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STEREOSELECTIVE ALKYLATION OF OXATHIAZINANE *N,O*-KETALS FOR THE CONSTRUCTION OF AZA-QUATERNARY CARBON CENTERS

Hisanori Nambu, Eri Tanaka, Mai Okada, Chiaki Hirosawa, Narumi Noda, Tomoya Fujiwara, and Takayuki Yakura*

Faculty of Pharmaceutical Sciences, University of Toyama, Sugitani, Toyama 930-0194, Japan. E-mail address: yakura@pha.u-toyama.ac.jp

Dedicated to Professor Yasuyuki Kita on the occasion of his 77th birthday

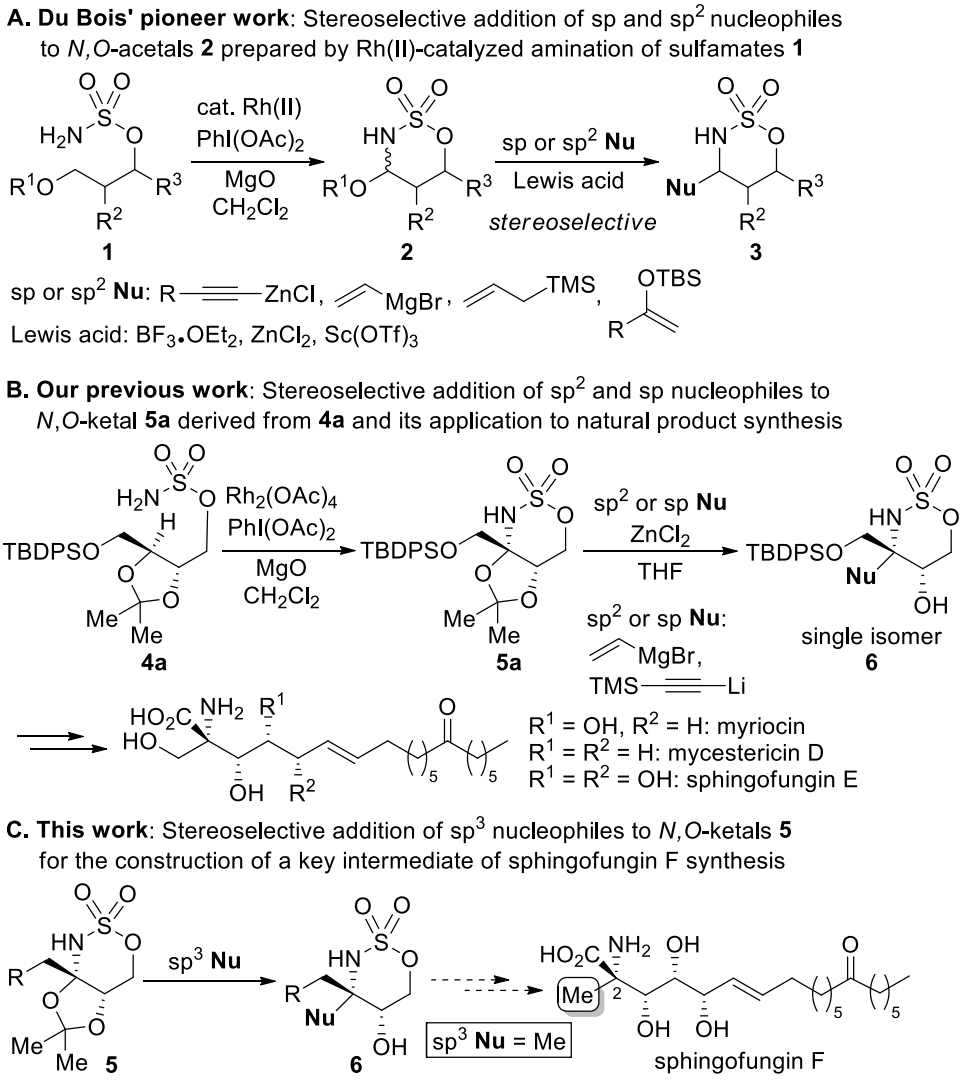
Abstract – Stereoselective construction of aza-quaternary carbon centers was achieved using the alkylation of oxathiazinane *N*,*O*-ketals prepared by Rh(II)-catalyzed C–H amination of sulfamates. The addition of alkyl Grignard reagents into *N*,*O*-ketals in the absence of any Lewis acid proceeded stereoselectively to provide the corresponding alkylated products with an aza-quaternary carbon center in high yields. The obtained product could be converted into an α-amino alcohol derivative, which is a potential synthetic intermediate for sphingofungin F and its derivatives.

INTRODUCTION

Aza-quaternary carbon centers (α-tertiary amines) are present in a wide range of biologically active natural and synthetic products such as natural alkaloids, unnatural amino acids, and pharmaceuticals.[1] To date, the stereoselective construction of an aza-quaternary carbon center is one of the most challenging subjects in synthetic organic chemistry.[2] The total synthesis of sphingolipid-related natural products such as myriocin, mycestericin D, and sphingofungin E, which possess an aza-quaternary carbon center, has recently been achieved using Du Bois Rh(II)-catalyzed C–H amination–alkylation. Du Bois *et al.* group has developed stereoselective additions of nucleophiles into *N*,*O*-acetals **2** prepared by Rh(II)-catalyzed C–H amination of sulfamates **1** to obtain the corresponding alkylated products **3** with aza-tertiary carbon centers (Scheme 1, A).[3] The Du Bois procedure can be extended to the formation of a quaternary center, and the alkenylation and alkynylation of **5a** derived from **4a** proceed smoothly and stereoselectively to

afford **6** as a single isomer, which can be successfully converted into myriocin, mycestericin D, and sphingofungin E (Scheme 1, B).[4–6]

Sphingofungin F is a member of the myriocin family, and it has a methyl group at the C2 position. For a comprehensive synthesis of these natural products, a stereoselective methylation of oxathiazinane *N*,*O*-ketal **5a** with sp^3 methyl nucleophile is necessary (Scheme 1, C). However, there have been no reports of using any simple sp^3 nucleophiles such as methyl and ethyl nucleophiles in the Du Bois procedure. Herein, we report the stereoselective alkylation of oxathiazinane *N*,*O*-ketals **5** with various sp^3 nucleophiles for the construction of aza-quaternary carbon centers (Scheme 1, C).

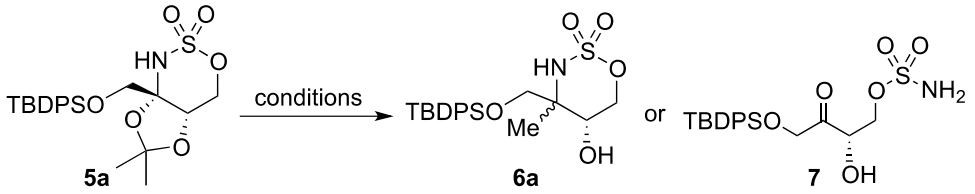


Scheme 1. Stereoselective alkylations of oxathiazinane *N*,*O*-acetals **2** and ketals **5**

RESULTS AND DISCUSSION

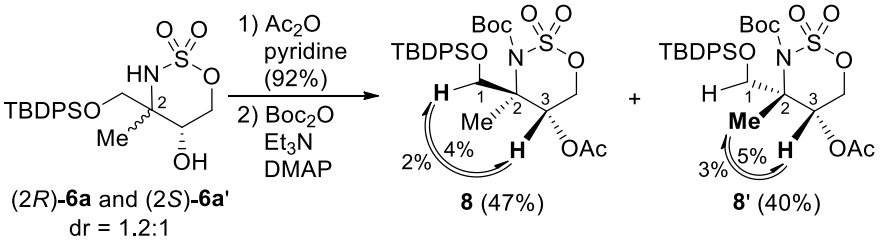
We initially examined the reaction of oxathiazinane *N*,*O*-ketal **5a**[4,5] under various methylating conditions (Table 1). According to the ethynylation of **5a** (Scheme 1, B),[4,5] the reaction of **5a** with methyllithium (MeLi) in the presence of zinc chloride ($ZnCl_2$) and boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) in tetrahydrofuran (THF) at room temperature was investigated; however, it did not proceed at all (entry 1). The use of scandium(III) triflate ($Sc(OTf)_3$) as a Lewis acid resulted in decomposition products (entry 2). Methylmagnesium chloride (MeMgCl)—instead of MeLi—in the presence of $ZnCl_2$ afforded hydrolyzed product **7** of **5a** in 64% yield (entry 3). The addition of $BF_3{\cdot}OEt_2$ into the reaction with methylmagnesium bromide (MeMgBr) and $ZnCl_2$ underwent decomposition (entry 4). The use of trimethylaluminum (Me_3Al) at 50 °C gave hydrolyzed product **7** in 22% yield (entry 5). When $BF_3{\cdot}OEt_2$ was added to the reaction of **5a** with Me_3Al, no reaction was observed (entry 6). Thus, all attempts to synthesize methylated product **6a** by employing various combinations of methylating reagents and Lewis acids were unsuccessful. Methylated product **6a** was obtained under Ellman's conditions for the methylation of *N*-sulfinyl ketimines.[7] The reaction of **5a** with MeLi and Me_3Al in toluene at room temperature afforded **6a** in 86% yield with a disappointingly low diastereoselectivity (entry 7, dr = 1.2:1).

Table 1. Methylation of oxathiazinane *N*,*O*-ketal **5a**



entry	reagents	solvent	temp.	time (h)	product (yield)
1	MeLi, $ZnCl_2$, $BF_3{\cdot}OEt_2$	THF	rt	24	no reaction
2	MeLi, $ZnCl_2$, $Sc(OTf)_3$	THF	rt	24	decomp.
3	MeMgCl, $ZnCl_2$	THF	rt	4	**7** (64%)
4	MeMgBr, $ZnCl_2$, $BF_3{\cdot}OEt_2$	THF	rt	24	decomp.
5	Me_3Al	THF	50 °C	24	**7** (22%)
6	Me_3Al, $BF_3{\cdot}OEt_2$	THF	50 °C	24	no reaction
7	MeLi, Me_3Al	toluene	rt	0.5	**6a** (86%) [dr = 1.2:1]

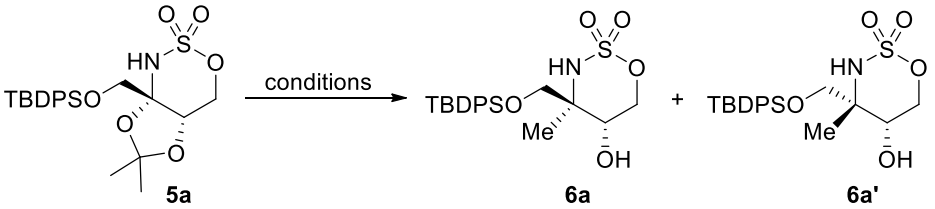
Since **6a** and its diastereomer **6a'** could not be separated by column chromatography on silica gel, their stereochemistries were determined using ^{1}H nuclear Overhauser effect (^{1}H NOE) experiments of their derivatives **8** and **8'**, respectively (Scheme 2). The acetylation of the hydroxy group in **6a** and **6a'** followed by *tert*-butoxycarbonyl (Boc) protection of the amino group yielded separable isomers **8** and **8'**. Significant NOE interactions between C1–H and C3–H in **8** and between C2–Me and C3–H in **8'** allowed assigning 2*R* and 2*S* as the stereochemistries of **6a** and **6a'**, respectively. The stereochemistry of **6a** was consistent with those of the previously reported alkenylation and alkynylation products.[4,5]



Scheme 2. Determination of stereochemistries of **6a** and **6a'**

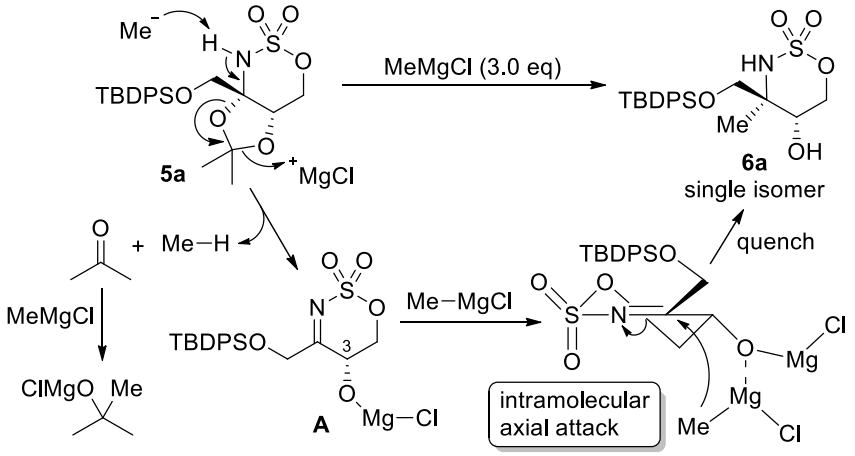
Next, the reaction to further enhance the diastereoselectivity was examined, because the methylated product **6a** could be obtained (Table 2). The use of MeMgBr instead of MeLi in the presence of Me_3Al in toluene at room temperature increased the product yield and diastereoselectivity (93% yield, **6a**:**6a'** = 2:1, entry 2). Surprisingly, the reaction of **5a** with 3.0 equivalents (eq) of MeMgBr in the absence of Me_3Al afforded **6a** as a single isomer in 65% yield (entry 3). Thus, Lewis acid was not required for this reaction of *N*,*O*-ketal **5a**. Changing the Grignard reagent from MeMgBr to MeMgCl increased the product yield to 85% (entry 4). When the amount of MeMgCl was reduced from 3.0 eq to 2.0 or 1.0 eq, sharp drops in product yields were observed (45% and 7% yields for entries 5 and 6, respectively). These results indicated that the use of 3.0 eq of Grignard reagent was crucial for high yield. In contrast, the reaction with 3.0 eq of MeLi resulted in the formation of a complex mixture of products (entry 7). A survey of solvents using 3.0 eq of MeMgCl revealed that THF was the optimal solvent for this reaction to produce **6a** in 87% yield (entries 4, 8, 9, and 10). Increasing the amount of MeMgCl to 3.3 eq improved the product yield to 95% (entry 11). Thus, we achieved a stereoselective construction of an aza-quaternary carbon center by employing the reaction of oxathiazinane *N*,*O*-ketal with the Grignard reagent in the absence of Lewis acids.

Table 2. Stereoselective methylation of oxathiazinane *N*,*O*-ketal **5a**



entry	reagents	solvent	time (h)	yield (dr)
1	MeLi (2.5 eq), Me_3Al (1.2 eq)	toluene	0.5	86% (**6a**:**6a'** = 1.2:1)
2	MeMgBr (2.5 eq), Me_3Al (1.2 eq)	toluene	0.5	93% (**6a**:**6a'** = 2:1)
3	MeMgBr (3.0 eq)	toluene	1.5	65% (**6a** only)
4	MeMgCl (3.0 eq)	toluene	1.5	85% (**6a** only)
5	MeMgCl (2.0 eq)	toluene	4	45% (**6a** only)
6	MeMgCl (1.0 eq)	toluene	5	7% (**6a** only)
7	MeLi (3.0 eq)	toluene	1.5	complex mixture
8	MeMgCl (3.0 eq)	CH_2Cl_2	3.5	14% (**6a** only)
9	MeMgCl (3.0 eq)	Et_2O	0.5	86% (**6a** only)
10	MeMgCl (3.0 eq)	THF	0.5	87% (**6a** only)
11	MeMgCl (3.3 eq)	THF	0.5	95% (**6a** only)

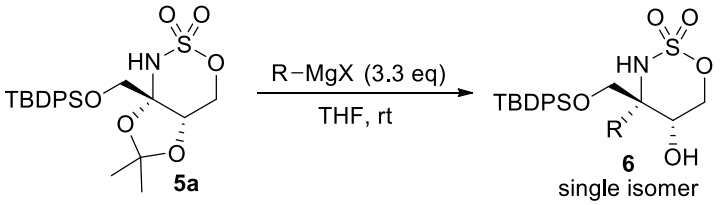
A plausible mechanism of the methylation of **5a** with MeMgCl is shown in Scheme 3. The deprotonation of acidic N–H proton in **5a** by the first MeMgCl would produce a ketimine intermediate **A** and acetone, which would react with the second MeMgCl to produce a tertiary alcohol.[8] After the third MeMgCl coordinates with the C3 oxygen atom in **A**, an intramolecular axial attack of MeMgCl to ketimine would proceed, and after quenching, it would provide product **6a** as a single isomer. Thus, it is necessary to use 3 eq of the Grignard reagent to complete the reaction.

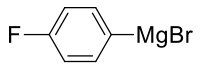
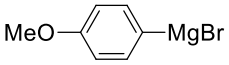
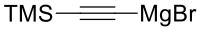


Scheme 3. Plausible mechanism of stereoselective methylation of **5a** using MeMgCl

The scope of the reaction with respect to the Grignard reagent was investigated with an optimal set of reaction conditions (Table 3). The reaction of **5a** with ethyl- and butylmagnesium halides as sp^3 nucleophiles afforded the corresponding alkylated products **6b** and **6c** as single isomers in 84% and 91% yields, respectively (entries 1 and 2). The use of isopropylmagnesium chloride resulted in the low yield of **6d** (19%, entry 3), probably because of steric hindrance. Next, the reaction with sp^2 and sp nucleophiles was examined. Further, aryl Grignard reagents were effective and provided arylated products **6e**–**g** in 75%–97% yields (entries 4–6). Although the alkenylation of **5a** with vinylmagnesium bromide in the presence of $ZnCl_2$ as a Lewis acid was already reported,[4,5] the reaction without any Lewis acid proceeded smoothly to furnish vinylated product **6h** in 93% yield (entry 7). Alkynylation with trimethylsilylethynylmagnesium bromide also proceeded without Lewis acid and provided **6i** in 94% yield (entry 8). All above products were obtained as single isomers. In contrast, the reaction with benzyl and allyl Grignard reagents gave a mixture of diastereomers (entries 9 and 10). While the reason for the low diastereoselectivity is currently unclear, benzyl and allyl Grignard reagents afforded the corresponding products **6j** + **6j'** and **6k** + **6k'** in 90% and 73% yields, respectively.

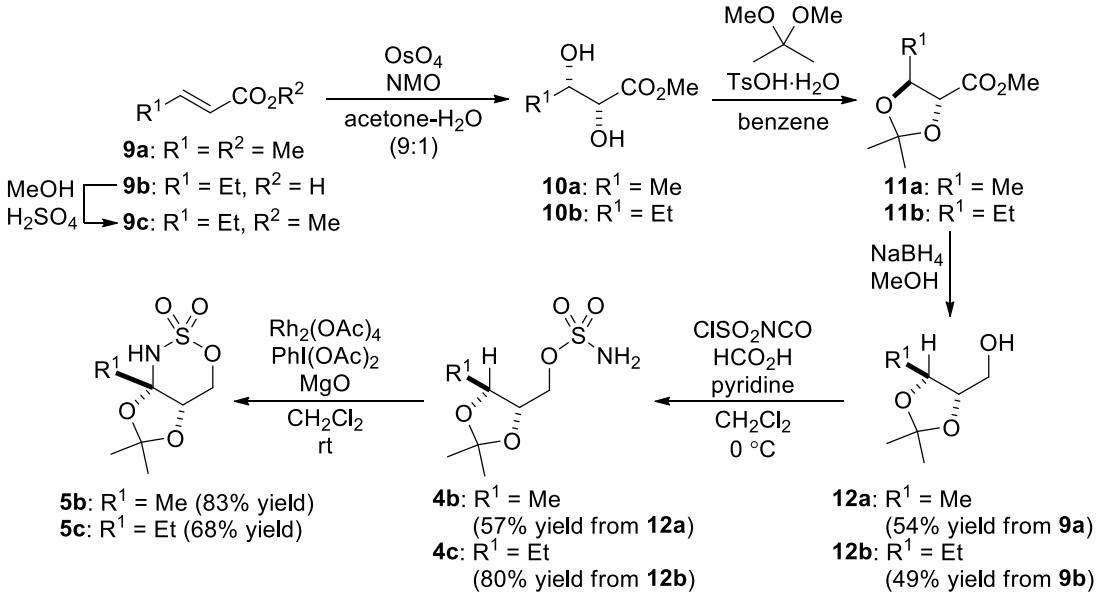
Table 3. Stereoselective alkylation of oxathiazinane *N*,*O*-ketals **5a** with various Grignard reagents



entry	R-MgX	time (h)	product	yield (%)
1	EtMgBr	1	**6b**	84
2	BuMgCl	0.5	**6c**	91
3	^{i}PrMgCl	1.5	**6d**	19
4	PhMgBr	0.5	**6e**	85
5		1.5	**6f**	75
6		0.5	**6g**	97
7	vinyl-MgBr	1	**6h**	93
8[a]		1	**6i**	94
9	BnMgCl	1	**6j** + **6j'**[b]	90[b]
10	allyl-MgBr	1	**6k** + **6k'**[c]	73[c]

[a] 6.0 eq. of Grignard reagent was used.
[b] A mixture of **6j** and **6j'** was obtained (**6j**:**6j'** = 1.6:1).
[c] A mixture of **6k** and **6k'** was obtained (**6k**:**6k'** = 1:1.5).

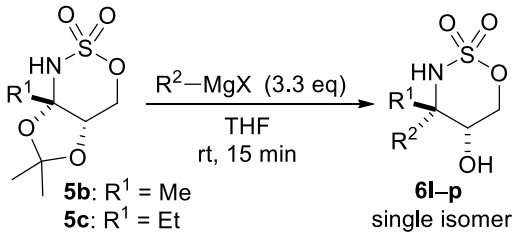
To investigate the scope of oxathiazinane *N*,*O*-ketal **5**, racemic methyl- and ethyl-substituted substrates **5b** and **5c** were synthesized (Scheme 4). The osmium-catalyzed dihydroxylation of methyl crotonate (**9a**) followed by the protection of the resulting diol **10a** as an acetonide and the subsequent reduction of ester **11a** with sodium borohydride furnished primary alcohol **12a** in 54% yield from **9a**. The reaction of **12a** with chlorosulfonyl isocyanate, formic acid, and pyridine afforded sulfamate ester **4b** in 57% yield. C–H amination of **4b** with phenyliodine(III) diacetate and magnesium oxide in the presence of a catalytic amount of dirhodium(II) tetraacetate provided oxathiazinane *N*,*O*-ketal **5b** in 83% yield. The synthesis of ethyl-substituted *N*,*O*-ketal **5c** from methyl *trans*-2-pentenoate (**9c**), which was prepared from *trans*-2-pentenoic acid (**9b**), could be achieved by the same procedure used for the preparation of **5b**.



Scheme 4. Preparation of oxathiazinane *N*,*O*-ketals **5b** and **5c**

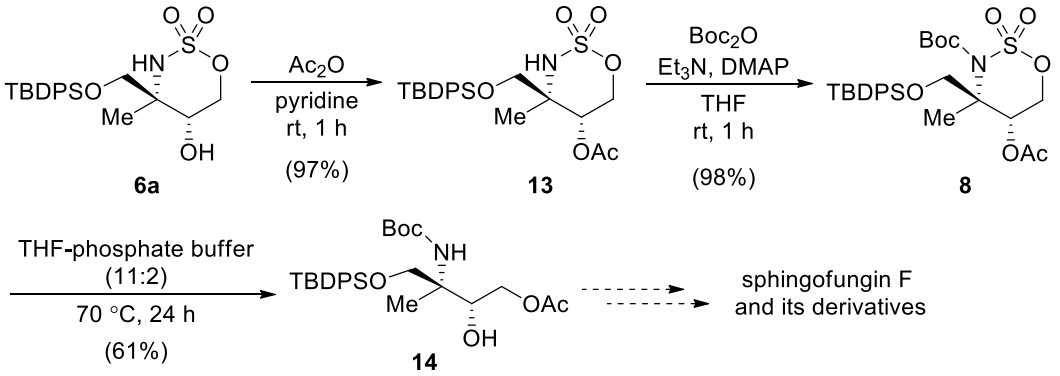
The alkylation of the *N*,*O*-ketals **5b** and **5c** with various Grignard reagents was then investigated (Table 4). The reaction of methyl-substituted compound **5b** (R^1 = Me) with ethylmagnesium bromide proceeded smoothly to afford an ethylated product **6l** in 84% yield (entry 1). As a result, a perfect stereoselectivity was obtained even by using the substrate possessing a small substituent R^1. The use of butylmagnesium chloride in the reaction of **5b** provided **6m** in 95% yield (entry 2). Similar to the previous example (Table 3, entry 3), the use of isopropylmagnesium chloride resulted in the low yield of **6n** (39%, entry 3). The reaction of an ethyl-substituted compound **5c** (R^1 = Et) with methyl- and butylmagnesium chlorides furnished products **6o** and **6p** in 84% and 91% yields, respectively (entries 4 and 5).

Table 4. Stereoselective alkylation of oxathiazinane *N*,*O*-ketals **5b** and **5c** with Grignard reagents



entry	substrate	R^2-MgX	product	R^1	R^2	yield (%)
1	**5b**	EtMgBr	**6l**	Me	Et	84
2	**5b**	BuMgCl	**6m**	Me	Bu	95
3	**5b**	^{i}PrMgCl	**6n**	Me	^{i}Pr	39
4	**5c**	MeMgCl	**6o**	Et	Me	84
5	**5c**	BuMgCl	**6p**	Et	Bu	91

Finally, the conversion of the obtained product **6a** into an α-amino alcohol derivative **14** according to myriocin synthesis was investigated (Scheme 5).[4,5] The acetylation of the hydroxy group in **6a** followed by Boc protection of the amine in **13** afforded fully protected oxathiazinane **8**. The reaction of **8** in THF–phosphate buffer (11:2) at 70 °C led to ring opening and a 1,2-acetyl group shift to provide secondary alcohol **14**, which would be a potential synthetic intermediate for sphingofungin F and its derivatives.[4,5]



Scheme 5. Conversion of **6a** into an α-amino alcohol derivative **14**

In conclusion, a stereoselective construction of aza-quaternary carbon centers employing alkylation of oxathiazinane *N*,*O*-ketals prepared by Rh(II)-catalyzed C–H amination of sulfamates was developed. The addition of alkyl Grignard reagents into *N*,*O*-ketals in the absence of Lewis acid proceeded stereoselectively to provide the corresponding alkylated products with an aza-quaternary carbon center in high yields. The obtained product could be converted into α-amino alcohol derivatives, which would be a potential synthetic intermediate for sphingofungin F. The present method is expected to provide high

flexibility for analogue synthesis. The synthesis of sphingofungin F and its analogues is currently in progress.

EXPERIMENTAL

General. Melting points are uncorrected. IR spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer and absorbance bands are reported in wavenumber (cm^{-1}). ^1H NMR spectra were recorded on JEOL JNM-ECX400P (400 MHz) spectrometer. Chemical shifts are reported relative to internal standard (tetramethylsilane at δ_H 0.00 or $CDCl_3$ at δ_H 7.26). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, br = broad), coupling constant and integration. ^{13}C NMR spectra were recorded on JEOL JNM-ECX400P (100 MHz) spectrometer. The following internal reference was used ($CDCl_3$ at δ 77.0). All ^{13}C NMR spectra were determined with complete proton decoupling. High-resolution mass spectra were determined with JEOL JMS-AX505HAD instrument. Column chromatography was performed on Silica Gel 60 PF_{254} (Nacalai Tesque) and Kanto silica gel 60 N (63–210 mesh) under pressure. Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates. Visualization was accomplished with UV light and phosphomolybdic acid stain solution followed by heating.

Unless otherwise noted, reagents were obtained from commercial suppliers and used without further purification. Dehydrated THF, toluene, CH_2Cl_2, Et_2O, benzene, MeOH, and pyridine were purchased from Kanto Chemical Co., Inc. and FUJIFILM Wako Pure Chemical Corporation. (4*S*,5*S*)-4-(*tert*-Butyldiphenylsilyloxy)methyl-(2,2-dimethyl-1,3-dioxolo)[4,5-*d*][1,2,3]oxathiazinane 2,2-dioxide (**5a**) was prepared according to our reported procedure.[4,5] The spectral data of (4*R*,5*R*)-4-(*tert*-butyl-diphenylsilyloxy)methyl-5-hydroxy-4-vinyl-1,2,3-oxathiazinane 2,2-dioxide (**6h**) and (4*R*,5*R*)-4-(*tert*-butyldiphenylsilyloxy)methyl-5-hydroxy-4-[2-(trimethylsilyl)ethynyl]-1,2,3-oxathiazinane 2,2-dioxide (**6i**) were reported in our previous literatures.[4,5]

Determination of stereochemistries of 6a and 6a': (4*R*,5*R*)- and (4*S*,5*R*)-4-[(*tert*-Butyldiphenylsilyloxy)-methyl]-3-(1,1-dimethylethoxycarbonyl)-4-methyl-5-hydroxy-1,2,3-oxathiazinane 2,2-dioxides (8) and (8')

Me_3Al (0.18 mL, 0.25 mmol, 1.4 M in hexane) was added to a solution of **5a** (100 mg, 0.21 mmol) in toluene (1.1 mL) at 0 °C. After stirring at this temperature for 5 min, MeLi (0.17 mL, 0.52 mmol, 3.1 M in dimethoxyethane) was added to the reaction mixture. After stirring at room temperature for 0.5 h, the reaction was quenched with saturated aqueous potassium sodium tartrate (10 mL) and the whole mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue

was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide an inseparable mixture of diastereomers **6a** (79 mg, 86%, dr = 1.2:1) as a white solid. The spectral data of **6a** were described below.

Acetic anhydride (2.1 mL, 22.2 mmol) was added to a solution of **6a** (300 mg, 0.69 mmol) in pyridine (2.1 mL) at room temperature. After stirring for 1.5 h, the solvent was removed in vacuo. The resulting residue was diluted with EtOAc (15 mL) and washed with water (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 15% EtOAc in hexane) to provide an inseparable mixture of diastereomers (302 mg, 92%) as a white solid.

Boc_2O (0.29 mL, 1.46 mmol), Et_3N (0.31 mL, 2.22 mmol), and DMAP (16 mg, 0.13 μmol) were added to a solution of the acetate (302 mg, 0.63 mmol) in THF (6.3 mL) at room temperature. After stirring for 1 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the whole mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 8% EtOAc in hexane) to provide **8** (173 mg, 47%) as a white solid and **8'** (147 mg, 40%) as a white solid. **8**: mp 117–118 °C; $[\alpha]_D^{25}$ +22.0 (*c* 1.0, $CHCl_3$); IR (KBr) cm^{-1}: 1733, 1473, 1428, 1391, 1303, 1225, 1187, 1149, 1115; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.63–7.60 (m, 4H), 7.46–7.36 (m, 6H), 5.51 (t, *J* = 6.6 Hz, 1H), 4.87 (dd, *J* = 11.4, 6.9 Hz, 1H), 4.38 (d, *J* = 10.5 Hz, 1H), 4.12 (dd, *J* = 11.4, 6.9 Hz, 1H), 3.61 (d, *J* = 10.5 Hz, 1H), 1.77 (s, 3H), 1.50 (s, 3H), 1.52 (s, 9H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.4, 149.7, 135.9, 135.7, 132.5, 130.0, 127.8, 127.7, 85.0, 70.4, 68.4, 65.8, 62.5, 27.8, 26.8, 20.3, 19.2, 17.2; HRMS (FAB) *m/z* calcd for $C_{28}H_{40}O_8NSSi$ $(M + H)^+$ 578.2244, found 578.2264. **8'**: mp 117–118 °C; $[\alpha]_D^{21}$ +12.3 (*c* 0.07, $CHCl_3$); IR (KBr) cm^{-1}: 1739, 1472, 1391, 1232, 1105; ^1H-NMR (400 MHz, $CDCl_3$) δ: 7.63–7.59 (m, 4H), 7.47–7.26 (m, 6H), 5.29 (dd, *J* = 3.2, 2.4 Hz, 1H), 4.94 (ddd, *J* = 6.0, 3.2, 1.2 Hz, 1H), 4.61 (dd, *J* = 10.0, 2.4 Hz, 1H), 4.32 (d, *J* = 7.4 Hz, 1H), 3.98 (d, *J* = 7.4 Hz, 1H), 2.01 (s, 3H), 1.65 (s, 3H), 1.42 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1, 150.3, 135.7, 135.6, 132.6, 132.5, 130.02, 129.98, 127.8, 85.6, 71.3, 68.8, 68.4, 65.7, 27.6, 26.8, 20.8, 19.8, 19.1; HRMS (FAB) *m/z* calcd for $C_{28}H_{40}O_8NSSi$ $(M + H)^+$ 578.2244, found 578.2294.

Typical procedure for alkylation of oxathiazinane *N,O*-ketals 5 with Grignard reagents: (4*R*,5*R*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-4-methyl-5-hydroxy-1,2,3-oxathiazinane 2,2-dioxide (6a)

MeMgCl (0.23 mL, 0.69 mmol, 3.0 M in THF) was added to a solution of **5a** (100 mg, 0.21 mmol) in THF (1.2 mL) at 0 °C. After stirring at room temperature for 0.5 h, the reaction was cooled to 0 °C and quenched with saturated aqueous NH_4Cl (10 mL). The whole mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over

anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 20% EtOAc in hexane) to provide **6a** (87 mg, 95%) as a white solid: mp 109–111 °C; $[\alpha]_D^{22}$ −11.5 (*c* 1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3568, 3258, 1471, 1427 1349, 1186, 1111, 1082; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.68–7.60 (m, 4H), 7.50–7.41 (m, 6H), 5.00 (s, 1H), 4.43 (dd, *J* = 11.6, 10.4 Hz, 1H), 4.25 (dd, *J* = 11.6, 4.4 Hz, 1H), 4.11 (dd, *J* = 10.4, 7.2 Hz, 1H), 3.69 (d, *J* = 10.4 Hz, 1H), 3.51 (d, *J* = 10.4 Hz, 1H), 1.68 (dd, *J* = 10.4, 7.2 Hz, 1H), 1.27 (s, 3H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.6, 135.5, 132.3, 131.9, 130.5, 130.4, 128.2, 128.1, 69.3, 66.2, 62.7, 61.5, 27.0, 19.2, 15.0; HRMS (FAB) *m/z* calcd for $C_{21}H_{30}O_5NSSi$ $(M + H)^+$ 436.1614, found 436.1637.

(4*R*,5*R*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-4-ethyl-5-hydroxy-1,2,3-oxathiazinane 2,2-dioxide (6b)

According to the typical procedure for the alkylation of oxathiazinane *N*,*O*-ketals with Grignard reagents, **6b** was prepared from **5a** (100 mg, 0.21 mmol) with EtMgBr (0.23 mL, 0.69 mmol, 3.0 M in Et_2O) for 1 h. The crude product was purified by column chromatography (silica gel, 20% EtOAc in hexane) to provide **6b** (79 mg, 84%) as a colorless amorphous: $[\alpha]_D^{24}$ −11.6 (*c* 1.0, $CHCl_3$); IR (neat) cm^{-1}: 3532, 3300, 1462, 1427, 1362, 1191, 1113, 1089; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.68–7.60 (m, 4H), 7.49–7.42 (m, 6H), 4.74 (s, 1H), 4.45 (dd, *J* = 11.8, 9.8 Hz, 1H), 4.22 (dd, *J* = 11.8, 4.4 Hz, 1H), 4.07 (m, 1H), 3.68 (dd, *J* = 18.0, 10.8 Hz, 2H), 2.05 (m, 1H), 1.42 (m, 1H), 1.33 (d, *J* = 6.4 Hz, 1H), 1.11 (s, 9H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.6, 135.5, 132.2, 132.0, 130.4, 130.3, 128.10, 128.07, 69.7, 64.0, 63.3, 63.0, 60.5, 26.9, 21.0, 20.5, 19.2, 14.1, 6.8; HRMS (FAB) *m/z* calcd for $C_{22}H_{31}O_5NSSi$ $(M)^+$ 449.1692, found 449.1711.

(4*R*,5*R*)-4-Butyl-4-[(*tert*-butyldiphenylsilyloxy)methyl]-5-hydroxy-1,2,3-oxathiazinane 2,2-dioxide (6c)

According to the typical procedure for the alkylation of oxathiazinane *N*,*O*-ketals with Grignard reagents, **6c** was prepared from **5a** (100 mg, 0.21 mmol) with EtMgBr (0.345 mL, 0.69 mmol, 2.0 M in THF) for 0.5 h. The crude product was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **6c** (88 mg, 91%) as a colorless amorphous: $[\alpha]_D^{24}$ −7.7 (*c* 1.0, $CHCl_3$); IR (neat) cm^{-1}: 3531, 3299, 1470, 1427, 1362, 1190; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.68–7.65 (m, 2H), 7.62–7.60 (m, 2H), 7.51–7.42 (m, 6H), 4.73 (s, 1H), 4.46 (dd, *J* = 11.8, 9.4 Hz, 1H), 4.22 (dd, *J* = 11.8, 4.2 Hz, 1H), 4.05 (m, 1H), 3.69 (dd, *J* = 20.0, 10.8 Hz, 2H), 1.97 (m, 1H), 1.55 (s, 2H), 1.41–1.24 (m, 4H), 1.11 (s, 9H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.6, 135.5, 132.2, 132.0, 130.4, 130.3, 128.13, 128.10, 69.6, 63.9, 63.5, 63.4, 60.5, 27.3, 27.0, 24.3, 23.0, 19.2, 14.2, 13.9; HRMS (FAB) *m/z* calcd for $C_{24}H_{36}O_5NSSi$ $(M + H)^+$ 478.2083, found 478.2102.

(4*R*,5*R*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-4-(propan-2-yl)-5-hydroxy-1,2,3-oxathiazinane 2,2-dioxide (6d)

According to the typical procedure for the alkylation of oxathiazinane *N*,*O*-ketals with Grignard reagents, **6d** was prepared from **5a** (100 mg, 0.21 mmol) with ^{i}PrMgCl (0.345 mL, 0.69 mmol, 2.0 M in THF) for 1.5 h. The crude product was purified by column chromatography (silica gel, 20% EtOAc in hexane) to provide **6d** (18 mg, 19%) as a white solid: mp 118–119 °C; $[\alpha]_D^{23}$ +60.2 (*c* 0.5, $CHCl_3$); IR (KBr) cm^{-1}: 3526, 3271, 2961, 1473, 1427, 1363, 1189, 1113, 1090; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 6.8 Hz, 4H), 7.50–7.41 (m, 6H), 4.53 (s, 1H), 4.34 (dd, *J* = 12.4, 5.0 Hz, 1H), 4.23 (dd, *J* = 12.4, 5.0 Hz, 1H), 4.07 (m, 1H), 4.02 (d, *J* = 11.2 Hz, 1H), 3.91 (d, *J* = 11.2 Hz, 1H), 2.20 (m, 1H), 1.94 (m, 1H), 1.10 (s, 12H), 1.00 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.7, 132.2, 132.1, 130.35, 130.27, 128.1, 128.0, 72.3, 66.8, 63.2, 61.0, 32.2, 27.0, 19.1, 18.3, 16.9; HRMS (FAB) *m/z* calcd for $C_{23}H_{34}O_5NSSi$ $(M + H)^+$ 464.1927, found 464.1920.

(4*R*,5*R*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-4-phenyl-5-hydroxy-1,2,3-oxathiazinane 2,2-dioxide (6e)

According to the typical procedure for the alkylation of oxathiazinane *N*,*O*-ketals with Grignard reagents, **6e** was prepared from **5a** (100 mg, 0.21 mmol) with PhMgBr (0.69 mL, 0.69 mmol, 1.0 M in THF) for 0.5 h. The crude product was purified by column chromatography (silica gel, 20% EtOAc in hexane) to provide **6e** (89 mg, 85%) as a white solid: mp 160–161 °C; $[\alpha]_D^{22}$ +1.3 (*c* 1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3556, 3510, 1720, 1449, 1470, 1449, 1436, 1345, 1181, 1112, 1081; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, *J* = 5.2 Hz, 2H), 7.47–7.31 (m, 13H), 5.07 (s, 1H), 4.62–4.57 (m, 2H), 4.46 (td, *J* = 4.8, 2.2 Hz, 1H), 3.90 (d, *J* = 10.8 Hz, 1H), 4.16 (d, *J* = 10.8 Hz, 1H), 1.83 (d, *J* = 4.8 Hz, 1H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.5, 135.4, 132.09, 132.05, 130.2, 130.1, 128.7, 128.5, 128.0, 127.9, 126.8, 71.4, 68.5, 67.0, 63.4, 26.8, 19.1; HRMS (FAB) *m/z* calcd for $C_{26}H_{33}O_5NSSi$ $(M + 2H)^{2+}$ 499.1849, found 499.1942.

(4*R*,5*R*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-4-(4-fluorophenyl)-5-hydroxy-1,2,3-oxathiazinane 2,2-dioxide (6f)

According to the typical procedure for the alkylation of oxathiazinane *N*,*O*-ketals with Grignard reagents, **6f** was prepared from **5a** (100 mg, 0.21 mmol) with 4-fluorophenylmagnesium bromide (0.69 mL, 0.69 mmol, 1.0 M in THF) for 1.5 h. The crude product was purified by column chromatography (silica gel, 20% EtOAc in hexane) to provide **6f** (83 mg, 75%) as a white solid: mp 141–143 °C; $[\alpha]_D^{23}$ −6.7 (*c* 1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3291, 3169, 1608, 1514, 1348, 1183, 1112, 1078; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (dd, *J* = 8.6, 5.0 Hz, 2H), 7.51–7.45 (m, 6H), 7.41–7.36 (m, 4H), 7.04 (t, *J* = 8.6 Hz, 2H), 5.12 (s, 1H), 4.57 (dd, *J* = 12.0, 7.4 Hz, 1H), 4.49–4.45 (m, 2H), 3.85 (d, *J* = 10.8 Hz, 1H), 4.00 (d, *J* = 10.8 Hz, 1H), 1.75 (d, *J* = 6.0 Hz, 1H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.48, 135.46, 132.7, 132.0,

131.9, 130.4, 129.3, 129.2, 128.1, 115.5, 115.3, 71.0, 67.7, 67.2, 64.1, 26.9, 19.2; HRMS (FAB) *m/z* calcd for $C_{26}H_{31}O_5SiFSN$ $(M + H)^+$ 516.1676, found 516.1692.

(4*R*,5*R*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-4-(4-methoxyphenyl)-5-hydroxy-1,2,3-oxathiazinane 2,2-dioxide (6g)

According to the typical procedure for the alkylation of oxathiazinane *N*,*O*-ketals with Grignard reagents, **6g** was prepared from **5a** (100 mg, 0.21 mmol) with 4-methoxyphenylmagnesium bromide (1.38 mL, 0.69 mmol, 0.5 M in THF) for 0.5 h. The crude product was purified by column chromatography (silica gel, 20% EtOAc in hexane) to provide **6g** (104 mg, 97%) as a pale yellow solid: mp 166–167 °C; $[\alpha]_D^{23}$ −6.7 (*c* 1.0, $CHCl_3$); IR (KBr) cm^{-1}: 3554, 3170, 2933, 1516, 1431, 1348, 1248, 1184, 1114; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.50–7.33 (m, 13H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.05 (s, 1H), 4.59 (dd, *J* = 11.9, 6.0 Hz, 1H), 4.51 (dd, *J* = 11.9, 2.3 Hz, 1H), 4.43 (dd, *J* = 6.0, 2.3 Hz, 1H), 4.09 (d, *J* = 10.5 Hz, 1H), 3.86 (d, *J* = 10.5 Hz, 1H), 3.82 (s, 3H), 1.67 (br s, 1H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.5, 135.50, 135.48, 132.2, 132.1, 130.21, 130.17, 129.0, 128.3, 127.98, 127.95, 114.0, 99.9, 71.2, 68.0, 67.1, 63.7, 55.3, 26.9, 19.2; HRMS (FAB) *m/z* calcd for $C_{27}H_{34}O_6SiNS$ $(M + H)^+$ 528.1876, found 528.1910.

(4*R*,5*R*)- and (4*S*,5*R*)-4-Benzyl-4-[(*tert*-butyldiphenylsilyloxy)methyl]-5-hydroxy-1,2,3-oxathiazinane 2,2-dioxides (6j) and (6j')

According to the typical procedure for the alkylation of oxathiazinane *N*,*O*-ketals with Grignard reagents, **6j** and **6j'** were prepared from **5a** (100 mg, 0.21 mmol) with benzylmagnesium chloride (0.69 mL, 0.69 mmol, 1.0 M in Et_2O) for 1 h. The crude product was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **6j** (59 mg, 56%) as a colorless oil and **6j'** (36 mg, 34%) as a colorless oil. **6j**: $[\alpha]_D^{22}$ −19.0 (*c* 0.8, $CHCl_3$); IR (neat) cm^{-1}: 3528, 3295, 2931, 1589, 1471, 1455, 1362, 1188, 1114, 1085; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 6.4 Hz, 2H), 7.52–7.35 (m, 8H), 7.25–7.23 (m, 5H), 4.70 (s, 1H), 4.47 (dd, *J* = 12.0, 8.8 Hz, 1H), 4.16 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.06 (dd, *J* = 8.8, 4.0 Hz, 1H), 3.63 (d, *J* = 10.8 Hz, 1H), 3.47 (d, *J* = 10.8 Hz, 1H), 3.47 (d, *J* = 15.0 Hz, 1H), 2.82 (d, *J* = 15.0 Hz, 1H), 1.72 (br s, 1H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.6, 135.5, 134.4, 132.3, 131.9, 131.1, 130.4, 130.3, 128.6, 128.21, 128.16, 128.14, 128.12, 128.06, 127.0, 126.9, 70.0, 64.2, 63.5, 63.4, 32.7, 27.0, 19.2; HRMS (FAB) *m/z* calcd for $C_{27}H_{34}O_5SiNS$ $(M + H)^+$ 512.1927, found 512.1931. **6j'**: $[\alpha]_D^{23}$ +14.0 (*c* 0.05, $CHCl_3$); IR (neat) cm^{-1}: 3446, 3315, 2931, 1589, 1427, 1361, 1189, 1114, 1090; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.58–7.56 (m, 4H), 7.49–7.44 (m, 2H), 7.41–7.36 (m, 4H), 7.25–7.23 (m, 5H), 4.91 (d, *J* = 13.8 Hz, 1H), 4.77 (d, *J* = 13.8 Hz, 1H), 4.45 (s, 1H), 3.82 (d, *J* = 10.4 Hz, 1H), 3.77 (t, *J* = 4.0 Hz, 1H), 3.62 (d, *J* = 13.8 Hz, 1H), 3.59 (d, *J* = 10.4 Hz, 1H), 3.47 (d, *J* = 5.2 Hz, 1H), 2.77 (d, *J* = 13.8 Hz, 1H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.51, 135.50, 133.9, 130.8, 130.5, 130.4, 128.4, 128.2, 128.1, 127.3, 72.6, 66.1, 65.5, 63.6, 37.6, 26.9, 19.1; HRMS (FAB) *m/z* calcd for $C_{27}H_{34}O_5SiNS$ $(M + H)^+$ 512.1927, found 512.1925.

(4*R*,5*R*)- and (4*S*,5*R*)-4-Allyl-4-[(*tert*-butyldiphenylsilyloxy)methyl]-5-hydroxy-1,2,3-oxathiazinane 2,2-dioxides (6k) and (6k')

According to the typical procedure for the alkylation of oxathiazinane *N*,*O*-ketals with Grignard reagents, **6k** and **6k'** were prepared from **5a** (100 mg, 0.21 mmol) with allylmagnesium bromide (0.69 mL, 0.69 mmol, 1.0 M in THF) for 1 h. The crude product was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **6k** (28 mg, 29%) as a colorless oil and **6k'** (43 mg, 44%) as a colorless oil. **6k**: $[\alpha]_D^{20}$ −30.5 (*c* 0.2, $CHCl_3$); IR (neat) cm^{-1}: 3523, 3298, 1471, 1427, 1189, 1113; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.63 (dd, *J* = 23.6, 6.8 Hz, 2H), 7.50–7.44 (m, 6H), 5.92–5.81 (m, 1H), 5.10 (d, *J* = 17.6 Hz, 1H), 5.07 (d, *J* = 12.0 Hz, 1H), 4.80 (s, 1H), 4.45 (dd, *J* = 12.0, 9.6 Hz, 1H), 4.23 (dd, *J* = 12.0, 4.4 Hz, 1H), 4.06–4.01 (m, 1H), 3.72 (d, *J* = 10.6 Hz, 1H), 3.66 (d, *J* = 10.6 Hz, 1H), 2.86 (dd, *J* = 14.8, 5.6 Hz, 1H), 2.18 (dd, *J* = 14.8, 9.0 Hz, 1H), 1.45 (br s, 1H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.6, 135.5, 132.3, 132.0, 131.8, 130.5, 130.4, 128.2, 128.1, 119.6, 69.7, 63.6, 63.2, 63.1, 32.3, 27.0, 19.2; HRMS (FAB) *m/z* calcd for $C_{23}H_{32}O_5NSSi$ $(M + H)^+$ 462.1770, found 462.1791. **6k'**: $[\alpha]_D^{23}$ +40.0 (*c* 0.05, $CHCl_3$); IR (neat) cm^{-1}: 3544, 3289, 2931, 1589, 1427, 1362, 1190, 1114, 1028; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.64–7.62 (m, 4H), 7.51–7.41 (m, 6H), 5.80–5.70 (m, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 5.03 (d, *J* = 17.2 Hz, 1H), 4.86 (d, *J* = 12.4 Hz, 1H), 4.69 (s, 1H), 4.49 (dd, *J* = 12.4, 3.2 Hz, 1H), 3.81 (d, *J* = 10.4 Hz, 1H), 3.73 (d, *J* = 10.4 Hz, 1H), 3.64 (d, *J* = 12.4 Hz, 1H), 2.87 (dd, *J* = 14.4, 5.2 Hz, 1H), 2.30 (dd, *J* = 14.4, 8.8 Hz, 1H), 1.40 (d, *J* = 8.8 Hz, 1H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.52, 135.50, 131.3, 131.1, 131.0, 130.6, 130.5, 128.23, 128.15, 120.3, 72.9, 66.2, 63.0, 36.5, 26.8, 19.1; HRMS (FAB) *m/z* calcd for $C_{23}H_{32}O_5NSSi$ $(M + H)^+$ 462.1770, found 462.1729.

Preparation of oxathiazinane *N*,*O*-ketals 5b and 5c (Scheme 4)

***rac*-(4*S*,5*S*)-4-Hydroxymethyl-2,2,5-trimethyl-1,3-dioxolane (12a)**

OsO_4 (0.95 mL, 0.15 mmol, 4% in H_2O) and 4-methylmorpholine *N*-oxide (4.2 mL, 18.0 mmol, 50% in H_2O) were added to a solution of methyl crotonate (**9a**) (1.50 g, 15.0 mmol) in acetone–H_2O (9:1, 72 mL) at room temperature. After stirring for 15 h, the reaction was quenched with 10% aqueous $NaHSO_3$ (20 mL) and the whole mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (10 mL). Then, the aqueous layer was saturated with NaCl and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 30% EtOAc in hexane) to provide the corresponding diol with residual solvent because of a low boiling point of the product.

2,2-Dimethoxypropane (1.8 mL, 14.6 mmol) and $TsOH \cdot H_2O$ (6.0 mg, 0.32 mmol) were added to a solution of the crude product in benzene (4.9 mL). The reaction mixture was stirred at 85 °C for 1 h and then at reflux for 10 min. After cooling to room temperature, K_2CO_3 (20 mg) was added to the reaction mixture. The mixture was diluted with EtOAc (30 mL) and washed with 5% aqueous $NaHCO_3$ (15 mL),

water (15 mL), and brine (15 mL), and dried over anhydrous Na_2SO_4. Filtrate was concentrated in vacuo to provide the crude product (1.88 g), which was used in the next step without further purification.

$NaBH_4$ (815 mg, 21.6 mmol) was added to a solution of the crude product in MeOH (27 mL) at 0 °C. After stirring at room temperature for 1.5 h, the solvent was removed in vacuo. The resulting residue was diluted with EtOAc (30 mL) and washed with water (15 mL), and brine (15 mL), and dried over anhydrous Na_2SO_4. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 30% EtOAc in hexane) to provide **12a** (1.18 g, 54% from **9a**) as a colorless oil: IR (neat) cm^{-1}: 3445, 2985, 2934, 2876, 1456, 1380, 1371, 1248, 1222, 1174, 1092, 1052, 990, 845; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.02 (m, 1H), 3.81 (m, 1H), 3.70–3.56 (m, 2H), 2.16 (br t, J = 4.6 Hz, 1H), 1.43 (s, 3H), 1.41 (s, 3H), 1.30 (d, J = 5.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 108.4, 82.7, 72.7, 61.4, 27.3, 26.9, 17.6; HRMS (FAB) *m/z* calcd for $C_7H_{15}O_3$ $(M+H)^+$ 147.1021, found 147.1056.

***rac*-(4*S*,5*S*)-2,2,5-Trimethyl-4-sulfamoyloxymethyl-1,3-dioxolane (4b)**

Formic acid (1.2 mL, 32.1 mmol) was added dropwise to neat chlorosulfonyl isocyanate (2.8 mL, 32.1 mmol) at 0 °C with rapid stirring. The resulting viscous suspension was stirred at 0 °C for 5 min. CH_2Cl_2 (20 mL) was added to the mixture and the solution was stirred at 0 °C for 20 min and then at room temperature for 7 h. The reaction mixture was cooled to 0 °C, and a solution of **12a** (1.18 g, 8.03 mmol) and pyridine (2.9 mL, 36.1 mmol) in CH_2Cl_2 (5 mL) was added via cannula. The reaction mixture was warmed to room temperature and stirred for 10 min. The reaction was quenched with EtOAc (20 mL) and H_2O (20 mL). The organic phase was collected and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 30% EtOAc in hexane) to provide **4b** (1.04 g, 57%) as a colorless oil: IR (neat) cm^{-1}: 3255, 1374, 1254, 1221, 1183, 1095, 993; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.09 (s, 2H), 4.29 (d, J = 4.4 Hz, 2H), 4.01–3.96 (m, 1H), 3.87–3.83 (m, 1H), 1.43 (d, J = 10.4 Hz, 6H), 1.35 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 109.5, 79.7, 73.4, 69.7, 27.2, 26.6, 17.7; HRMS (FAB) *m/z* calcd for $C_7H_{16}O_5NS$ $(M + H)^+$ 226.0749, found 226.0743.

***rac*-(4*S*,5*S*)-4-Methyl-(2,2-dimethyl-1,3-dioxolo)[4,5-*d*][1,2,3]oxathiazinane 2,2-dioxide (5b)**

$Rh_2(OAc)_4$ (60 mg, 0.14 mmol), $PhI(OAc)_2$ (1.61 g, 4.99 mmol) and MgO (421 mg, 10.4 mmol) were added to a solution of sulfamate **4b** (1.02 g, 4.54 mmol) in CH_2Cl_2 (28 mL). After stirring at room temperature for 1 h, the reaction mixture was filtered through a pad of Celite. The filter cake was rinsed with CH_2Cl_2, and the combined filtrates were concentrated in vacuo. The residue was purified by column chromatography (silica gel, 30% EtOAc in hexane) to provide **5b** (846 mg, 83%) as a white solid: mp 99–102 °C; IR (KBr) cm^{-1}: 3317, 1724, 1384, 1199, 1120; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.74 (t, J = 1.4 Hz,

2H), 4.26 (s, 1H), 3.83 (t, *J* = 1.4 Hz, 1H), 1.74 (s, 3H), 1.54 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.5, 92.9, 73.2, 67.8, 28.0, 25.7, 23.5; HRMS (FAB) *m/z* calcd for $C_7H_{14}O_5NS$ $(M + H)^+$ 224.0593, found 224.0593.

***rac*-(4*S*,5*S*)-2,2-Dimethyl-4-ethyl-5-hydroxymethyl-1,3-dioxolane (12b)**

H_2SO_4 (4.5 mL) was added to a solution of *trans*-2-pentenoic acid (**9b**) (1.50 g, 15.0 mmol) in MeOH (30 mL) at room temperature. The reaction mixture was stirred at reflux for 45 min. After cooling to room temperature, water (105 mL) was added to the reaction mixture. The mixture was extracted with Et_2O (2 x 30 mL) and washed with 5% aqueous $NaHCO_3$ (30 mL), water (30 mL), and brine (30 mL), and dried over anhydrous Na_2SO_4. Filtrate was concentrated in vacuo to provide the crude product **9c** (3.29 g), which was used in the next step without further purification.

Alcohol **12b** was prepared from the crude ester **9c** by the same procedure used for the preparation of **12a** from **9a**. **12b** (1.17 g, 49% from **9b**) was obtained as a colorless oil: IR (neat) cm^{-1}: 3447, 2985, 2936, 2879, 1459, 1379, 1371, 1246, 1219, 1171, 1106, 1066, 1001, 855; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.87–3.72 (m, 3H), 3.60 (m, 1H), 2.14 (br s, 1H), 1.66–1.57 (m, 2H), 1.42 (s, 6H), 1.04–0.97 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 108.6, 81.2, 78.0, 62.2, 27.3, 27.0, 25.9, 10.1; HRMS (FAB) *m/z* calcd for $C_8H_{17}O_3$ $(M+H)^+$ 161.1178, found 161.1211.

***rac*-(4*S*,5*S*)-2,2-Dimethyl-4-ethyl-5-sulfamoyloxymethyl-1,3-dioxolane (4c)**

According to the procedure for the preparation of sulfamate **4b** from alcohol **12a**, **4c** was prepared from **12b** (770 mg, 4.81 mmol). **4c** (919 mg, 80%) was obtained as a white solid: mp 66–67 °C; IR (KBr) cm^{-1}: 3386, 3275, 1373, 1250, 1179, 1093, 996; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.92 (s, 2H), 4.34–4.26 (m, 2H), 3.97–3.93 (m, 1H), 1.66 (quint, *J* = 7.3 Hz, 2H), 1.42 (d, *J* = 3.2 Hz, 6H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 109.7, 78.6, 78.4, 70.7, 27.3, 26.8, 25.9, 9.9; HRMS (FAB) *m/z* calcd for $C_8H_{18}O_5NS$ $(M + H)^+$ 240.0906, found 240.0912.

***rac*-(4*S*,5*S*)-4-Ethyl-(2,2-dimethyl-1,3-dioxolo)[4,5-*d*][1,2,3]oxathiazinane 2,2-dioxide (5c)**

According to the procedure for the Rh(II)-catalyzed C–H amination of sulfamate **4b**, **5c** was prepared from **4c** (900 mg, 3.76 mmol). **5c** (609 mg, 68%) was obtained as a white solid: mp 100–102 °C; IR (KBr) cm^{-1}: 3188, 1713, 1340, 1210, 1174, 1111; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.72 (d, *J* = 1.6 Hz, 2H), 4.24 (s, 1H), 3.86 (t, *J* = 1.6 Hz, 1H), 2.22 (sext, *J* = 7.6 Hz, 1H), 1.80 (sextd, *J* = 7.6, 0.8 Hz, 1H), 1.58 (s, 3H), 1.40 (s, 3H), 1.08 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.4, 95.3, 72.1, 67.9, 28.8, 28.0, 25.8, 7.3; HRMS (FAB) *m/z* calcd for $C_8H_{16}O_5NS$ $(M + H)^+$ 238.0749, found 238.0750.

***rac*-(4*S*,5*R*)-4-Ethyl-4-methyl-5-hydroxy-1,2,3-oxathiazinane 2,2-dioxide (6l)**

According to the typical procedure for the alkylation of oxathiazinane *N*,*O*-ketals with Grignard reagents, **6l** was prepared from **5b** (48 mg, 0.23 mmol) with EtMgBr (0.25 mL, 0.75 mmol, 3.0 M in Et_2O) for 15 min. The crude product was purified by column chromatography (silica gel, 20% EtOAc in hexane) to

provide **6l** (40 mg, 84%) as a white solid: mp 78–79 °C; IR (KBr) cm^{-1}: 3454, 3207, 1433, 1352, 1170, 1140, 1031; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.94 (dd, *J* = 12.4, 1.2 Hz, 1H), 4.74 (s, 1H), 4.49 (dd, *J* = 12.4, 3.2 Hz, 1H), 3.43 (s, 1H), 2.84 (br s, 1H), 1.66 (q, *J* = 7.3 Hz, 2H), 1.46 (s, 3H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.1, 65.8, 63.0, 30.9, 20.6, 7.0; HRMS (FAB) *m/z* calcd for $C_6H_{14}O_4NS$ $(M + H)^+$ 196.0644, found 196.0651.

***rac*-(4*S*,5*R*)-4-Butyl-4-methyl-5-hydroxy-1,2,3-oxathiazinane 2,2-dioxide (6m)**

According to the typical procedure for the alkylation of oxathiazinane *N*,*O*-ketals with Grignard reagents, **6m** was prepared from **5b** (49 mg, 0.23 mmol) with BuMgCl (0.38 mL, 0.76 mmol, 2.0 M in THF) for 15 min. The crude product was purified by column chromatography (silica gel, 20% EtOAc in hexane) to provide **6m** (46 mg, 95%) as a white solid: mp 69–70 °C; IR (KBr) cm^{-1}: 3480, 3202, 1444, 1353, 1186, 1142, 1090, 1035; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.94 (d, *J* = 12.8 Hz, 1H), 4.50 (s, 1H), 4.48 (dd, *J* = 12.8, 2.8 Hz, 1H), 3.42 (s, 1H), 2.84 (br s, 1H), 1.63–1.56 (m, 2H), 1.47 (s, 3H), 1.36–1.34 (m, 4H), 0.93 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.1, 66.1, 62.8, 37.9, 24.6, 22.9, 21.2, 13.9; HRMS (FAB) *m/z* calcd for $C_8H_{18}O_4NS$ $(M + H)^+$ 224.0957, found 224.0954.

***rac*-(4*S*,5*R*)-4-Methyl-4-(propan-2-yl)-5-hydroxy-1,2,3-oxathiazinane 2,2-dioxide (6n)**

According to the typical procedure for the alkylation of oxathiazinane *N*,*O*-ketals with Grignard reagents, **6n** was prepared from **5b** (50 mg, 0.24 mmol) with ^{i}PrMgCl (0.39 mL, 0.78 mmol, 2.0 M in THF) for 15 min. The crude product was purified by column chromatography (silica gel, 20% EtOAc in hexane) to provide **6n** (18 mg, 39%) as a white solid: mp 157–159 °C; IR (KBr) cm^{-1}: 3464, 3202, 1434, 1353, 1190, 1033; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.01 (d, *J* = 12.8 Hz, 1H), 4.46 (dd, *J* = 12.8, 2.3 Hz, 1H), 4.40 (s, 1H), 3.48 (s, 1H), 2.35 (br s, 1H), 2.05 (sext, *J* = 6.8 Hz, 1H), 1.34 (s, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.5, 64.9, 33.6, 16.4, 15.3, 14.7; HRMS (FAB) *m/z* calcd for $C_7H_{16}O_4NS$ $(M + H)^+$ 210.0800, found 210.0808.

***rac*-(4*R*,5*R*)-4-Ethyl-4-methyl-5-hydroxy-1,2,3-oxathiazinane 2,2-dioxide (6o)**

According to the typical procedure for the alkylation of oxathiazinane *N*,*O*-ketals with Grignard reagents, **6o** was prepared from **5c** (49 mg, 0.21 mmol) with MeMgCl (0.23 mL, 0.69 mmol, 3.0 M in THF) for 15 min. The crude product was purified by column chromatography (silica gel, 50% EtOAc in hexane) to provide **6o** (36 mg, 84%) as a white solid: mp 108–111 °C; IR (KBr) cm^{-1}: 3495, 3217, 1356, 1183, 1140, 1038; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.90 (dd, *J* = 12.4, 1.4 Hz, 1H), 4.47 (dd, *J* = 12.4, 3.6 Hz, 1H), 4.26 (s, 1H), 3.46–3.43 (m, 1H), 2.12–2.03 (m, 1H), 1.58–1.49 (m, 1H), 1.30 (s, 3H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 72.5, 66.8, 63.1, 29.1, 21.2, 7.4; HRMS (FAB) *m/z* calcd for $C_6H_{14}O_4NS$ $(M + H)^+$ 196.0644, found 196.0641.

***rac*-(4*S*,5*R*)-4-Butyl-4-ethyl-5-hydroxy-1,2,3-oxathiazinane 2,2-dioxide (6p)**

According to the typical procedure for the alkylation of oxathiazinane *N*,*O*-ketals with Grignard reagents, **6p** was prepared from **5c** (50 mg, 0.21 mmol) with BuMgCl (0.35 mL, 0.70 mmol, 2.0 M in THF) for 15 min. The crude product was purified by column chromatography (silica gel, 20% EtOAc in hexane) to provide **6p** (45 mg, 91%) as a white solid: mp 97–99 °C; IR (KBr) cm^{-1}: 3464, 3200, 1438, 1343, 1182, 1138; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.98 (d, *J* = 12.4 Hz, 1H), 4.47 (dd, *J* = 12.4, 2.0 Hz, 1H), 4.30 (s, 1H), 3.43 (s, 1H), 2.39 (br d, *J* = 3.2 Hz, 1H), 2.15 (sext, *J* = 7.2 Hz, 1H), 1.61 (m, 1H), 1.51 (sext, *J* = 7.2 Hz, 2H), 1.39–1.23 (m, 4H), 0.97 (t, *J* = 7.6 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.4, 65.9, 65.0, 32.7, 24.4, 24.0, 22.8, 13.9, 7.0; HRMS (FAB) *m/z* calcd for $C_9H_{20}O_4NS$ $(M + H)^+$ 238.1113, found 238.1118.

(2*R*,3*R*)-1-Acetoxy-4-(*tert*-butyldiphenylsilyloxy)-3-(1,1-dimethylethoxycarbonyl)amino-3-methyl-butan-2-ol (14)

Phosphate buffer (0.32 mL, 0.1 M) was added to a solution of **8** (68 mg, 0.12 mmol) in THF (1.8 mL) at room temperature. After stirring at 70 °C for 24 h, the reaction was quenched with 5% $NaHCO_3$ (5 mL) and the whole mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **14** (37 mg, 61%) as a colorless oil: $[\alpha]_D^{25}$ −15.0 (*c* 1.0, $CHCl_3$); IR (neat) cm^{-1}: 3419, 3072, 2932, 1724, 1692, 1497, 1113, 1062, 937; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 7.2 Hz, 4H), 7.47–7.38 (m, 6H), 5.07 (s, 1H), 4.59 (br s, 1H), 4.25 (dd, *J* = 11.8, 2.6 Hz, 1H), 4.00 (dd, *J* = 11.8, 8.0 Hz, 1H), 3.77 (t, *J* = 8.0 Hz, 1H), 3.70 (d, *J* = 10.2 Hz, 1H), 3.63 (d, *J* = 10.2 Hz, 1H), 2.03 (s, 3H), 1.43 (s, 9H), 1.36 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.2, 156.4, 135.6, 132.5, 132.4, 130.0, 127.89, 127.87, 80.2, 73.5, 67.5, 66.5, 58.8, 28.3, 26.8, 21.0, 19.3, 19.1; HRMS (FAB) *m/z* calcd for $C_{28}H_{42}NO_6Si$ $(M+H)^+$ 516.2781, found 516.2774.

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8. We confirmed that 2-arylpropan-2-ols were obtained in the reaction of **5a** with aryl Grignard reagents (Table 3, entries 6–8).