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A NEW TEMPLATE OF MITSUNOBU ACYLATE CLEAVABLE IN NON-ALKALINE CONDITIONS

Yoshimichi Sakakibara, Yusuke Sai, Yasumitsu Uraki, Makoto Ubukata, and Kengo Shigetomi*

Research Faculty of Agriculture, Hokkaido University, Kita-9, Nishi-9, Kita-Ku, Sapporo, Hokkaido 060-8589, Japan
E-mail: sgtm@for.agr.hokudai.ac.jp

Abstract – The Mitsunobu inversion is one of the reliable methods for stereospecific substitution of chiral alcohols, but its deacylation step has limited the substrate scope. Here, we propose a new template of the Mitsunobu acylate that can be deacylated in non-alkaline treatments. The 3,4-dihydroxy-2-methylenebutanoate was selected as a template structure, and its acetonide- or bisTBS derivatives were synthesized. The latter especially showed excellent inversion efficiency (up to >99% ee) and good elimination performance for a series of secondary alcohols in near-neutral conditions. The results demonstrated the applicability of the new template for the substrates labile in alkaline conditions, such as α-hydroxyesters.

INTRODUCTION

The Mitsunobu reaction is a condensation reaction that enables highly stereospecific inversion of various functional groups.[1] Especially, the reaction has been widely used for the inversion of the stereochemistry of secondary alcohols by combining nucleophilic substitution with acids and the following deacylation.[2] As well as its usefulness, the reaction is also known to have several defects to be solved, such as i) lower reactivities for weak acids,[3] ii) multiple side reactions,[4] iii) complicated by-products that make purification harder. In addition, the deacylation process has limited the application for substrates labile in basic conditions because the hydrolysis is mostly performed in alkaline conditions. Enormous efforts have been made to solve the former three problems to date,[5] but no efficient resolution for the last issue is proposed.

6-Tuliposide B, an antibacterial compound occurring mainly in the anthers of tulips, is a nonglycosidic sugar ester comprised of D-glucose and 3,4-dihydroxy-2-methylenebutanoate (DHMB).[6] The acidic

treatment of this compound, likewise other 4-hydroxyesters, can give a lactone, known as tulipalin B,[7–9] and it is also proved that the same conversion can proceed enzymatically.[10] In addition, it was empirically known that this lactonization could proceed even under neutral aqueous conditions and be prevented under weakly acidic conditions (Figure 1). In the total synthesis of 6-tuliposide B, this spontaneous heterocyclization had hampered the effective deprotection in the final step, which was eventually achieved by the use of *t*-butyldimethylsilyl (TBS) and 2-(trimethylsilyl)ethyl groups as protecting groups.[8] This structural vulnerability, however, implies the possibility of this structure as a new template of the acid in the Mitsunobu inversion. The strategy is as follows: 1) DHMB-based carboxylic acids having "cap" structures on their 4-*O* position are introduced to chiral alcohols as an acid of the Mitsunobu reaction. 2) The "cap"s are removed by corresponding conditions. 3) The resulting free 4-hydroxy groups, or correctly 4-alkoxide, undergo spontaneous lactonization liberating sterically inverted alcohols. This process will enable the deacylation that depends on not alkaline conditions but the deprotecting conditions. In this study, we first evaluated the cyclization performance of DHMB-based analogs to optimize the structure of the aimed carboxylic acid. As candidates of acids in the Mitsunobu reaction, the acetonides-type and bisTBS-type of DHMB acids were next synthesized, and their introduction to chiral secondary alcohols and elimination were examined to discuss their practicalities.

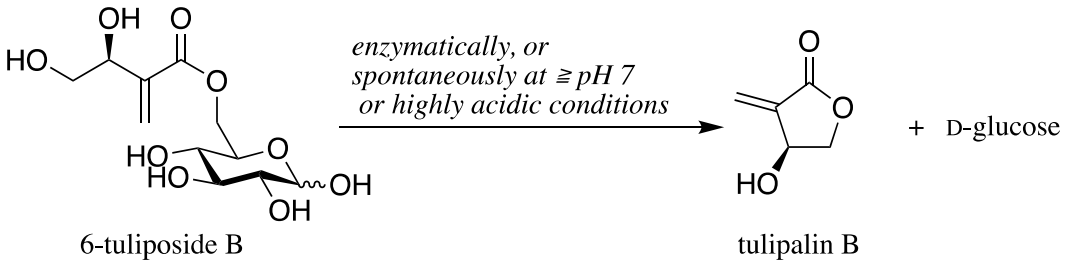


Figure 1. 6-Tuliposide B and lactonization of its side chain

RESULTS AND DISCUSSION

EVALUATION OF CYCLIZATION PERFORMANCE OF DHMB ANALOGS

While the side chain of 6-tuliposide B was known to show a cyclization in aqueous media, its competency as the aimed template was not fully evaluated. Especially, its structural necessity had to be verified to simplify the preparation procedure of the target acids. Thus, we first synthesized a series of DHMB analogs and evaluated their cyclization performance in acidic to neutral aqueous solutions. Methyl ester of DHMB (**1**) was prepared by the Baylis-Hillman reaction of TBS-protected glycolaldehyde and methyl acrylate followed by the desilylation with TBAF/AcOH.[9] 3-*O*-Methyl analog (**2**) was synthesized by the methylation of the Baylis-Hillman adduct, and 3-deoxy analog (**3**) was prepared by the methanolysis of α-methylene-γ-butyrolactone (tulipalin A).[6] The hydrogenation of tulipalin B followed by the benzylation

gave a dihydro-3-deoxy analog (**4**), and the same benzylation treatment was applied for γ-butyrolactone to obtain 4-hydroxybutanoate (**5**). 4-Methyl analog (**6**) was prepared by the Baylis-Hillman reaction of methyl acrylate and TBS-protected lactaldehyde.[11] The cyclization performance of these compounds were evaluated at different pH conditions. Substrates (**1**, **2**, **4** as racemates and **6** as a diastereomeric mixture) were incubated in citrate–phosphate buffers containing 5% MeCN as a cosolvent, and the remaining linear structures were quantified by PDA-HPLC. The results are shown in Figure 2. As expected, DHMB (**1**) showed rapid cyclization at the neutral condition ($t_{1/2}$ = 2.4 h), and the acidic environments clearly suppressed the reaction (Figure 2a). This tendency was true for all analogs tested, and **6** showed outstanding reactivity ($t_{1/2}$ = 0.7 h at pH 7.0) compared with **2**–**5** ($t_{1/2}$ = 4.2–9.8 h). The superior reactivities of **1** and **6** will be achieved by both the 3-hydroxy- and alkyl-substituents. The effect of the 3-hydroxy group is typically seen in the difference between **1** and **3**, and which might be explained by the hydrogen-bond relay between 1-*O*, 3-OH, and 4-OH that gives an enhanced nucleophilicity on 4-oxygen. The alkyl substituents will destabilize the linear structures in the aqueous media and facilitate the cyclization to minimize its hydrophobic surface (compare **1** with **6**, or **4** with **5**).

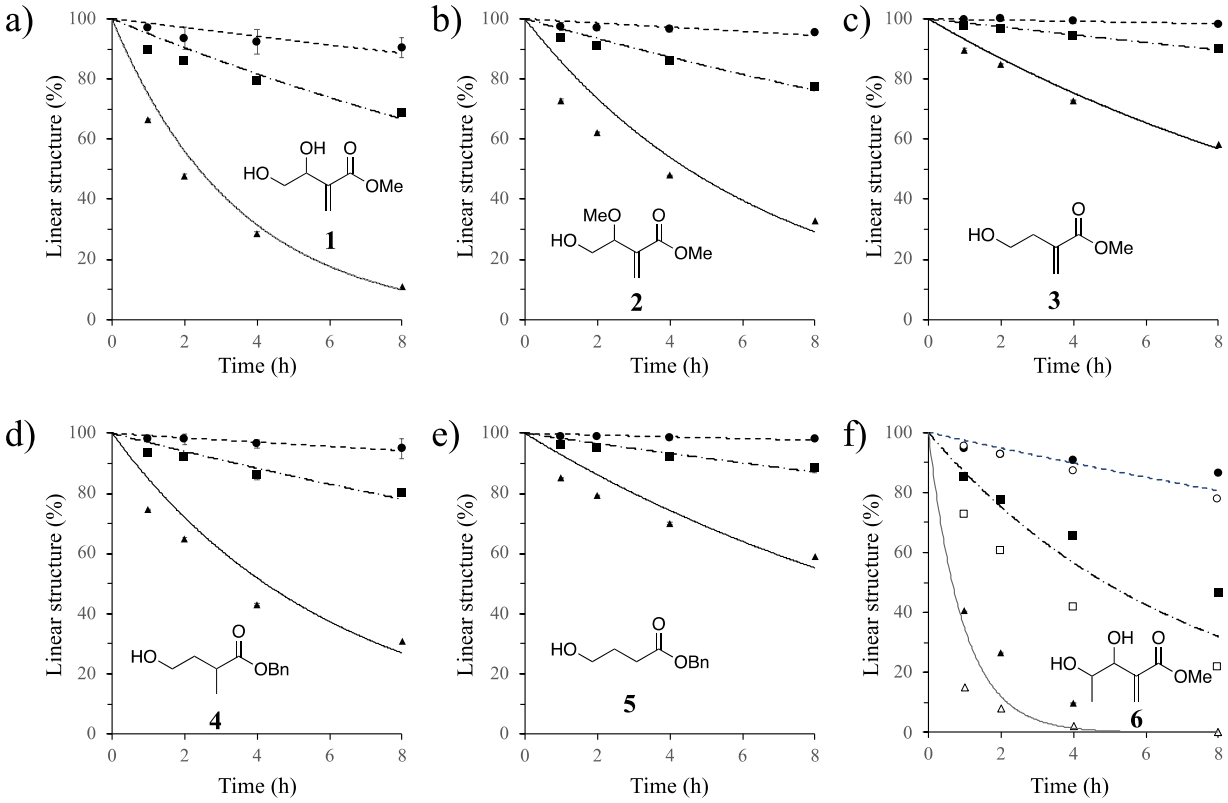


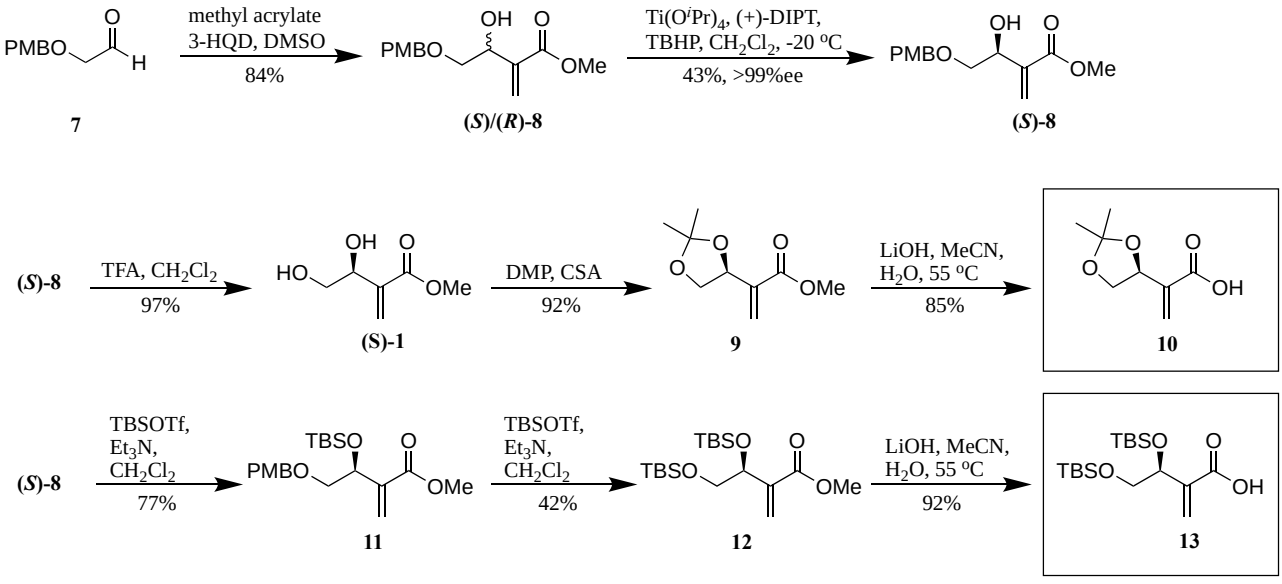
Figure 2. Remaining linear structures after the incubation of compounds **1**–**6** in the buffers adjusted at pH 5.0 (●), 6.0 (■), and 7.0 (▲). a) DHMB Me ester (**1**); b) 3-*O*-methyl analog (**2**); c) 3-deoxy analog (**3**); d) dihydro-3-deoxy analog (**4**); e) 4-hydroxybutanoate (**5**); 4-methyl analog (**6**). Closed and open symbols in the panel f represent the values of major and minor diastereomers, respectively. Approximation curves for

respective conditions were shown as continuous (pH 5.0), long dashed dotted (pH 6.0), and dashed (pH 7.0) lines. Curves in the panel f were prepared for the average values of diastereomers.

Although the compound **6** with the fastest cyclization performance was attractive as an aiming template, it had three disadvantages in comparison with **1**, *i.e.*, i) the rapid cyclization lowered the yield in its preparation (only 18% in the desilylation step); ii) the 4-methyl group gives an additional chiral center that makes the following reactions complicated; iii) the deprotection of secondary hydroxy group generally requires harsher conditions. Therefore, we eventually selected the original DHMB structure as a target template. Although the 2-methylene group negatively affected at least in the 3-deoxy analog **3** (compare with **4**), this moiety was considered preferable in the Mitsunobu reaction because it can lower the p*Ka* of the resulting acids like other acrylates and can avoid another chiral center on 2-position.

PREPARATION OF DHMB-BASED ACIDS FOR THE MITSUNOBU REACTION

Two types of DHMB-based acids for the Mitsunobu reaction were synthesized following the procedures previously developed.[13] As protecting groups for acids, isopropylidene and TBS groups were selected, which can be deprotected under acidic or near-neutral conditions, respectively. In addition, the enantiomerically pure acids were prepared to avoid complexity in the spectral analysis of diastereomers resulting from the Mitsunobu reaction.



Scheme 1. Preparation of DHMB-based acids furnishing isopropylidene and bisTBS as protective groups

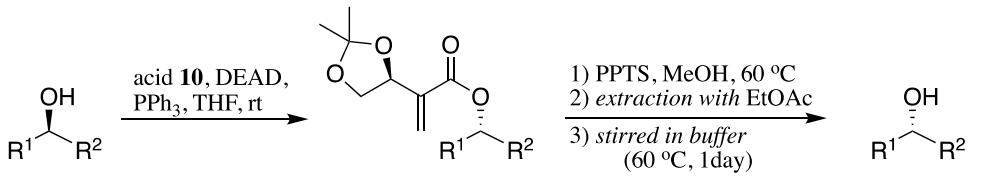
PMB-protected glycolaldehyde (**7**)[12] was synthesized from *cis*-2-butene-1,4-diol and was subjected to the Baylis–Hillman reaction to afford racemic adduct (*S*)/(*R*)-**8**. The (*S*)-**8** was selectively recovered by Katsuki–Sharpless kinetic resolution (>99% ee).[13,14] The PMB group was deprotected in an acidic

condition, and an isopropylidene group was introduced using 2,2-dimethoxypropane/camphorsulfonic acid to form **9**. The hydrolysis of **9** gave acetonide-type acid **10** in good yields. The bisTBS-type acid **13** was similarly prepared from (*S*)-**8** through stepwise silylation and the subsequent hydrolysis.

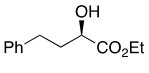
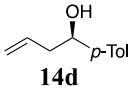
MITSUNOBU REACTION AND DEACYLATION WITH ACETONIDE-TYPE ACID

To investigate the substrate scopes of the DHMB-based acids, the Mitsunobu reaction and the following deacylation treatment were performed using enantiomerically pure secondary alcohols. The acetonide-type acid **10** was first tested (Table 1). The inversion efficiencies were evaluated based on the diastereomeric excesses (% de) of the Mitsunobu products and the enantiomeric excesses (% ee) of the deacylated products, which were measured by chiral HPLC. Fortunately, the use of enantiomerically pure acids enabled the facile detection of undesired diastereomers *epi*-15**a**–**g** on ^{1}H NMR spectra (typical for signals of 4-CH_2 at 3.6 and 4.4 ppm), and the results were well consistent with those in chiral HPLC. In the acylation step, the acylates were easily introduced at room temperature, mostly in good yields and selectivities. In the Mitsunobu reaction, the substrates with a bulky substituent at the α-position often result in low yields,[15] and which was seen with **14f** (Table 1, entry 6). Interestingly, structurally similar **14e** and **14g** showed sufficient reactivities (entries 5 and 7). As an attempt to remove acyl moiety, isopropylidene of the adduct **15a** was first deprotected by PPTS. Since the resulting product retained a 3,4-diol linear chain in its structure, the crude product was recovered by EtOAc extraction and treated in the same buffer as that used in the cyclization experiment (condition A) at 60 °C for 1 day. Surprisingly, this condition could not remove DHMB and an alcohol *ent*-**14a** was not obtained. Thus, a series of buffers were next examined (data not shown), and the MeOH-THF-buffer system (condition B) was found to successfully give the product *ent*-**14a** (83%). The different reactivities in the buffer from that in Figure 2 suggested that the alkoxy moiety of the ester also affected the efficiency of the cyclization.

Table 1. Substrate scope of acetonide-type acid **10**



14a–g **15a–g** *ent*-**14a–e**, 1-*epi*-**14f**, **g**

Entry	Substrate	Acylation step			Deacylation step			
		Product	Yield (%)	de (%) [a]	Product	Buffer condition	Yield (%)	ee (%) [a]
1	 **14a**	**15a**	81	88	*ent*-**14a**	A	n.r. [b]	–
						B	83	82
						C	64	89
2	 **14b**	**15b**	88	>99	*ent*-**14b**	B	87	99
3	 **14c**	**15c**	95	>99	*ent*-**14c**	B	n.r.	–
						C	8	99
4	 **14d**	**15d**	96	>99	*ent*-**14d**	B	n.r.	–
						C	5	99
5	 **14e**	**15e**	69	>99	*ent*-**14e**	B or C	n.r.	–
6	 **14f**	**15f**	39	94	1-*epi*-**14f**	B or C	n.r.	–
7	 **14g**	**15g**	95	>99	1-*epi*-**14g**	B or C	n.r.	–

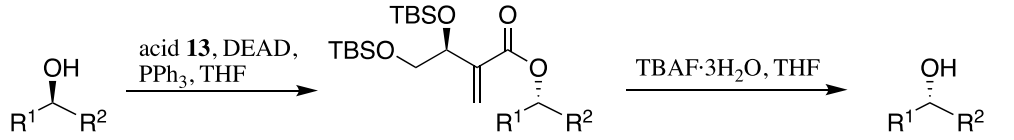
Buffer condition A: MeCN/citrate–phosphate buffer (pH 7.0) = 5:95; B: THF/MeOH/phosphate buffer (pH 7.0) = 2:3:4; C: condition B + cat.TBAI. [a] Determined by chiral HPLC; [b] No reaction.

Although condition B also worked for **15b** (*ent*-**14b**: 87%), it was disappointing that it was not effective for other substrates (entries 3–7). The addition of TBAI as a phase-stimulating agent partly promoted the deacylation of **15c** and **15d** (entries 3 and 4), but this condition was not effective for **15e**–**g** at least by 1 day-treatment. Hence, although the deprotection followed by buffer treatment was shown to work as the deacylation strategy, it was also proved that the buffers must be carefully modulated depending on the substrates. The acetonide-type acid **10** will be applicable as a new Mitsunobu acid for a part of alcohols, but it seemed to be unfavorable, especially for the alcohols on ring structures. This may suggest that not only hydrophobicity but also the conformational flexibility of the alkoxy moieties can agitate the cyclization of acylate.

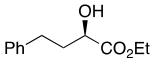
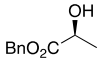
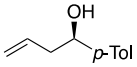
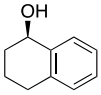
MITSUNOBU REACTION AND DEACYLATION WITH BISTBS-TYPE ACID

The bisTBS-type acid **13** was likewise tested (Table 2). The diastereomeric excesses (% de) of the Mitsunobu products were determined by ^{1}H NMR because chiral HPLC could not separate the diastereomers due to low polarities. The same substrates as those in Table 1 were subjected to the acylation.

Table 2. Substrate scope of bisTBS-type acid **13**



14a–g **15a–g** *ent*-**14a–e**, 1-*epi*-**14f**, **g**

Entry	Substrate	Acylation step			Deacylation step		
		Product	Yield (%)	de (%) [a]	Product	Yield (%)	ee (%) [b]
1	 **14a**	**16a**	52	>99	*ent*-**14a**	97	89
2	 **14b**	**16b**	75	>99	*ent*-**14b**	78	99
3	 **14c**	**16c**	66	>99	*ent*-**14c**	73	99
4	 **14d**	**16d**	82	>99	*ent*-**14d**	72	99
5	 **14e**	**16e**	53 [c]	88	*ent*-**14e**	70 [e]	72
6	 **14f**	**16f**	n.r. [d]	–	1-*epi*-**14f**	–	–
7	 **14g**	**16g**	93 [d]	>99	1-*epi*-**14g**	43 [f]	96

[a] Estimated based on the signals of 4-CH_2 in ^{1}H NMR. ">99%" denotes that no signals of uninverted products were found.; [b] Determined by chiral HPLC; [c] Additional 4.0 eq. of DEAD and PPh_3 were used. [d] The reactions were performed at 60 °C. [e] 10% of 3,4-diol remained.; [f] 55% of 3,4-diol remained.

The yields tended to become lower than those with **10** and a part of substrates required elevated temperature or additional reagents (entries 5 and 7). The acylation for the substrate **14f** did not proceed, probably due to the steric hindrance of α-position as seen with **10**. However, the stereochemistry of the resulting acylates underwent an efficient inversion from the original alcohols (>88% de). Therefore, the bisTBS moiety will not have a critical effect on steric inversion, even if it affects the efficiency of the acylation. The following deacylation step was carried out with TBAF hydrate. Interestingly, inverted alcohols were successfully recovered from corresponding acylates without additional buffer treatments (up to 97% yield). This result suggested that the desilylated 4-alkoxide directly attacked the carbonyl without being stabilized as 4-OH. Thus, the basic species locally formed will play a key role in this reaction and, in that sense, this may not strictly be the reaction at neutral condition. However, since neither transesterification nor racemization has occurred in the substrates **16b** and **16c**, the temporal formation of the alkoxide must not affect the pH of the whole system. In addition, the good yields in these substrates will reflect the results that the desired 5-*exo*-type cyclization selectively proceeded without accompanying 5-*endo*- or 8-*exo*-type ring closure that can not liberate the alcohols. Although residual 3,4-diol products were observed in the deacylation of **14e** and **14g** (10 and 55%, respectively), the use of anhydrous TBAF may improve the yields based on this mechanism. In total, the bisTBS-type acid **13** was demonstrated to be applicable as an aiming Mitsunobu acid cleavable without basic reagents, though a part of bulky alcohols can not be good substrates.

CONCLUSION

To develop the new acids that can be cleaved without basic conditions in the Mitsunobu inversion, the application of 3,4-dihydroxy-2-methylenebutanoate (DHMB)-based structure was examined being inspired by the spontaneous lactonization of 6-tuliposide B. The DHMB, which showed rapid cyclization in neutral aqueous solvent, was selected as a template structure and two types of protected acids were prepared. The acetonide-type acid **10** successfully inverted the stereochemistry of the chiral alcohols, but the subsequent deprotection followed by the buffer treatment worked only for the limited substrates. While the reactivity of bisTBS-type acid **13** tended to be lower than acetonide-type, the inverted alcohols were easily obtained only by desilylation treatment. These results demonstrated the capability of DHMB as a template structure of the new acids for the Mitsunobu inversion. It should be noteworthy that the application of these acids enabled the inversion of α-hydroxy esters (**14b** and **14c**) that can be epimerized or hydrolyzed in basic conditions conventionally used. Although isopropylidene and TBS groups were used in this study, the protecting groups can be diversified depending on the substructure in substrates. In the present study, we have also confirmed that the racemic acids exhibit comparable reactivities to that of the pure enantiomers. However, the use of enantiomers will have advantages in terms of the easy analyses

of Mitsunobu products and the possibility of recrystallization that can enhance optical purity. Despite recent advances in asymmetric reactions, we still run into products with unexpected stereochemistry. The use of the DHMB template can be a good option to invert the undesired stereochemistry, even if substrates had the moieties labile in alkaline conditions.

EXPERIMENTAL

MATERIALS AND METHODS

Unless otherwise stated, chemicals of the highest commercial purity were used without further purification. NMR spectra were recorded on a JEOL EX-270. Chemical shifts are defined using tetramethylsilane as the internal standard. Coupling constants (*J*) are given in Hz. Mass spectra were acquired with FI or FD techniques using JMS-T100GCV (JEOL, Tokyo, Japan). HPLC analyses were performed on the system D7000 (Hitachi, Tokyo, Japan). Thin layer and column chromatography (CC) were performed with Silicagel 70 F_{254} (Fujifilm Wako Pure Chemical Co., Tokyo, Japan) and Silica Gel 60 N spherical, neutral (Kanto Chemicals Co., Tokyo, Japan), respectively. Optical rotations were measured on a P-2000 polarimeter (Jasco., Tokyo, Japan). THF and CH_2Cl_2 were distilled from sodium/benzophenone ketyl and phosphorous oxide, respectively.

SYNTHESIS OF METHYL 3,4-DIHYDROXY-2-METHYLENEBUTANOATE (1)

To a solution of 4-{[*t*-butyl(dimethyl)silyl]oxy}-3-hydroxy-2-methylenebutanoate[9] (108.2 mg, 0.42 mmol) in 5.0 mL of THF, a mixture of TBAF·$3H_2O$ (126 mg) and AcOH (50 μL) in THF (1.0 mL) was added. After stirring for 24 h at room temperature, the solvent was removed *in vacuo* and the resulting crude product was purified by silica gel CC (MeOH/$CHCl_3$ 1:4) to give **1** as a colorless syrup (52.6 mg, 87%). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 3.60 (1H, dd, *J* = 11.2, 6.9 Hz, H-4a), 3.79 (3H, s, OCH_3), 3.83 (1H, dd, *J* = 11.3, 3.6 Hz, H-4b), 4.61 (1H, br s, H-3), 5.97 (1H, br s, olefinic), 6.37 (1H, br s, olefinic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 52.0 (OCH_3), 65.9 (C-4), 71.3 (C-3), 126.8 (C=$\underline{C}H_2$), 139.2 (C-2), 166.6 (C-1); FI-MS: *m*/*z* =147.1 $[M+H]^+$.

SYNTHESIS OF METHYL 4-HYDROXY-3-METHOXY-2-METHYLENEBUTANOATE (2)

To a solution of 4-{[*t*-butyl(dimethyl)silyl]oxy}-3-hydroxy-2-methylenebutanoate[9] (353.5 mg, 1.36 mmol) in 5.0 mL of CH_2Cl_2 were added Ag_2O (3.79 g, 16.4 mmol) and MeI (1.0 mL, 16.1 mmol) and the mixture was refluxed for 5 h. The insoluble part was removed by silica-pad, and the solvent was evaporated. The crude product was purified by silica gel CC (EtOAc/hexane 1:4) to give a methylated product (233.5 mg, 63%). The product was then dissolved in THF (2.5 mL), and AcOH (120 μL) and TBAF·$3H_2O$ (268.8 mg) were added to the solution. After stirring for 24 h at room temperature, the mixture was partitioned between 0.25 M aqueous citric acid and Et_2O. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Finally, silica gel CC (MeOH/$CHCl_3$ 2:98) afforded 80.7 mg of **2** (59%). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 3.36 (3H, s, OCH_3), 3.47 (1H, dd, *J* = 11.5,

6.9 Hz, H-4a), 3.72–3.78 (4H, m, H-4b and $COOCH_3$), 4.26 (1H, dd, *J* = 6.9, 3.3 Hz, H-3), 5.91 (1H, t, *J* = 1.3 Hz, olefinic), 6.43 (1H, d, *J* = 1.3 Hz, olefinic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 51.9 ($COOCH_3$), 57.2 (OCH_3), 65.4 (C-4), 80.4 (C-3), 126.9 (C=$\underline{C}H_2$), 136.9 (C-2), 166.4 (C-1); FI-MS: *m*/*z* =161.1 $[M+H]^+$.

SYNTHESIS OF METHYL 4-HYDROXY-2-METHYLENEBUTANOATE (3)

To a solution of α-methylene-γ-butyrolactone (136.4 mg, 1.39 mmol) in MeOH (10.0 mL), a catalytic amount of Amberlyst R-15 was added. The mixture was allowed to stir at 68 °C for 4 h. The resins were filtered off and MeOH was removed by evaporation. The crude product was purified by silica gel CC (MeOH/$CHCl_3$ 3:97) and 90.4 mg of **3** was obtained as a colorless syrup (50%). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.58 (2H, t, *J* = 6.3 Hz, H-3), 3.72–3.77 (5H, m, H-4 and OCH_3), 5.69 (1H, s, olefinic), 6.24 (1H, s, olefinic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 35.4 (C-3), 51.9 (OCH_3), 61.4 (C-4), 127.2 (C=$\underline{C}H_2$), 137.2 (C-2), 167.8 (C-1); FI-MS: *m*/*z* =130.1 $[M]^+$.

SYNTHESIS OF BENZYL 4-HYDROXY-2-METHYLBUTANOATE (4)

To a solution of α-methylene-γ-butyrolactone (193.2 mg, 2.01 mmol) in CH_2Cl_2 (2.0 mL) was added 69.7 mg of Pd/C and the reaction was allowed to stir under H_2 atmosphere. After the completion of the reaction, the solid was removed by celite-filtration and the solvent was removed by evaporation. The crude product (153.7 mg) was dissolved in 3.0 mL of an aqueous solution containing NaOH (52.0 mg, 1.30 mmol). The mixture was treated at 70 °C for 24 h. After that, the solvent was removed azeotropically with toluene, and 3.0 mL of acetone was added to the residue. After the addition of tetrabutylammonium bromide (21.6 mg, 0.067 mmol) and BnBr (187.1 μL, 1.58 mmol), the mixture was again stirred at 60 °C for 24 h. The mixture was washed with several milliliters of EtOAc, and which was washed with 1 M aqueous $NaHSO_4$, saturated aqueous $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4 and purified by silica gel CC after evaporation (EtOAc/hexane, 1:2) to afford **4** (120.6 mg, 29% in 3 steps). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.21 (3H, d, *J* = 6.9 Hz, CH_3), 1.63–1.75 (1H, m, H-3a), 1.86–2.01 (1H, m, H-3b), 2.69 (1H, sext, *J* = 7.0 Hz, H-2), 3.65 (2H, br d, H-4), 5.12 (2H, s, benzyl), 7.33 (5H, m, Ph); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ:16.9 (CH_3), 36.1 (C-3), 36.3 (C-2), 60.2 (C-4), 66.1 (benzyl), 127.9 (aromatic), 128.0 (aromatic), 128.4 (aromatic), 135.9 (aromatic), 176.5 (C-1); FI-MS: *m*/*z* =208.1 $[M]^+$.

SYNTHESIS OF BENZYL 4-HYDROXYBUTANOATE (5)

The same procedure as the synthesis of **4** except the hydrogenation step was applied for γ-butyrolactone. From 864.5 mg (10.05 mmol) of starting material, 1.23 g of **5** was obtained (63% in 2 steps). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.90 (2H, quin, *J* = 6.3 Hz, H-3), 2.49 (2H, t, *J* = 7.1 Hz, H-2), 3.67 (2H, t, *J* = 6.1 Hz, H-4), 5.12 (1H, s, benzyl), 7.35(5H, m, aromatic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 27.7 (C-3), 31.0

(C-2), 62.0 (C-4), 66.3 (benzyl), 128.16 (aromatic), 128.21 (aromatic), 128.5 (aromatic), 135.9 (aromatic), 173.7 (C-1)； FI-MS: *m*/*z* =194.1 $[M]^+$.

SYNTHESIS OF METHYL 3,4-DIHYDROXY-2-METHYLENEPENTANOATE (6)

To a solution of 2-{[*t*-butyl(dimethyl)silyl]oxy}propanal[11] (4.28 g, 22.8 mmol) in a mixed solvent consisted of methyl acrylate (40 mL) and DMSO (4.0 mL), DABCO (2.59 g, 23.1 mmol) was added. The mixture was allowed to stir for 48 h at room temperature and partitioned between Et_2O (x 3) and saturated aqueous NH_4Cl. The combined organic layer was washed with brine and the solvent was removed *in vacuo*. The subsequent silica gel CC (EtOAc/hexane, 1:9) gave 2.31 g of methyl 4-{[*t*-butyl(dimethyl)silyl]oxy}-3-hydroxy-2-methylenepentanoate (37%). A portion of this product (326.7 mg, 1.19 mmol) was dissolved in 3.0 mL of THF, and to this solution, AcOH (136 μL, 2.38 mmol) and TBAF·$3H_2O$ (375.5 mg, 1.19 mmol) were added in this order. After stirring for 24 h at room temperature, Et_2O was added to the reaction, and which was washed with 0.25 M aqueous citric acid and then brine. The evaporation was followed by silica gel CC (MeOH/$CHCl_3$, 5:95) to afford 33.5 mg of **6** as a diastereomeric mixture (0.21 mmol, 18%). The diastereomer ratio determined by the integration values of signals at 5.92 and 5.97 ppm in ^{1}H NMR was approximately 3:2. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.10 (d, *J* = 6.3 Hz, H-5$_{major}$), 1.17 (d, *J* = 6.3 Hz, H-5$_{minor}$), 3.78 (s, OCH_3 $_{major}$), 3.79 (s, OCH_3 $_{minor}$), 3.84–3.93 (m, H-4$_{minor}$), 3.99–4.08 (m, H-4$_{major}$), 4.23 (dd, *J* = 4.8, 0.9 Hz, H-3$_{minor}$), 4.51 (br d, *J* = 3.9 Hz, H-3$_{major}$), 5.92 (t, *J* = 1.0 Hz, olefinic $_{minor}$), 5.97 (t, *J* = 1.3 Hz, olefinic $_{major}$), 6.34–6.36 (m, olefinic $_{major}$ and $_{minor}$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 16.9 and 18.0 (C-5), 51.8 and 52.0 (OCH_3), 69.2 and 69.6 (C-4), 74.5 and 76.5 (C-3), 126.9 and 127.3 (C=$\underline{C}H_2$), 139.0 and 140.9 (C-2), 167.1 and 167.7 (C-1); FI-MS: *m*/*z* =161.1 $[M+H]^+$.

EVALUATION OF CYCLIZATION PERFORMANCE

Compounds **1**–**6** were dissolved in MeCN to make 10% (*w*/*v*) solutions. Ten microliters of these samples were mixed with 990 μL of the buffers (pH 5.0, 6.0, and 7.0) prepared with 0.25 M citric acid and 0.50 M Na_2HPO_4 aqueous solutions. Each sample was vigorously shaken at 30 ºC (600 rpm), and a portion was sampled at 1, 2, 4, and 8 h to subject to the HPLC analyses. For HPLC, the following conditions were used; column: Mightysil RP-18GP 250-4.6 (Kanto Chemical. Co. Inc.); temp.: 30 ºC; flow rate: 0.5 mL/min; detector: UV 210 nm. The elution was performed isocratically with MeOH:H_2O in the ratio **1**: 5:95; **2**: 20:80; **3**: 20:80; **4**: 55:45; **5**: 50:50; **6**: 5:95. The areas of untreated samples were defined as 100% and remaining linear structures (%) were calculated based on these values.

SYNTHESIS OF METHYL (*S*)-2-(2',2'-DIMETHYL-1',3'-DIOXOLAN-4'-YL)PROPENOATE (9)

The preparation of **(*S*)-1** is described in reference 13. Compound **(*S*)-1** (416 mg, 2.85 mmol) was dissolved in 20 mL of 2,2-dimethoxypropane and a catalytic amount of camphorsulfonic acid was added to the solution. After stirring overnight at room temperature, the solvent was removed *in vacuo*. The

resulting precipitate was purified by silica gel CC (EtOAc/hexane, 1:4) to give 489 mg of **9** (2.63 mmol, 92%). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.40 and 1.44 (6H, s, CCH_3), 3.62 (1H, dd, *J* = 8.4, 7.0 Hz, H-5'a), 3.77 (3H, s, OCH_3), 4.38 (1H, dd, *J* = 8.1, 7.0 Hz, H-5'b), 4.87 (1H, tt, *J* = 6.9, 1.6 Hz, H-4'), 6.06 (1H, t, *J* = 1.6 Hz, olefinic), 6.31 (1H, t, *J* = 1.6 Hz, olefinic).

SYNTHESIS OF (*S*)-2-(2',2'-DIMETHYL-1',3'-DIOXOLAN-4'-YL)PROPENIC ACID (10)

To a solution of **9** (87.3 mg, 0.469 mmol) in 4.0 mL of H_2O:MeCN = 1:1(*v*/*v*), 44.4 mg of LiOH· H_2O (1.05 mmol) was added. The mixture was stirred at 55 ℃ overnight, and the mixture was partitioned between Et_2O (x 3) and aqueous citric acid. Combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The subsequent silica gel CC (MeOH/$CHCl_3$, 1:9) gave acid **10** (85%, 0.397 mmol). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.44 and 1.47 (6H, s, CCH_3), 3.65 (1H, dd, *J* = 8.4, 7.0 Hz, H-5'a), 4.38 (1H, dd, *J* = 8.4, 6.8 Hz, OCH2), 4.87 (1H, tt, *J* = 6.9, 1.5 Hz, H-4'), 6.17 (1H, t, *J* = 1.6 Hz, olefinic), 6.45 (1H, t, *J* = 1.5 Hz, olefinic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 25.5 (CCH_3), 26.3 (CCH_3), 70.1 (C-5'), 73.8 (C-4'), 109.6 (C-2'), 127.1 (C-3), 138.5 (C-2), 169.7 (C-1); HR-FD-MS: *m*/*z* $[M+H]^+$ calcd for $C_8H_{13}O_4$,173.08138; found, 173.08218.

SYNTHESIS OF METHYL 3-{[*t*-BUTYL(DIMETHYL)SILYL]OXY}-4-(*p*-METHOXYBENZYLOXY)-2-METHYLENEBUTANOATE (11)

The crude product of Katsuki-Shaprpless[13] kinetic resolution consisting of (***S***)-**8** (344 mg, 1.39 mmol) and (+)-DIPT (456 mg, 2.09 mmol) was used. This mixture was dissolved in 30 mL of CH_2Cl_2, and triethylamine (800 μL, 6.02 mmol) and TBSOTf (1.60 g, 6.02 mmol) were added dropwise in this order at 0 ºC. After the overnight reaction, the mixture was diluted with Et_2O, and which was washed with saturated aqueous $NaHCO_3$. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The resulting mixture was subjected to silica gel CC (EtOAc/hexane, 1:9) giving 376 mg of **11** (0.987 mmol, 77%). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.04 and 0.09 (12H, s, $Si(CH_3)_2$), 0.90 (18H, s, *t*-Bu), 3.37 (1H, dd, *J* = 10.2, 6.6 Hz, H-4a), 3.51 (1H, dd, *J* = 10.2, 3.3 Hz, H-4b), 3.73 (3H, s, OCH_3), 3.80 (3H, s, $ArOCH_3$), 4.42–4.53 (2H, m, benzyl), 4.81 (1H, m, H-3), 6.01 (1H, d, *J* = 1.7 Hz, olefinic), 6.31 (1H, d, *J* = 1.7 Hz, olefinic), 6.86 (2H, d, *J* = 8.6 Hz, aromatic), 7.24 (2H, d, *J* = 8.6 Hz, aromatic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: -5.0 and -4.1 ($Si(CH_3)_2$), 18.2 ($\underline{C}(CH_3)_3$), 25.8 ($C(\underline{C}H_3)_3$), 51.7 (OCH_3), 55.3 ($ArOCH_3$), 70.4 (C-4), 72.8 (C-3), 74.7 (benzyl), 113.6 (aromatic), 126.1 ($C=\underline{C}H_2$), 129.08 (aromatic), 130.6 (aromatic), 141.2 (C-2), 159.0 (aromatic), 166.5 (C-1).

SYNTHESIS OF METHYL 3,4-BIS{[*t*-BUTYL(DIMETHYL)SILYL]OXY}-2-METHYLENEBUTANOATE (12)

To a solution of **11** (376 mg, 0.987 mmol) in CH_2Cl_2 (30 mL), TBSOTf (264 mg, 1.00 mmol) was added dropwise at 0 °C. After the color turned to deep red, to the solution was added triethylamine (140 μL, 1.00 mmol). The mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$ followed by brine. The organic layer was dried over anhydrous Na_2SO_4 and the resultant crude product was purified by silica gel CC (EtOAc/hexane, 1:19) to give 156 mg of **12** (0.416 mmol, 42%). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.03, 0.04, 0.09 (12H, s, $Si(CH_3)_2$), 0.88 and 0.89 (18H, s, *t*-Bu), 3.44 (1H, dd, *J* = 10.0, 6.8 Hz, H-4a), 3.62 (1H, dd, *J* = 10.0, 3.8 Hz, H-4b), 3.76 (3H, s, OCH_3), 4.66 (1H, dd, *J* = 6.6, 3.6 Hz, H-3), 5.98 (1H, d, *J* = 1.6 Hz, olefinic), 6.29 (1H, d, *J* = 0.8 Hz, olefinic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: -5.41, -5.39, -5.0 and -4.7 ($Si(CH_3)_2$), 18.2 and 18.4 ($\underline{C}(CH_3)_3$), 25.8 and 26.0 ($C(\underline{C}H_3)_3$), 51.7 (OCH_3), 68.4 (C-4), 72.0 (C-3), 126.1 ($C=\underline{C}H_2$), 141.6 (C-2), 166.5 (C-1).

SYNTHESIS OF 3,4-BIS{[*t*-BUTYL(DIMETHYL)SILYL]OXY}-2-METHYLENEBUTANOIC ACID (13)

Following the same procedure as the synthesis of **10**, 1.00 g (2.67 mmol) of **12** was hydrolyzed. The final silica gel CC was performed with MeOH/$CHCl_3$, 5:95 as an eluent, which gave 885 mg of acid **13** (2.46 mmol, 92%). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.02, 0.05, 0.06 and 0.11 (12H, s, $Si(CH_3)_2$), 0.88 and 0.91 (18H, s, *t*-Bu), 3.54 (1H, dd, *J* = 10.2, 5.9 Hz, H-4a), 3.64 (1H, dd, *J* = 10.2, 4.3 Hz, H-4b), 4.62 (1H, br d, *J* = 5.1 Hz, H-3), 5.97 (1H, br s, olefinic), 6.42 (1H, br s, olefinic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: -5.49, -5.45, -5.02 and -4.81 ($Si(CH_3)_2$), 18.2 and 18.4 ($\underline{C}(CH_3)_3$), 25.8 and 26.0 ($C(\underline{C}H_3)_3$), 68.3 (C-4), 72.5 (C-3), 128.1 ($C=\underline{C}H_2$), 140.9 (C-2), 170.1 (C-1); HR-FD-MS: *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{37}O_4Si_2$, 361.22304; found, 361.22139.

GENERAL PROCEDURE FOR THE MITSUNOBU REACTION

To the THF solutions of the secondary alcohols (0.1 mmol/mL), 4.0 eq. of the carboxylic acid and triphenylphosphine were added. Diethyl azodicarboxylate (4.0 eq.) was added dropwise to the solution at 0 °C, and the reaction was allowed to stir at room temperature or 60 °C. The reaction was monitored by TLC. After completion, the mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The crude products were finally purified by silica gel CC using appropriate eluents.

GENERAL PROCEDURE FOR DEPROTECTION OF ACETONIDE-TYPE ACYLATES

The acylates were dissolved in MeOH (0.1 mmol/mL) and 4 eq. of PPTS was added. The mixture was stirred at 60 °C until the completion of the reaction. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The aqueous layer was washed another trice with EtOAc. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The evaporated crude products were dissolved in 1.0 mL of the buffers described in Table 1. The production of inverted alcohols were

monitored by reverse-phase HPLC, and the enantiomeric excesses were determined by chiral HPLC using ChiralPak IA column (Daicel, Osaka, Japan) with eluting EtOH/hexane (10:90–15:85) solvent system.

GENERAL PROCEDURE FOR DEPROTECTION OF BISTBS-TYPE ACYLATES

The acylates were dissolved in THF (0.1 mmol/mL) and 4 eq. of TBAF·$3H_2O$ was added. The mixture was stirred at room temperature overnight. THF was removed i*n vacuo*, and the crude products were dissolved in 1.0 mL of MeOH/phosphate buffer 1:1 for HPLC analyses. The HPLC analyses of the products were performed similarly to the above-mentioned methods.

PHYSICOCHEMICAL PROPERTIES OF ACYLATES

(4'*S*, 1''*S*)-1''-Phenyleth-1''-yl 2-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)propenoate (15a): $[\alpha]_D^{25}$ +7.11 (*c* 1.19, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.44 and 1.45 (6H, s, CH_3), 1.58 (3H, d, *J* = 6.8 Hz, H-2''), 3.61 (1H, dd, *J* = 8.0, 7.2 Hz, H-5'a), 4.37 (1H, dd, *J* = 8.4, 6.8 Hz, H-5'b), 4.88 (1H, t, *J* = 6.8 Hz, H-4'), 5.97 (1H, q, *J* = 6.8 Hz, H-1''), 6.06 (1H, s, H-3a), 6.36 (1H, s, H-3b), 7.35 (5H, m, aromatic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 22.2 (C-2''), 25.5 (CH_3), 26.2 (CH_3), 70.2 (C-5'), 72.9 (C-1''), 74.1 (C-4'), 109.4 (C-2'), 124.5 (C-3), 125.9, 128.0 and 128.6 (aromatic), 139.6 (C-2), 141.3 (aromatic), 164.8 (C-1); HR-FI-MS: *m*/*z* $[M]^+$ calcd for $C_{18}H_{20}O_4$, 276.13616; found, 276.13618.

(4'*S*, 1''*S*)-1''-Ethyloxycarbonyl-3''-phenylprop-1''-yl 2-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)propenoate (15b): $[\alpha]_D^{25}$ +19.1 (*c* 0.11, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.26 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.45 and 1.47 (6H, s, CH_3), 2.22 (2H, q, *J* = 7.9 Hz, H-2''), 2.76 (2H, t, *J* = 7.9 Hz, H-3''), 3.66 (1H, dd, *J* = 8.3, 7.0 Hz, H-5'a), 4.19 (1H, m, $C\underline{H}_2CH_3$), 4.38 (1H, dd, *J* = 8.2, 6.9 Hz, H-5'b), 4.91 (1H, t, *J* = 6.9 Hz, H-4'), 5.06 (1H, t, *J* = 6.4 Hz, H-1''), 6.14 (1H, t, *J* = 1.3 Hz, H-3a), 6.38 (1H, t, *J* = 1.3 Hz, H-3b), 7.16–7.33 (5H, m, aromatic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 14.1 ($CH_2\underline{C}H_3$), 25.5 and 26.3 (CH_3), 31.4, (C-3''), 32.7 (C-2''), 61.5 ($\underline{C}H_2CH_3$), 70.2 (C-5'), 72.1 (C-1''), 73.9 (C-4'), 109.6 (C-2'), 125.5 (C-3), 126.3, 128.4 and 128.6 (aromatic), 138.7 (C-2), 140.2 (aromatic), 165.0 (C-1), 169.7 (carbnyl); HR-FD-MS: *m*/*z* $[M]^+$ calcd for $C_{20}H_{26}O_6$, 362.17163; found, 362.17294.

(4'*S*, 1''*R*)-1''-(Benzyloxycarbonyl)eth-1''-yl 2-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)propenoate (15c): $[\alpha]_D^{27}$ +30.4 (*c* 0.51, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.43 and 1.45 (6H, s, CH_3), 1.54 (3H, d, *J* = 6.9 Hz, H-2''), 3.64 (1H, dd, *J* = 8.6, 6.9 Hz, H-5'a), 4.36 (1H, dd, *J* = 8.4, 6.8 Hz, H-5'b), 4.87 (1H, t, *J* = 6.8 Hz, H-3'), 5.17–5.24 (3H, m, H-1'' and benzyl), 6.11 (1H, s, H-3a), 6.40 (1H, s, H-3b), 7.26–7.36 (5H, m, aromatic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 16.9 (C-2''), 25.5 and 26.2 (CH_3), 67.1 (benzyl), 69.0 (C-1''), 70.2 (C-5'), 74.0 (C-4'), 109.5 (C-2'), 125.7 (C-3), 125.7, 128.2, and 128.6 (aromatic), 135.2 (C-2), 138.7 (aromatic), 164.8 (C-1), 170.3 (carbonyl); HR-FI-MS: *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{23}O_6$, 335.14946; found, 335.14845.

(4'*S*, 1''*S*)-1''-(*p*-Tolyl)but-3''-en-1''-yl 2-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)propenoate (15d): $[\alpha]_D^{27}$ +13.5 (*c* 1.19, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.42 and 1.44 (6H, s, CH_3), 2.34 (3H, s, tolyl-CH_3), 2.53–2.75 (2H, m, H-2''), 3.59 (1H, dd, *J* = 8.2, 7.2 Hz, H-5'a), 4.36 (1H, dd, *J* = 8.2, 6.6 Hz, H-5'b), 4.84 (1H, t, *J* = 7.0 Hz, H-4'), 5.63–5.76 (1H, m, H-3''), 5.81 (1H, dd, *J* = 7.6, 5.9 Hz, H-1''), 6.04 (1H, d, *J* = 1.6 Hz, H-3a), 6.34 (1H, s, H-3b), 7.14–7.26 (5H, m, aromatic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 21.2 (tolyl-CH_3), 25.6 and 26.3 (CH_3), 40.7 (C-2''), 70.3 (C-5'), 74.1 (C-4'), 75.8 (C-1''), 109.4 (C-2'), 118.2 (C-4''), 124.5, 126.4, 129.2, 133.2, 136.7, 137.9 and 139.6 (C-2, C-3, C-3'' and aromatic), 164.8 (C-1); HR-FI-MS: *m*/*z* $[M]^+$ calcd for $C_{19}H_{24}O_4$, 316.16746; found, 316.16614.

(4'*S*, 1''*S*)-1'',2'',3'',4''-Tetrahydronaphth-1''-yl 2-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)propenoate (15e): $[\alpha]_D^{25}$ +49.7 (*c* 1.10, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.41 and 1.43 (6H, s, CH_3), 1.87–2.04 (4H, m, H-3'' and H-4''), 2.76–2.88 (2H, m, H-2''), 3.59 (1H, dd, *J* = 8.4, 7.0 Hz, H-5'a), 4.26 (1H, dd, *J* = 8.4, 6.8 Hz, H-5'b), 4.87 (1H, t, *J* = 7.0 Hz, H-4'), 6.03 (1H, d, *J* = 1.6 Hz, H-3a), 6.08 (1H, t, *J* = 4.6 Hz, H-1''), 6.31 (1H, d, *J* = 1.6 Hz, H-3b), 7.16–7.26 (5H, m, aromatic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 18.9 (C-3''), 25.6 and 26.3 (CH_3), 28.9, 29.1 (C-2'' and C-4''), 70.2 (C-5'), 70.6 (C-1''), 74.2 (C-4'), 109.4 (C-2'), 124.7 (C-3), 126.1, 128.2, 129.1, 129.4, 134.1, 137.9 and 139.7 (aromatic and C-2), 165.1 (C-1); HR-FI-MS: *m*/*z* $[M]^+$ calcd for $C_{18}H_{22}O_4$, 302.15181; found, 302.15297.

(4'*S*, 1''*S*, 2''*S*)-2''-Methylcyclohex-1''-yl 2-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)propenoate (15f): $[\alpha]_D^{25}$ +36.5 (*c* 0.02, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.88 (3H, d, *J* =7.0 Hz, cyclohexyl-CH_3), 1.44 and 1.47 (6H, s, acetonide-CH_3), 1.22–1.93 (9H, m, H-2'', H-3'', H-4'', H-5'' and H-6''), 3.62 (1H, dd, *J* = 8.4, 7.0 Hz, H-5'a), 4.37 (1H, dd, *J* = 8.4 Hz, 7.0 Hz, H-5'b), 4.89 (1H, t, *J* = 6.9 Hz, H-4'), 5.02–5.06 (1H, m, H-1''), 6.02 (1H, d, *J* = 1.6 Hz, H-3a), 6.30 (1H, d, *J* = 1.6 Hz, H-3b); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 17.5 (cyclohexyl-CH_3), 21.0 (cyclohexyl-CH_2), 25.5 and 26.3 (acetonide-CH_3), 24.6, 29.6 and 29.8 (cyclohexyl-CH_2), 34.7 (C-2''), 70.4 (C-5'), 74.1 (C-4'), 77.2 (C-1''), 109.4 (C-2''), 124.1 (C-3), 139.8 (C-2), 165.4 (C-1); HR-FI-MS: *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{25}O_4$, 269.17528; found, 269.17452.

(4'*S*, 1''*S*, 2''*S*)-2''-Phenylcyclohex-1''-yl 2-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)propenoate (15g): $[\alpha]_D^{25}$ +145 (*c* 1.02, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.41 and 1.44 (6H, s, acetonide-CH_3), 1.49–2.13 (8H, m, cyclohexyl-CH_2), 2.84 (1H, br d, *J* = 12.7 Hz, H-2''), 3.38 (1H, dd, *J* = 8.1, 7.3 Hz, H-5'a), 4.24 (1H, dd, *J* = 8.1, 7.0 Hz, H-5'b), 4.74 (1H, t, *J* = 7.0 Hz, H-4'), 5.30 (1H, H-1''), 5.96 (1H, s, H-3a), 6.24 (1H, s, H-3b), 7.17–7.29 (5H, m, aromatic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 20.4 (cyclohexyl-CH_2), 25.5 (acetonide-CH_3), 25.9 (cyclohexyl-CH_2), 26.0 (cyclohexyl-CH_2), 26.3 (acetonide-CH_3), 30.7 (cyclohexyl-CH_2), 46.5 (C-2''), 70.2 (C-5'), 73.9 (C-4'), 74.0 (C-1''), 109.3 (C-2'), 123.7 (aromatic), 126.5 (C-3), 127.6 and 128.2 (aromatic), 139.8 (C-2), 142.8 (aromatic), 164.6 (C-1); HR-FI-MS: *m*/*z* $[M]^+$ calcd for $C_{20}H_{26}O_4$, 330.18311; found, 330.18357.

(4*S*, 1'*S*)-1'-Phenyleth-1'-yl 3,4-bis{[*t*-butyl(dimethyl)silyl]oxy}-2-methylenebutanoate (16a): $[\alpha]_D^{25}$ +6.40 (*c* 1.10, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ: -0.01, 0.02, 0.07 and 0.08 (12H, s, $Si(CH_3)_2$), 0.85 and 0.89 (18H, s, *t*-Bu), 1.58 (3H, d, *J* = 6.5 Hz, H-2'), 3.42 (1H, dd, *J* = 10.3, 7.0 Hz, H-4a), 3.63 (1H, dd, *J* =10.3, 3.2 Hz, H-4b), 4.67 (1H, br s, H-3), 5.95–5.97 (2H, m, H-1' and C=C$\underline{H}_2$), 6.34 (1H, d, *J* = 1.6 Hz, C=C$\underline{H}_2$), 7.26–7.36 (5H, m, aromatic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: -5.41, -5.37, -4.9 and -4.7 ($Si(CH_3)_2$), 18.3 and 18.4 ($\underline{C}(CH_3)_3$), 22.4 (C-2'), 25.8 and 26.0 ($C(\underline{C}H_3)_3$), 68.3 (C-4), 72.3 (C-3), 75.5 (C-1'), 125.9 (aromatic), 126.3 (C=$\underline{C}H_2$), 127.8 and 128.5 (aromatic), 141.71, 141.72 (aromatic and C-2), 165.3 (C-1); HR-FI-MS: *m*/*z* $[M+H]^+$ calcd for $C_{25}H_{45}O_4Si_2$, 465.28564; found, 465.28743.

(4'*S*, 1'*S*)-1'-Ethyloxycarbonyl-3'-phenylprop-1'-yl 3,4-bis{[*t*-butyl(dimethyl)silyl]oxy}-2-methylenebutanoate (16b): $[\alpha]_D^{25}$ +10.7 (*c* 0.99, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.04, 0.05, 0.07 and 0.10 (12H, s, $Si(CH_3)_2$), 0.88 and 0.91 (18H, s, *t*-Bu), 1.25 (3H, t, *J* = 7.3 Hz, $CH_2C\underline{H}_3$), 2.18–2.26 (2H, m, H-2'), 2.76 (2H, t, *J* = 7.7 Hz, H-3'), 3.43 (1H, dd, *J* =10.1, 6.9 Hz, H-4a), 3.68 (1H, dd, *J* =10.3, 3.0 Hz, H-4b), 4.18 (2H, q, *J* = 7.0 Hz, $C\underline{H}_2CH_3$), 4.79 (1H, br s, H-3), 5.04 (1H, t, *J* = 6.3 Hz, H-1'), 6.07 (1H, s, C=C$\underline{H}_2$), 6.39 (1H, s, C=C$\underline{H}_2$), 7.16–7.29 (5H, m, aromatic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: -5.4, -5.3, -4.9 and -4.7 ($Si(CH_3)_2$), 14.1 ($CH_2\underline{C}H_3$), 18.3 and 18.4 ($\underline{C}(CH_3)_3$), 25.9 and 26.0 ($C(\underline{C}H_3)_3$), 31.4 (C-2'), 32.8 (C-3'), 61.3 ($\underline{C}H_2CH_3$), 68.2 (C-4), 72.0, 72.2 (C-3 and C-1''), 126.3 (aromatic), 127.4 (C=$\underline{C}H_2$), 128.4 and 128.5 (aromatic), 140.4, 140.7 (aromatic and C-2), 165.5 (C-1), 169.9 (carbonyl); HR-FI-MS: *m*/*z* $[M]^+$ calcd for $C_{29}H_{50}O_6Si_2$, 550.31459; found, 550.31453.

(4*S*, 1'*R*)-1'-(Benzyloxycarbonyl)eth-1'-yl 3,4-bis{[*t*-butyl(dimethyl)silyl]oxy}-2-methylenebutanoate (16c): $[\alpha]_D^{27}$ +174.5 (*c* 1.5, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.0–0.1 (12H, s, $Si(CH_3)_2$), 0.87 and 0.89 (18H, s, *t*-Bu), 1.54 (3H, d, *J* = 6.9 Hz, H-2'), 3.42 (1H, dd, *J* =10.2, 6.6 Hz, H-4a), 3.68 (1H, dd, *J* =10.2, 3.3 Hz, H-4b), 4.66 (1H, q, *J* = 3.4 Hz, H-3), 5.19 (3H, m, benzyl and H-1'), 6.05 (1H, s, C=C$\underline{H}_2$), 6.39 (1H, s, C=C$\underline{H}_2$), 7.34 (5H, m, aromatic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: -5.4 and -5.0 ($Si(CH_3)_2$), 16.9 (C-2'), 18.2 and 18.4 ($\underline{C}(CH_3)_3$), 25.8 and 25.9 ($C(\underline{C}H_3)_3$), 67.0 (benzyl), 68.2 (C-4), 68.7 (C-1'), 72.0 (C-3), 127.2 (aromatic), 128.1 (C=$\underline{C}H_2$), 128.4 and 128.6 (aromatic), 135.3 (C-1') 140.8 (aromatic), 165.4 (C-1), 170.5 (carbonyl); HR-FI-MS: *m*/*z* $[M+H]^+$ calcd for $C_{27}H_{47}O_6Si_2$, 523.29112; found, 523.29136.

(4*S*, 1'*S*)-1'-(*p*-Tolyl)but-3'-en-1'-yl 3,4-bis{[*t*-butyl(dimethyl)silyl]oxy}-2-methylenebutanoate (16d): $[\alpha]_D^{27}$ +66.7 (*c* 0.15, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.0–0.1 (12H, s, $Si(CH_3)_2$), 0.85–0.89 (18H, s, *t*-Bu), 2.33 (3H, s, tolyl-CH_3), 2.53–2.74 (2H, m, H-2'), 3.39 (1H, dd, *J* =10.2, 6.9 Hz, H-4a), 3.64 (1H, dd, *J* =10.2, 3.0 Hz, H-4b), 4.65 (1H, q, *J* = 3.0 Hz, H-3), 5.02–5.11 (2H, m, H-4' and H-1'), 5.97 (1H, t, *J* = 1.6 Hz, C=C$\underline{H}_2$), 6.34 (1H, s, C=C$\underline{H}_2$), 7.12–7.26 (5H, m, aromatic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: -5.0 and -0.2 ($Si(CH_3)_2$), 18.2 and 18.4 ($\underline{C}(CH_3)_3$), 21.1 (tolyl-CH_3), 25.8 and 26.0

(C(CH$_3$)$_3$), 40.9 (C-2'), 68.2 (C-4), 72.3 (C-3), 75.3 (C-1'), 118.2 (C-4'), 126.35, 126.44, 129.1, 133.4, 137.1 and 141.5 (C=CH$_2$, C-3' and aromatic) 165.2 (C-1); HR-FI-MS: *m*/*z* [M+H]$^+$ calcd for $C_{28}H_{49}O_4Si_2$, 505.31694; found, 505.31592.

(4*S*, 1'*S*)-1',2',3',4'-Tetrahydronaphth-1'-yl 3,4-bis{[*t*-butyl(dimethyl)silyl]oxy}-2-methylenebutanoate (16e): $[\alpha]_D^{25}$ +25.3 (*c* 1.20, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ: -0.02, 0.01, 0.02 and 0.08 (12H, s, Si(CH$_3$)$_2$), 0.85 and 0.88 (18H, s, *t*-Bu), 1.78–2.07 (4H, m, cyclohexyl-CH$_2$), 2.70–2.93 (2H, m, H-4'), 3.43 (1H, dd, *J* = 9.9, 6.5 Hz, H-4a), 3.62 (1H, dd, *J* = 9.9, 3.1 Hz, H-4b), 4.66 (1H, q, *J* =3.3 Hz, H-3), 5.95 (1H, t, *J* = 1.6 Hz, C=CH$_2$), 6.09 (1H, t, *J* = 4.7 Hz, H-1'), 6.29 (1H, d, *J* = 1.6 Hz, C=CH$_2$), 7.11–7.26 (5H, m, aromatic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: -5.44, -5.41, -4.9 and -4.7 (Si(CH$_3$)$_2$), 18.3 and 18.4 (C(CH$_3$)$_3$), 19.0 (C-3'), 25.8 and 26.0 (C(CH$_3$)$_3$), 29.0, 29.2 (C-2' and C-4'), 68.2 (C-4), 70.2 (C-1'), 72.3 (C-3), 126.1, 126.5, 128.0 and 129.0 (C-5', C-6', C-7', C-8' and C=CH$_2$), 134.6, 137.9, 141.7 (C-2', C-4'a and C-8'a) 165.8 (C-1); HR-FI-MS: *m*/*z* [M+H]$^+$ calcd for $C_{27}H_{47}O_4Si_2$, 491.30129; found, 491.29992.

(4*S*, 1'*S*, 2'*S*)-2'-Phenylcyclohex-1'-yl 3,4-bis{[*t*-butyl(dimethyl)silyl]oxy}-2-methylenebutanoate (16g): $[\alpha]_D^{25}$ +84.0 (*c* 1.63, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ: -0.04, 0.01 and 0.07 (12H, s, Si(CH$_3$)$_2$), 0.88 (18H, s, *t*-Bu), 1.53–2.13 (8H, m, cyclohexyl-CH$_2$), 2.83 (1H, dt, *J* = 12.4, 2.9 Hz, H-2'), 3.24 (1H, dd, *J* = 10.2, 7.2 Hz, H-4a), 3.54 (1H, dd, *J* = 10.2, 2.3 Hz, H-4b), 4.56 (1H, br d, *J* = 6.9 Hz, H-3), 5.27 (1H, br s, H-1'), 5.90 (1H, d, *J* = 1.6 Hz, C=CH$_2$), 6.25 (1H, t, *J* = 1.7 Hz, C=CH$_2$), 7.16–7.26 (5H, m, aromatic); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: -5.5, -5.4, -5.0 and -4.7 (Si(CH$_3$)$_2$), 18.2 and 18.3 (C(CH$_3$)$_3$), 20.4 (cyclohexyl-CH$_2$), 25.8 (cyclohexyl-CH$_2$), 26.0 (cyclohexyl-CH$_2$), 30.6 (cyclohexyl-CH$_2$), 46.5 (C-2'), 68.5 (C-4), 72.5 (C-3), 73.7 (C-1'), 126.0 (aromatic), 126.4 (C=CH$_2$), 127.7 and 128.2 (aromatic), 141.5 (C-2), 143.0 (aromatic), 165.0 (C-1); HR-FI-MS: *m*/*z* [M+H]$^+$ calcd for $C_{29}H_{51}O_4Si_2$, 519.33259; found, 519.33272.

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