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Synthesis of trans-fused tetrahydrooxepins: stereoselective allylation of sulfur or fluoro-substituted tetrahydrooxepins

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Abstract—An efficient route to the trans-fused tetrahydrooxepin corresponding to the E ring of ciguatoxin was developed. Wide screening of allylation reactions of sulfur or fluoro-substituted tetrahydrooxepin revealed that the optimum method for obtaining the β-allylation product selectively was the use of a combination of allyltrimethylsilane and $TiCl_4$ with 6-fluoro-7-hydroxytetrahydrooxepin.

Keywords: Allylation; Tetrahydrooxepin; Titanium tetrachloride; Ciguatoxin

1. Introduction

During the course of our recent synthetic studies of ciguatoxin (**1**),[1] the principal toxin responsible for ciguatera seafood poisoning, we have continuously worked on the development of an efficient route to trans-fused tetrahydrooxepin, which corresponds to the E ring of **1** (Fig. 1). In particular, by considering the structurally simplified and readily accessible bicyclic model **3** as an alternative to the DE ring, we developed a strategy which ultimately resulted in the first synthesis of the ABCDE ring segment (**2**) of **1**.[2,3]

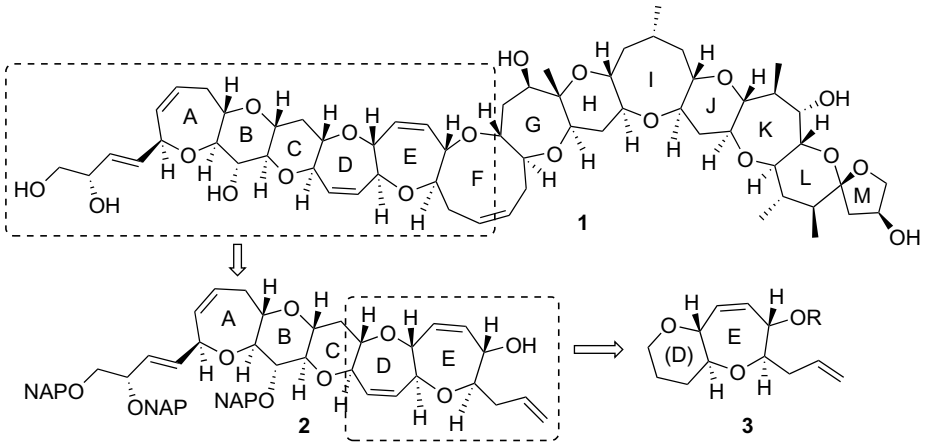

Figure 1. Structures of ciguatoxin (**1**), the ABCDE ring segment (**2**), and the DE ring model (**3**). NAP = 2-naphthylmethyl.

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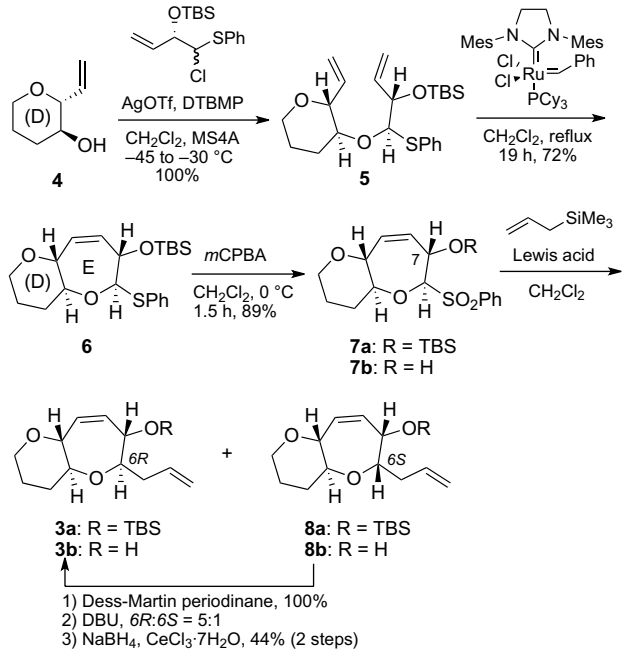


Scheme 1. Strategy for constructing trans-fused tetrahydrooxepin. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, TBS = *tert*-butyldimethylsilyl, *m*CPBA = *m*-chloroperbenzoic acid, TBAF = tetrabutylammonium fluoride.

Our strategy to access **3** involved three key transformations, as shown in Scheme 1: (1) AgOTf-mediated *O*,*S*-acetal formation[4] (**4** to **5**), (2) ring-closing metathesis[5] (**5** to **6**), and (3) Lewis acid-mediated allylation of anomeric sulfone[6] (**7** to **3**). Although this approach is fast and offers a high yield, stereocontrol at the anomeric center has been a formidable challenge, because Lewis acid-mediated substitution normally occurs from the α-side due to the anomeric effect of the ring oxygen. For instance, allylation of **7a** provided the α-adduct **8a** rather than the β-adduct **3a**, regardless of the type of Lewis acid used. In our previous communication, we discovered that the β-adduct **3b** was formed preferentially when $TiCl_4$ was employed with the C-7-hydroxyl derivative **7b**.[2] However, these conditions could not be applied to the highly functionalized ABCDE ring segment **2**, since they were accompanied by side reactions arising from the depressed reactivity of the C-7-hydroxyl sulfone.[2] Therefore, we continued our screening of allylation reactions using other substrates and a variety of activators. Herein, we provide a summary of allylation reactions of sulfur- or fluoro-substituted tetrahydrooxepins and our development of a method for obtaining the β-adduct selectively using 6-fluoro-7-hydroxytetrahydrooxepin.

2. Results and discussion

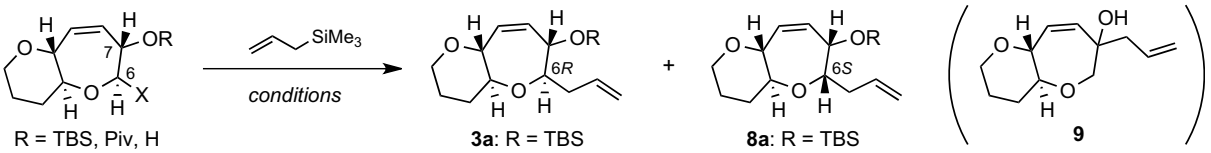
Our experiments are summarized in Table 1. Direct allylation of TBS-protected phenyl sulfide with NBS/TfOH[7] or NIS/AgOTf[8] activators afforded the α-allylation product **8a** exclusively in moderate yields (entries 1 and 2). Similarly high α-selectivity was observed in the case of sulfoxides, irrespective of the type of C-7-protective group used (entries 3 and 4). To the best of our knowledge, this is the first application of the Tf_2O/DTBMP activation system[9] to a C-nucleophile. As reported previously,[2] allylation of the corresponding sulfone also gave α-product **8a** predominately (entries 5 and 6), while a reversal of α/β selectivity was observed for the C-7-hydroxyl sulfone (entries 7 and 8). In addition to this remarkable β-selectivity, it should be pointed out that addition of the C-nucleophile proceeded in preference to intermolecular O-alkylation (dimerization) even in the presence of free hydroxyl groups. Since the time-consuming processes in entry 8 provoked side reactions when applied to functionalized molecules,[2] we next examined anomeric fluoride, a stable and highly reactive glycosydation precursor.[10] Application of the activators $Cp_2HfCl_2/AgClO_4$ or $Cp_2TiCl_2/AgClO_4$,[11] or the use of $BF_3{\cdot}Et_2O$,[12] generated allylation product **8a** in high yield with α-selectivity (entries 9–11). Since neighboring ester groups and polar solvents have been known to facilitate β-nucleophilic attack by stabilizing the cationic intermediate, we attempted to use C-7-pivalate and CH_3CN (entries 12 and 13). However, only a marginal improvement in selectivity was observed as the reaction time was prolonged (entry 13). Eventually, we again focused our attention on the C-7-hydroxyl substrate. Whereas the application of $Cp_2HfCl_2/AgClO_4$ or $BF_3{\cdot}Et_2O$ activators gave disappointing results due to competition with intermolecular O-alkylation (entry 14), the use of $TiCl_4$ gave rise to the desired β-adduct **3b** in 70% yield with good selectivity (entry 16). Notably, allylation was completed within 10 min even at −100 °C, and α/β selectivity was independent of the C-6-stereochemistry of the starting fluoride.

Since some alkylmagnesium and alkylaluminum reagents can react with glycosyl fluorides in the absence of a Lewis acid,[13,14] we also examined allylation reactions with allylmetal species (entries 17–21). However, the desired isomers (**3a** or **3b**) were not obtained preferentially under any of the conditions examined.[†]

It has been well established in previous studies[15] that formation of the α-product **8a** in the C-8-OTBS series can be rationalized by the anomeric effect, which causes the C-nucleophile to approach from the pseudo-axial side (Fig. 2).[16] In contrast, in the case of the C-7-unprotected alcohol, the cationic intermediate is stabilized by

[†] We expected the formation of **3b** in the reaction of the C-7-hydroxyl substrate with allylmagnesium bromide (entry 20) through an epoxide-like intermediate akin to **11** (see Fig. 2). However, the only product obtained was homoallyl alcohol **9**, which presumably arose from abstraction of the C-7-hydrogen followed by enol-keto tautomerization and allylation to the resulting enone.

Table 1. Allylation of sulfur- or fluoro-substituted tetrahydrooxepins[a,b]



Entry	X	R	Activators	Solvent	Temperature (°C)	Time (h)	Yield[c] (%)	Ratio (**3**:**8**)[d]
1	SPh	TBS	NBS, TfOH, MS 4 Å	CH_2Cl_2	−50 to 0	8.5	53	<5:>95
2	SPh	TBS	NIS, AgOTf	CH_2Cl_2	−25	22	57	<5:>95
3	S(O)Ph	TBS	Tf_2O, DTBMP	CH_2Cl_2	−78	1.3	62	<5:>95
4	S(O)Ph	Piv	Tf_2O, DTBMP	CH_2Cl_2	−78 to −15	19	<33	<5:>95[e]
5	SO_2Ph	TBS	$EtAlCl_2$	CH_2Cl_2	−78 to −60	0.8	73	20:80
6	SO_2Ph	TBS	$TiCl_4$	CH_2Cl_2	−78	0.3	74	31:69
7	SO_2Ph	H	$AlCl_3$	CH_2Cl_2	−78 to 0	17	81	60:40
8	SO_2Ph	H	$TiCl_4$	CH_2Cl_2	−78	11	62	84:16
9	F	TBS	Cp_2HfCl_2, $AgClO_4$, MS 4 Å	CH_2Cl_2	−78 to −50	1.2	92	<5:>95
10	F	TBS	Cp_2TiCl_2, $AgClO_4$, MS 4 Å	CH_2Cl_2	−78 to 10	17	90	<5:>95
11	F	TBS	$BF_3{\cdot}Et_2O$	CH_2Cl_2	−30	0.5	87	<5:>95
12	F	TBS	$BF_3{\cdot}Et_2O$	CH_3CN	−30	0.5	54	12:88
13	F	Piv	$BF_3{\cdot}Et_2O$	CH_2Cl_2	−50 to 15	15	56	34:66[e]
14	F	H	$BF_3{\cdot}Et_2O$	CH_2Cl_2	−30	0.4	<49	57:43
15	F	H	TMSOTf	CH_2Cl_2	−78 to 15	48	84	13:87
16[f]	F	H	$TiCl_4$	CH_2Cl_2	−100	0.2	70	87:13
17	F	TBS	$CH_2{=}CHCH_2MgBr$	CH_2Cl_2	20	0.5	100	39:61
18	F	TBS	$CH_2{=}CHCH_2MgBr$	Et_2O	20	1.5	92	41:59
19[g]	F	TBS	$(CH_2{=}CHCH_2)_3Al$	Et_2O	0 to 20	3	30	60:40
20	F	H	$CH_2{=}CHCH_2MgBr$	Et_2O	20	1.5	**9** (86)	
21[g]	F	H	$(CH_2{=}CHCH_2)_3Al$	Et_2O	0 to 20	2	**3b** (15),	**9** (56)

[a] For fluorotetrahydrooxepins, a 1:1.7 (β-fluoride:α-fluoride) mixture was used.
[b] For entries 17–21, reactions were performed in the absence of allyltrimethylsilane.
[c] Isolated yield.
[d] Determined by ^1H NMR (500 MHz, $CDCl_3$).
[e] Determined after cleavage of pivalate by DIBAL at −60 °C.
[f] For entry 16, the same results were obtained from each C-6-stereoisomer.
[g] Triallylaluminum was prepared in situ from 3 equiv of allylmagnesium bromide and 1 equiv of $AlCl_3$ in Et_2O.

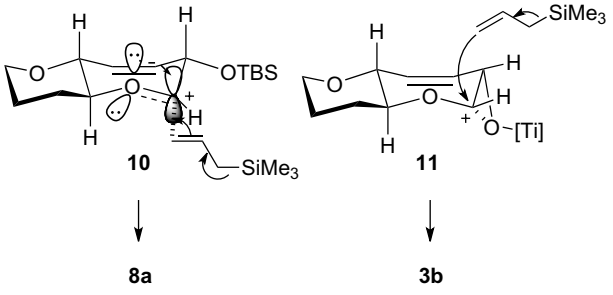
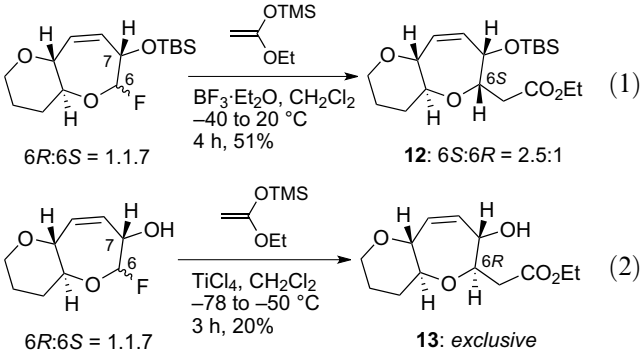


Figure 2. A possible model to explain the stereochemical outcome.

partial epoxide formation (**11**), which allows S_N2-like attack of the C-nucleophile, generating the β-isomer **3b**.[17] It is unclear, however, whether the conformational difference between the TBS ether and the unprotected alcohol plays a role in the stereochemical outcome. However, it is clear that the C-7-protective group, as well as the presence of a Lewis acid, is a critical factor in deciding stereoselectivity.

To evaluate the generality of $TiCl_4$-mediated β-selective allylation, other C-nucleophiles were tested. In contrast to the C-7-protected fluorotetrahydroxepin, which afforded the α-adduct **12** predominantly (Eq. 1), $TiCl_4$-mediated alkylation of the corresponding C-7-alcohol with trimethylsilylketene acetal furnished the β-adduct



13 exclusively (Eq. 2). It appears that the lower yield may be attributed to the depressed nucleophilicity of trimethylsilylketene acetal compared to allyltrimethylsilane.

3. Conclusion

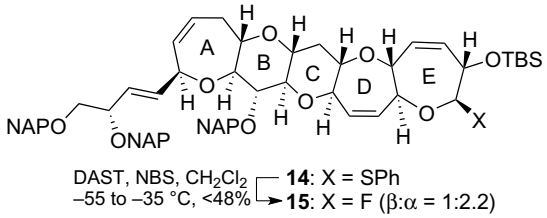
In conclusion, an efficient route to the trans-fused tetrahydrooxepin, which corresponds to the E ring of ciguatoxin, was developed.[‡] This work demonstrated that allylation of fluorotetrahydrooxepin bearing an adjacent hydroxyl group is a viable synthesis method, although it has so far been limited to the substrates used herein. We are currently testing the further applicability of this methodology to fluorotetrahydropyrans and fluorotetrahydrofurans as well as its potential for synthesizing other C-glycosides.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 200 (200 MHz), a Varian 400MR (400 MHz), a Varian INOVA-500 (500 MHz), or a JEOL JNM-ECP500 spectrometer. IR spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR spectrometer. Matrix assisted laser desorption ionization time-of-flight mass spectra (MALDI-TOFMS) were recorded on an Applied Biosystems Voyager DE STR SI-3 instrument using α-cyano-4-hydroxy cinnamic acid as a matrix. Electron spray ionization time-of-flight mass spectra (ESI-TOFMS) were recorded on an Applied Biosystems Mariner instrument. Electron ionization mass spectra (EI MS) were recorded on a JEOL MS700 spectrometer. High resolution electron spray ionization Fourier-transform ion cyclotron resonance mass spectra (HR-ESI FT-ICR MS) were recorded on a Bruker Daltonics APEX III instrument. Optical rotations were recorded on a JASCO DIP-370 digital polarimeter. Flash column chromatography was performed with 40–50 μm Silica Gel 60N (Kanto Chemical Co., Inc.). All reactions sensitive to air or moisture were carried out under argon or nitrogen atmosphere in dry, freshly distilled solvents under anhydrous conditions. Dry solvents purchased from Kanto Chem. Co. were also used.

[‡] Although we wished to apply the newly developed allylation conditions to the preparation of a fully functionalized ABCDE ring segment (**15**), we faced a serious problem in converting phenyl sulfide into the corresponding fluoride. Fluorination proceeded in less than 48% yield even under carefully chosen conditions. It appears that the diallylic moiety of the A ring is highly sensitive to fluorination conditions. In the event, we were unable to obtain sufficient quantities of fluoride to test this methodology.



4.2. Preparation of allylation precursors

4.2.1. ((1*R*,2*S*)-1-(Phenylthio)-1-((2*R*,3*S*)-2-vinyltetrahydro-2*H*-pyran-3-yloxy)but-3-en-2-yloxy)-*tert*-butyldimethylsilane (5). To a solution of (*2S*)-1-phenylthio-2-*tert*-butyldimethylsilyloxy-3-butene (427 mg, 1.45 mmol) in CCl_4 (6 mL) was added *N*-chlorosuccinimide (233 mg, 1.74 mmol). The mixture was stirred for 1 h at room temperature and the precipitate was filtered. Concentration of the filtrate gave the corresponding α-chlorosulfide. To a suspension of alcohol **4** (93.0 mg, 0.726 mmol) and MS 4 Å (powdered, activated, 320 mg) in CH_2Cl_2 (4 mL) were added AgOTf (369 mg, 1.67 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (417 mg, 2.03 mmol) at −45 °C. After being stirred for 10 min, a solution of α-chlorosulfide in CH_2Cl_2 (4 mL) was added and the resulting mixture was stirred for 40 min at −30 °C. The mixture was eluted (hexane/EtOAc = 0.67) through a short plug of silica gel to give a pale yellow oil that was further purified by flash column chromatography (silica gel, hexane/EtOAc = 150 to 100 to 50) to give *O,S*-acetal **5** (305 mg, 100%). Compound **5**: $[\alpha]_D^{27.0}$ +7.2 (*c* 0.40, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.01 (s, 3H, $SiMe_3$), 0.02 (s, 3H, $SiMe_3$), 0.89 (s, 9H, *t*Bu), 1.35–1.44 (m, 1H, H-4′), 1.50–1.65 (m, 2H, H-5′), 2.16–2.22 (m, 1H, H-4′), 3.27 (ddd, 1H, *J* = 10.0, 9.0, 4.5 Hz, H-3′), 3.33 (dt, 1H, *J* = 11.5, 2.5 Hz, H-6′), 3.57 (br dd, 1H, *J* = 9.0, 6.0 Hz, H-2′), 3.85–3.90 (m, 1H, H-6′), 4.32–4.34 (m, 1H, H-2), 4.81 (d, 1H, *J* = 3.5 Hz, H-1), 5.15 (ddd, 1H, *J* = 11.0, 2.0, 1.0 Hz, H-4), 5.23 (dt, 1H, *J* = 10.5, 1.5 Hz, *CH*$_2$=CH–), 5.28 (dt, 1H, *J* = 8.0, 1.5 Hz, H-4), 5.32 (dt, 1H, *J* = 7.5, 1.5 Hz, *CH*$_2$=CH–), 5.91 (ddd, 1H, *J* = 17.5, 10.5, 6.0 Hz, CH$_2$=*CH*–), 5.98 (ddd, 1H, *J* = 17.0, 10.5, 6.0 Hz, H-3), 7.21–7.47 (m, H-5, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.6, −4.4, 18.4, 25.4, 26.0, 31.0, 67.4, 76.8, 78.0, 81.4, 95.8, 116.9, 127.3, 129.1, 132.6, 135.8, 136.6, 137.6; FT-IR (neat) *ν* 3076, 2954, 2927, 2855, 1645, 1584, 1472, 1439, 1362, 1254, 1216, 1089 cm^{-1}; MALDI-TOFMS $[M+Na]^+$ calcd for $C_{23}H_{36}NaO_3SiS$: 443.3; found, 443.2; HRMS (EI, 70 eV) $[M-SPh]^+$ calcd for $C_{17}H_{31}O_3Si$: 311.2042; found, 311.2027.

4.2.2. ((4a*S*,6*R*,7*S*,9a*R*)-6-(Phenylthio)-3,4,4a,6,7,9a-hexahydro-2*H*-1,5-dioxa-benzocyclohepten-7-yloxy)-*tert*-butyldimethylsilane (6). A solution of diene **5** (181 mg, 0.431 mmol) and second generation Grubbs' catalyst

(36.6 mg, 0.0431 mmol) in CH_2Cl_2 (43 mL) was refluxed for 19 h. Et_3N (170 μL) was added and the mixture was concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 200 to 50) to give a seven-membered ring **6** (122 mg, 72%). Compound **6**: $[\alpha]_D^{27.0}$ +110 (*c* 0.990, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.14 (s, 3H, $SiMe_3$), 0.18 (s, 3H, $SiMe_3$), 0.94 (s, 9H, *t*Bu), 1.40–1.47 (m, 1H, H-4), 1.53–1.60 (m, 2H, H-3), 1.72–1.78 (m, 1H, H-4), 3.16 (ddd, 1H, $J = 11.1$, 9.0, 4.5 Hz, H-4a), 3.25–3.30 (m, 1H, H-2), 3.77 (ddd, 1H, $J = 9.0$, 4.5, 2.0 Hz, H-9a), 3.82–3.86 (m, 1H, H-2), 4.39 (ddd, 1H, $J = 9.0$, 4.0, 2.0 Hz, H-7), 4.91 (d, 1H, $J = 9.0$ Hz, H-6), 5.58 (dt, 1H, $J = 13.0$, 2.0 Hz, H-8), 5.69 (dt, 1H, $J = 13.0$, 2.5 Hz, H-9), 7.22–7.30 (m, 3H, Ph), 7.45–7.48 (m, 2H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.5, −4.3, 18.3, 25.4, 26.0, 30.3, 67.6, 74.1, 80.5, 80.7, 93.5, 127.3, 128.7, 132.5, 132.8, 134.3, 134.5; FT-IR (neat) *v* 3059, 2951, 2885, 2856, 1731, 1584, 1472, 1463, 1439, 1389, 1361, 1258, 1217, 1186, 1091, 1039 cm^{-1}; HR-ESI FT-ICR MS $[M+Na]^+$ calcd for $C_{21}H_{32}NaO_3SSi$: 415.1734; found, 415.1734.

4.2.3. ((4a*S*,6*R*,7*S*,9a*R*)-6-Benzenesulfonyl-3,4,4a,6,7,9a-hexahydro-2*H*-1,5-dioxa-benzocyclohepten-7-yloxy)-*tert*-butyldimethylsilane (7a). To a solution of sulfide **6** (27.6 mg, 0.0704 mmol) in CH_2Cl_2 (1.4 mL) was added *m*CPBA (41.1 mg, 0.154 mmol) at 0 °C. The mixture was stirred for 1.4 h at 0 °C and quenched with Et_3N (118 μL, 0.844 mmol). After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 5) to give sulfone **7a** (26.5 mg, 89%). Compound **7a**: $[\alpha]_D^{26.5}$ +45.1 (*c* 0.724, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.18 (s, 3H, $SiMe_3$), 0.24 (s, 3H, $SiMe_3$), 0.96 (s, 9H, *t*Bu), 1.04–1.11 (m, 1H, H-4), 1.15–1.25 (m, 1H, H-3), 1.34–1.49 (m, 2H, H-3, H-4), 3.00 (ddd, 1H, $J = 10.5$, 8.5, 4.5 Hz, H-4a), 3.20 (dt, 1H, $J = 11.5$, 3.0 Hz, H-2), 3.67 (ddd, 1H, $J = 9.0$, 4.5, 2.0 Hz, H-9a), 3.78 (br d, 1H, $J = 11.0$, 4.5 Hz, H-2), 4.39 (d, 1H, $J = 8.0$ Hz, H-6), 4.90 (ddd, 1H, $J = 8.0$, 4.5, 2.3 Hz, H-7), 5.54 (dt, 1H, $J = 13.0$, 2.3 Hz, H-8), 5.67 (dt, 1H, $J = 13.0$, 2.5 Hz, H-9), 7.52 (t, 2H, $J = 8.8$ Hz, Ph), 7.62 (br t, 1H, $J = 7.5$ Hz, Ph), 7.90 (d, 2H, $J = 7.5$ Hz, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, −4.4, 18.3, 25.1, 26.0, 29.6, 67.5, 70.5, 79.9, 80.6, 95.7, 128.7, 129.5, 132.4, 133.5, 133.6, 138.2; FT-IR (film) *v* 2951, 2857, 1472, 1328, 1259, 1155, 1116, 1014 cm^{-1}; MALDI-TOFMS $[M+Na]^+$ calcd for $C_{21}H_{32}NaO_5SiS$: 447.2; found, 447.1.

4.2.4. (4a*S*,6*R*,7*S*,9a*R*)-6-Benzenesulfonyl-3,4,4a,6,7,9a-hexahydro-2*H*-1,5-dioxa-benzocyclohepten-7-ol (7b). TBAF (1.0 M solution in THF, 488 μL, 0.488 mmol) was added to a solution of TBS ether **6** (128 mg, 0.325 mmol) in THF (3.3 mL). The mixture was stirred for 12.5 h at ambient temperature and quenched with saturated NH_4Cl solution. The aqueous phase was extracted with EtOAc, and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 3.6) to give a corresponding alcohol (73.4 mg, 0.264 mmol, 81%).

*m*CPBA (199 mg, 0.750 mmol) was added to a solution of the above alcohol (73.4 mg, 0.264 mmol) in CH_2Cl_2 (2.6 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C and quenched with Et_3N (368 μL, 2.64 mmol). After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 2) to give sulfone **7b** (66.4 mg, 81%). Compound **7b**: $[\alpha]_D^{27.0}$ +15 (*c* 0.98, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.37–1.46 (m, 1H, H-4), 1.47–1.63 (m, 2H, H-3), 1.64–1.70 (m, 1H, H-4), 3.15 (ddd, 1H, $J = 11.0$, 9.5, 5.0 Hz, H-4a), 3.26 (dt, 1H, $J = 11.5$, 3.0 Hz, H-2), 3.68 (br d, 1H, $J = 9.5$ Hz, H-9a), 3.73 (br s, 1H, OH), 3.83 (br dd, 1H, $J = 11.5$, 4.5 Hz, H-2), 4.34 (d, 1H, $J = 9.0$ Hz, H-6), 4.74 (br d, 1H, $J = 9.5$ Hz, H-7), 5.60 (s, 2H, H-8, H-9), 7.59 (t, 2H, $J = 8.5$ Hz, Ph), 7.72 (br t, 1H, $J = 7.0$ Hz, Ph), 7.95 (br d, 2H, $J = 8.0$ Hz, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.1, 30.0, 67.6, 69.4, 79.8, 82.1, 95.8, 129.1, 129.9, 130.8, 132.2, 134.6, 136.0; FT-IR (KBr) *v* 3408, 3069, 3031, 2974, 2945, 2855, 2822, 1655, 1584, 1449, 1388, 1323, 1292, 1278, 1266, 1242, 1211, 1150, 1084 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%): 169 ($[M-SO_2Ph]^+$, 27), 151 (21), 125 (19), 123 (16), 97 (20), 95 (16), 84 (42), 81 (42), 77 (80), 71 (100).

4.2.5. ((4a*S*,6*R*,7*S*,9a*R*)-6-(Phenylsulfinyl)-3,4,4a,6,7,9a-hexahydro-2*H*-1,5-dioxa-benzocyclohepten-7-yloxy)-*tert*-butyldimethylsilane. To a solution of sulfide **6** (20.0 mg, 0.0510 mmol) in CH_2Cl_2 (1 mL) was added *m*CPBA (40.6 mg, 0.153 mmol) at −50 °C. The mixture was stirred for 1 h at –50 °C and quenched with saturated $Na_2S_2O_3$ solution. The aqueous phase was extracted with EtOAc, and the combined organic phase was washed with saturated $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 3 to 2) to give a corresponding sulfoxide (20.8 mg, 100%) as a 2.5:1 diastereomeric mixture. ^1H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 6H, TBS minor), 0.21 (s, 3H, TBS major), 0.28 (s, 3H, TBS major), 0.93 (s, 9H, TBS minor), 0.98 (s, 9H, TBS), 1.06–1.90 (m, 8H, H-3, H-4 major and minor), 2.78 (td, 1H, $J = 9.7$, 4.9 Hz, H-4a), 3.17–3.25 (m, 1H, H-2 major), 3.25–3.32 (m, 1H, H-2 minor), 3.63 (br d, 1H, J = 9.0 Hz, H-9a minor), 3.69–3.79 (m, 3H, H-2 major, H-9a major, H-4a minor), 3.84–3.91 (m, 1H, H-2 minor), 3.91 (d, 1H, $J = 9.3$ Hz, H-6 major), 4.40 (d, 1H, $J = 6.4$ Hz, H-6 minor), 4.61 (br t, 1H, $J = 5.5$ Hz, H-7 minor), 4.81 (dq, 1H, $J = 9.0$, 2.2 Hz,

H-7 major), 4.81 (br d, 1H, $J = 13$, 2.2 Hz, H-8 major), 5.69 (dt, 1H, $J = 13$, 2.3 Hz, H-9 major), 5.75 (br d, 1H, $J = 12$ Hz, H-9 minor), 5.86 (ddd, 1H, $J = 12$, 4.6, 2.4 Hz, H-8 minor); FT-IR (film) ν 3059, 2951, 2929, 2855, 1471, 1443, 1389, 1362, 1307, 1257, 1217, 1108, 1092, 1047, 1015, 953, 864 cm^{-1}; MS (EI, 70 eV) m/z (%): 351 ([M−*t*Bu]$^+$, 11), 283 (74), 211 (60), 156 (65), 139 (62), 75 (100), 73 (99), 71 (94).

4.2.6. (4a*S*,6*R*,7*S*,9a*R*)-6-(Phenylsulfinyl)-3,4,4a,6,7,9a-hexahydro-2*H*-1,5-dioxa-benzocyclohepten-7-yl pivalate. To a solution of 7-hydroxy-6-phenylthiotetrahydrooxepin (101 mg, 0.364 mmol) in CH_2Cl_2 (3.6 mL) were added pyridine (294 μL, 3.64 mmol) and PivCl (134 μL, 1.09 mmol). The mixture was stirred for 5 days at room temperature and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 5) to give a corresponding pivalate (132 mg, 100%).

To a solution of the above pivalate (15.4 mg, 0.0425 mmol) in CH_2Cl_2 (0.8 mL) was added *m*CPBA (33.8 mg, 0.127 mmol) at −40 °C. The mixture was stirred for 30 min at −40 °C and quenched with saturated $Na_2S_2O_3$ solution, then saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc and the organic phase was dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 1.5) to give a corresponding sulfoxide (16.1 mg, 100%) as a 1.3:1 diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H, Piv), 1.31 (s, 9H, Piv), 1.30–1.70 (m, 7H, H-3, H-4), 2.00–2.05 (m, 1H, H-4 major), 2.90–2.98 (m, 1H, H-4a minor), 3.21–3.31 (m, 2H, H-2 major and minor), 3.43–3.50 (m, 1H, H-4a major), 3.65 (br d, 1H, $J = 9.3$ Hz, H-9a major), 3.77–3.90 (m, 3H, H-2 major and minor, H-9a minor), 4.25 (d, 1H, $J = 9.5$ Hz, H-6 major), 4.64 (br d, 1H, $J = 8.6$ Hz, H-6 minor), 5.39 (br d, 1H, $J = 8.6$ Hz, H-7 minor), 5.52 (br d, 1H, $J = 13$ Hz, H-8 major), 5.55 (br d, 1H, $J = 12$ Hz, H-8 minor), 5.63 (br d, 1H, $J = 13$ Hz, H-9 major), 5.72 (br d, 1H, $J = 12.0$ Hz, H-9 minor), 5.72 (br d, 1H, $J = 8.6$ Hz, H-7 minor); FT-IR (film) ν 3066, 2955, 2926, 2853, 1735, 1574, 1479, 1443, 1397, 1278, 1140, 1092, 1041, 956, 750 cm^{-1}.

4.2.7. ((4a*S*,6*R*,7*S*,9a*R*)-6-Fluoro-3,4,4a,6,7,9a-hexahydro-2*H*-1,5-dioxa-benzocyclohepten-7-yloxy)-*tert*-butyldimethylsilane. To a solution of sulfide **6** (142 mg, 0.362 mmol) in CH_2Cl_2 (5.6 mL) were added DAST (81.4 μL, 0.616 mmol) and NBS (83.5 mg, 0.471 mmol) at −50 °C. The mixture was gradually warmed to −30 °C over 40 min with stirring and quenched with saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc and the combined organic phase was washed with saturated $Na_2S_2O_3$ solution and brine, and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 20) to give fluoride as a 1.7:1 diastereomeric mixture (99.2 mg, 91%, 6*S*:6*R* = 1.7:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 6H, $SiMe_3$), 0.10 (s, 6H, $SiMe_3$), 0.90 (s, 9H, *t*Bu), 0.90 (s, 9H, *t*Bu), 1.42–1.51 (m, 1H, H-4 major), 1.54–1.63 (m, 1H, H-4 minor), 1.64–1.72 (m, 4H, H-3 major and minor), 2.00–2.06 (m, 1H, H-4 major), 2.14–2.19 (m, 1H, H-4 minor), 3.27–3.37 (m, 2H, H-2 major and minor), 3.43 (ddd, 1-H, $J = 10.5$, 9.0, 4.5 Hz, H-4a minor), 3.71 (dt, 1H, $J = 9.0$, 2.0 Hz, H-9a minor), 3.83–3.92 (m, 4H, H-2, H-4a, H-9a major, and H-2 minor), 4.25–4.30 (m, 1H, H-7 minor), 4.46 (br d, 1H, $J = 25$ Hz, H-7 major), 5.03 (dd, 1H, $J = 51$, 7.0 Hz, H-6 minor), 5.34 (br d, 1H, $J = 51$ Hz, H-6 major), 5.44–5.49 (m, 1H, H-9 minor), 5.52 (br d, 1H, $J = 12.0$ Hz, H-9 major), 5.62 (br d, 1H, $J = 13.0$ Hz, H-8 minor), 5.65 (br d, 1H, $J = 12.0$, 2.0 Hz, H-8 major); FT-IR (film) ν 2952, 2930, 2856, 1471, 1439, 1389, 1362, 1257, 1219, 1099, 1062, 1005, 962, 938, 911 cm^{-1}; HRMS (EI, 70 eV) [M]$^+$ calcd for $C_{15}H_{27}FO_3Si$: 302.1714; found, 302.1667.

4.2.8. (4a*S*,6*R*,7*S*,9a*R*)-6-Fluoro-3,4,4a,6,7,9a-hexahydro-2*H*-1,5-dioxa-benzocyclohepten-7-ol. To a solution of 7-*tert*-butyldimethylsilyloxy-6-fluorotetrahydrooxepin (6*S*:6*R* = 1.7:1, 108 mg, 0.357 mmol) in THF (4 mL) was added TBAF (1.0 M solution in THF, 535 μL, 0.535 mmol). The mixture was stirred for 30 min at room temperature and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 5 to 3 to 1) to give a corresponding C-7-alcohol as a 1.7:1 diastereomeric mixture (60.6 mg, 90%, 6*S*:6*R* = 1.7:1). Separation of the C-6-epimer was performed after acetylation of the C-7-alcohol with Ac_2O and pyridine in the presence of DMAP. Methanolysis of each C-7-acetate with K_2CO_3 reproduced the diastereomerically pure C-6-fluorides. (6*S*)-Isomer: $[\alpha]_D^{27.0}$ −88 (*c* 0.11, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48–1.55 (m, 1H, H-4), 1.65–1.75 (m, 2H, H-3), 2.02–2.07 (m, 1H, H-4), 2.08 (d, 1H, $J = 10$ Hz, OH), 3.29–3.34 (m, 1H, H-2), 3.84 (br dd, 1H, $J = 9.0$, 2.0 Hz, H-9a), 3.88–3.93 (m, 1H, H-2), 3.94 (td, 1H, $J = 9.5$, 5.0 Hz, H-4a), 4.44 (br dd, 1H, $J = 25$, 9.0 Hz, H-7), 5.52 (br d, 1H, $J = 52$ Hz, H-6), 5.53–5.57 (m, 1H, H-9), 5.70 (dt, 1H, $J = 12.0$, 2.5 Hz, H-8); FT-IR (film) ν 3294, 3168, 2945, 2928, 2853, 2819, 1466, 1424, 1372, 1349, 1262, 1170, 1103, 1076, 1049, 984, 957 cm^{-1}; HRMS (EI, 70 eV) [M]$^+$ calcd for $C_9H_{13}FO_3$: 188.0849; found, 188.0846. (6*R*)-Isomer: $[\alpha]_D^{27.0}$ −32 (*c* 0.724, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58–1.66 (m, 1H, H-4), 1.65–1.74 (m, 2H, H-3), 2.18–2.22 (m, 1H, H-4), 2.20 (s, 1H, OH), 3.32–3.37 (m, 1H, H-2), 3.41 (td, 1H, $J = 10$, 5.0 Hz, H-4a), 3.73 (br dd, 1H, $J = 9.0$, 2.0 Hz, H-9a), 3.90–3.95 (m, 1H, H-2), 4.31–4.37 (m, 1H, H-7), 5.06 (dd, 1H, $J = 51$, 7.0 Hz, H-6),

5.51–5.56 (m, 1H, H-9), 5.69 (br d, 1H, $J = 13.5$ Hz, H-8); FT-IR (film) ν 3332, 3228, 2916, 2852, 1464, 1397, 1335, 1284, 1265, 1222, 1149, 1108, 1054, 1039, 1019, 957 cm^{-1}. Anal. Calcd for $C_9H_{13}FO_3$: C, 57.44; H, 6.96. Found: C, 57.38; H, 7.32.

4.2.9. (4a*S*,6*R*,7*S*,9aR)-6-Fluoro-3,4,4a,6,7,9a-hexahydro-2*H*-1,5-dioxa-benzocyclohepten-7-yl pivalate. To a solution of 6-fluoro-7-hydroxytetrahydrooxepin (6*S*:6*R* = 1.7:1, 14.4 mg, 0.0765 mmol) in CH_2Cl_2 (2 mL) were added pyridine (471 μL, 3.83 mmol) and PivCl (236 μL, 1.91 mmol). The mixture was stirred for 7 days at room temperature and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 20:5) to give a corresponding C-8-pivalate as a 1.7:1 diastereomeric mixture (19.0 mg, 91%, 9*S*:9*R* = 1.7:1). ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (s, 9H, Piv), 1.23 (s, 9H, Piv), 1.47–1.55 (m, 1H, H-4 major), 1.58–1.66 (m, 1H, H-4 minor), 1.66–1.74 (m, 4H, H-3 major and minor), 2.02–2.07 (m, 1H, H-4 major), 2.16–2.21 (m, 1H, H-4 minor), 3.29–3.39 (m, 2H, H-2 major and minor), 3.53 (td, 1H, $J = 10.5$, 5.0 Hz, H-4a minor), 3.81 (dt, 1H, $J = 9.5$, 2.0 Hz, H-9a minor), 3.88–3.95 (m, 4H, H-1, H-4a, H-9a major, and H-2 minor), 5.29 (dd, 1H, $J = 51$, 7.5 Hz, H-6 minor), 5.35–5.39 (m, 1H, H-9 minor), 5.42 (br d, 1H, $J = 13.0$ Hz, H-9 major), 5.43 (br d, 1H, $J = 51$ Hz, H-6 major), 5.44–5.49 (m, 1H, H-7 minor), 5.52 (br d, 1H, $J = 25$ Hz, H-7 major), 5.76 (br d, 2H, $J = 13.0$ Hz, H-6 major and minor); FT-IR (film) ν 2959, 2853, 1736, 1480, 1461, 1397, 1149, 1116, 1099, 1065, 1043, 1022, 958 cm^{-1}.

4.3. Allylation of sulfide, sulfoxide, sulfone, and fluoride

4.3.1. Allylation of 6 with NBS/TfOH activators. To a suspension of sulfide **6** (1 equiv) and MS 4 Å (powdered, activated, 200 wt % of **6**) in CH_2Cl_2 (15 mL/mmol) were added allyltrimethylsilane (5 equiv), NBS (1.5 equiv), and TfOH (0.1 equiv) at −50 °C. The mixture was stirred for 1.7 h at −50 °C and allyltrimethylsilane (5 equiv), NBS (1.5 equiv) and TfOH (0.1 equiv) were further added to the mixture in four portions at intervals of 1.7 h. The reaction mixture was stirred for 8.5 h at −50 °C to 0 °C, and then quenched with saturated $Na_2S_2O_3$ solution, then saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc, and the organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 20) to give allylation product **8a** (53%) and recovery of **6** (24%). The C-6-stereochemistry of **8a** was identified by NOE experiments after removal of TBS group with TBAF.

4.3.2. Allylation of 6 with NIS/AgOTf activators. To a solution of sulfide **6** (1 equiv) in CH_2Cl_2 (23 mL/mmol) were added allyltrimethylsilane (10 equiv), NIS (3 equiv), and AgOTf (1.5 equiv) at −25 °C. The mixture was stirred for 22 h at −25 °C and quenched with saturated $Na_2S_2O_3$ solution, then saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc, and the organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 20) to give allylation product **8a** (57%) and recovery of **6** (24%).

4.3.3. General procedure for allylation of sulfoxide with Tf_2O/DTBMP activators. To a solution of sulfoxide (1 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (5.2 equiv) in CH_2Cl_2 (40 mL/mmol) was added Tf_2O (2.6 equiv) at −78 °C. The mixture was stirred for 3 min at −78 °C followed by addition of allyltrimethylsilane (20 equiv). The resulting mixture was stirred for the indicated times at the indicated temperatures, as shown in Table 1, and then quenched with saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc, and the organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to give allylation product **8a** or **8c**.

4.3.4. General method for allylation of sulfone with Lewis acid. To a solution of sulfone **7a** or **7b** (1 equiv) in CH_2Cl_2 (25 mL/mmol) were added allyltrimethylsilane (3–6 equiv) and Lewis acid (3–6 equiv) at −78 °C. The mixture was stirred at the indicated temperature for the indicated times as shown in Table 1 and quenched with saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc, and the organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to give allylation products **3a**, **8a**, **3b**, or **8b**.

4.3.5. Allylation of fluoride with Cp_2HfCl_2/$AgClO_4$ activators. To a suspension of Cp_2HfCl_2 (3 equiv), $AgClO_4$ (6 equiv), and MS 4 Å (powdered, activated, 200 wt % of fluoride) in CH_2Cl_2 (20 mL/mmol) was added allyltrimethylsilane (20 equiv). The mixture was stirred for 10 min at room temperature and cooled to −78 °C. A solution of anomeric fluoride (1 equiv) in CH_2Cl_2 (20 mL/mmol) was added and the mixture was stirred for 1.2 h at −78 °C to −50 °C. The reaction mixture was quenched with saturated $NaHCO_3$ solution and filtered through a pad of Celite. The filter cake was washed with EtOAc and the filtrate was dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 20) to give allylation product **8a** (92%).

4.3.6. Allylation of fluoride with $Cp_2TiCl_2/AgClO_4$ activators. To a suspension of Cp_2TiCl_2 (3 equiv), $AgClO_4$ (6 equiv), and MS 4 Å (powdered, activated, 200 wt % of fluoride) in CH_2Cl_2 (20 mL/mmol) was added allyltrimethylsilane (20 equiv). The mixture was stirred for 10 min at room temperature and cooled to −78 °C. A solution of anomeric fluoride (1 equiv) in CH_2Cl_2 (20 mL/mmol) was added and the mixture was gradually warmed to 10 °C over 17 h with stirring. The reaction mixture was quenched with saturated $NaHCO_3$ solution and filtered through a pad of Celite. The filter cake was washed with EtOAc and the filtrate was dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 20) to give allylation product **8a** (90%).

4.3.7. General method for allylation of fluoride with $BF_3{\cdot}Et_2O$. To a solution of fluoride (1 equiv) in CH_2Cl_2 (25 mL/mmol) or CH_3CN (25 mL/mmol) were added allyltrimethylsilane (20 equiv) and $BF_3{\cdot}Et_2O$ (3 equiv). The mixture was stirred at the indicated temperature for the indicated times as shown in Table 1 and quenched with saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc, and the organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to give allylation products **3a**–**c** and **8a**–**c**.

4.3.8. Allylation of fluoride with TMSOTf. To a solution of fluoride (1 equiv) in CH_2Cl_2 (30 mL/mmol) were added allyltrimethylsilane (20 equiv) and TMSOTf (1.5 equiv) at −78 °C. The mixture was stirred for 1 h at −78 °C and TMSOTf (3 equiv) was further added to the mixture. The reaction mixture was stirred for 48 h at −78 °C to 10 °C and quenched with saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc, and the organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 6 to 1.5) to give allylation products **3b** and **8b** (84%).

4.3.9. Allylation of fluoride with $TiCl_4$. To a solution of fluoride (1 equiv) in CH_2Cl_2 (20 mL/mmol) were added allyltrimethylsilane (6 equiv) and $TiCl_4$ (1.0 M solution in toluene, 4 equiv) at −100 °C. The mixture was stirred for 10 min at −100 °C and quenched with saturated $NaHCO_3$ solution. The resulting suspension was filtered through a pad of Celite and washed with EtOAc. The filtrate was extracted with EtOAc, and the organic phase was washed with water, brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 4) to give allylation products **3b** and **8b** (70%).

4.3.10. General method for allylation of fluoride with allylmagnesium bromide. To a solution of fluoride (1 equiv) in CH_2Cl_2 (50 mL/mmol) or Et_2O was added allylmagnesium bromide (0.82 M solution in Et_2O, 4 equiv). The mixture was stirred at 20 °C for the indicated times as shown in Table 1 and quenched with saturated NH_4Cl solution. The aqueous phase was extracted with EtOAc, and the organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to give allylation products **3a**–**c**, **8a**–**c**, or **9**.

4.3.11. General method for allylation of fluoride with triallylaluminum. Allylmagnesium bromide (0.6 M solution in Et_2O, 15 equiv) was added to $AlCl_3$ (5 equiv) and the mixture was stirred for 1 h at 0 °C. A solution of fluoride (1 equiv) in Et_2O (100 mL/mmol) was added and the mixture was stirred at 0 °C to 20 °C for the indicated times as shown in Table 1. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with EtOAc. The organic phase was washed with saturated NH_4Cl_4, water, and brine, and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to give allylation products **3a**, **8a**, **3b**, or **9**.

4.3.12. (4a*S*,6*S*,7*S*,9a*R*)-6-Allyl-3,4,4a,6,7,9a-hexahydro-2*H*-1,5-dioxa-benzocyclohepten-7-ol (8b). $[\alpha]_D^{30.0}$ +9.1 (*c* 0.31, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.40–1.49 (m, 1H, H-4), 1.63–1.70 (m, 2H, H-3), 1.95–1.99 (m, 1H, H-4), 2.30–2.36 (m, 1H, allyl), 2.54–2.60 (m, 1H, allyl), 3.28–3.33 (m, 1H, H-2), 3.57 (ddd, 1H, J = 11.0, 9.5, 4.8 Hz, H-4a), 3.87–3.97 (m, 3H, H-1, H-6, H-9a), 4.40 (dd, 1H, J = 4.3, 2.3 Hz, H-7), 5.08–5.17 (m, 2H, allyl), 5.64 (s, 2H, H-8, H-9), 5.80–5.88 (m, 1H, allyl); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 31.5, 33.4, 67.9, 72.5, 72.7, 76.6, 79.4, 117.2, 130.8, 132.9, 135.3; FT-IR (neat) ν 3354, 3265, 2924, 2848, 2819, 1642, 1447, 1421, 1375, 1262, 1223, 1124, 1092, 1070, 1051, 1010, 963, 942, 917, 889, 849 cm^{-1}; ESI-TOFMS $[M+Na]^+$ calcd for $C_{12}H_{18}NaO_3$: 233.1154; found, 233.1151.

4.3.13. (4a*S*,6*R*,7*S*,9a*R*)-6-Allyl-3,4,4a,6,7,9a-hexahydro-2*H*-1,5-dioxa-benzocyclohepten-7-ol (3b). $[\alpha]_D^{24.0}$ +27.2 (*c* 0.520, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.41–1.49 (m, 1H, H-4), 1.63–1.68 (m, 2H, H-3), 2.02–2.07 (m, 1H, H-4), 2.23–2.29 (m, 1H, allyl), 2.53–2.59 (m, 1H, allyl), 3.19 (ddd, 1H, J = 11.5, 9.0, 4.5 Hz, H-4a), 3.28–3.34 (m, 1H, H-2), 3.38 (dt, 1H, J = 8.0, 3.0 Hz, H-6), 3.71 (ddd, 1H, J = 9.0, 4.0, 2.5 Hz, H-9a), 3.87–3.91 (m, 1H, H-2), 4.13 (ddd, 1H, J = 9.0, 4.0, 2.5 Hz, H-7), 5.07–5.15 (m, 2H, allyl), 5.57 (dt, 1H, J = 13.0, 2.0 Hz, H-8), 5.65 (dt, 1H,

$J = 13.0$, 2.3 Hz, H-9), 5.91–5.99 (m, 1H, allyl); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 31.0, 37.9, 67.7, 73.9, 80.0, 81.2, 84.3, 117.0, 132.3, 133.8, 135.3; FT-IR (neat) ν 3418, 3075, 2943, 2868, 1641, 1436, 1335, 1313, 1262, 1218, 1112, 1039, 992, 959, 915, 849 cm^{-1}; ESI-TOFMS $[M+Na]^+$ calcd for $C_{12}H_{18}NaO_3$: 233.1154; found, 233.1163.

4.3.14. (4a*S*,9a*R*)-7-Allyl-3,4,4a,6,7,9a-hexahydro-2*H*-1,5-dioxa-benzocyclohepten-7-ol (9). For major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44–1.54 (m, 1H, H-4), 1.64–1.72 (2H, H-3), 2.05–2.12 (m, 1H, H-4), 2.45 (dd, 1H, $J = 12$, 7.4 Hz, allyl), 2.50 (dd, 1H, $J = 12$, 7.3 Hz, allyl), 3.20–3.26 (m, 1H, H-4a), 3.29–3.35 (m, 1H, H-2), 3.51 (d, 1H, $J = 11.9$ Hz, H-6), 3.71 (d, 1H, $J = 11.9$ Hz, H-6), 3.82 (br d, 1H, $J = 9.2$ Hz, H-9a), 3.86–3.92 (m, 1H, H-2), 5.20 (d, 1H, $J = 17.4$ Hz, allyl), 5.23 (d, 1H, $J = 8.7$ Hz, allyl), 5.51 (br d, 1H, $J = 12.8$ Hz, H-8), 5.67 (d, 1H, $J = 12.8$ Hz, H-9), 5.81–5.90 (m, 1H, allyl); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 31.1, 42.3, 67.7, 75.1, 77.3, 80.9, 81.1, 120.4, 131.4, 132.8, 136.8; FT-IR (film) ν 3435, 3075, 2942, 2861, 1639, 1434, 1372, 1312, 1262, 1218, 1129, 1093, 1063, 1038, 999, 963, 917, 849 cm^{-1}; HR-ESI FT-ICR MS $[M+Na]^+$ calcd for $C_{12}H_{18}NaO_3$: 233.1148; found, 233.1149.

4.4. Alkylation of fluoride with trimethylsilylketene acetal

4.4.1. Alkylation of 7-*tert*-butyldimethylsilyloxy-6-fluorotetrahydrooxepin with $BF_3{\cdot}Et_2O$. To a solution of 7-*tert*-butyldimethylsilyloxy-6-fluorotetrahydrooxepin (6*R*:6*S* = 1:1.7, 12.5 mg, 0.0413 mmol) and 1-ethoxy-1-[(trimethylsilyl)oxy]ethane (132 mg, 0.826 mmol) in CH_2Cl_2 (1.5 mL) was added $BF_3{\cdot}Et_2O$ (10.5 μL, 0.0826 mmol) at −40 °C. The mixture was stirred for 4 h at −40 °C to −20 °C and quenched with saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc and the combined organic phase was dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 5 to 3) to give a 2.5:1 mixture of alkylation product **12** (7.8 mg, 51%, 6*S*:6*R* = 2.5:1). The C-6-stereochemistry of the major isomer was identified by NOE experiments after removal of TBS group with TBAF. C-7-alcohol of (6*S*)-**12**: $[\alpha]_D^{25.5}$ +8.5 (*c* 0.082, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, 3H, $J = 7.5$ Hz, Et), 1.50–1.68 (m, 3H, H-3, H-4), 1.88–1.94 (m, 1H, H-4), 2.12 (br d, 1H, $J = 8.0$ Hz, OH), 2.58 (dd, 1H, $J = 15.5$, 4.5 Hz, CH_2CO_2Et), 2.80 (dd, 1H, $J = 15.5$, 9.0 Hz, CH_2CO_2Et), 3.29–3.34 (m, 1H, H-2), 3.58 (td, 1H, $J = 10$, 4.5 Hz, H-4a), 3.86–3.91 (m, 1H, H-2), 4.04 (br dd, 1H, $J = 9.0$, 2.0 Hz, H-9a), 4.11–4.22 (m, 2H, Et), 4.34–4.38 (m, 1H, H-7), 4.41 (ddd, 1H, $J = 9.0$, 4.5, 2.0 Hz, H-6), 5.62–5.68 (m, 2H, H-8, H-9); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 25.6, 31.3, 36.0, 60.9, 67.9, 72.8, 73.3, 74.0, 78.8, 130.0, 133.2, 172.0; FT-IR (film) ν 3449, 3033, 2938, 2854, 1735, 1443, 1372, 1260, 1177, 1092, 1034, 968 cm^{-1}; HR-ESI FT-ICR MS $[M+Na]^+$ calcd for $C_{13}H_{20}NaO_5$: 279.1203; found, 279.1203.

4.4.2. Alkylation of 6-fluoro-7-hydroxytetrahydrooxepin with $TiCl_4$. To a solution of 6-fluoro-7-hydroxytetrahydrooxepin (6*R*:6*S* = 1:1.7, 10.4 mg, 0.0553 mmol) in CH_2Cl_2 (2 mL) were added 1-ethoxy-1-[(trimethylsilyl)oxy]ethane (177 mg, 1.11 mmol) and $TiCl_4$ (24.4 μL, 0.221 mmol) at −78 °C. The mixture was stirred for 3 h at −78 °C to −50 °C and quenched with saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc, and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 3 to 2) to give β-alkylation product **13** (2.8 mg, 20%). Compound **13**: $[\alpha]_D^{27.0}$ +20 (*c* 0.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, 3H, $J = 7.5$ Hz, Et), 1.40–1.44 (m, 1H, H-4), 1.45–1.68 (m, 2H, H-3), 1.95 (br d, 1H, $J = 7.0$ Hz, OH), 1.96–2.03 (m, 1H, H-4), 2.51 (dd, 1H, $J = 15$, 8.0 Hz, CH_2CO_2Et), 2.84 (dd, 1H, $J = 15$, 3.5 Hz, CH_2CO_2Et), 3.25 (ddd, 1H, $J = 11.5$, 9.0, 5.0 Hz, H-4a), 3.26–3.32 (m, 1H, H-2), 3.71 (br dd, 1H, $J = 9.0$, 2.0 Hz, H-9a), 3.83 (td, 1H, $J = 9.0$, 4.0 Hz, H-6), 3.85–3.90 (m, 1H, H-2), 4.11–4.17 (m, 1H, H-7), 4.17 (q, 2H, $J = 7.5$ Hz, Et), 5.60 (br d, 1H, $J = 13.5$ Hz, H-8), 5.67 (dt, 1H, $J = 13.5$, 2.0 Hz, H-9); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 25.5, 31.0, 39.6, 60.8, 67.7, 73.8, 80.1, 81.1, 81.7, 132.8, 133.7, 172.2; FT-IR (film) ν 3428, 3070, 3048, 2929, 2856, 1723, 1464, 1428, 1375, 1261, 1219, 1113, 1042, 959, 849 cm^{-1}; HR-ESI FT-ICR MS $[M+Na]^+$ calcd for $C_{13}H_{20}NaO_5$: 279.1203; found, 279.1203.

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