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Diastereoselective synthesis of 2,5-disubstituted tetrahydrofuran derivatives

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Abstract

5-Substituted lactol **1** was converted to 2,5-disubstituted tetrahydrofuran derivatives by a Lewis acid-promoted reaction with allylsilanes. High *trans* selectivity (12:1) was obtained when hindered allylsilane **8** was employed. 5-Substituted lactol **16** was transformed into 2,5-*cis*-disubstituted tetrahydrofuran **17b** (6:1 ratio) by a $TiCl_4$-promoted intramolecular allyl transfer process. Additionally, 2,5-*cis*-disubstituted tetrahydrofuran derivatives were obtained in good yields and diastereoselectivities after alkyllithium addition to lactone **6**, followed by $Et_3SiH/BF_3{\cdot}OEt_2$ reduction of the corresponding hemiketals.

1. Introduction

Functionalized tetrahydrofurans moieties are found in many biologically important natural products including pheromones,[1] polyether antibiotics[2] and acetogenins.[3,4] In particular, the stereoselective synthesis of 2,5-disubstituted tetrahydrofurans has received much attention. Although widely used in carbohydrate chemistry,[5] the Lewis acid-promoted substitution at the anomeric carbon of γ-lactols via oxocarbenium ions was rarely applied to the diastereoselective synthesis of 2,5-disubstituted tetrahydrofurans.[6–9]

Suzuki and co-workers reported that the replacement of the hydroxyl group of 5-substituted γ-lactols by the alkyl group of organometallic reagents such R_2Zn and R_3Al, via an oxocarbenium ion intermediate, proceeded with *trans* selectivity.[10] Meanwhile, Yoda and co-workers reported that the direct conversion of 5-substituted γ-lactones to 2,5-disubstituted tetrahydrofurans via Lewis acid-induced reduction of hemiketal intermediates with Et_3SiH displayed low *cis* selectivity[11] (Scheme 1).

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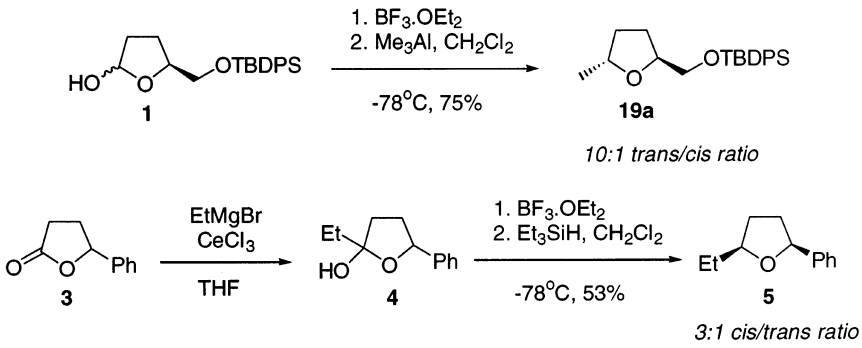
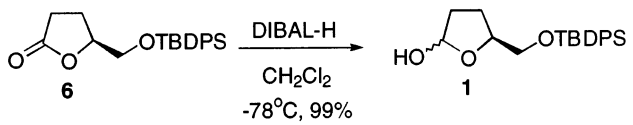


Scheme 1.

In order to investigate the stereochemical outcome of the inter- and intramolecular addition of allylsilanes to chiral cyclic oxocarbenium ions, we elected lactol **1** due to its strategic relevance for the asymmetric synthesis of tetrahydrofuran-containing natural products.

2. Results and discussion

Lactol **1**,[12] readily available from (*S*)-glutamic acid via lactone **6**,[13–15] was prepared by DIBAL-H reduction at low temperature as a 2:1 epimeric mixture (Scheme 2).

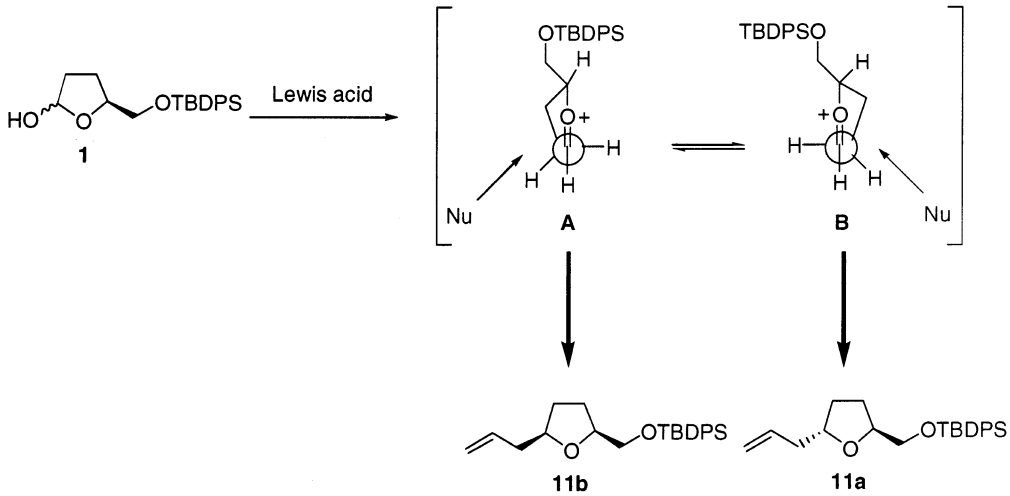


Scheme 2.

We initially investigated the influence of the Lewis acid in the nucleophilic addition of commercially available allylsilane **7** to lactol **1**. Good yields of 2,5-disubstituted tetrahydrofurans **11a**/**11b** were obtained in the reactions promoted by $BF_3{\cdot}OEt_2$, $TiCl_4$ and TiF_4, but modest *trans* selectivity was observed (Table 1, entries 1–3). These results contrast with the large *trans* preference reported by Suzuki and co-workers[10] when lactol **1** reacted with organometallic compounds in the presence of $BF_3{\cdot}OEt_2$ ascribed to the rather remote orientation of the C-5 substituent in the intermediate oxocarbenium ion.[7]

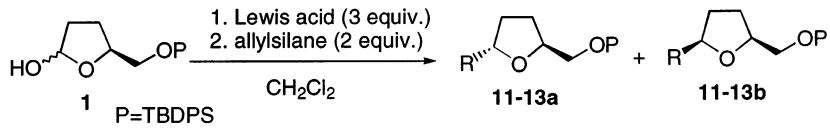
The intermediate oxocarbenium ion derived from lactol **1** may adopt pseudo-chair conformations **A** and **B**, which differ in their reactivity to a small extent. Since the $-CH_2OTBDPS$ group is located at a remote position from the electrophilic center, low diastereoselection is expected (Scheme 3).

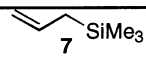
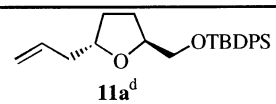
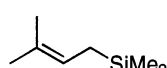
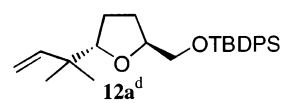
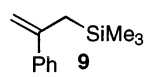
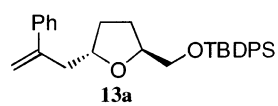
In order to evaluate the effect of the bulkiness of the nucleophile, we examined the addition of allylsilanes **8** and **9**[16] (entries 4–5). Allylsilane **9** produced **13a**/**13b** in good yield but with low *trans*-2,5 preference, while terminally disubstituted allylsilane **8** produced *trans*-2,5-tetrahydrofuran **12a** in good yield and diastereoisomeric ratio (*trans*/*cis* = 12:1). It is apparent that an increase in the steric bulkiness near to the nucleophilic center brings about an overriding interaction with the $-CH_2OTBDPS$ group at the 5-position of the oxocarbenium ion. These



Scheme 3.

Table 1
Nucleophilic addition of allylsilanes to lactol **1**



Entry	Lewis Acid	Allylsilane	T (°C)	Major isomer	*trans/cis* (%Yield)
1	$BF_3.OEt_2$	 **7**	-78~rt	 **11a**[d]	2:1[a] (94)
2	$TiCl_4$	**7**	-78	**11a**[d]	2:1[a] (88)
3	TiF_4[c]	**7**	-78	**11a**[d]	3:1[a] (90)
4	$BF_3.OEt_2$	 **8**	-78~rt	 **12a**[d]	12:1[b] (74)
5	$BF_3.OEt_2$	 **9**	-78~rt	 **13a**	2:1[b] (73)

[a]Ratio determined by GC/MS analysis after desilylation; [b]Ratio determined by ^{1}H-NMR analysis;

[c]TiF_4 in CH_3CN solution was employed; [d]Major diastereoisomer was isolated and fully characterized.

results are also consistent with a recent report by Worpel[8] on a large increase in *trans*-1,2 selectivity when a more hindered nucleophile was employed.

The major diastereoisomer **11a** was isolated by column chromatography on silica gel and its *trans* stereochemistry was assigned by NOE experiments after comparison with the NOE data obtained for *cis*-**11b** prepared from **17b** (Scheme 5). The major isomer **12a** was isolated by column chromatography on silica gel and its *trans* stereochemistry was unambiguously characterized by NOE experiments (Fig. 1). Irradiation of H-5 led to a 2.4% enhancement in the H_a signal, while irradiation of H-2 led to a 2.1 and 2.9% enhancement in the aromatic hydrogens. No increment in the H-2 signal was observed upon irradiation of H-5 and vice-versa. The relative stereochemistry of the major isomer **13a** was tentatively assigned as *trans* based on comparison of the ^1H and ^{13}C NMR data for a mixture of *trans*-**13a** and *cis*-**13b** with those of **12a**.

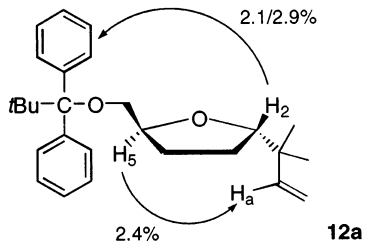
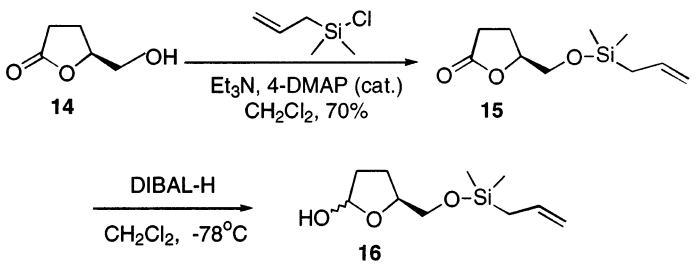


Figure 1.

Tetrahydrofuran derivatives **11a** and **11b** containing functional groups at C-2 and C-5 amenable to further functionalization are valuable synthetic intermediates, but their efficient preparation through the intermolecular addition of allylsilanes to the oxocarbenium ion derived from **1** seems to be limited to heavily substituted allylsilanes.

Reetz developed a different strategy for the allylation of β-hydroxyaldehydes, which relies on the intramolecular allyl transfer by a silyloxy tether.[17,18] The advantages of the intramolecular reaction over the corresponding intermolecular version are well documented.[19] The decrease in the entropic demands often lead to higher reaction rates and milder reaction conditions. Reduction in the degree of freedom of the unimolecular transition state often results in higher levels of asymmetric induction by the resident stereogenic center.

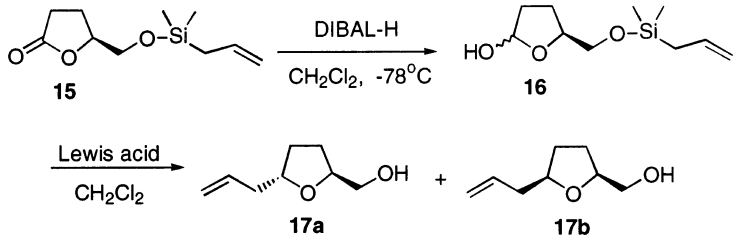
In order to test such an approach, lactol **16** was prepared after *O*-allyldimethylsilylation of lactone **14**, followed by its DIBAL-H reduction (Scheme 4).



Scheme 4.

Labile lactol **16** was immediately treated with Lewis acid to afford 2,5-disubstituted tetrahydrofurans **17a**/**17b** in good yields and *cis*-2,5 preference (Table 2).

Table 2
Intramolecular allylation of lactol **16**



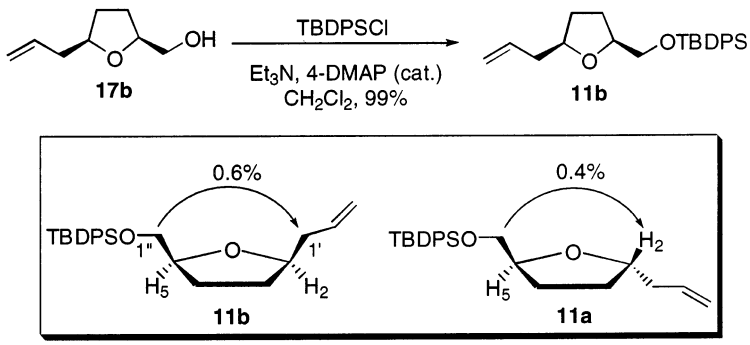
Entry	Lewis acid[a]	*T* (°C)	Dilution (M)	Yield[b] (%)	**17a**/**17b**[c]
1	$TiCl_4$	−78	0.5	73	1:1.5
2	$TiCl_4$	−78	5×10^{-3}	77	1:6
3	$TiCl_4$	−78	1×10^{-3}	–[d]	1:6
4	$SnCl_4$	−78	5×10^{-3}	72	1:3
5	$BF_3{\cdot}OEt_2$	−78 to rt	5×10^{-3}	76	1:3
6	TiF_4[e]	−78	5×10^{-3}	75	1.5:1

[a] 3 equiv. employed.
[b] Yields for two steps.
[c] Ratio determined by GC/MS analysis.
[d] Only 50% of conversion was observed by GC analysis.
[e] TiF_4 in CH_3CN solution was employed.

Compared with the intermolecular additions (Table 1), which displayed poor *trans* stereoselectivity (except when the more hindered allylsilane **8** was employed, entry 4), the intramolecular allylation of lactol **16** provided a preparatively useful approach to *cis*-2,5-disubstituted tetrahydrofuran **17b**.

The diastereoselection proved to be dependent on the dilution condition employed: when the reaction was carried out at a 0.5 M concentration (entry 1), almost no diastereoselection was observed probably due to the intervention of intermolecular allyl transfer. However, when the reaction was carried out at higher dilution, a significant increase in the *cis*-selectivity was observed (entries 2, 4–5). Among the Lewis acid tested at 5×10^{-3} M dilution, $TiCl_4$ performed better (6:1, entry 2) than $SnCl_4$ and $BF_3{\cdot}OEt_2$ and a 6:1 mixture of **17b**/**17a** was obtained in 77% yield with $TiCl_4$ as Lewis acid at 5×10^{-3} M dilution. At 1×10^{-3} M concentration the same *cis*/*trans* ratio was observed but with lower conversion rate (entry 3). Surprisingly, the use of TiF_4 produced 2,5-*trans*-disubstituted tetrahydrofuran **17a** as the major isomer probably due to fluoride desilylation of lactol **16** and the occurrence of intermolecular addition reaction.

The major diastereoisomer **17b** was isolated by column chromatography on silica gel and its *cis* stereochemistry was planned to be assigned by NOE experiments, but no definitive evidence emerged from these experiments. To circumvent this, **17b** was converted to *cis*-**11b** and the *cis* stereochemistry was confirmed by NOE experiments after comparison with the data obtained for *trans*-**11a** (Scheme 5): irradiation of H-1″ in *cis*-**11b** led to a 0.6% enhancement in the signal of the allylic hydrogens while no increment was observed in the H-2 signal. Irradiation of H-1″

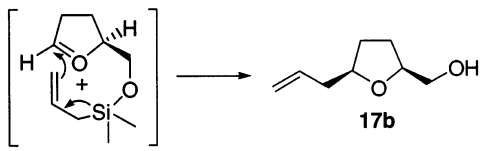


Scheme 5.

in *trans*-**11a** led to a 0.4% enhancement in the H-2 signal while no increment was observed for the allylic hydrogens.

The *cis* preference can be explained by taking into account that the intramolecular attack of the allyl group to the *si* face of the oxocarbenium carbon is geometrically favored (Scheme 6).

The conversion of lactones to cyclic ethers via Lewis acid-induced reduction of the corresponding lactols with Et_3SiH has been extensively studied in the domain of the synthesis of *C*-glycosides and it is of potential utility for the preparation of *cis*-2,5-disubstituted tetrahydrofurans with substituents at C-5 other than the allylated ones.



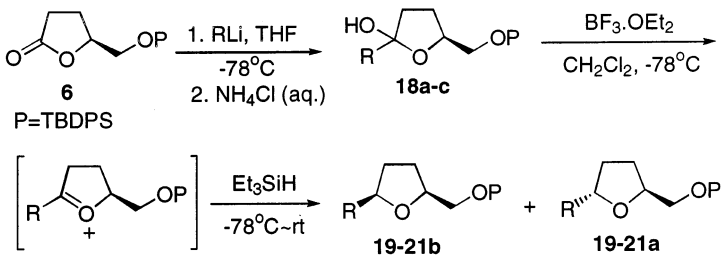
Scheme 6.

In order to evaluate the feasibility of this strategy for the preparation of *cis*-2,5-disubstituted tetrahydrofurans, we examined the addition of some alkyllithium reagents to lactone **6** followed by Lewis acid-promoted Et_3SiH deoxygenation (Table 3).

As shown in Table 3, the addition of alkyllithium reagents to lactone **6** afforded hemiketals **18a–c**, which were reduced with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ to afford 2,5-*cis*-disubstituted tetrahydrofurans **19b–21b** in moderate yields. The *cis* preference increased with the steric requirement of the R group (Table 3) and a single isomer was observed when R = Ph. The major diastereoisomers were isolated by column chromatography on silica gel and the *cis* stereochemistry of **20b** and **21b** was assigned by NOE experiments (NOESY 1D). As shown in Fig. 2, strong NOE correlations were observed between H-2/H-5 in the NOESY-1D spectra of **20b** and **21b** while for **19b** weak NOE increments were observed in H-2 signal upon irradiation at H-5.

Tetrahydrofuran *trans*-**19a** was independently prepared according to the procedure reported by Suzuki and co-workers.[10] Comparison of the ^1H and ^{13}C NMR data for *trans*-**19a** with those of **19b** confirm the *cis* stereochemistry of the major isomer formed in the Et_3SiH reduction of lactol **18a**.

Table 3
Nucleophilic addition of alkyllithium reagents to lactone **6** followed by deoxygenation



Entry	RLi	Hemiketal	Major isomer[a,b]	Yield[b] (%)	*cis*/*trans*[c]
1	MeLi	**18a**	**19b**	54	3:1
2	*n*-BuLi	**18b**	**20b**	54	5:1
3	PhLi	**18c**	**21b**	51	>95:5

[a] Yields for two steps.
[b] The major diastereoisomers were isolated and characterized.
[c] Ratio determined by ^{1}H NMR analysis.

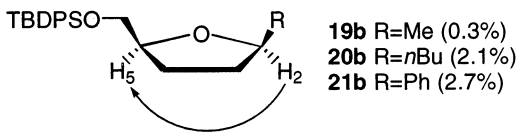


Figure 2.

3. Conclusions

In summary, we have demonstrated that the synthesis of 2,5-disubstituted tetrahydrofuran derivatives can be achieved in good yields and divergent diastereoselectivity by intermolecular or intramolecular replacement of the hydroxyl group of 5-substituted γ-lactols by the allyl group. Furthermore, Lewis acid-induced reduction of hemiketals derived from the lactone **6** is an alternative method to synthesize 2,5-*cis*-disubstituted tetrahydrofurans. These strategies provide a new synthetic opportunity for the synthesis of biologically active natural products.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 and 75 MHz, respectively, using a Varian Gemini 2000 spectrometer and at 500 and 125 MHz, respectively, using a Varian Inova 500 spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane followed by multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet), coupling constant (Hz) and number of protons. The values in parentheses refer to the chemical shift of the minor isomer. Infrared spectra were recorded on a Nicolet

Impact 410 spectrophotometer. High resolution mass spectra were obtained via electron impact (70 eV) on a VG Autospec spectrometer. Optical rotations were measured at 24°C in a Polamat A (Carl Zeiss). GC analyses were performed in a Hewlett-Packard 5890 series II chromatograph equipped with flame ionization detector, nitrogen as the carrier gas and capillary columns (30 m×0.53 mm) with 1% phenylmethylsilicone (HP-1) or cross-linked polyethyleneglycol (Carbowax 20M) as stationary phases. GC–MS analyses were performed on a Hewlett-Packard 5890 series II gas chromatograph coupled to a MSD 5970 mass detector equipped with a capillary column (Carbowax 20M, 25 m×0.20 mm×0.33 μm). Column chromatography was performed using silica gel (70-230 mesh), except when stated otherwise, and reactions were monitored by TLC (plates from Macherey–Nagel, Germany).

Tetrahydrofuran was treated with sodium/benzophenone and distilled immediately prior to use. Dichloromethane and triethylamine were treated with calcium hydride and distilled immediately prior to use. $BF_3{\cdot}OEt_2$, $TiCl_4$ and $SnCl_4$ were distilled prior to use. The remaining reagents employed were purchased from commercial suppliers and used without further purification. The reactions involving anhydrous solvents were carried out under argon atmosphere.

4.2. Preparation of γ-lactol ***1***

*4.2.1. (5*S*)-(*tert*-Butyldiphenylsilyloxymethyl)-tetrahydrofuran-2-ol* ***1***

A CH_2Cl_2 solution (5.4 mL) of lactone **6** (0.959 g, 2.70 mmol) was cooled to −78°C, treated with DIBAL-H (3.24 mL, 1.0 M in toluene, 3.24 mmol) and stirred at −78°C for 1 h. The reaction was quenched by the addition of AcOEt (6.5 mL) and warmed to room temperature. Then, saturated solution of sodium potassium tartarate (6.5 mL) were added and the mixture was stirred for 2 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×2 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$, filtered and concentrated to afford an anomeric mixture of **1** (0.953 g, 2.67 mmol, 99% yield, 2:1 ratio) as a clear oil, which was used in the next step without further purification (R_f 0.45 in 30% AcOEt–hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05 and 1.08 (s, 9H), 1.72–2.12 (m, 5H), 3.55–3.90 (m, 2H), 4.10–4.40 (m, 1H), 5.26–5.60 (m, 1H), 7.20–7.45 (m, 6H), 7.66–7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.0, 25.3 (23.6), 26.6, 31.8 (34.6), 66.0 (66.2), 78.6 (80.2), 100.8 (98.6), 127.8 (128.0), 129.8 (130.1), 135.8 (133.9), 135.9 (136.0); IR (film) 3415, 2929, 2856, 1471, 1427, 1112 cm^{-1}; LRMS (EI) m/z 199 (100%), 299 (15%); HRMS (IE) m/z calcd for $C_{17}H_{19}O_3Si$ $[M-C_4H_9]^+$ 299.11035. Found: 299.11038.

4.3. General procedure for the allylation of γ-lactol ***1***

To a 0.5 M CH_2Cl_2 solution of lactol **1** (1.0 equiv.) at −78°C was added Lewis acid (3.0 equiv.) followed by allylsilane (2.0 equiv.). The reaction mixture was stirred for 3 h at the temperature indicated in Table 1. The reaction was quenched by the addition of saturated aqueous NH_4Cl, the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude mixture was purified by column chromatography as indicated below.

*4.3.1. (2*S*,5*S*)-2-Allyl-5-(*tert*-butyldiphenylsilyloxymethyl)-tetrahydrofuran* ***11a***

Chromatography on silica gel (5% AcOEt in hexanes, v/v) afforded a diastereoisomeric mixture of **11a**/**11b** in 94% yield and 2:1 *trans*/*cis* ratio. An analytically pure sample of **11a** was

obtained as a colorless oil (R_f 0.50 in 10% AcOEt–hexanes). $[\alpha]_D^{24}$ +15.2 (*c* 0.3, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.50–1.58 (m, 1H), 1.80–1.88 (m, 1H), 1.97–2.05 (m, 2H), 2.20–2.26 (m, 1H), 2.32–2.37 (m, 1H), 3.62 (dd, $J=5.1$, 10.5 Hz, 1H), 3.66 (dd, $J=4.5$, 10.5 Hz, 1H), 3.99–4.04 (m, 1H), 4.13–4.18 (m, 1H), 5.02–506 (m, 1H), 5.10 (dq, $J=17.0$, 1.7 Hz, 1H), 5.82 (ddt, $J=17.0$, 10.0, 7.1 Hz, 1H), 7.37–7.42 (m, 6H), 7.67–7.70 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 26.8, 28.0, 31.3, 40.2, 66.5, 78.8, 79.1, 116.6, 127.6, 129.5, 133.7, 135.2, 135.6; IR (film) 3070, 2956, 2929, 2852, 1641, 1115 cm^{-1}; LRMS (EI) *m*/*z* 199 (100%), 323 (36%); HRMS (IE) *m*/*z* calcd for $C_{20}H_{23}O_2Si$ $[M-C_4H_9]^+$ 323.14673. Found: 323.14674.

4.3.2. (2S,5S)-2-(1,1-Dimethyl-2-propenyl)-5-(tert-butyldiphenylsilyloxymethyl)-tetrahydrofuran **12a**

Chromatography on silica gel (1% AcOEt in hexanes, v/v) afforded a diastereoisomeric mixture of **12a**/**12b** in 74% yield and 12:1 *trans*/*cis* ratio. An analytically pure sample of **12a** was obtained as a colorless oil (R_f 0.38 in 5% AcOEt–hexanes). $[\alpha]_D^{24}$ −4.8 (*c* 4.2, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.05 (s, 3H), 1.06 (s, 9H), 1.56–1.72 (m, 1H), 1.73–2.05 (m, 3H), 3.67 (m, 2H), 3.77 (dd, $J=5.5$, 8.8 Hz, 1H), 4.07–4.13 (m, 1H), 4.96–5.06 (m, 2H), 5.91 (dd, $J=10.3$, 18.0 Hz, 1H), 7.32–7.48 (m, 6H), 7.64–7.78 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 22.7, 23.7, 26.6, 27.1, 28.3, 40.3, 66.6, 79.8, 86.7, 112.0, 127.8, 129.7, 134.0, 135.9, 145.4; IR (film) 3070, 2958, 2929, 2856, 1605, 1589, 1471, 1427, 1112 cm^{-1}; LRMS (EI) *m*/*z* 199 (100%), 351 (20%); HRMS (EI) *m*/*z* calcd for $C_{22}H_{27}O_2Si$ $[M-C_4H_9]^+$ 351.17803. Found: 351.17828.

4.3.3. (2S,5S)-2-(Phenyl-2-propenyl)-5-(tert-butyldiphenylsilyloxymethyl)-tetrahydrofuran **13a**

Chromatography on silica gel (1% AcOEt in hexanes, v/v) afforded the product as a clear oil (R_f 0.30 in 1% AcOEt–hexanes) in 73% yield (2:1 *trans*/*cis* selectivity). Major diastereoisomer (**13a**): ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 9H), 1.34–1.52 (m, 2H), 1.62–1.78 (m, 2H), 2.41 (dd, $J=14.2$, 7.3 Hz, 1H), 2.78 (dd, $J=14.2$, 5.5 Hz, 1H), 3.41–3.54 (m, 2H), 3.78–3.91 (m, 2H), 4.97 (d, $J=1.5$ Hz, 1H), 5.17 (d, $J=1.5$ Hz, 1H), 7.02–7.30 (m, 11H), 7.49–7.58 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 26.7, 27.5, 30.6, 41.7, 66.4, 78.4, 79.5, 114.4, 126.4, 127.1, 127.8, 128.5, 129.8, 133.9, 135.9, 141.3, 145.8; IR (film) 3070, 2956, 2929, 2856, 1624, 1598, 1112 cm^{-1}; LRMS (EI) *m*/*z* 199 (100%), 399 (19%); HRMS (EI) *m*/*z* calcd for $C_{26}H_{27}O_2Si$ $[M-C_4H_9]^+$ 399.17803. Found: 399.17809.

4.4. Preparation of **17b** and **11b**

4.4.1. (5S)-(Allyldimethylsilyloxymethyl)-tetrahydrofuran-2-one **15**

A solution of lactone **14** (0.568 g, 4.89 mmol) in CH_2Cl_2 (10 mL) was treated with triethylamine (0.818 mL, 5.87 mmol), a catalytic amount of *N*,*N*-dimethyl-4-aminopyridine (0.0597 g, 0.489 mmol) and allyldimethysilyl chloride (0.857 mL, 5.87 mmol). The mixture was stirred 1 h at room temperature and poured into water. The layers were separated and the organic phase was washed with saturated NH_4Cl solution (3 mL), brine (3 mL), dried over $MgSO_4$ and concentrated. Chromatography on silica gel (30% AcOEt in hexanes, v/v) of the crude product afforded **15** (0.734 g, 3.42 mmol, 70% yield) as a colorless oil (R_f 0.42 in 30% AcOEt–hexanes). $[\alpha]_D^{24}$ +27.5 (*c* 5.9, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 1.57 (d, $J=8.1$ Hz, 2H), 1.98–2.27 (m, 2H), 2.40–2.60 (m, 2H), 3.63 (dd, $J=3.3$, 11.4 Hz, 1H), 3.78 (dd, $J=3.0$, 11.4 Hz, 1H), 4.49–4.55 (m, 1H), 4.81–4.88 (m, 2H), 5.65–5.79 (m, 1H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ −2.9, −2.8, 23.4, 24.0, 28.4, 64.5, 79.9, 114.0, 133.6, 177.6; IR (film) 3076, 2958, 2871, 1778, 1630 cm^{-1}; LRMS (EI) m/z 129 (100%), 173 (40%); HRMS (EI) m/z calcd for $C_7H_{13}O_3Si$ $[M-C_3H_5]^+$ 173.06340. Found: 173.06338.

*4.4.2. General procedure for the preparation of (2*R,*5*S*)-2-allyl-5-(hydroxymethyl)-tetrahydrofuran* ***17b***

A CH_2Cl_2 solution (0.5 M) of lactone **15** was cooled to −78°C, treated with DIBAL-H (1.0 M in toluene, 1.2 equiv.) and stirred at −78°C for 1 h. The reaction was quenched by the addition of AcOEt, warmed to room temperature and saturated solution of sodium potassium tartarate was added. After 2 h the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. To a 0.5 M solution of lactol **16** (1.0 equiv.) in dry CH_2Cl_2 at −78°C were added 3.0 equiv. of Lewis acid (Table 2) and the mixture was stirred for 3 h at temperature indicated in Table 2. The reaction was quenched by the addition of saturated aqueous NH_4Cl, the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude mixture was purified by silica gel chromatography (50% AcOEt in hexanes, v/v) to afford **17a**/**17b** as a clear oil (see Table 2, for yields and *cis*/*trans* ratios). An analytically pure sample of the major diastereoisomer **17b** was isolated and characterized (R_f 0.21 in 40% AcOEt–hexanes). $[\alpha]_D^{24}$ −31.3 (*c* 0.3, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.52–2.06 (m, 5H), 2.19–2.42 (m, 2H), 3.49 (dd, $J=5.5$, 11.7 Hz, 1H), 3.71 (dd, $J=3.3$, 11.7 Hz, 1H), 3.94–4.06 (m, 2H), 5.05–5.14 (m, 2H), 5.82 (ddt, $J=17.2$, 10.2, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.8, 30.7, 40.0, 65.1, 79.1, 79.4, 117.2, 134.8; IR (film) 3423, 3076, 2931, 2871, 1641 cm^{-1}; LRMS (EI) m/z 57 (100%), 142 (05%); HRMS (EI) m/z calcd for $C_8H_{14}O_2$ $[M]^+$ 142.09937. Found: 142.09959.

*4.4.3. (2*R,*5*S*)-2-Allyl-5-(*tert*-butyldiphenylsilyloxymethyl)-tetrahydrofuran* ***11b***

A solution of **17b** (0.200 g, 1.41 mmol) in CH_2Cl_2 (3.0 mL) was treated with triethylamine (0.24 mL, 1.7 mmol), a catalytic amount of *N*,*N*-dimethyl-4-aminopyridine (0.0172 g, 0.141 mmol) and *tert*-butyldiphenylsilyl chloride (0.44 mL, 1.7 mmol). The mixture was stirred 1 h at room temperature and poured into water. The layers were separated and the organic phase was washed with saturated NH_4Cl solution (1 mL), brine (1 mL), dried over $MgSO_4$ and concentrated. Chromatography on silica gel (10% AcOEt in hexanes, v/v) of the crude product afforded **11b** (0.531 g, 1.40 mmol, 99% yield) as a colorless oil (R_f 0.50 in 10% AcOEt–hexanes). $[\alpha]_D^{24}$+7.8 (*c* 1.3, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.50–1.62 (m, 1H), 1.86–1.98 (m, 3H), 2.21–2.28 (m, 1H), 2.34–2.41 (m, 1H), 3.63 (dd, $J=5.2$, 10.5 Hz, 1H), 3.67 (dd, $J=4.4$, 10.5 Hz, 1H), 3.92–3.96 (m, 1H), 4.03–4.05 (m, 1H), 5.01–5.05 (m, 1H), 5.05–5.11 (m, 1H), 5.83 (ddt, $J=17.3$, 10.0, 7.0 Hz, 1H), 7.36–7.45 (m, 6H), 7.60–7.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 26.8, 27.7, 30.6, 40.3, 66.4, 79.3, 79.5, 116.6, 127.6, 129.6, 133.7, 135.2, 135.6; IR (film) 3070, 2956, 2929, 2852, 1641, 1115 cm^{-1}; LRMS (EI) m/z 199 (100%), 323 (35%); HRMS (IE) m/z calcd for $C_{20}H_{23}O_2Si$ $[M-C_4H_9]^+$ 323.14673. Found: 323.14674.

4.5. General procedure for tandem alkyllithium addition to lactone ***6****/Et₃SiH reduction*

A 0.5 M THF solution of lactone **6** was cooled to −78°C, treated with alkyllithium reagent (1.2 equiv.) and stirred at −78°C for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl, the layers were separated and the aqueous layer was extracted with Et_2O. The

combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. A solution of crude hemiketal in dry CH_2Cl_2 (0.5 M) was cooled to −78°C, treated with $BF_3{\cdot}OEt_2$ (3.0 equiv.) and Et_3SiH (2.0 equiv.). The mixture was stirred 3 h at −78°C and the reaction was quenched by the addition of saturated aqueous NH_4Cl, the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude mixture was purified as indicated below.

*4.5.1. (2*S,*5*S*)-2-Methyl-5-(*tert-*butyldiphenylsilyloxymethyl)-tetrahydrofuran* ***19b***

Chromatography on silica gel (1% AcOEt in hexanes, v/v) afforded the product as a clear oil in 54% yield (3:1 *cis*/*trans*). An analytically pure sample of the major diastereoisomer **19b** was isolated and characterized (R_f 0.35 in 5% AcOEt–hexanes). $[\alpha]_D^{24}$ −12.3 (*c* 0.81, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6) δ 1.13 (d, $J=5.9$ Hz, 3H), 1.17 (s, 9H), 1.52–1.61 (m, 4H), 3.64 (dd, $J=4.9$, 10.7 Hz, 1H), 3.68 (dd, $J=4.4$, 10.7 Hz, 1H), 3.82–3.86 (m, 1H), 3.95–4.00 (m, 1H), 7.21–7.25 (m, 6H), 7.79–7.83 (m, 4H); ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.23 (d, $J=5.9$ Hz, 3H), 1.44–1.48 (m, 1H), 1.87–1.97 (m, 3H), 3.60 (dd, $J=5.6$, 10.5 Hz, 1H), 3.68 (dd, $J=4.4$, 10.5 Hz, 1H), 3.98–4.05 (m, 2H), 7.35–7.42 (m, 6H), 7.68–7.71 (m, 4H); ^{13}C NMR (125 MHz, CCl_4) δ 22.4, 24.1, 29.8, 30.9, 35.9, 69.3, 78.2, 82.0, 130.3, 132.2, 136.9, 138.4; IR (film) 2962, 2929, 2856, 1113 cm^{-1}; LRMS (EI) *m*/*z* 199 (100%), 297 (70%); HRMS (EI) *m*/*z* calcd for $C_{18}H_{21}O_2Si$ $[M-tBu]^+$ 297.13108. Found: 297.13101.

*4.5.2. (2*S,*5*S*)-2-*n*-Butyl-5-(*tert-*butyldiphenylsilyloxymethyl)-tetrahydrofuran* ***20b***

Chromatography on silica gel (5% AcOEt in hexanes, v/v) afforded the product as a clear oil in 54% yield (5:1 *cis*/*trans*). An analytically pure sample of the major diastereoisomer **20b** was isolated and characterized (R_f 0.39 in 5% AcOEt–hexanes). $[\alpha]_D^{24}$ +8.3 (*c* 0.3, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, $J=7.0$ Hz, 3H), 1.05 (s, 9H), 1.28–1.64 (m, 7H), 1.85–1.95 (m, 3H), 3.60 (dd, $J=5.4$, 10.5 Hz, 1H), 3.67 (dd, $J=4.4$, 10.5 Hz, 1H), 3.82–3.86 (m, 1H), 4.00–4.03 (m, 1H), 7.35–7.43 (m, 6H), 7.68–7.71 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 19.3, 22.8, 26.8, 27.9, 28.5, 31.1, 35.7, 66.5, 79.2, 80.1, 127.6, 129.5, 133.7, 135.6; IR (film) 2956, 2929, 2858, 1113 cm^{-1}; LRMS (IE) *m*/*z* 199 (100%), 339 (75%); HRMS (EI) *m*/*z* calcd for $C_{21}H_{27}O_2Si$ $[M-tBu]^+$ 339.17803. Found: 339.17810.

*4.5.3. (2*R,*5*S*)-2-Phenyl-5-(*tert-*butyldiphenylsilyloxymethyl)-tetrahydrofuran* ***21b***

Chromatography on silica gel (4% AcOEt in hexanes, v/v) afforded the product as a clear oil (R_f 0.28 in 5% AcOEt–hexanes) and 51% yield (single isomer detected by ^1H NMR). $[\alpha]_D^{24}$ +34.9 (*c* 0.86, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.76–1.89 (m, 1H), 1.96–2.13 (m, 2H), 2.22–2.33 (m, 1H), 3.80 (d, $J=4.4$ Hz, 2H), 4.18–4.25 (m, 1H), 4.91 (dd, $J=6.2$, 8.1 Hz, 1H), 7.23–7.43 (m, 11H), 7.69–7.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 26.8, 28.0, 34.4, 66.2, 79.9, 81.4, 125.9, 127.2, 127.7, 128.2, 129.7, 133.7, 135.7, 143.2; IR (film) 2958, 2929, 2856, 1113 cm^{-1}; LRMS (EI) *m*/*z* 199 (100%), 359 (20%); HRMS (EI) *m*/*z* calcd for $C_{23}H_{23}O_2Si$ $[M-tBu]^+$ 359.14673. Found: 359.14679.

*4.6. (2*R,*5*S*)-2-Methyl-5-(*tert-*butyldiphenylsilyloxymethyl)-tetrahydrofuran* ***19a***

To a solution of lactol **1** (0.180 g, 0.505 mmol) in dry CH_2Cl_2 (2.0 mL) at −78°C was added $BF_3{\cdot}OEt_2$ (0.186 mL, 1.51 mmol) and Me_3Al (0.090 mL, 1.0 mmol). The mixture was stirred for

3 h at −78°C and the reaction was quenched by the addition of saturated aqueous NH_4Cl (2 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×1 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$, filtered and concentrated. Chromatography on silica gel (5% AcOEt in hexanes, v/v) afforded **19a**/**19b** (0.148 g, 0.417 mmol, 83% yield) as a clear oil (8:1 *trans*/*cis*). An analytically pure sample of the major diastereoisomer **19a** was isolated and characterized (R_f 0.37 in 5% AcOEt–hexanes). $[\alpha]_D^{24}$ −8.2 (*c* 1.22, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.21 (d, J=6.1 Hz, 3H), 1.41–1.47 (m, 1H), 1.81–1.86 (m, 1H), 1.99–2.05 (m, 2H), 3.61 (dd, J=5.4, 10.5 Hz, 1H), 3.66 (dd, J=4.6, 10.5 Hz, 1H), 4.05–4.09 (m, 1H), 4.13–4.18 (m, 1H), 7.35–7.43 (m, 6H), 7.67–7.71 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 21.1, 26.9, 28.4, 33.7, 66.7, 75.3, 79.0, 127.6, 129.5, 133.8, 135.6; IR (film) 2962, 2929, 2856, 1113 cm^{-1}; LRMS (EI) m/z 199 (100%), 297 (70%); HRMS (EI) m/z calcd for $C_{18}H_{21}O_2Si$ [M−*t*Bu]$^+$ 297.13108. Found: 297.13122.

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