2.03 (d, *J* = 5.0 Hz, 1 H, 1-H), 3.72 (s, 3 H, OCH_3), 3.50 (d, *J* = 14.8 Hz, 1 H, NC*H*$_2$Ph), 3.72 (d, *J* = 11.7 Hz, 1 H, 2-H), 3.83 (d, *J* = 2.2 Hz, 1 H, 5-H), 4.08 (dd, *J* = 5.0, 11.7 Hz, 1 H, 2-H), 4.14 (t, *J* = 7.6 Hz, 1 H, 5′-H), 4.18 (t, *J* = 7.6 Hz, 1 H, 5′-H), 4.35 (d, *J* = 14.8 Hz, 1 H, NC*H*$_2$Ph), 4.87 (dt, *J* = 2.2, 7.6 Hz, 1 H, 4′-H), 7.13–7.29 (m, 5 H, C_6H_5).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 23.5, 26.0 (2 q, CH_3), 30.7 (d, C-1), 40.1 (s, C-7), 57.0 (q, OCH_3), 59.1 (t, N*C*H_2Ph), 63.9 (s, C-5′), 64.1 (t, C-2), 65.0 (t, C-5), 66.6 (s, C-6), 74.3 (d, C-4′), 108.0 (s, C-2′), 126.8, 128.1, 128.2, 139.4 (3 d, s, C_6H_5).

MS (EI, 80 eV, 80 °C): *m*/*z* (%) = 477 (M^+, <1), 462 (M^+ – Me, 3), 476 (M^+ – $C_5H_9O_2$, 9), 101 ($C_5H_9O_2^+$, 63), 91 (CH_2Ph^+, 100).

Anal. Calcd for $C_{18}H_{23}Br_2NO_4$ (477.2): C, 45.31; H, 4.86; N, 2.94. Found: C, 45.77; H, 5.04; N, 2.91.

***anti*-3b (Minor Diastereomer)**

Colorless oil.

IR (film): 3090–3050 (=C–H), 2990–2940 (C–H), 1060 cm^{-1} (C–O–C).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.35, 1.45 (2 s, 3 H each, CH_3), 2.14 (dd, *J* = 3.1, 8.8 Hz, 1 H, 1-H), 3.47 (s, 3 H, OCH_3), 3.49 (d, *J* = 3.1 Hz, 1 H, 5-H), 3.60 (d, *J* = 14.5 Hz, 1 H, NC*H*$_2$Ph), 3.75 (dd, *J* = 3.1, 12.2 Hz, 1 H, 2-H), 3.94 (t, *J* = 8.0 Hz, 1 H, 5′-H), 4.15 (d, *J* = 14.5 Hz, 1 H, NC*H*$_2$Ph), 4.18 (t, *J* = 8.0 Hz, 1 H, 5′-H), 4.25 (dd, *J* = 8.8, 12.2 Hz, 1 H, 2-H), 4.77 (dt, *J* = 3.1, 8.0 Hz, 1 H, 4′-H), 7.23–7.34 (m, 5 H, C_6H_5).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 23.5, 26.0 (2 q, CH_3), 30.7 (d, C-1), 40.1 (s, C-7), 57.0 (q, OCH_3), 59.1 (t, N*C*H_2Ph), 62.8 (t, C-5), 64.1 (t, C-2), 64.5 (s, C-6), 66.4 (s, C-5′), 73.6 (d, C-4′), 108.0 (s, C-2′), 126.8, 127.9, 128.1, 137.5 (3 d, s, C_6H_5).

MS (EI, 80 eV, 80 °C): *m*/*z* (%) = 477 (M^+, <1), 462 (M^+ – Me, 3), 476 (M^+ – $C_5H_9O_2$, 9), 101 ($C_5H_9O_2^+$, 63), 91 (CH_2Ph^+, 100).

Dibromocarbene Addition to 1,2-Oxazines 1, Followed by Solvolysis; General Procedure 1 (GP1)

A solution of NaOH (9 equiv) and KF (2.5 g/mmol) in H_2O (2.5 mL/mmol) was added to a vigorously stirred solution of 1,2-oxazine **1** (1 equiv) in $CHBr_3$ (1.6 mL/ mmol) containing $BnEt_3NCl$ (3.5 mg/mmol). The biphasic mixture was stirred for 2 d at r.t., then diluted with H_2O (5 mL/mmol) and extracted with Et_2O (3 × 5 mL/mmol). The combined Et_2O extracts were washed with brine (5 mL/mmol), dried (Na_2SO_4), and concentrated. The excess of $CHBr_3$ was removed under high vacuum. The residue was purified by column chromatography. The resulting diastereomeric mixture of dibromocyclopropanes was refluxed with anhyd K_2CO_3 (3.8 equiv) in MeOH (4 mL/mmol) for 20 h under argon. The reaction mixture was cooled to r.t., diluted with H_2O (5 mL/mmol), and extracted with CH_2Cl_2 (3 × 5 mL/mmol). The combined organic extracts were dried (Na_2SO_4) and concentrated. The product was purified by column chromatography.

(3*R*,4′*S*)-2-Benzyl-5-bromo-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-4-methoxy-4-[2-(trimethylsilyl)ethoxy]-2,3,4,7-tetrahydro-[1,2]oxazepine (*anti*-4a)

A solution of NaOH (500 mg) and KF (3.10 g) in H_2O (3 mL) was added to a vigorously stirred solution of *anti*-**1a** (490 mg, 1.25

mmol) in $CHBr_3$ (2.1 mL) containing $BnEt_3NCl$ (4.2 mg) as described in GP1. The resulting residue was purified by column chromatography (hexane–EtOAc, 8:1) to give 386 mg (55%, dr = 65:35) of *anti*-**3a**. The diastereomeric mixture of dibromocyclopropane derivative *anti*-**3a** was refluxed with anhyd K_2CO_3 (541 mg, 3.92 mmol) in MeOH (7 mL) for 20 h under argon. The product was purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to give pure *anti*-**4a** in 220 mg (62%) as a colorless oil; $[\alpha]_D^{22}$ –76.5 (*c* 0.32, $CHCl_3$).

IR (film): 3090–3030 (=C–H), 2985–2845 (C–H), 1670 cm^{-1} (C=C).

^1H NMR (500 MHz, $CDCl_3$): δ = 0.03 [s, 9 H, $Si(CH_3)_3$], 0.85–0.98 (m, 2 H, CH_2Si), 1.33, 1.34 (2 s, 3 H each, CH_3), 3.18 (s, 3 H, OCH_3), 3.34 (d, *J* = 5.2 Hz, 1 H, 3-H), 3.47 (ddd, *J* = 6.2, 9.1, 10.7 Hz, 1 H, CH_2O), 3.68 (ddd, *J* = 5.9, 9.1, 10.7 Hz, 1 H, CH_2O), 4.06 (dd, *J* = 6.4, 8.7 Hz, 1 H, 5′-H), 4.09 (dd, *J* = 8.1, 8.7 Hz, 1 H, 5′-H), 4.24–4.28 (m, 2 H, 4′-H, NCH_2Ph), 4.30 (d, *J* = 11.3 Hz, 1 H, NCH_2Ph), 4.36 (dd, *J* = 1.3, 13.5 Hz, 1 H, 7-H), 4.44 (d, *J* = 13.5 Hz, 1 H, 7-H), 6.69 (br s, 1 H, 6-H), 7.20–7.37 (m, 5 H, C_6H_5).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = –1.4 [q, $Si(CH_3)_3$], 17.8 (t, CH_2Si), 25.8, 26.5 (2 q, CH_3), 49.3 (q, OCH_3), 58.2 (t, NCH_2Ph), 58.4 (t, OCH_2), 63.6 (t, C-7), 67.3 (d, C-3), 67.5 (t, C-5′), 75.0 (d, C-4′), 99.2 (s, C-4), 108.3 (s, C-2′), 108.8 (d, C-6), 127.1, 128.1, 128.2, 138.3 (3 d, s, C_6H_5), 135.6 (s, C-5).

MS (EI, 80 eV, 110 °C): *m*/*z* (%) = 515 (M^+, <1), 513 (M^+, <1), 500 (M^+ – Me, 1), 498 (M^+ – Me, 1), 442 (M^+ – $SiMe_3$, 1), 440 (M^+ – $SiMe_3$, 1), 101 ($C_5H_9O_2^+$ 18), 91 (CH_2Ph^+, 100), 73 ($SiMe_3^+$, 74).

HRMS: *m*/*z* [M^+ – Me] calcd for $C_{22}H_{30}{}^{79}BrNO_5Si$: 498.1311; found: 498.1332.

(3*R*,4′*S*)-2-Benzyl-5-bromo-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-4,4-dimethoxy-2,3,4,7-tetrahydro[1,2]oxazepine (*anti*-4b)

A solution of NaOH (600 mg) and KF (4.10 g) in H_2O (4 mL) was added to a vigorously stirred solution of *anti*-**1b** (500 mg, 1.64 mmol) in $CHBr_3$ (2.7 mL) containing $BnEt_3NCl$ (5.5 mg) as described in GP1. The resulting residue was purified by column chromatography (hexane–EtOAc, 4:1) to give 511 mg (65%, dr = 68:32) of *anti*-**3b**. The diastereomeric mixture of dibromocyclopropane derivative *anti*-**3b** was refluxed with anhyd K_2CO_3 (872 mg, 6.27 mmol) in MeOH (7 mL) for 20 h under argon. The product was purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to afford 241 mg (53%) of pure *anti*-**4b** as a colorless oil; $[\alpha]_D^{22}$ –84.2 (*c* 0.45, $CHCl_3$).

IR (film): 3090–3030 (=C–H), 2985–2845 (C–H), 1635 cm^{-1} (C=C).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.33, 1.36 (2 s, 3 H each, CH_3), 3.19, 3.29 (2 s, 3 H each, OCH_3), 3.28 (d, *J* = 5.6 Hz, 1 H, 3-H), 4.07 (dd, *J* = 6.4, 8.7 Hz, 1 H, 5′-H), 4.11 (dd, *J* = 7.9, 8.7 Hz, 1 H, 5′-H), 4.29 (m_c, 1 H, 4′-H), 4.30, 4.34 (2 d, *J* = 14.0 Hz, 1 H each, NCH_2Ph), 4.37 (dd, *J* = 1.1, 13.5 Hz, 1 H, 7-H), 4.47 (d, *J* = 13.5 Hz, 1 H, 7-H), 6.70 (br s, 1 H, 6-H), 7.24–7.40 (m, 5 H, C_6H_5).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 25.7, 26.3 (2 q, CH_3), 49.0, 49.1 (2 q, OCH_3), 58.1 (t, NCH_2Ph), 63.6 (t, C-7), 66.7 (d, C-3), 67.2 (t, C-5′), 74.9 (d, C-4′), 99.2 (s, C-4), 108.5 (d, C-6), 108.9 (s, C-2′), 127.1, 128.2, 128.6, 138.0 (3 d, s, C_6H_5), 135.3 (s, C-5).

MS (EI, 80 eV, 100 °C): *m*/*z* (%) = 429 (M^+, 1), 427 (M^+, 1), 414 (M^+ – Me, 1), 412 (M^+ – Me, 1), 398 (M^+ – OMe, <1), 396 (M^+ – OMe, <1), 329 (M^+ – $C_5H_9O_2$, 6), 327 (M^+ – $C_5H_9O_2$, 6), 91 (CH_2Ph^+, 100).

HRMS: *m*/*z* [M^+] calcd for $C_{19}H_{26}{}^{79}BrNO_5$: 427.0994; found: 427.0995.

Anal. Calcd for $C_{19}H_{26}BrNO_5$ (428.3): C, 53.28; H, 6.12; N, 3.27. Found: C, 53.10; H, 5.91; N, 2.68.

(3*S*,4′*S*)-2-Benzyl-5-bromo-3-(2′,2′dimethyl-1′,3′-dioxolan-4′-yl)-4-methoxy-4-[2-(trimethylsilyl)ethoxy]-2,3,4,7-tetrahydro-[1,2]oxazepine (*syn*-4a)

1,2-Oxazine *syn*-**1a** (200 mg, 0.510 mmol) and *t*-BuOK (170 mg, 1.53 mmol) were suspended in anhyd Et_2O (2 mL) at –40 °C followed by the dropwise addition of $CHBr_3$ (0.30 mL, 3.38 mmol). The reaction mixture was warmed slowly to r.t. and stirred overnight. The residue was purified by column chromatography (hexane–EtOAc, 8:1). The resulting diastereomeric mixture (64:36) of dibromocyclopropane *syn*-**3a** was refluxed with anhyd K_2CO_3 (880 mg, 0.640 mmol) in MeOH (1 mL) for 12 h under argon as described in GP1. The product was purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to yield 107 mg (41% from *syn*-**1a**) of pure *syn*-**4a** as a colorless oil; $[\alpha]_D^{22}$ +13.0 (*c* 0.49, $CHCl_3$).

IR (film): 3090–3030 (=C–H), 2985–2845 (C–H), 1670 cm^{-1} (C=C).

^1H NMR (500 MHz, $CDCl_3$): δ = 0.03 [s, 9 H, $Si(CH_3)_3$], 0.75–0.98 (m, 2 H, CH_2Si), 1.39, 1.40 (2 s, 3 H each, CH_3), 3.12 (s, 3 H, OCH_3), 3.37 (d, *J* = 6.7 Hz, 1 H, 3-H), 3.51–3.57 (m, 2 H, CH_2O), 3.75–3.79 (m, 1 H, 5′-H), 4.01 (d, *J* = 14.6 Hz, 1 H, CH_2Ph), 4.02 (dd, *J* = 5.4, 8.5 Hz, 1 H, 5′-H), 4.22 (dd, *J* = 1.2, 12.8 Hz, 1 H, 7-H), 4.33 (d, *J* = 14.6 Hz, 1 H, CH_2Ph), 4.50 (ddd, *J* = 5.1, 5.4, 6.7 Hz, 1 H, 4′-H), 4.62 (d, *J* = 12.8 Hz, 1 H, 7-H), 6.58 (br s, 1 H, 6-H), 7.25–7.40 (m, 5 H, C_6H_5).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = –1.4 [q, $Si(CH_3)_3$], 17.8 (t, CH_2Si), 26.3, 26.8 (2 q, CH_3), 49.3 (q, OCH_3), 58.6 (t, OCH_2), 59.7 (t, NCH_2Ph), 67.2 (t, C-5′), 67.8 (d, C-3), 68.3 (t, C-7), 73.4 (d, C-4′), 99.7 (s, C-2′), 108.0 (d, C-6), 109.0 (s, C-4), 126.9, 128.1, 128.3, 138.6 (3 d, s, C_6H_5), 136.9 (s, C-5).

MS (EI, 80 eV, 110 °C): *m*/*z* (%) = 513 (M^+, <1), 514 (M^+ + H, 1), 412 (M^+ – TMSE, 1), 101 (TMSE$^+$, 17), 91 (CH_2Ph^+, 53), 73 (Me_3Si^+, 100).

Anal. Calcd for $C_{23}H_{33}BrNO_5Si$ (514.5): C, 53.69; H, 7.05; N, 2.72. Found: C, 53.11; H, 6.82; N, 2.66.

(3*S*,4′*S*)-2-Benzyl-5-bromo-3-(2,2-dimethyl-1,3-dioxolan-4′-yl)-4,4-dimethoxy-2,3,4,7-tetrahydro[1,2]oxazepine (*syn*-4b)

A solution of NaOH (600 mg) and KF (4.10 g) in H_2O (4 mL) was added to a vigorously stirred solution of *syn*-**1b** (500 mg, 1.64 mmol) in $CHBr_3$ (2.7 mL) containing $BnEt_3NCl$ (5.5 mg) as described in GP1. The resulting residue was purified by column chromatography (hexane–EtOAc, 4:1) to give 420 mg (54%, dr = 70:30) of *syn*-**3b**. The diastereomeric mixture of dibromocyclopropane *syn*-**3b** was refluxed with anhyd K_2CO_3 (590 mg, 4.28 mmol) in MeOH (7 mL) for 20 h and under argon. The product was purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to give pure *syn*-**4b** in 185 mg (49%) as a colorless oil; $[\alpha]_D^{22}$ +21.5 (*c* 1.3, $CHCl_3$).

IR (film): 3090–3030 (=C–H), 2985–2845 (C–H), 1635 cm^{-1} (C=C).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.40, 1.405 (2 s, 3 H each, CH_3), 3.12, 3.24 (2 s, 3 H each, OCH_3), 3.34 (d, *J* = 6.4 Hz, 1 H, 3-H), 3.76 (dd, *J* = 8.2, 9.1 Hz, 1 H, 5′-H), 4.00 (dd, *J* = 5.5, 8.2 Hz, 1 H, 5′-H), 4.03 (d, *J* = 14.9 Hz, 1 H, NCH_2Ph), 4.21 (dd, *J* = 1.5, 12.8 Hz, 1 H, 7-H), 4.35 (d, *J* = 14.9 Hz, 1 H, NCH_2Ph), 4.43–4.53 (m, 1 H, 4′-H), 4.62 (d, *J* = 12.8 Hz, 1 H, 7-H), 6.59 (br s, 1 H, 6-H), 7.20–7.43 (m, 5 H, C_6H_5).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 26.3, 26.5 (2 q, CH_3), 49.2, 49.4 (2 q, OCH_3), 59.5 (t, NCH_2Ph), 66.7 (d, C-3), 67.0 (t, C-5′), 68.8 (t, C-7), 72.9 (d, C-4′), 99.5 (s, C-4), 107.4 (d, C-6), 108.3 (s, C-2′), 126.8, 128.1, 128.3, 138.6 (3 d, s, C_6H_5), 136.3 (s, C-5).

MS (EI, 80 eV, 130 °C): *m*/*z* (%) = 429 (M^+, <1), 427 (M^+, <1), 414 (M^+ – Me, 2), 412 (M^+ – Me, 2), 329 (M^+ – $C_5H_9O_2$, 18), 327 (M^+ –

$C_5H_9O_2$, 18), 194 ($C_6H_9O_2{}^{81}Br^+$, 61), 192 ($C_6H_9O_2{}^{79}Br^+$, 62), 91 (CH_2Ph^+, 100).

HRMS: *m/z* [M^+] calcd for $C_{19}H_{26}{}^{79}BrNO_5$: 427.0994; found: 427.0957.

Anal. Calcd for $C_{19}H_{26}BrNO_5$ (428.3): C, 53.28; H, 6.12; N, 3.27. Found: C, 53.22; H, 6.12; N, 3.20.

(3*S*,4′*S*)-2-Benzyl-5-bromo-3-(1′,4′-dioxaspiro[4.5]dec-2′-yl)-4,4-dimethoxy-2,3,4,7-tetrahydro[1,2]oxazepine (*syn*-4c)

According to GP1, *syn*-**1c** (0.371 g, 1.07 mmol) and $BnEt_3NCl$ (7 mg) in $CHBr_3$ (2.7 mL) was treated with NaOH (380 mg) and KF (2.71 g) in H_2O (4 mL). The resulting residue was purified by column chromatography (hexane–EtOAc, 4:1) to give 182 mg (33%, dr = 60:40) of *syn*-**3c**. Then *syn*-**3c** (95 mg, 0.183 mmol) was refluxed with anhyd K_2CO_3 (152 mg, 1.10 mmol) in MeOH (3 mL) for 20 h under argon. Purification by column chromatography (silica gel, hexane–EtOAc, 4:1) gave 43 mg (51%) of *syn*-**4c** as a pale yellow oil; $[\alpha]_D^{22}$ –14.0 (*c* 0.15, $CHCl_3$).

***syn*-3c**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33–1.75 (m, 10 H, CH_2), 1.94 (d, *J* = 5.2 Hz, 0.6 H, 1-H), 2.13 (dd, *J* = 3.5, 8.5 Hz, 0.4 H, 1-H), 3.39 (s, 1.2 H, OCH_3), 3.42–3.46 (m, 1 H, 5-H), 3.52 (s, 1.8 H, OCH_3), 3.56, 3.64 (2 d, *J* = 15.0 Hz, 1 H each, NCH_2Ph), 3.74 (dd, *J* = 3.6, 12.4 Hz, 0.4 H, 2-H), 3.79 (br d, *J* = 11.9 Hz, 0.6 H, 2-H), 3.83–3.92, 4.05–4.15, 4.19–4.29, 4.36–4.47, 4.58–4.66 (5 m, 1 H, 1H, 2 H, 1 H, 1 H), 7.20–7.40 (m, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.2, 25.3*, 35.3, 35.8*, 36.1, 36.4* (6 t, CH_2), 31.2, 33.4* (2 d, C-1), 38.7*, 40.7 (2 s, C-7), 57.0 (q, OCH_3), 60.0, 60.2* (2 t, NCH_2Ph), 63.8*, 64.1 (2 s, C-6), 65.0*, 65.7, 66.6*, 68.4 (4 t, C-5, C-2), 65.7*, 67.0 (2 s, C-5′), 73.9, 74.3* (2 d, C-4′), 109.9*, 110.0 (2 s, C-2′), 126.8, 128.2, 128.3, 138.8*, 139.0 (3 d, 2 s, C_6H_5). Signals of the minor diastereomer are marked with *.

***syn*-4c**

IR (film): 3090–3030 (=C–H), 2935–2860 (C–H), 1635 cm^{-1} (C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.75 (m, 10 H, CH_2), 3.13, 3.24 (2 s, 3 H each, OCH_3), 3.34 (br d, *J* = 6.9 Hz, 1 H, 3-H), 3.74 (dd, *J* = 8.4, 9.3 Hz, 1 H, 3′-H), 4.02 (dd, *J* = 5.4, 8.4 Hz, 1 H, 3′-H), 4.05 (d, *J* = 15.1 Hz, 1 H, NCH_2Ph), 4.22 (dd, *J* = 1.3, 12.8 Hz, 1 H, 7-H), 4.39 (d, *J* = 15.1 Hz, 1 H, NCH_2Ph), 4.48 (ddd, *J* = 5.4, 6.9, 9.3 Hz, 1 H, 2′-H), 4.64 (d, *J* = 12.8 Hz, 1 H, 7-H), 6.58 (br s, 1 H, 6-H), 7.22–7.46 (m, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.1, 24.2, 25.2, 35.7, 36.3 (5 t, CH_2), 49.3, 49.4 (2 q, OCH_3), 59.8 (t, NCH_2Ph), 66.8 (t, C-3′), 67.2 (d, C-3), 68.9 (t, C-7), 72.4 (d, C-2′), 99.6 (s, C-4), 108.1 (s, C-5′), 108.2 (d, C-6), 126.8, 128.1, 128.2, 138.8 (3 d, s, C_6H_5), 136.3 (s, C-5).

HRMS: *m/z* [M + Na^+] calcd for $C_{22}H_{30}{}^{81}BrNO_5$ + Na: 492.1185; found: 492.1192.

(3*S*,4′*S*)-2-Benzyl-4-benzyloxy-5-bromo-3-(2,2-dimethyl-1,3-dioxolan-4′-yl)-4-methoxy-2,3,4,7-tetrahydro[1,2]oxazepine (*syn*-4d)

According to GP1, *syn*-**1d** (0.626 g, 1.64 mmol) and $BnEt_3NCl$ (10 mg) in $CHBr_3$ (5.2 mL) was treated with NaOH (589 mg) and KF (4.16 g) in H_2O (5 mL). The resulting residue was purified by column chromatography (hexane–EtOAc, 4:1) to give 442 mg (49%, dr = 55:45) of *syn*-**3d** as a pale yellow oil. Then *syn*-**3d** (100 mg, 0.180 mmol) was refluxed with anhyd K_2CO_3 (150 mg, 1.09 mmol) in MeOH (3 mL) for 20 h under argon. Purification by column chromatography (silica gel, hexane–EtOAc = 4:1) gave 49 mg (54%, dr = 82:18) of *syn*-**4d** as a colorless oil.

***syn*-3d**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32, 1.35, 1.38, 1.44 (4 s, 1.65 H, 1.65 H, 1.35 H, 1.35 H, CH_3), 2.05 (d, *J* = 5.2 Hz, 0.55 H, 1-H), 2.25 (dd, *J* = 4, 8.5 Hz, 0.45 H, 1-H), 3.54–3.69, 3.77–3.90, 4.11–4.39, 4.55–4.79 (4 m, 2 H, 2 H, 4 H, 3 H), 7.22–7.41 (m, 10 H, C_6H_5).

***syn*-4d (Major Isomer)**

IR (film): 3090–3030 (=C–H), 2985–2895 (C–H), 1635 cm^{-1} (C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35, 1.39 (2 s, 3 H each, CH_3), 3.15 (s, 3 H, OCH_3), 3.47 (d, *J* = 6.5 Hz, 1 H, 3-H), 3.87 (dd, *J* = 8.4, 8.8 Hz, 1 H, 5′-H), 3.99 (dd, *J* = 5.6, 8.4 Hz, 1 H, 5′-H), 4.07 (d, *J* = 14.8 Hz, 1 H, NCH_2Ph), 4.29 (dd, *J* = 1.4, 12.9 Hz, 1 H, 7-H), 4.37 (d, *J* = 14.8 Hz, 1 H, NCH_2Ph), 4.52–4.69 (m, 4 H, 4′-H, 7-H, OCH_2Ph), 6.67 (br s, 1 H, 6-H), 7.23–7.47 (m, 10 H, C_6H_5).

^{1}H NMR (400 MHz, $CDCl_3$): δ (additional data for the minor isomer of *syn*-**4d**) = 1.40, 1.43 (2 s, 3 H each, CH_3), 3.30 (s, 3 H, OCH_3), 3.43 (d, *J* = 6.8 Hz, 1 H, 3-H), 3.80 (dd, *J* = 8.5, 8.8 Hz, 1 H, 5′-H), 4.15 (dd, *J* = 1.5, 12.8 Hz, 1 H, 7-H), 6.71 (br s, 1 H, 6-H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 26.2, 26.3*, 26.6*, 26.7 (4 q, CH_3), 49.5, 49.8* (2 q, OCH_3), 59.5 (t, NCH_2Ph), 63.2, 63.7* (2 d, C-3), 66.7*, 67.0*, 67.2, 67.4 (4 t, C-5′, OCH_2Ph), 68.9 (t, C-7), 73.02, 73.08* (2 d, C-4′), 100.1 (s, C-4), 107.46, 107.48* (2 s, C-2′), 108.3, 108.8* (2 d, C-6), 126.9*, 127.0, 127.5*, 127.8, 128.0, 128.1*, 128.2, 128.3, 128.4, 128.5, 128.55*, 137.4, 137.7*, 138.5, 138.7* (11 d, 4 s, C_6H_5), 136.5, 136.7* (2 s, C-5). Signals of the minor diastereomer are marked with *.

HRMS: *m/z* [M + Na^+] calcd for $C_{25}H_{30}{}^{81}BrNO_5$ + Na: 528.1185; found: 528.1194.

(3*S*,4′*S*,5′*R*,4″*R*)-2-Benzyl-5-bromo-3-(2′,2′,2″,2″-tetramethyl-[4′,4″]bi[1′,3′-dioxolanyl]-5′-yl)-4-methoxy-4-[2-(trimethylsilyl)ethoxy]-2,3,4,7-tetrahydro[1,2]oxazepine (*syn*-4e)

According to GP1, *syn*-**1e** (0.344 g, 0.727 mmol) and $BnEt_3NCl$ (6 mg) in $CHBr_3$ (2.3 mL) was treated with NaOH (260 mg) and KF (1.83 g) in H_2O (2 mL). The resulting residue was purified by column chromatography (hexane–EtOAc, 8:1) to give 163 mg (35%, dr = 60:40) of *syn*-**3e**. Then *syn*-**3e** (91 mg, 0.137 mmol) was refluxed with anhyd K_2CO_3 (114 mg, 0.831 mmol) in MeOH (2.5 mL) for 20 h under argon. Purification by column chromatography (silica gel, hexane–EtOAc, 4:1) gave 49 mg (58%, dr = 60:40) of *syn*-**4e** as a colorless resin.

***syn*-3e**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04, 0.05 [2 s, 9 H, $Si(CH_3)_3$], 0.96–1.10 (m, 2 H, $SiCH_2$), 1.34, 1.37*, 1.39, 1.41*, 1.44*, 1.48*, 1.55 (7 s, 12 H, CH_3), 2.06 (d, *J* = 5.0 Hz, 0.6 H, 1-H), 2.13 (dd, *J* = 1.5, 7.2 Hz, 0.4 H, 1-H), 3.58–3.75, 3.91–4.34 (2 m, 3 H, 8.4 H), 4.39 (d, *J* = 13.5 Hz, 0.6 H, NCH_2Ph), 7.21–7.38 (m, 5 H, C_6H_5).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = –1.4*, –1.37 [2 q, $Si(CH_3)_3$], 18.4 (t, CH_2Si), 25.3, 25.6*, 26.3*, 26.8, 26.85*, 26.9, 27.4, 27.6* (8 q, CH_3), 31.5 (d, C-1), 42.3 (s, C-7), 58.34, 58.41* (2 t, NCH_2Ph), 63.6 (d, C-5), 64.2 (t, C-2), 65.5 (s, C-6), 66.8 (t, C-5″), 67.6 (t, OCH_2), 77.1, 77.8 (2 d, C-4″, C-5′), 79.9 (d, C-4′), 109.6, 109.9 (2 s, C-2′, C-2″), 126.8, 128.1, 128.2, 128.6*, 138.6 (4 d, s, C_6H_5). Signals of the minor diastereomer are marked with *.

***syn*-4e**

IR (film): 3090–3040 (=C–H), 2990–2895 (C–H), 1630 cm^{-1} (C=C).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.03*, 0.05 [2 s, 9 H, $Si(CH_3)_3$], 0.83–1.05 (m, 2 H, $SiCH_2$), 1.20*, 1.255, 1.26, 1.29*, 1.33*, 1.36, 1.40, 1.45* (8 s, 12 H, CH_3), 3.16, 3.17* (2 s, 3 H, OCH_3), 3.19*, 3.36 (2 m_c, 1 H, 3-H), 3.38–3.79, 3.85–4.25, 4.30–4.65 (3 m, 3 H, 5

H, 3 H, 7-H), 6.60, 6.77* (2 br s, 0.6 H, 0.4 H, 6-H), 7.21–7.48 (m, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –1.38, –1.34* [2 q, $Si(CH_3)_3$], 17.6*, 17.9 (2 t, CH_2Si), 25.3, 25.7*, 26.3*, 26.4*, 26.5, 27.0, 27.1*, 27.5 (8 q, CH_3), 48.84*, 48.87 (2 q, OCH_3), 57.1*, 57.9, 58.5*, 59.7 (4 t, N*C*H_2Ph, OCH_2), 63.6, 63.8* (2 t, C-7), 65.4, 67.5* (2 d, C-3), 67.9 (t, C-5″), 75.5*, 76.6, 77.5, 77.7, 77.8*, 79.1* (6 d, C-4′, C-4″, C-5′), 98.9, 99.2* (2 s, C-4), 107.1, 109.7* (2 d, C-6), 108.8*, 109.1, 109.3*, 110.1 (4 s, C-2′, C-2″), 127.0, 127.4, 128.26, 128.33, 128.6, 129.1, 137.6*, 138.7 (6 d, 2 s, C_6H_5), 135.3*, 136.0 (2 s, C-5). Signals of the minor diastereomer are marked with *.

HRMS: *m*/*z* [M + Na^+] calcd for $C_{28}H_{44}{}^{79}BrNO_7$ + Na: 636.1968; found: 636.1947.

(3*R*,4′*S*,5′*R*,4″*R*)-2-Benzyl-5-bromo-3-(2′,2′,2″,2″-tetramethyl-[4′,4″]bi[1′,3′-dioxolanyl]-5′-yl)-4,4-dimethoxy-2,3,4,7-tetrahydro[1,2]oxazepine (*anti*-4f)

According to GP1, *anti*-**1f** (1.05 g, 2.58 mmol) and $BnEt_3NCl$ (9 mg) in $CHBr_3$ (4.7 mL) was treated with NaOH (940 mg) and KF (6.50 g) in H_2O (7 mL). The resulting residue was purified by column chromatography (hexane–EtOAc, 4:1) to give 692 mg (46%, dr = 70:30) of *anti*-**3f** as colorless crystals; mp 136–139 °C. Then, *anti*-**3f** (682 mg, 1.18 mmol) was refluxed with anhyd K_2CO_3 (622 mg, 4.44 mmol) in MeOH (8 mL) for 22 h under argon. Purification by column chromatography (silica gel, hexane–EtOAc, 4:1) gave 465 mg (74%) of *anti*-**4f** as a colorless resin; $[\alpha]_D{}^{22}$ +130.5 (*c* 0.3, $CHCl_3$).

***anti*-3f**

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.34, 1.35, 1.40, 1.43, 1.52, 1.54 (6 s, 12 H, CH_3), 2.08–2.10 (m, 1 H, 1-H), 3.56 (s, 3 H, OCH_3), 3.59–3.76 (m, 1 H), 3.78 (d, *J* = 14.0 Hz, 1 H, NCH_2Ph), 3.87–4.19 (m, 5 H), 4.27 (d, *J* = 14.0 Hz, 1 H, NCH_2Ph), 4.37 (dd, *J* = 3.9, 7.1 Hz, 0.3 H, 4′-H), 4.45–4.53 (m, 0.7 H, 4′-H), 7.19–7.39 (m, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.5*, 25.6, 26.5, 26.76*, 26.8, 27.1*, 27.2, 27.3* (8 q, CH_3), 31.6, 31.8* (2 d, C-1), 41.55*, 41.6 (2 s, C-7), 57.2 (q, OCH_3), 57.2 (t, N*C*H_2Ph), 62.1*, 62.2 (2 d, C-5), 65.3 (s, C-6), 65.6, 66.1* (2 t, C-2), 67.3*, 67.6 (2 t, C-5″), 76.9, 77.3* (2 d, C-4″), 78.2, 78.6 (2 d, C-4′, C-5′), 109.1, 109.9 (2 s, C-2′, C-2″), 127.0, 127.05*, 128.0*, 128.1, 128.4, 137.5, 137.55* (5 d, 2 s, C_6H_5). Signals of the minor diastereomer are marked with *.

Anal. Calcd for $C_{23}H_{31}Br_2NO_6$ (577.3): C, 47.85; H, 5.41; N, 2.43. Found: C, 47.66; H, 5.44; N, 2.49.

***anti*-4f**

IR (film): 3090–3035 (=C–H), 2985–2890 (C–H), 1630 cm^{-1} (C=C).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.15, 1.36, 1.38, 1.45 (4 s, 3 H each, CH_3), 3.11 (d, *J* = 7.3 Hz, 1 H, 3-H), 3.18, 3.26 (2 s, 3 H each, OCH_3), 3.74 (dd, *J* = 7.3, 7.5 Hz, 1 H, 5′-H), 3.92 (d, *J* = 7.3 Hz, 2 H, 5″-H), 4.35 (d, *J* = 13.1 Hz, 1 H, NCH_2Ph), 4.40, 4.41 (AB system, J_{AB} = 13.0 Hz, 1 H each, 7-H), 4.47 (dt, *J* = 2.6, 7.3 Hz, 1 H, 4′-H), 4.49 (d, *J* = 13.1 Hz, 1 H, NCH_2Ph), 4.61 (dd, *J* = 2.6, 7.5 Hz, 1 H, 4″-H), 6.78 (s, 1 H, 6-H), 7.24–7.26, 7.30–7.33, 7.39–7.42 (3 m, 1 H, 2 H, 2 H, C_6H_5).

^{13}C NMR (176.1 MHz, $CDCl_3$): δ = 25.6, 26.15, 26.17, 27.1 (4 q, CH_3), 48.6, 49.1 (2 q, OCH_3), 56.9 (t, N*C*H_2Ph), 61.5 (t, C-7), 63.8 (t, C-5″), 66.3 (d, C-3), 75.6 (d, C-4″), 76.6 (d, C-5′), 77.8 (d, C-4′), 99.5 (s, C-4), 108.8, 109.2 (2 s, C-2′, C-2″), 109.7 (d, C-6), 127.3, 128.3, 129.3, 137.2 (3 d, s, C_6H_5), 134.9 (s, C-5).

HRMS: *m*/*z* [M + Na^+] calcd for $C_{24}H_{34}{}^{79}BrNO_7$ + Na: 552.1392; found: 552.1421.

Sonogashira Cross-Coupling Reactions of 1,2-Oxazepines 4; General Procedure 2 (GP2)

A reaction flask containing 1,2-oxazepine derivative **4** (1 equiv), Ph_3P (0.2 equiv), $Pd(OAc)_2$ (5 mol%), and CuI (5 mol%) was degassed and filled with argon. DMF (5 mL/mmol) and *i*-Pr_2NH (2.5 mL/mmol) were added followed by an alkyne (1.2–1.7 equiv). After stirring at r.t. for 10 h, the mixture was diluted with H_2O (8 mL/mmol) and extracted with Et_2O (3 × 5 mL/mmol). The combined organic extracts were washed with H_2O (5 mL/mmol) and brine (5 mL/mmol), dried (Na_2SO_4), and concentrated to dryness.

(3*S*,4′*S*)-2-Benzyl-4,4-dimethoxy-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-5-phenylethynyl-2,3,4,7-tetrahydro[1,2]oxazepine (*syn*-5)

A reaction flask containing *syn*-**4b** (50 mg, 0.117 mmol), Ph_3P (6.2 mg, 0.024 mmol), $Pd(OAc)_2$ (1.3 mg, 0.006 mmol), and CuI (1.1 mg, 0.006 mmol) was degassed and filled with argon. DMF (0.54 mL) and *i*-Pr_2NH (0.27 mL) were added followed by phenylacetylene (14 mg, 0.140 mmol) as described in GP2. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to afford pure *syn*-**5** (50 mg, 95%) as a colorless oil; $[\alpha]_D{}^{22}$ +192.4 (*c* 0.53, $CHCl_3$).

IR (film): 3080–3030 (=C–H), 2985–2850 (C–H), 1685, 1600 cm^{-1} (C=C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40, 1.41 (2 s, 3 H each, CH_3), 3.15, 3.28 (2 s, 3 H each, OCH_3), 3.43 (d, *J* = 6.9 Hz, 1 H, 3-H), 3.80 (dd, *J* = 8.5, 9.1 Hz, 1 H, 5′-H), 4.06 (d, *J* = 13.8 Hz, 1 H, NCH_2Ph), 4.07 (m_c, 1 H, 5′-H), 4.38 (d, *J* = 13.8 Hz, 1 H, NCH_2Ph), 4.40 (m_c, 1 H, 7-H), 4.54 (ddd, *J* = 5.5, 6.9, 9.1 Hz, 1 H, 4′-H), 4.82 (d, *J* = 12.8 Hz, 1 H, 7-H), 6.15 (s, 1 H, 6-H), 7.24–7.47 (m, 10 H, C_6H_5).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 26.4, 26.6 (2 q, CH_3), 49.2, 49.4 (2 q, OCH_3), 59.6 (t, N*C*H_2Ph), 67.4 (t, C-5′), 67.5 (d, C-3), 68.4 (t, C-7), 73.1 (d, C-4′), 84.4 (s, C≡C), 96.6 (s, C-4), 98.3 (s, C≡C), 107.4 (s, C-2′), 109.1 (d, C-6), 122.8 (s, C-5), 126.8, 128.1, 128.2, 128.3, 128.5, 131.4, 138.8, 143.5 (6 d, 2 s, C_6H_5).

MS (EI, 80 eV, 90 °C): *m*/*z* (%) = 449 (M^+, 3), 434 (M^+ – Me, 2), 348 ($M^+ - C_5H_9O_2$, 5), 214 (100), 91 (CH_2Ph^+, 30).

HRMS: *m*/*z* [M^+] calcd for $C_{27}H_{31}NO_5$: 449.2202; found: 449.2219.

Anal. Calcd for $C_{27}H_{31}NO_5$ (449.6): C, 72.14; H, 6.95; N, 3.12. Found: C, 71.44; H, 6.67; N, 2.93.

(3*R*,4′*S*)-2-Benzyl-4,4-dimethoxy-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-5-phenylethynyl-2,3,4,7-tetrahydro[1,2]oxazepine (*anti*-5)

A reaction flask containing *anti*-**4b** (50 mg, 0.117 mmol), Ph_3P (6.2 mg, 0.024 mmol), $Pd(OAc)_2$ (1.3 mg, 0.006 mmol), and CuI (1.1 mg, 0.006 mmol) was degassed and filled with argon. DMF (0.54 mL) and *i*-Pr_2NH (0.27 mL) were added followed by phenylacetylene (14 mg, 0.140 mmol) as described in GP2. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to afford pure *anti*-**5** (50 mg, 95%) as a colorless oil; $[\alpha]_D{}^{22}$ –241.9 (*c* 0.85, $CHCl_3$).

IR (film): 3080–3030 (=C–H), 2985–2835 (C–H), 1685 cm^{-1} (C=C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35, 1.38 (2 s, 3 H each, CH_3), 3.21, 3.31 (2 s, 3 H each, OCH_3), 3.33 (d, *J* = 6.0 Hz, 1 H, 3-H), 4.12 (dd, *J* = 6.6, 8.8 Hz, 1 H, 5′-H), 4.15 (dd, *J* = 7.8, 8.8 Hz, 1 H, 5′-H), 4.31–4.36 (m, 2 H, NCH_2Ph, 4′-H), 4.39 (d, *J* = 13.9 Hz, 1 H, NCH_2Ph), 4.57 (dd, *J* = 1.0, 13.4 Hz, 1 H, 7-H), 4.63 (d, *J* = 13.4 Hz, 1 H, 7-H), 6.26 (s, 1 H, 6-H), 7.25–7.45 (m, 10 H, C_6H_5).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 25.7, 26.3 (2 q, CH_3), 48.9, 49.1 (2 q, OCH_3), 57.8 (t, N*C*H_2Ph), 62.9 (t, C-7), 67.3 (d, C-3), 67.4 (t, C-5′), 74.9 (d, C-4′), 84.4 (s, C≡C), 96.5 (s, C-4), 98.0 (s, C≡C),

108.5 (s, C-2′), 109.8 (d, C-6), 122.9 (s, C-5), 127.1, 128.2, 128.3, 128.5, 128.7, 131.4, 138.2, 142.3 (6 d, 2 s, C_6H_5).

MS (EI, 80 eV, 140 °C): *m*/*z* (%) = 449 (M^+, 3), 434 (M^+ – Me, 3), 348 ($M^+ - C_5H_9O_2$, 2), 214 (100), 91 (CH_2Ph^+, 35).

HRMS: *m*/*z* [M^+] calcd for $C_{27}H_{31}NO_5$: 449.2202; found: 449.2197.

(3*R*,4′*S*)-2-Benzyl-4,4-dimethoxy-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-5-(3-methoxyprop-1-yn-1-yl)-2,3,4,7-tetrahydro[1,2]oxazepine (*anti*-6)

A reaction flask containing *anti*-**4b** (50 mg, 0.117 mmol), Ph_3P (6.2 mg, 0.024 mmol), $Pd(OAc)_2$ (1.3 mg, 0.006 mmol), and CuI (1.1 mg, 0.006 mmol) was degassed and filled with argon. DMF (0.54 mL) and *i*-Pr_2NH (0.27 mL) were added followed by methyl propargyl ether (14 mg, 0.200 mmol) as described in GP2. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to afford pure *anti*-**6** (35 mg, 72%) as a colorless oil; $[\alpha]_D^{22}$ –148.2 (*c* 0.66, $CHCl_3$).

IR (film): 3080–3030 (=C–H), 2985–2835 (C–H), 1685 cm^{-1} (C=C).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.31, 1.35 (2 s, 3 H each, CH_3), 3.15, 3.28, 3.37 (3 s, 3 H each, OCH_3), 3.27 (d, *J* = 6.3 Hz, 1 H, 3-H), 4.07 (dd, *J* = 6.7, 8.9 Hz, 1 H, 5′-H), 4.10 (dd, *J* = 8.0, 8.9 Hz, 1 H, 5′-H), 4.21 (m_c, 2 H, OCH_2), 4.28 (ddd, *J* = 6.3, 6.7, 8.0 Hz, 1 H, 4′-H), 4.31, 4.32 (AB system, J_{AB} = 14.0 Hz, 1 H each, NC*H*$_2$Ph), 4.47, 4.49 (AB system, J_{AB} = 13.5 Hz, 1 H each, 7-H), 6.07 (br s, 1 H, 6-H), 7.24–7.38 (m, 5 H, C_6H_5).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 25.8, 26.3 (2 q, CH_3), 48.9, 49.0, 57.7 (3 q, OCH_3), 57.7 (t, N*C*H$_2$Ph), 60.3 (t, OCH_2), 62.8 (t, C-7), 67.2 (d, C-3), 67.4 (t, C-5′), 75.0 (d, C-4′), 81.3, 92.3 (2 s, C≡C), 97.8 (s, C-4), 108.5 (s, C-2′), 109.8 (d, C-6), 127.1, 128.2, 128.7, 138.2, 143.0 (3 d, 2 s, C_6H_5, C-5).

MS (EI, 80 eV, 80 °C): *m*/*z* (%) = 417 (M^+, <1), 402 (M^+ – Me, 2), 316 ($M^+ - C_5H_9O_2$, 2), 182 (100), 91 (CH_2Ph^+, 26).

HRMS: *m*/*z* [M^+] calcd for $C_{23}H_{31}NO_6$: 417.2152; found: 417.2136.

(3*R*,4′*S*)-2-Benzyl-4,4-dimethoxy-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-5-phenyl-2,3,4,7-tetrahydro[1,2]oxazepine (*anti*-7)

A reaction flask containing *anti*-**4b** (50 mg, 0.117 mmol), Ph_3P (6.2 mg, 0.024 mmol), and $Pd(OAc)_2$ (1.3 mg, 0.006 mmol), was degassed and filled with argon. DMF (0.54 mL) and K_2CO_3 (24 mg, 0.176 mmol) were added, followed by phenylboronic acid (16 mg, 0.129 mmol). After stirring at 70 °C for 10 h, the mixture was diluted with H_2O (1.5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to afford pure *anti*-**7** (40 mg, 80%) as a colorless oil; $[\alpha]_D^{22}$ –109.0 (*c* 0.65, $CHCl_3$).

IR (film): 3085–3030 (=C–H), 2985–2840 (C–H), 1600 cm^{-1} (C=C).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.35, 1.38 (2 s, 3 H each, CH_3), 3.27, 3.36 (2 s, 3 H each, OCH_3), 3.41 (d, *J* = 5.1 Hz, 1 H, 3-H), 4.08 (dd, *J* = 6.5, 8.5 Hz, 1 H, 5′-H), 4.19 (dd, *J* = 8.1, 8.5 Hz, 1 H, 5′-H), 4.33 (d, *J* = 14.4 Hz, 1 H, NC*H*$_2$Ph), 4.38 (d, *J* = 14.4 Hz, 1 H, NC*H*$_2$Ph), 4.43 (ddd, *J* = 5.1, 6.4, 8.6 Hz, 1 H, 4′-H), 4.48 (d, *J* = 13.3 Hz, 1 H, 7-H), 4.57 (dd, *J* = 1.0, 13.3 Hz, 1 H, 7-H), 7.07 (br s, 1 H, 6-H), 7.15–7.40 (m, 10 H, C_6H_5).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 25.7, 26.3 (2 q, CH_3), 48.9, 49.0 (2 q, OCH_3), 58.3 (t, N*C*H$_2$Ph), 62.3 (t, C-7), 67.2 (t, C-5′), 67.4 (d, C-3), 75.2 (d, C-4′), 98.2 (s, C-4), 108.3 (s, C-2′), 129.8 (d, C-6), 126.9, 127.4, 128.3, 128.5, 128.7, 131.4, 131.8, 135.8, 136.6 (6 d, 3 s, C_6H_5, C-5).

MS (EI, 80 eV, 90 °C): *m*/*z* (%) = 425 (M^+, 1), 410 (M^+ – Me, 2), 190 (100), 91 (CH_2Ph^+, 56).

HRMS: *m*/*z* [M^+] calcd for $C_{25}H_{31}NO_5$: 425.2202; found: 425.2198.

(3*R*,4′*S*)-2-Benzyl-4,4-dimethoxy-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-5-vinyl-2,3,4,7-tetrahydro[1,2]oxazepine (*anti*-8)

A reaction flask containing *anti*-**4b** (40 mg, 0.094 mmol) in DMF (0.5 mL) was degassed and filled with argon. Ph_3P (4.9 mg, 0.019 mmol) and $Pd(OAc)_2$ (2.1 mg, 0.009 mmol) were added followed by addition of vinyltributyltin (32.8 mg, 0.103 mmol). After stirring at 65 °C for 3 h, the mixture was taken up in EtOAc (1.5 mL), washed with H_2O (2 × 2 mL) and brine (2 mL). The organic layer was dried (Na_2SO_4) and concentrated to dryness. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 6:1) to afford pure *anti*-**8** (33 mg, 94%) as a colorless oil; $[\alpha]_D^{22}$ –99.9 (*c* 1.36, $CHCl_3$).

IR (film): 3085–3030 (=C–H), 2985–2835 (C–H), 1650, 1605 cm^{-1} (C=C).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.32, 1.35 (2 s, 3 H each, CH_3), 3.15, 3.29 (2 s, 3 H each, OCH_3), 3.30 (s, 1 H, 3-H), 4.04 (dd, *J* = 6.4, 8.7 Hz, 1 H, 5′-H), 4.12 (dd, *J* = 8.2, 8.7 Hz, 1 H, 5′-H), 4.29–4.34 (m, 3 H, NC*H*$_2$Ph, 4′-H), 4.36 (d, *J* = 13.2 Hz, 1 H, 7-H), 4.44 (d, *J* = 13.2 Hz, 1 H, 7-H), 5.28 (d, *J* = 9.5 Hz, 1 H, 2″-H), 5.42 (d, *J* = 15.9 Hz, 1 H, 2″-H), 6.52 (dd, *J* = 9.5, 15.9 Hz, 1 H, 1″-H), 6.53 (s, 1 H, 6-H), 7.21–7.39 (m, 5 H, C_6H_5).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 25.8, 26.3 (2 q, CH_3), 48.8, 48.9 (2 q, OCH_3), 57.9 (t, N*C*H$_2$Ph), 60.8 (t, C-7), 67.2 (d, C-3), 67.3 (t, C-5′), 75.6 (d, C-4′), 98.0 (s, C-4), 108.4 (s, C-2′), 121.0 (t, C-2″), 129.1 (d, C-6), 127.1, 128.2, 128.7, 130.8 (3 d, s, C_6H_5), 130.3 (d, C-1″), 138.4 (s, C-5).

MS (EI, 80 eV, 40 °C): *m*/*z* (%) = 375 (M^+, 19), 360 (M^+ – Me, 100), 344 (M^+ – OMe, 42).

HRMS: *m*/*z* [M^+] calcd for $C_{21}H_{29}NO_5$: 375.2046; found: 375.2044.

Anal. Calcd for $C_{21}H_{29}NO_5$ (375.5): C, 67.18; H, 7.79; N, 3.73. Found: C, 67.61; H, 7.15; N, 3.15.

(3*R*,4′*S*)-3-{2-Benzyl-4,4-dimethoxy-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2,3,4,7-tetrahydro[1,2]oxazepin-5-yl}acrylic Acid Methyl Ester (*anti*-9)

A reaction flask containing *anti*-**4b** (80 mg, 0.187 mmol) in DMF (0.9 mL) was degassed and filled with argon. LiCl (24 mg, 0.561 mmol) and Et_3N (0.03 mL, 0.187 mmol) were added followed by methyl acrylate (0.013 mL, 0.187 mmol) and $Pd(OAc)_2$ (2.1 mg, 0.009 mmol). After stirring at 70 °C for 10 h, the mixture was taken up in EtOAc (1.5 mL), washed with H_2O (2 × 2 mL) and brine (2 mL). The organic layer was dried (Na_2SO_4) and concentrated to dryness to give 85 mg of the crude product. This was purified by column chromatography (silica gel, hexane–EtOAc, 4:1) to afford pure *anti*-**9** (66 mg, 82%) as colorless crystals; mp 102–104 °C; $[\alpha]_D^{22}$ –134.4 (*c* 1.2, $CHCl_3$).

IR (KBr): 3085–3030 (=C–H), 2985–2840 (C–H), 1700 (C=O), 1650, 1615 cm^{-1} (C=C).

^1H NMR (500 MHz, $CDCl_3$): δ = 1.29, 1.33 (2 s, 3 H each, CH_3), 3.14, 3.30 (2 s, 3 H each, OCH_3), 3.28 (d, *J* = 6.4 Hz, 1 H, 3-H), 3.74 (s, 3 H, CO_2CH_3), 4.03 (dd, *J* = 6.4, 8.7 Hz, 1 H, 5″-H), 4.07 (dd, *J* = 7.7, 8.7 Hz, 1 H, 5″-H), 4.25 (td, *J* = 6.4, 7.7 Hz, 1 H, 4″-H), 4.34, 4.36 (AB system, J_{AB} = 14.0 Hz, 1 H each, NC*H*$_2$Ph), 4.47, 4.51 (AB system, J_{AB} = 13.5 Hz, 1 H each, 7-H), 6.06 (d, *J* = 15.1 Hz, 1 H, 6-H), 6.69 (d, *J* = 12.1 Hz, 1 H, 2″-H), 7.22–7.38 (m, 5 H, C_6H_5), 7.46 (dd, *J* = 12.1, 15.1 Hz, 1 H, 1″-H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 25.7, 26.2 (2 q, CH_3), 48.9, 51.7 (2 q, CO*C*H$_3$), 57.8 (t, N*C*H$_2$Ph), 60.6 (t, C-7), 67.2 (d, C-3), 67.4 (t, C-5′), 74.6 (d, C-4′), 97.9 (s, C-4), 108.6 (s, C-2′), 109.8 (d, C-6),

126.0 (d, C-2″), 127.1, 128.2, 128.7, 136.2 (3 d, s, C_6H_5), 137.9 (d, C-1″), 139.4 (s, C-5).

MS (EI, 80 eV, 100 °C): *m*/*z* (%) = 433 (M^+, <1), 418 (M^+ – Me, 1), 332 ($M^+ - C_5H_9O_2$, 2), 139 (100), 91 (CH_2Ph^+, 47).

HRMS: *m*/*z* [M^+] calcd for $C_{23}H_{31}NO_7$: 433.2101; found: 433.2105.

(3*R*,4′*S*,5′*R*,4″*R*)-2-Benzyl-3-(2′,2′,2″,2″-tetramethyl[4′,4″]-bi[1′,3′-dioxolanyl]-5′-yl)-4,4-dimethoxy-5-phenyl-2,3,4,7-tetrahydro[1,2]oxazepine (*anti*-10)

According to the preparation of *anti*-**7**, *anti*-**4f** (166 mg, 0.313 mmol), Ph_3P (17 mg, 0.065 mmol), $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), K_2CO_3 (64 mg, 0.471 mmol), and phenylboronic acid (43 mg, 0.345 mmol) in DMF (1.5 mL) was stirred at 70 °C for 12 h. After workup, the resulting residue was purified by column chromatography (silica gel, hexane–EtOAc, 4:1) to afford pure *anti*-**10** (112 mg, 68%) as a colorless resin; $[\alpha]_D^{22}$ +85.1 (*c* 0.21, $CHCl_3$).

IR (film): 3100–3030 (=C–H), 2990–2840 (C–H), 1600 cm^{-1} (C=C).

^1H NMR (250 MHz, $CDCl_3$): δ = 1.17, 1.31, 1.41, 1.42 (4 s, 3 H each, CH_3), 3.21 (d, *J* = 7.4 Hz, 1 H, 3-H), 3.23, 3.33 (2 s, 3 H each, OCH_3), 3.84–3.97, 4.39–4.53 (2 m, 3 H, 4 H), 4.58 (d, *J* = 12.7 Hz, 1 H, 7-H), 4.67–4.71 (m, 1 H), 7.15–7.45 (m, 11 H, 6-H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.6, 26.14, 26.19, 27.2 (4 q, CH_3), 48.4, 49.0 (2 q, OCH_3), 57.0 (t, N*C*H_2Ph), 59.8 (t, C-7), 63.8 (t, C-5″), 66.7 (d, C-3), 75.6 (d, C-4′), 77.1, 77.6 (2 d, C-4″, C-5′), 98.0 (s, C-4), 108.9, 109.3 (2 s, C-2′, C-2″), 115.3 (d, C-6), 127.3, 127.5, 128.3, 128.4, 128.8, 129.4, 131.4, 135.6, 137.6 (6 d, 3 s, C_6H_5, C-5).

HRMS: *m*/*z* [M + Na^+] calcd for $C_{30}H_{39}NO_7$ + Na: 548.2624; found: 548.2710.

(3*R*,4′*S*,5′*R*,4″*R*)-2-Benzyl-3-(2′,2′,2″,2″-tetramethyl[4′,4″]-bi[1′,3′-dioxolanyl]-5′-yl)-4,4-dimethoxy-5-(phenylethynyl)-2,3,4,7-tetrahydro[1,2]oxazepine (*anti*-11)

According to GP2, *anti*-**4f** (120 mg, 0.227 mmol), Ph_3P (16 mg, 0.065 mmol), $Pd(OAc)_2$ (2.4 mg, 0.011 mmol), and CuI (1.8 mg, 0.011 mmol) was degassed and filled with argon. Then, DMF (0.7 mL) and *i*-Pr_2NH (0.4 mL) were added followed by phenylacetylene (39 mg, 0.385 mmol). The resulting residue was purified by column chromatography (silica gel, hexane–EtOAc, 4:1) to afford pure *anti*-**11** (79 mg, 63%) as a colorless resin; $[\alpha]_D^{23}$ +233.9 (*c* 0.23, $CHCl_3$).

IR (film): 3090–3030 (=C–H), 2980–2830 (C–H), 1620 cm^{-1} (C=C).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.20, 1.35, 1.37, 1.44 (4 s, 3 H each, CH_3), 3.19, 3.29 (2 s, 3 H each, OCH_3), 3.20 (d, *J* = 7.6 Hz, 1 H, 3-H), 3.77 (t, *J* = 7.4 Hz, 1 H, 4′-H), 3.91–3.98 (m, 2 H, 5′-H), 4.35 (d, *J* = 13.2 Hz, 1 H, N*C*H_2Ph), 4.50 (d, *J* = 13.2 Hz, 1 H, N*C*H_2Ph), 4.53 (m_c, 1 H, 4′-H), 4.55 (d, *J* = 12.8 Hz, 1 H, 7-H), 4.62–4.66 (m, 2 H, 7-H, 4″-H), 6.32 (s, 1 H, 6-H), 7.24–7.35, 7.39–7.45 (2 m, 6 H, 4 H, C_6H_5).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.6, 26.21, 26.25, 27.1 (4 q, CH_3), 48.6, 49.1 (2 q, OCH_3), 56.9 (t, N*C*H_2Ph), 61.2 (t, C-7), 63.8 (t, C-5″), 67.3 (d, C-3), 75.7 (d, C-4″), 76.7 (d, C-5′), 77.9 (d, C-4′), 84.4, 97.9 (2 s, C≡C), 96.5 (s, C-4), 108.8, 109.3 (2 s, C-2′, C-2′), 110.6 (d, C-6), 122.8, 127.3, 128.3, 128.5, 129.3, 131.4, 137.5, 141.8 (s, 5 d, 2 s, C_6H_5, C-5).

HRMS: *m*/*z* [M + Na^+] calcd for $C_{32}H_{39}NO_7$ + Na: 572.2624; found: 572.2628.

Acknowledgment

Generous support of this work by the Deutsche Forschungsgemeinschaft, the Deutsche Akademische Austauschdienst (fellowship to A. A.-H.), the Fonds der Chemischen Industrie, and the Bayer Schering Pharma AG is most gratefully acknowledged. We also thank Dr. Wolfgang Schade (Technische Universität Dresden) for preliminary studies on the dihalocarbene cycloadditions and Valentin Kunz for his experimental assistance.

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