HETEROCYCLES, Vol. 72, 2007, pp. 103 - 110. © The Japan Institute of Heterocyclic Chemistry
Received, 4th October, 2006, Accepted, 27th November, 2006, Published online, 28th November, 2006. COM-06-S(K)9

STEREOSELECTIVE MANNICH-LIKE REACTIONS OF ESTER ENOLATES GENERATED ON SUGAR TEMPLATES: A NOVEL ACCESS TO A KEY INTERMEDIATE FOR 1β-METHYLCARBAPENEM SYNTHESIS‡

Daisuke Sasaki,[a] Daisuke Sawamoto,[a] Ken-ichi Takao,[a] Kin-ichi Tadano,[a]* Masayuki Okue,[b] and Keiichi Ajito[b]

[a]Department of Applied Chemistry, Keio University, 3-14-1, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan. [b]Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd., 760 Morooka-cho, Kohoku-ku, Yokohama 222-8567, Japan

Abstract – The Mannich-like reactions of the enolates generated from 2,3-di-*O*-protected 6-deoxy-4-*O*-propionyl-α-D-glucopyranosides with (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]azetidin-2-one were investigated. The corresponding 2,3-di-*O*-methyl derivative provided the Mannich adduct in good to excellent stereoselectivity. From the major adduct, the azetidin-2-one incorporating an α-methyl acetic acid side chain at the C-4 position with β-configuration was obtained by alkaline hydrolysis. This product, (3*S*,4*S*)-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-4-[(*R*)-1-carboxyethyl]azetidin-2-one, is a useful intermediate for the 1β-methylcarbapenem synthesis.

INTRODUCTION

Since the discovery of (+)-thienamycin (**1**)[1] (Figure 1), particularly during the 1980s, the chemical and pharmacological development of carbapenems has been a focus in modern medicinal chemistry. Through the chemical modifications of thienamycin to improve the intrinsic chemical stability, the Merck group synthesized 1β-methylthienamycin (**2**), in which a methyl group with β(*R*)-configuration is introduced at the C-1 of the carbapenem nucleus.[2] Since then, a number of 1β-methylcarbapenems have been synthesized, and some 1β-methylthienamycin congeners, such as meropenem (**3**)[3], have come into the

‡ This paper is dedicated to Professor Yoshito Kishi (Harvard University), with respect and admiration, on the occasion of his 70th birthday.

market.

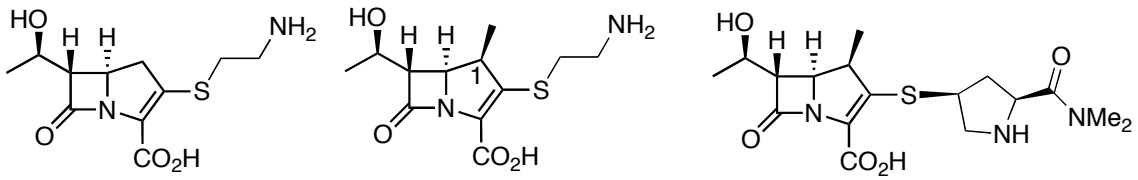
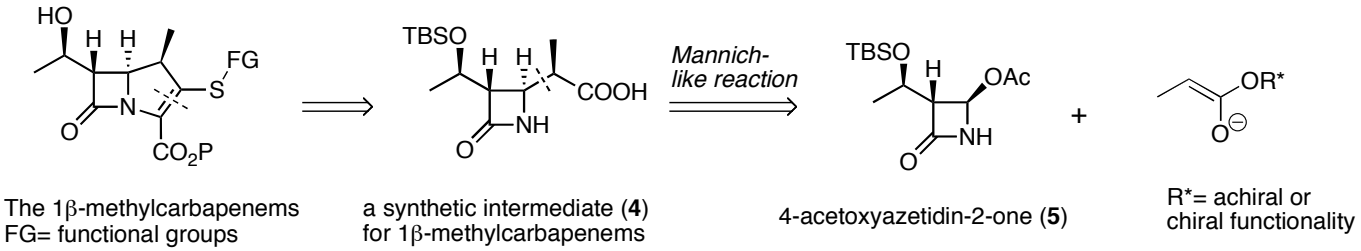


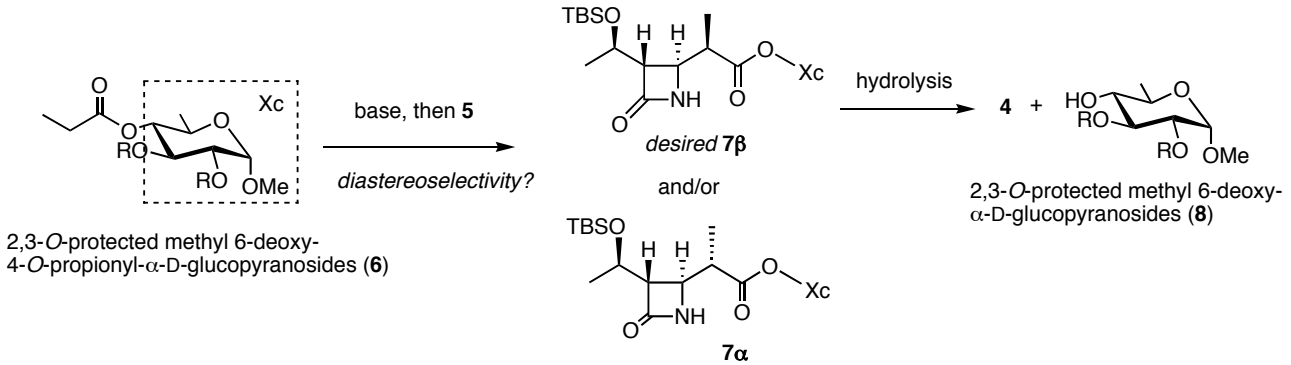
Figure 1

As concerns the chemical synthesis of 1β-methylcarbapenems, numerous synthetic approaches have been developed during the last two decades.[4] The most common approach is a late-stage ring closure for the bicyclic skeleton construction by using a *C*-4 functionalized azetidin-2-one, such as **4**, namely (3*S*,4*S*)-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-4-[(*R*)-1-carboxyethyl]azetidin-2-one, which in turn would be constructed via the Mannich-like coupling reaction of commercial (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]azetidin-2-one (**5**) with the enolates generated from achiral or chiral propionic acid esters (Scheme 1).[5,6]



Scheme 1. Most commonly employed synthetic approach to 1β-methylcarbapenems

In this decade, we have studied the asymmetric carbon-carbon bond-forming reactions by using a variety of glycopyranose-based templates as efficient chiral auxiliaries.[7] As an extension of this sugar template strategy, we have explored the stereoselective Mannich-like reaction of **5** with a number of 2,3-*O*-protected methyl 6-deoxy-4-*O*-propionyl-α-D-glucopyranosides (**6**) as the sources of chiral propionyl

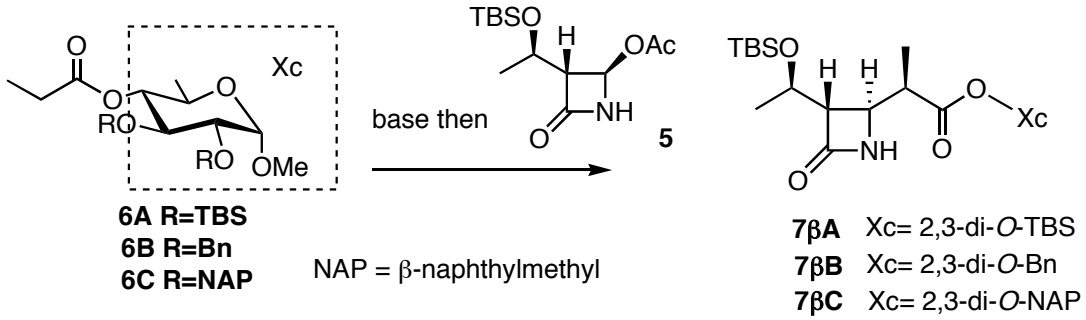


Scheme 2. Our concept for the synthesis of **4** by using sugar templates

enolates (Scheme 2). The desired Mannich-adduct (**7β**), if it could be obtained efficiently, would then be hydrolyzed to isolate the key intermediate (**4**) along with the recovery of the 4-*O*-unprotected sugar templates (**8**).

RESULTS AND DISCUSSION

We started the Mannich-like carbon-carbon bond-forming reaction by using the 2,3-di-*O*-TBS-type compound (**6A**), the most promising substrate for the stereoselective α-alkylation of the propionyl ester evidenced in our previous studies.[7f,7h] After a brief treatment of **6A** with a base, azetidin-2-one (**5**) was added to the thus formed enolate, and the solution was then quenched (Scheme 3). The representative results are shown in Table 1. In most cases, disappointing results were obtained (entries 1-3). Thus, decomposition or recovery of **6A** occurred predominantly. In one case (entry 2), the Mannich-adduct was isolated in a far from satisfactory yield of 6%. The adduct was **7αA** (not shown) instead of the desired **7βA**. The stereochemistry of the newly introduced contiguous chiral centers in the adduct was determined by ^{1}H NMR analysis.[8] When 2,3-di-*O*-benzyl-4-*O*-propionate (**6B**)[9] was used as substrate, mixtures of the desired 1β-adduct (**7βB**) and the 1α-isomer were obtained (entries 4 and 5). The ratio



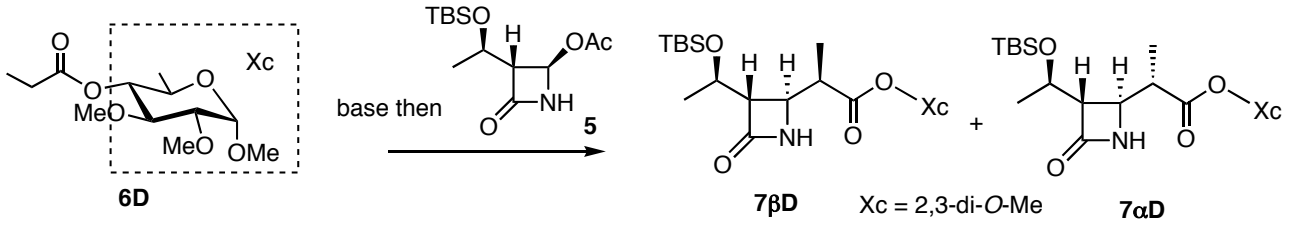
Scheme 3. Mannich-like reactions using the sugar templates (**6A**), (**6B**), or (**6C**)

Table 1.

Entry	Substrate	Base, Additive, Solvent, Temperature	Combined yield (**7β**:**7α**)	Recovery of **6**
1	**6A**	NaHMDS, THF, -18 °C	decomposition	
2	**6A**	LiHMDS (5.0 eq), THF, -78 °C	6%(**7αA** only)	79% **6A**
3	**6A**	LiHMDS (5.0 eq), LiCl (2.5 eq), THF, -78 °C		83% **6A**
4	**6B**	LiHMDS (5.0 eq), THF, -78 °C	52% (1.7:1)	45% **6B**
5	**6B**	LiHMDS (3.0 eq), LiCl (3.0 eq), THF, -78 °C	23% (2.3:1)	75% **6B**
6	**6C**	LiHMDS (5.0 eq), THF, -78 °C	18% (5:3)	55% **6C**
7	**6C**	LiHMDS (5.0 eq), LiCl (5.0 eq), THF, -78 °C	19% (5:3)	81% **6C**

of 1β- and 1α-isomer was varied depending on the reaction conditions. The additive LiCl was likely to be a somewhat stereocontrolling factor. Then, 2,3-di-*O*-(β-naphthylmethyl)-4-*O*-propionate (**6C**) was examined for the coupling with **5** (entries 6 and 7). However, we could not improve the ratio of the 1β-isomer, i.e., **7βC**, and the α-isomer. In contrast to our expectation, bulky substituents, such as OTBS (**6A**), OBn (**6B**), or ONAP (**6C**), at C-3 in the sugar-based substrates did not serve as a significant stereocontrolling element for the attempted Mannich-like reaction with **5**.

Then, we chose a new substrate, i.e., 2,3-di-*O*-methyl derivative (**6D**), which possesses a sterically less congested substituent OMe group at C-3 (Scheme 4). The representative results on the reaction of the enolate derived from the 4-*O*-propionate (**6D**) with **5** are summarized in Table 2. We were pleasantly surprised to see that, in many cases, the ratios of **7βD** and the α-isomer (**7αD**) were remarkably high in favor of the desired **7βD**.[10] We thoroughly examined the base, solvent, reaction temperature, and presence or absence of additives. Although the combined yields of **7βD** and **7αD** were not necessarily remarkable, the efficiency of the base regarding the stereoselectivity was significant in the cases of lithium hexamethyldisilazide (LiHMDS) (entries 1-3).[11] Importantly, unreacted **6D** was recovered without significant loss in many cases.[12] Sodium hexamethyldisilazide (NaHMDS) also served as an effective base, which predominantly provided **7βD** with a ratio of 14:1 in 42% yield in the presence of LiCl at –78 °C (entry 7).[13] We propose a plausible transition-state model for explanation of the observed the diastereoselectivities achieved using the new template (**6D**) (Scheme 5). Although we could not confirm

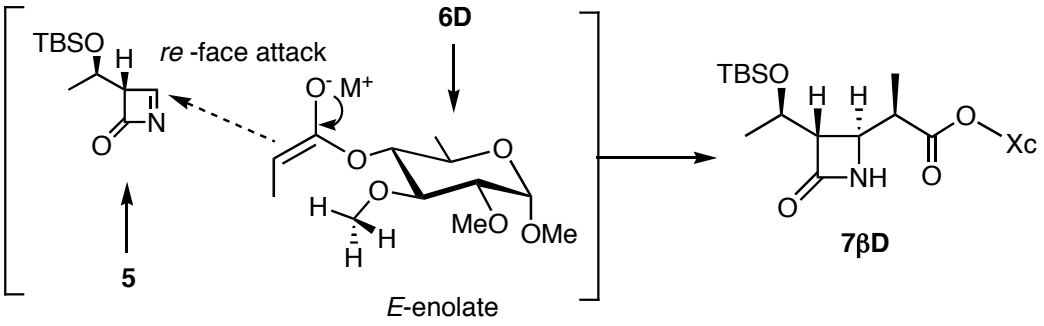


Scheme 4. Mannich-like reaction using the substrate (**6D**)

Table 2.

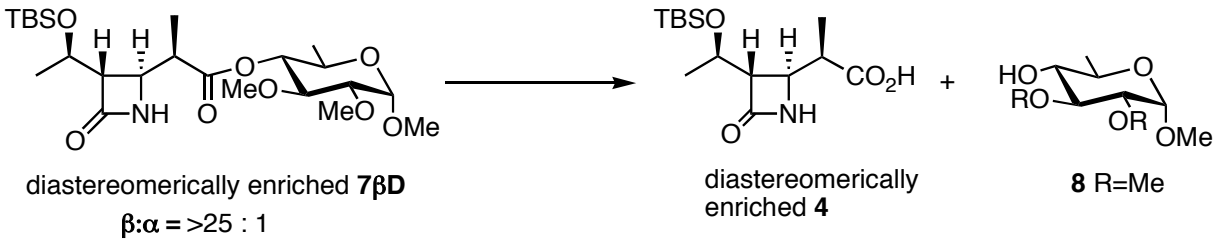
Entry	Base, Additive, Solvent, Temperature	Combined yield (**7βD**:**7αD**)	Recovery of **6D**
1	LiHMDS (2.5 eq), THF, -78 °C	44% (5.3:1)	56%
2	LiHMDS (2.0 eq), THF, -78 °C	29% (18:1)	64%
3	LiHMDS (1.2 eq), THF, -78 °C (100 mg scale)	11% (>25:1)	80%
4	NaHMDS (2.5 eq), THF, -78 °C, 2 h	50% (4.5:1)	32%
5	NaHMDS (2.5 eq), THF, -78 °C, 0.5 h	61% (4.3:1)	37%
6	NaHMDS (1.2 eq), THF, -78 °C, 2 h	23% (5.2:1)	67%
7	NaHMDS (2.5 eq), LiCl (2.5 eq), THF, -78 °C, 0.5 h	42% (14:1)	55%

the geometry of the metallated enolate derived from **6D**,[14] we consider the *E*-enolate might be formed, in contrast to the *Z*-enolate adopted for the enolate derived from the 2,3-*O*-TBS derivative (**6A**).[7f,7h] As depicted in Scheme 5, the resulting *E*-enolate attacked preferentially to the *re*-face of imine derived from **5**, which was placed in the less-congested rear side, thus leading to **7βD**.



Scheme 5. A plausible transition-state model for the diastereoselectivity achieved using **6D**

Finally, we explored the detachment of the sugar template from diastereomerically enriched **7βD** by alkaline hydrolysis (Scheme 6). The conditions and results of the hydrolysis are shown in Table 3. Unfortunately, 1 M aqueous LiOH-mediated hydrolysis in MeOH resulted in partial epimerization of the α-carbon of the ester moiety (entry 1). This drawback was overcome in the presence of aqueous hydrogen peroxide,[15] resulting in the efficient removal of the sugar template (**8**) (R=Me) without the troublesome epimerization (entries 2 and 3). The optimal conditions were a 0.2 M aqueous LiOH solution in the presence of 6.0 equivalents of H_2O_2. Using these conditions, almost pure **4** was obtained in 82% yield, and the sugar template (**8**) (R=Me) was recovered quantitatively in a 100 mg scale.[16]



Scheme 6. Removal of the sugar template (**8**) (R=Me) from the diastereomerically enriched **7βD**

Table 3.

Entry	Conditions	Yields of **4** (β:α ratio) and **8** (R=Me)
1	1 M aq. LiOH:MeOH =1:1	quant. (2.4:1) and 87%
2	1 M aq. LiOH:MeOH =1:1, aq. H_2O_2 (1.5 eq)	56% (>25:1) and 79%
3	0.2 M aq. LiOH:MeOH=1:1, aq. H_2O_2 (6.0 eq) (100 mg scale)	82% (>25:1) and quant.

In summary, we have developed a novel asymmetric synthesis of a key intermediate (**4**) for the 1β-methylcarbapenem synthesis. The Mannich-like reaction of D-glucose-derived 4-*O*-propionate (**6D)** and azetidin-2-one (**5**) produced the adduct (**7βD**) with high diastereoselectivity, from which the desired **4** was obtained after removal of the sugar template part.

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8. As previously disclosed in numerous reports, the attack of nucleophiles at the C-4 carbon in the azetidin-2-one ring occurred from the face opposite the C-3 side chain for steric reasons. This was the same in the cases of the nucleophilic attack of the enolates generated from **6**. The structures of

the adducts (**7β**) were confirmed after removal of the sugar-template, which produced known 1β-methylcarbapenem intermediate (**4**).

9. The hitherto unknown 4-*O*-propionates (**6B**-**6D**) were prepared from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside by the following reaction sequence; 1) 2,3-di-*O*-alkylation using respective alkyl halide in the presence of NaH, 2) acid hydrolysis for removal of the benzylidene acetal, 3) selective tosylation of the resulting primary hydroxyl group, 4) reductive removal of the tosyloxy group with $LiAlH_4$, and 5) 4-*O*-propionylation with propionic anhydride in pyridine with DMAP.
10. The structure of **7βD** was determined based on ^{1}H NMR spectral analysis. Furthermore, we synthesized authentic **7βD** by the esterification of the 4-OH derivative (**8**) (R=Me) with **4**, using a Yamaguchi protocol (**4**, 2,4,6-trichlorobenzoyl chloride, Et_3N, THF; then, DMAP, **8** (R=Me), toluene, reflux). Under these conditions, the yield of **7βD** was at most 13%, but we did not explore improvement of this esterification.
11. Mannich-like reaction using **6D** with **5** (Table 2, entry 3): The following reaction was carried out under Ar. To a cooled (–78 °C) stirred solution of **6D** (103 mg, 0.39 mmol) in THF (1.0 mL), LiHMDS (1.0 M solution in hexanes, 0.47 mL, 0.47 mmol) was added. The solution was stirred at –78 °C for 30 min, and then a solution of **5** (112 mg, 0.39 mmol) in THF (2 mL) was added for 15 min. After being stirred at –78 °C for 2 h, the reaction mixture was quenched with sat. aq. NH_4Cl (1 mL). The mixture was diluted with EtOAc (10 mL) and washed with sat. aq. NH_4Cl (5 mL × 3). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:3, repeatedly three times) to provide 20.5 mg (11%) of **7βD** (α:β = >25:1, ^{1}H NMR analysis) as white solids. 82.2 mg (80%) of **6D** was recovered. **7βD**: TLC, R_f 0.28 (EtOAc/hexane = 1:1); $[\alpha]^{24}_D$ +53.1 (c 1.12, $CHCl_3$): IR ν_{max} 2940, 1750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.066 (3H, s), 0.073 (3H, s), 0.87 (9H, s), 1.14 (3H, d, *J* = 6.3 Hz), 1.22 (3H, d, *J* = 6.3 Hz), 1.25 (3H, d, *J* = 7.3 Hz), 2.77 (1H, dq, *J* = 4.2, 7.3 Hz), 2.95 (1H, dd, *J* = 2.2, 4.8 Hz), 3.31 (1H, dd, *J* = 3.6, 9.6 Hz), 3.44 (3H, s), 3.51 (3H, s), 3.52 (3H, s), 3.54 (1H, t, *J* = 9.6 Hz). 3.77 (1H, dq, *J* = 6.3, 9.6 Hz), 4.00 (1H, dd, *J* = 2.2, 4.2 Hz), 4.20 (1H, dq, *J* = 4.8, 6.3 Hz), 4.67 (1H, t, *J* = 9.6 Hz), 4.80 (1H, d, *J* = 3.6 Hz), 5.90 (29/30H, s), 6.07 (1/30H, s); ^{13}C NMR (68 MHz, $CDCl_3$) δ –5.0, –4.3, 11.6, 17.4, 17.9, 22.5, 25.7 × 3, 41.8, 51.3, 55.3, 58.9, 61.2, 65.5, 75.1, 80.2, 82.0, 97.3, 168.0, 173.6; HRMS (EI) calcd for $C_{23}H_{43}NO_8Si$ (M^+) *m/z* 489.2758, found 489.2754.
12. For some entries in Table 2, the presence of excess LiHMDS or NaHMDS resulted in the significant decomposition of **5** prior to the desired Mannich-like reaction. Consequently, the yield of **7** decreased in these cases. Therefore, we could not recover the intact azetidinone (**5**) from the

reaction mixture in most cases. We could not find the optimal conditions for obtaining **7βD** in higher yields than those shown in Table 2.

13. We do not have a reasonable explanation for the remarkable improvement of diastereoselectivity observed in the presence of LiCl.
14. We tried to isolate the silyl enol ether derived from **6D**. All attempts for trapping the enolate with a silylating reagent were unsuccessful.
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16. Removal of the sugar template (Table 3, entry 3): To a stirred solution of MeOH (2.0 mL) and 0.2 M aqueous LiOH (2.0 mL, 0.40 mmol), 35% aqueous H_2O_2 (0.11 mL, 1.20 mmol) and **7βD** (β:α = >25:1) (98.7 mg, 0.202 mmol) were added. The solution was stirred at rt for 20 h, diluted with H_2O (10 mL), and washed with CH_2Cl_2 (10 mL × 8). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give 42.2 mg (quant.) of **8** (R=Me) as a colorless oil. To the aqueous layer, 1.0 M aqueous HCl (0.5 mL) (pH 2) was added. This was extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give 49.7 mg (82%) of **4** (β:α = >25:1, ^{1}H NMR) as white solids; TLC, R_f 0.13 (EtOAc/hexane = 1:1); $[\alpha]^{25}_D$ –25.9 (*c* 0.22, MeOH): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.066 (3H, s), 0.074 (3 H, s), 0.87 (9H, s), 1.20 (3H, d, *J* = 6.2 Hz), 1.26 (3H, d, *J* = 7.0 Hz), 2.74 (1H, dq, *J* = 5.1, 7.0 Hz), 3.03 (1H, dd, *J* = 2.2, 4.4 Hz), 3.95 (1H, dd, *J* = 2.2, 5.1 Hz), 4.20 (1H, dq, *J* = 4.4, 6.2 Hz), 6.40 (1H, s); ^{13}C NMR (68 Hz, $CDCl_3$) δ –5.0, –4.3, 12.1, 17.9, 22.4, 25.7 × 3, 41.8, 51.7, 61.1, 65.1, 169.4, 178.2; HRMS (EI) calcd for $C_{10}H_{18}NO_4Si$ ($M^+ - t$-C_4H_9) *m/z* 244.1005, found 244.1005.