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Improved catalytic and stereoselective glycosylation with glycosyl *N*-trichloroacetylcarbamate: application to various 1-hydroxy sugars

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ABSTRACT

Efficient catalytic and stereoselective glycosylation was achieved by activating a glycosyl *N*-trichloroacetylcarbamate with a catalytic amount of Lewis acid in the presence of a glycosyl acceptor and 5 Å molecular sieves. Catalytic one-pot dehydrative glycosylation of a 1-hydroxy carbohydrate was achieved stereoselectively by reaction with trichloroacetyl isocyanate, followed by activation with a catalytic amount of activators.

1. Introduction

O-Glycosylation is a crucial method for the construction of *O*-glycosyl bonds, which are found in natural products and biologically active compounds.[1] Many O-glycosylation methods have been disclosed[2] since the emergence of the Koenigs–Knorr procedure. For example, Schmidt and Kinzy have reviewed the glycosylation with trichloroacetimidate derivatives,[2c] which has two attractive features. One is the smooth promotion of the reaction by catalytic amounts of Lewis acid under mild conditions, and the other is the easy preparation of the glycosyl donor by treating a 1-hydroxy carbohydrate with trichloroacetonitrile in the presence of a base such as NaH or DBU.

A more convenient method for preparing glycosyl donors would be useful for generating the *O*-glycosyl bond. The high reactivity of trichloroacetyl isocyanate, which usually reacts with alcohols under neutral conditions to generate the corresponding *N*-trichloroacetyl carbamate, is an attractive approach. We were also interested in knowing whether the *N*-trichloroacetyl carbamate group would be a good leaving group for glycosylation. Some glycosylation reactions employing glycosyl carbamates as a glycosyl donor have been reported, and these are activated by using a stoichiometric amount of activators. Kunz and Zimmer reported the first example of employing a glycosyl carbamate for glycosylation, utilizing glycosyl *N*-allylcarbamates by activation of the allylic double bond with a soft electrophile, dimethylmethylthiosulfonium triflate (DMTST).[3] Lacombe and co-workers reported glycosylation using glycosyl *N*-phenylcarbamates and a stoichiometric amount of $BF_3{\cdot}Et_2O$.[4] Although Kiessling reported that glycosyl *N*-alkyl-*N*-*p*-toluenesulfonylcarbamates were activated with a catalytic amount of Me_3SiOTf, N-unalkylated sulfonylcarbamates were not activated under these conditions, and they required N-methylation or N-cyanomethylation for catalytic activation.[5]

Redlich and co-workers[6] were the first to report glycosylation using glycosyl *N*-trichloroacetyl carbamate, activated with a stoichiometric amount of Lewis acid. Jayakanthan and Vankar[7] reported catalytic glycosylation with glycosyl *N*-trichloroacetyl carbamate, but the α:β selectivity was low.

We believed that a more efficient and stereoselective glycosylation could be achieved using a glycosyl trichloroacetyl carbamate and by varying experimented conditions already reported by Redlich and co-workers[6] and Jayakanthan and Vankar.[7] Reaction conditions for catalytic and stereoselective glycosylation with glycosyl trichloroacetyl carbamate have been devised in our laboratory.[8] In this paper, we describe in detail catalytic and stereoselective glycosylation using a glycosyl *N*-trichloroacetylcar-

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bamate and the catalytic one-pot dehydrative glycosylation of a 1-hydroxy carbohydrate.

2. Results and discussion

2.1. Preparation of glycosyl *N*-trichloroacetylcarbamate

A glycosyl *N*-trichloroacetylcarbamate donor **2** was prepared from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **1** (α:β = 86:14, anomeric ratio determined by ^{1}H NMR spectroscopy in C_6D_6) by the reaction of 1.1 equiv of trichloroacetyl isocyanate in dry CH_2Cl_2 at room temperature (Scheme 1). The reaction was complete after 30 min, and evaporation of CH_2Cl_2 in vacuo gave **2** quantitatively as a mixture of anomers (α:β = 89:11, anomeric ratio determined by ^{1}H NMR spectroscopy in $CDCl_3$). Donor **2** was employed in the next glycosylation reaction without purification and could be stored in a refrigerator for several months. The α-anomer of **2** could be isolated in 72% yield by column chromatography on silica gel.

2.2. Glycosylation of 2,3,4,6-tetra-*O*-benzyl-D-glycosyl donors

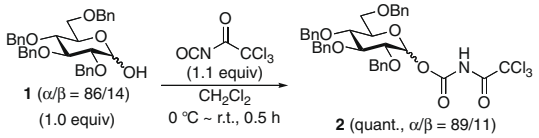
2.2.1. Optimization of reaction conditions

With glycosyl donor **2** in hand, activation conditions for the glycosylation of **2** with methyl 2,3,4-tri-*O*-benzoyl-D-glucopyranoside (**3**)[9] (1.0 equiv) were screened in CH_2Cl_2 over 5 Å molecular sieves (5 Å MS). Although $Zn(OTf)_2$ did not activate donor **2** (Table 1, entry 1), glycosylation proceeded moderately using TfOH and $Sc(OTf)_3$ (entries 2 and 3). The same reaction proceeded slowly using other Lewis acids such as $Mg(ClO_4)_2$ and $Cu(OTf)_2$, even at room temperature (entries 4 and 5). It was found that 1.2 equiv of TMSOTf smoothly activated the glycosylation process at 0 °C to afford the disaccharide **4**[10] in 95% yield as a mixture of anomers (α:β = 61:39, anomeric ratio determined by ^{1}H NMR spectroscopy in $CDCl_3$ and HPLC) (entry 6). The use of a catalytic amount of TMSOTf (0.2 equiv) promoted glycosylation in a yield similar to that obtained using stoichiometric conditions (92% yield, entry 7). Glycosylation using $SnCl_4$ as a promoter gave **4** in lower yield than when using either catalytic or stoichiometric amounts of TMSOTf (entries 8 and 9).

Next, we investigated the combination of solvent and Lewis acid for α-selective glycosylation with **2** and **3**. Good α-selectivity (α:β = 87:13) was observed for TMSOTf-catalyzed glycosylation in Et_2O (Table 2, entry 1). The α-selectivity ratio was further improved (α:β = 93:7) by changing the activator to $TMSClO_4$ (entry 2).[11] When a catalytic amount (20 mol %) of $TMSClO_4$ was employed, the reaction proceeded smoothly to give **4** in 97% yield and high α-selectivity (α:β = 94:6, entry 3). Even 10 mol % of $TMSClO_4$ catalyzed the glycosylation efficiently (α:β = 93:7, entry 4).

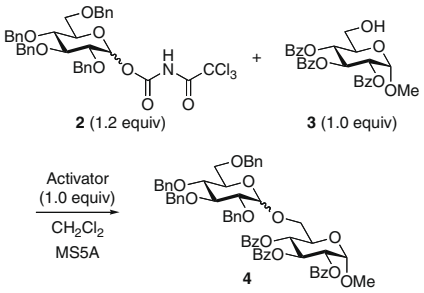
Purified α isomer of **2**, used in catalytic α-selective glycosylation with $TMSClO_4$ (Table 2, entry 4), provided the same α,β-selectivity as using an α,β-mixture of **2** (Table 2, entry 3). These results suggested that $TMSClO_4$ effectively activates the carbamate carbonyl group of **2**, resulting in the formation of an oxonium cation intermediate. Catalytic glycosylation required longer reaction times compared to stoichiometric glycosylation, but nearly quantitative yields of disaccharides **4** were obtained from both the stoichiometric and catalytic glycosylation reactions. Interestingly, catalytic glycosylation required the presence of 5 Å MS, since the $TMSClO_4$-catalyzed glycosylation did not proceed in the presence of 4 Å MS or 3 Å MS. The reasons for the outstanding effects of 5 Å MS are not clear, but similar effects of 5 Å MS have been observed in the catalytic glycosylation of glycosyl fluorides.[12]

Subsequently, we turned to β-selective glycosylation (α:β = 6:94) performed in MeCN[13] containing a stoichiometric amount of TMSOTf[14] (Table 3, entry 1) with **2** and **3**. The reaction proceeded at a lower temperature (−40 °C) than the α-selective reaction in Et_2O. When a catalytic amount of TMSOf was employed in MeCN, the desired glycoside was obtained with lower β-selectivity (13:87) and in lower yield (51%, entry 3). Efficient catalytic β-selective glycosylation was realized by using 20 mol % of TMSOTf in EtCN to afford disaccharide **4** in 99% yield, with a ratio of



Scheme 1. Preparation of glycosyl donor **2**.

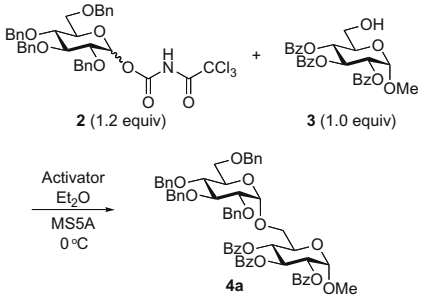
Table 1
Effect of Lewis acids in glycosylation with glycosyl donor **2**[a]



Entry	Activator	Temp. (°C)	Time	Yield (%)	α:β[b]
1	$Zn(OTf)_2$	rt	2 days	0	—
2	TfOH	rt	2 h	40	71:29
3	$Sc(OTf)_3$	rt	1.5 h	49	40:60
4	$Mg(ClO_4)_2$	rt	2.5 h	73	73:27
5	$Cu(OTf)_2$	rt	1.5 h	84	74:26
6	TMSOTf[c]	0	20 min	95	61:39
7	TMSOTf[d]	0	1 h	92	70:30
8	$SnCl_4$	0	20 min	61	47:53
9	$SnCl_4$	0	2 h	84	44:56

[a] The donor **2** (α:β = 89:11) was used unless otherwise noted.
[b] Determined by ^{1}H NMR spectroscopy (500 MHz) and HPLC.
[c] TMSOTf (1.2 equiv) was employed.
[d] TMSOTf (0.2 equiv) was employed.

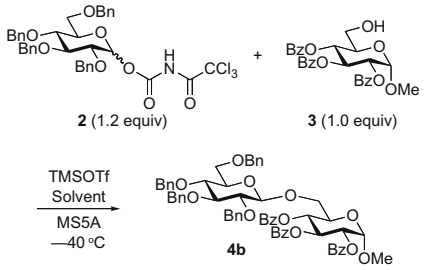
Table 2
α-Selective glycosylation with glycosyl donor **2**[a]



Entry	Activator (equiv)	Time (h)	Yield (%)	α:β[b]
1	TMSOTf (1.2)	8	98	87:13
2	$TMSClO_4$ (1.2)	1	99	93:7
3	$TMSClO_4$ (0.2)	3	97	94:6
4[c]	$TMSClO_4$ (0.1)	18	98	93:7

[a] The donor **2** (α:β = 89:11) was used unless otherwise noted.
[b] Determined by ^{1}H NMR spectroscopy (500 MHz) and HPLC.
[c] The α isomer of **2** was employed.

Table 3
β-Selective glycosylation with glycosyl donor **2**[a]



Entry	Activator (equiv)	Solvent	Temp. (°C)	Time	Yield (%)	α:β[b]
1	1.2	MeCN	−40	40 min	93	6:94
2	0.2	MeCN	—	—	0	—
3	0.2	MeCN	0 then rt	12 h 2.5 h	51	13:87
4[c]	0.2	EtCN	−40 then −23	40 min 1 h	93	7:93

[a] The donor **2** (α:β = 89:11) was used unless otherwise noted.
[b] Determined by ^{1}H NMR spectroscopy (500 MHz) and HPLC.
[c] The α isomer of **2** was employed.

α:β = 7:93 (entry 4). The use of EtCN as the solvent therefore greatly improved both β-selectivity and chemical yield.

2.2.2. One-pot dehydrative glycosylation

Most conventional glycosylation reactions have been conducted in two steps: (1) isolation of a glycosyl donor having a latent-leaving group at the anomeric position and (2) activation of the leaving group in the presence of a glycosyl acceptor. When glycosyl donors are unstable and difficult to isolate, it is desirable to perform the glycosylation by derivatizing a stable 1-hydroxy carbohydrate with a reactive glycosyl donor in situ, followed by activation in a one-pot manner. Since there are no side-products in the preparation of **2**, one-pot glycosylation (i.e., dehydrative glycosylation)[15] of the 1-hydroxy sugar **1** was investigated (Table 4). In this dehydrative glycosylation starting from **1**, CH_2Cl_2 was used as the co-solvent in the preparation of the carbamate donor **2** because of the low solubility of **1** in Et_2O and EtCN. Before adding $TMSClO_4$ or TMSOTf to the reaction mixture, acceptor **3** was added in either Et_2O or EtCN. By following this procedure, the stoichiometric one-pot glycosylation proceeded smoothly using 1.5 equiv of $TMSClO_4$ in Et_2O or TMSOTf in EtCN to afford the α- or β-glycoside, respectively, in high yields (entries 1 and 3). One-pot catalytic glycosylation in the absence of 5 Å MS did not proceed when using the previous procedure (entry 4). The procedure for the one-pot catalytic glycosylation was slightly modified to put 5 Å MS into the reaction medium after preparing the glycosyl donor. The catalytic one-pot dehydrative glycosylation proceeded stereoselectively in the presence of 5 Å MS (entries 2 and 5). We believe that the one-pot catalytic glycosylation might require 5 Å MS. The presence of 5 Å MS in catalytic reactions prevents the hydrolysis of Lewis acids by trace amounts of H_2O in the reaction medium. The ease of the present glycosylation method, especially for one-pot dehydrative glycosylation, will be useful in the synthesis of oligosaccharides or bioactive compounds having carbohydrate moieties.

2.2.3. Scope of stereoselective glycosylation with *N*-trichloroacetylcarbamate

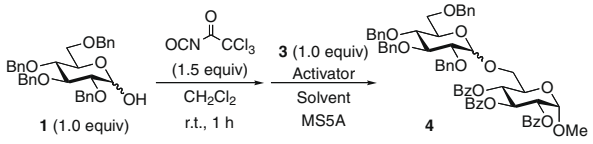
Next, the scope and limitations of catalytic and stereoselective glycosylation with **2** were investigated by using various glycosyl acceptors under α- and β selective glycosylation conditions (Table 5).

The glycosylation of 2,3,4-tri-O-benzylated acceptor **5**[16] bearing a primary hydroxy group proceeded smoothly to afford the corresponding disaccharides **11**.[17] The α and β selectivities were similar to those obtained using **3** as the glycosyl acceptor (entries 1 and 2). Glycosyl donors **6** and **7**,[13] which have a secondary hydroxy group, reacted similar to **3** and **5** under α-selective conditions ($TMSClO_4$ in Et_2O) (entries 3 and 5), whereas they reacted slowly in β-selective glycosylation conditions (TMSOTf in EtCN) and the observed β-selectivities were slightly lower (entries 4 and 6). Cholesterol (**8**), which does not have a sugar moiety, is also a good acceptor for α- and β-selective glycosylation (entries 7 and 8). Glycosylation with protected serine derivatives **9**[18] afforded the corresponding α isomer **15a** and β isomer **15b**[19] in high yields (entries 9 and 10). These results suggest that the present glycosylation method can be employed in glycoprotein research. When the acceptor has a tertiary hydroxy group, as in the case of *tert*-BuOH (**10**), the α-selective reaction proceeds efficiently, given a sufficiently long reaction time (entry 11). On the other hand, the β-selective reaction proceeds slowly to afford the corresponding glycoside in low yield and with only moderate β selectivity (entry 12).

2.3. Glycosylation of various glycosyl *N*-trichloroacetylcarbamates

2,3,4,6-Tetra-*O*-benzyl-D-galactosyl **18**, 2,3,4,6-tetra-*O*-benzyl-D-mannnosyl **20** and 2,3-di-*O*-benzyidene-D-mannnosyl donors **22** were prepared from the corresponding 1-hydroxy sugars, **17**,[20] **19**[21] and **21**[22] according to standard procedures (Scheme 2). The α- and β-selective glycosylations with galactosyl donor **18**

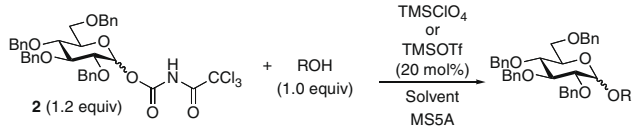
Table 4
One-pot dehydrative glycosylation[a]

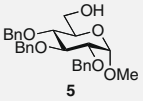
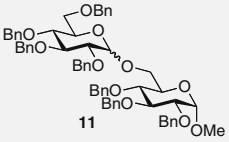
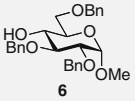
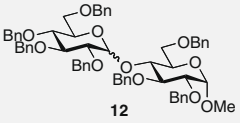
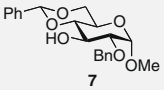
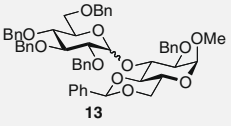
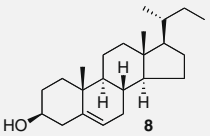
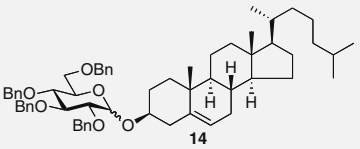
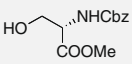
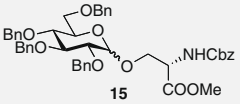
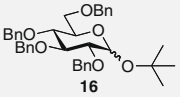


Entry	Activator (equiv)	Solvent[b]	Reaction conditions	Yield (%)	α:β[c]
1[d]	$TMSClO_4$ (1.5)	Et_2O	0 °C, 0.5 h	99	93:7
2	$TMSClO_4$ (0.2)	Et_2O	0 °C, 0.5 h	88	91:9
3[d]	TMSOTf (1.5)	EtCN	−40 °C, 0.5 h then −23 °C, 0.5 h	88	8:92
4[d]	TMSOTf (0.2)	EtCN	−40 °C, 0.5 h then −23 °C, 0.5 h	0	—
5	TMSOTf (0.2)	EtCN	−40 °C, 1 h then −23 °C, 1 h	85	12:88

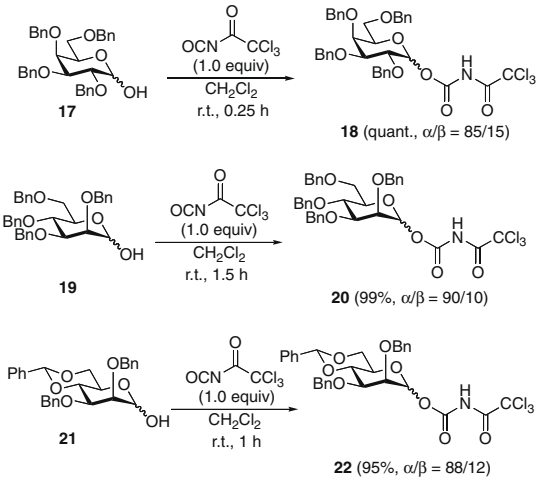
[a] The donor **2** (α:β = 89:11) was used unless otherwise noted.
[b] Solvent/CH_2Cl_2 = 5:1.
[c] Determined by ^{1}H NMR spectroscopy (500 MHz) and HPLC.
[d] 5 Å MS was not used.

Table 5
Stereoselective glycosylation of **2** with acceptor alcohol[a]



Entry	Acceptor	Activator	Solvent	Temp. (°C)	Time (h)	Product	Yield (%)	α:β[b]
1		$TMSCl_4$	Et_2O	0	4		98	94:6
2	5	TMSOTf	EtCN	−40 then −23	0.5 3	11	99	7:93
3		$TMSClO_4$	Et_2O	0	5		93	90:10
4	6	TMSOTf	EtCN	−40 then −23	1.5 16	12	83	15:85
5		$TMSClO_4$	Et_2O	0	3		86	96:4
6	7	TMSOTf	EtCN	−20	1	13	74	17:83
7		$TMSClO_4$	Et_2O	0	4		93	94:6
8	8	TMSOTf	EtCN	0 then rt	2 1	14	88	21:79
9		$TMSClO_4$	Et_2O	0	3		90	92:8
10	9	TMSOTf	EtCN	−40 then −23	0.5 4.5	15	88	20:80
11		$TMSClO_4$	Et_2O	0	19		89	86:14
12[c]	10	TMSOTf	EtCN	rt	96	16	38	39:61

[a] The donor **2** (α:β = 89:11) was used unless otherwise noted.
[b] Determined by ^1H NMR spectroscopy (500 MHz) and HPLC.
[c] Glycosyl donor **2** (1.0 equiv) and acceptor **10** (2.0 equiv) were employed.



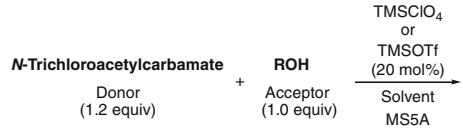
Scheme 2. Preparation of various glycosyl donors.

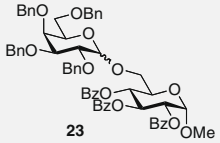
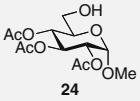
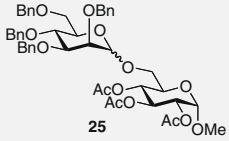
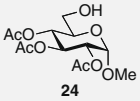
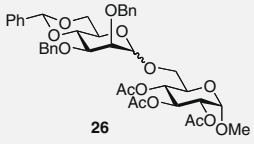
gave good yields and selectivities (Table 6, entries 1 and 2). The α-selective reaction between the mannosyl donor **20** and the acceptor **24**[23] smoothly proceeded in good yield and selectivity (entry 3). Glycosylation of mannosyl donor **20** with acceptor **24** using TMSOTf in MeCN proceeded smoothly, but the α glycoside was obtained as the major product (entry 4). In order to prepare the β glycoside more selectively, we employed the *O*-benzylidene-protected donor **22**.[24a] As expected, β selectivity was enhanced, but the yield was low when the reaction was carried out at −20 °C (entry 5). The same glycosylation at room temperature gave the desired glycosides in low yield because of the deprotection of the benzylidene acetal with TMSOTf (entry 6).

2.4. Model study for the construction of the glycosyl bond in natural products

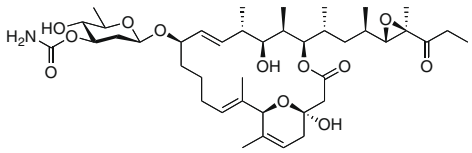
We are interested in the synthesis of irumamycin (**27**) (Fig. 1), initially isolated from culture broth of *Streptomyces subflavus* subsp., *Irumaensis* nov. subsp. AM-3603, and which exhibits high activity against phytopathogenic fungi.[25] The sugar moiety of irumamycin, 2-deoxy-D-rhamnose, is connected to the aglycon of irumamycin by a β-glycosidic bond. Roush and co-workers have already reported that the stereoselective construction of the 2-deoxy-D-rhamnose moiety was achieved by glycosylation with 2-SPh, 6-bromoglucose derivatives, followed by reduction of bromine and the thiophenyl group.[26] The selective glycosylation of 2-deoxysugars is still a challenging topic in synthetic organic

Table 6
Glycosylation of various glycosyl *N*-trichloroacetylcarbamates



Entry	Donor	Acceptor	Activator	Solvent	Temp. (°C)	Time (h)	Product	Yield (%)	α:β[a]
1	**18**[b]	**3**	$TMSClO_4$	Et_2O	0	1	 **23**	90	87:13
2			TMSOTf	EtCN	−40	20		96	19:81
3	**20**[c]	 **24**	TMSOTf	Et_2O	rt	0.25	 **25**	99	94:6
4			TMSOTf	MeCN	−40	0.5		99	76:24
5	**22**[d]	 **24**	TMSOTf[e]	CH_2Cl_2	−20	4	 **26**	25	27:73
6			TMSOTf[e]	CH_2Cl_2	rt	1.5		34	22:78

[a] Determined by ^1H NMR spectroscopy (500 MHz) and HPLC.
[b] Donor **18** (α:β = 85:15) was used.
[c] Donor **20** (α:β = 90:10) was used.
[d] Donor **22** (α:β = 88:12) was used.
[e] TMSOTf (1.2 equiv) was employed.



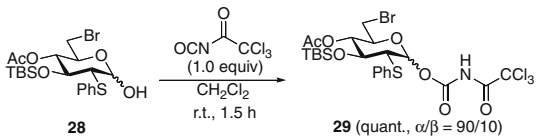
27

Figure 1. The structure of irumamycin (**27**).

chemistry. The glycosyl donor **29** was synthesized from 1-hydroxy sugar **28**[26] with *N*-trichloroacetylisocyanate in CH_2Cl_2 in quantitative yield using our general procedure (Scheme 3). The model study for the stereoselective construction of the β-glycosylic bond of irumamycin was performed using 2-propanol (**30**) as an acceptor. Undesired α-selectivity was observed when glycosylation was conducted at −5 °C (Table 7, entry 1), while the same glycosylation reaction at room temperature gave the product in improved yield as well as with the desired β selectivity (entry 2). Glycosylation at higher temperature (40 °C) using 1,2-dichlorethane as a solvent resulted in acceptable yield and β selectivity (entry 3).

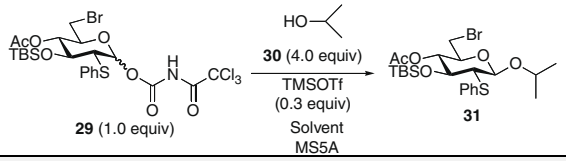
2.5. Plausible reaction mechanism

A mechanism for glycosylation with glycosyl *N*-trichloroacetylcarbamate by TMSOTf as an activator is proposed in Scheme 4. The carbonyl group of the glycosyl donor **33** is activated with TMSOTf



Scheme 3. The synthesis of glycosyl donor **31**.

Table 7
Model study for the construction of the glycosyl-bond of irumamycin[b]



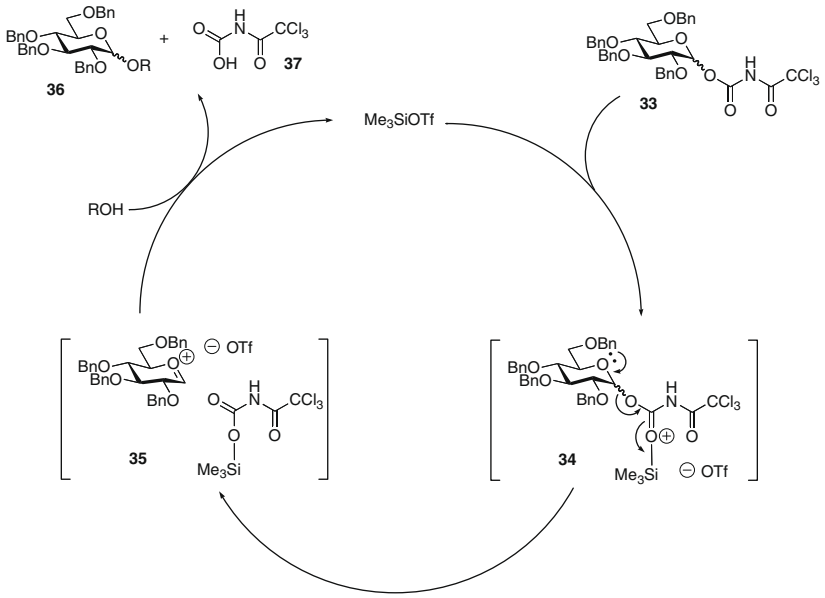
Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)	α:β[a]
1	CH_2Cl_2	−5	14	19	78:22
2	CH_2Cl_2	rt	19.5	56	20:80
3	1,2-Dichloroethane	40	0.25	70	19:81

[a] Determined by ^1H NMR spectroscopy (500 MHz) and HPLC.
[b] The donor **29** (α:β = 90:10) was used.

to form intermediate **34**, which collapses to an oxocarbenium cation intermediate along with trimethylsilyl *N*-trichloroacetyl carbamate (**35**). A glycosyl acceptor then reacts with intermediate **35** to give glycoside **36** and *N*-trichloroacetyl carbamic acid (**37**). The low reactivity and β selectivity obtained in the glycosylation of benzylidene-protected mannosyl donor **22** might be explained by the interaction of trimethylsilyl *N*-trichloroacetyl carbamate or *N*-trichloroacetyl carbamic acid.

3. Conclusions

The α- or β-selective glycosylation using glycosyl *N*-trichloroacetylcarbamate **2** as a glycosyl donor proceeded efficiently by activating the donor with a catalytic amount of $TMSClO_4$ in Et_2O or TMSOTf in EtCN in the presence of 5 Å MS. Preparation of **2** from a 1-hydroxy carbohydrate **1** and successive stereoselective and catalytic glycosylations were also realized in a one-pot manner, and the desired α or β glycoside was obtained directly from **1**. The ease of the present glycosylation approach, especially for the one-pot



Scheme 4. Plausible reaction mechanism of TMSOTf-catalyzed glycosylation of **33**.

dehydrative glycosylation, will be useful in the synthesis of oligosaccharides or other bioactive compounds having carbohydrate moieties.

4. Experimental

4.1. General methods

^{1}H NMR spectra were measured on a Varian VXR-300 (300 MHz) or on a JEOL JNM-ECP500 (500 MHz) spectrometer; chemical shifts (δ) are reported in parts per million relative to internal tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. ^{13}C NMR spectra were measured on a Varian VXR-300 (75 MHz) or on a JEOL JNM-ECP500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative to tetramethylsilane, using the residual solvent resonance as the internal standard ($CDCl_3$; 77.0 ppm, C_6D_6; 128.0 ppm). High-performance liquid chromatography (HPLC) was carried out using a Senshu UV–vis Detector (SSC-5410) and Senshu HPLC-pump (SSC-3461) with Senshu Pak PEGASIL Silica Gel 60-5 (normal phase: 4.6 ø × 250 mm). Analytical TLC was done on precoated (0.25 mm) Silica Gel 60 F254 plates (E. Merck). Thin-layer chromatography (TLC) was performed on Wakogel B-5F (Wako). Column chromatography was performed on Silica Gel 60 (Kanto Chemical Co., Inc. Silica Gel 60 N (63–210 mm)). All reactions were carried out under an argon atmosphere in dried glassware, unless otherwise noted. All reagents were purchased from Tokyo Kasei Kogyo, Kanto Chemical, Fluka or Sigma–Aldrich Chemical Co. and used without further purification, unless otherwise noted. Acetonitrile and propionitrile were distilled from P_2O_5 and then from CaH_2, and were stored over 4 Å molecular sieves. Dichloromethane was freshly distilled from CaH_2. Powdered and pre-dried molecular sieves 4 Å, and 5 Å were used in glycosylation. A 0.1 M solution of $TMSClO_4$ in Et_2O was prepared as follows: To a solution of $AgClO_4$ (38.4 mg, 185 μmol) in Et_2O (1.85 mL) at 0 °C was added TMSCl (20.5 mg, 189 μmol) and this mixture was stirred. After the mixture was left standing for 10 min without stirring, the supernatant was used for glycosylation as a catalyst. [Caution: Explosive reagent!]

4.2. Preparation of the glycosyl *N*-trichloroacetylcarbamate

4.2.1. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl *N*-trichloroacetylcarbamate (2a and 2b)

To the stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1**) (1.00 g, 1.85 mmol) in dry CH_2Cl_2 was added trichloroacetyl isocyanate (0.24 mL, 2.01 mmol) at 0 °C. After the reaction mixture was stirred at room temperature for 0.5 h, the solvent was evaporated in vacuo to give a mixture of **2a** and **2b** as colorless syrup (quant., α:β = 87:11, as determined by ^{1}H NMR spectroscopy). If necessary, the α isomer **2a** (R_f 0.40, 3:1 hexanes–AcOEt) and the β isomer **2b** (R_f 0.34, 3:1 hexanes–AcOEt) were separated, and the α isomer was isolated in 72% yield by column chromatography on silica gel (7:1 hexanes–AcOEt).

α Isomer (**2a**): ^{1}H NMR (300 MHz, C_6D_6): δ 8.11 (s, 1H, N–H), 7.05–6.75 (m, 20H, Ph–*H*), 6.33 (d, $J_{1,2}$ 3.5 Hz, 1H, H-1), 4.65 (d, *J* 11.4 Hz, 1H, CH_2Ph), 4.64 (d, *J* 11.1 Hz, 1H, CH_2Ph), 4.53 (d, *J* 11.4 Hz, 1H, CH_2Ph), 4.37 (d, *J* 11.1 Hz, 1H, CH_2Ph), 4.23 (d, *J* 11.4 Hz, 1H, CH_2Ph), 4.13 (d, *J* 11.4 Hz, 1H, CH_2Ph), 4.12 (d, *J* 12.0 Hz, 1H, CH_2Ph), 4.00 (d, *J* 11.1 Hz, 1H, CH_2Ph), 3.96 (m, 2H, H-3, H-5), 3.62 (dd, *J* 9.7, 9.5 Hz, 1H, H-4), 3.44 (dd, $J_{6a,6b}$ 11.0, $J_{5,6a}$ 3.2 Hz, 1H, H-6a), 3.29 (dd, $J_{6a,6b}$ 11.0, $J_{5,6b}$ 1.5 Hz, 1H, H-6b), 3.29 (dd, $J_{2,3}$ 9.5, $J_{1,2}$ 3.5 Hz, 1H, H-2). ^{13}C NMR (75 MHz); δ 158.0 (C═O), 150.0(C═O), 140.0, 138.4, 129.1, 129.0, 128.9, 128.84, 128.84, 128.81, 128.80, 128.79, 128.55, 128.54, 128.54, 128.49, 128.45, 128.23, 128.23, 128.1, 128.0, 95.0 (C-1), 92.5 (CCl_3), 82.3 (C-3), 79.7 (C-2), 77.6 (C-4), 76.0, 75.7, 74.9 (C-5), 73.98, 73.97, 68.9 (C-6).

β Isomer (**2b**): ^{1}H NMR (300 MHz, C_6D_6): δ 7.76 (s, 1H, N–H), 7.04–6.72 (m, 20H, Ph–H), 5.54 (d, $J_{1,2}$ 7.5 Hz, 1H, H-1), 4.58 (d, *J* 11.3 Hz, 1H, CH_2Ph), 4.54 (d, *J* 11.3 Hz, 1H, CH_2Ph), 4.51 (d, *J* 11.3 Hz, 1H, CH_2Ph), 4.47 (m, 2H, CH_2Ph), 4.30 (d, *J* 11.3 Hz, 1H, CH_2Ph), 4.10 (d, *J* 12.0 Hz, 1H, CH_2Ph), 3.95 (d, *J* 11.3 Hz, 1H, CH_2Ph), 3.59 (dd, $J_{4,5}$ 9.8, $J_{3,4}$ 9.4 Hz, 1H, H-4), 3.40–3.35 (m, 2H, H-2, H-3), 3.33 (dd, $J_{6a,6b}$ 10.8, $J_{5,6a}$ 3.1 Hz, 1H, H-6a), 3.28 (dd, $J_{6a,6b}$ 10.8, $J_{5,6b}$ 2.1 Hz, 1H, H-6b), 3.06 (ddd, $J_{4,5}$ 9.8, $J_{5,6a}$ 3.1, $J_{5,6b}$ 2.1 Hz, 1H, H-5). ^{13}C NMR (75 MHz): δ 157.7 (C═O), 149.1 (C═O), 139.4, 139.3, 139.1, 138.9, 129.00, 128.96, 128.91, 128.5, 128.41, 128.41, 128.2, 97.1 (C-1), 92.4 (CCl_3), 97.1 (C-3), 81.1 (C-2), 77.7 (C-4), 76.3 (C-5), 76.0, 75.3, 75.2, 74.0, 68.9 (C-6).

4.3. Glycosylation with 2,3,4,6-tetra-*O*-benzyl-D-glycosyl donors

4.3.1. Reaction optimization

4.3.1.1. Typical procedure for glycosylation with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl *N*-trichloroacetylcarbamate (2a and 2b): methyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (Table 1, entry 7). To a stirred suspension of 5 Å MS (118.1 mg, 5 Å MS:acceptor = 3 g/1 mmol), 2 (34.9 mg, 47.8 μmol) and acceptor 3 (20.1 mg, 39.7 μmol) in dry CH_2Cl_2 (2.5 mL) was added TMSOTf (1.4 μL, 7.93 μmol) at 0 °C. After the reaction mixture was stirred at 0 °C for 1 h, the reaction was quenched by adding satd $NaHCO_3$ solution, and the mixture was filtered through a Celite pad. The filtrate was extracted with AcOEt and the combined organic extracts were washed with H_2O and brine, dried over anhyd Na_2SO_4, and concentrated. The crude product was purified by preparative TLC (silica gel, 10:1 benzene–AcOEt) to afford known disaccharide 4[10] (a colorless oil, 37.6 mg, 36.5 μmol, 92%) as a mixture of anomers (α:β = 70:30 as determined by ^{1}H NMR spectroscopy (500 MHz).

α Isomer (**4a**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99–7.93 (m, 4H, Ph–*H*), 7.88–7.84 (m, 2H, Ph–*H*), 7.54–7.11 (m, 29H, Ph–*H*), 6.14 (t, $J_{2,3}$, $J_{3,4}$ 9.7 Hz, 1H, H-3), 5.52 (dd, $J_{4,5}$ 10.4 Hz, $J_{3,4}$ 9.7 Hz, 1H, H-4), 5.24–5.19 (m, 2H, 1-H, H-2), 4.91 (d, *J* 11.0 Hz, 1H, –C*H*$_2$Ph), 4.82 (d, *J* 11.0 Hz, 1H, –C*H*$_2$Ph), 4.77 (d, *J* 11.0 Hz, 1H, –C*H*$_2$Ph), 4.76 (d, *J* 12.3 Hz, 1H, –C*H*$_2$Ph), 4.74 (d, $J_{1',2'}$ 3.5 Hz, 1H, H-1′), 4.62 (d, *J* 12.3 Hz, 1H, –C*H*$_2$Ph), 4.54 (d, *J* 12.0 Hz, 1H, –C*H*$_2$Ph), 4.45 (d, *J* 11.0 Hz, 1H, –C*H*$_2$Ph), 4.37 (d, *J* 12.0 Hz, 1H, –C*H*$_2$Ph), 4.32 (ddd, $J_{4,5}$ 10.4 Hz, $J_{5,6a}$ 6.7 Hz, $J_{5,6b}$ 2.1 Hz, 1H, H-5), 3.96 (t, $J_{2,3}$, $J_{3,4}$ 9.2 Hz, 1H, H-3), 3.88–3.83 (m, 2H, H-6), 3.66–3.61 (m, 2H, H-4′, H-5′), 3.58 (dd, $J_{6'a,6'b}$ 11.0 Hz, $J_{5',6'a}$ 2.5 Hz, 1H, H-6′a), 3.53 (dd, $J_{1',2'}$ 9.7 Hz, 3.5 Hz, 1H, H-2′), 3.50 (dd $J_{6'a,6'b}$ 11.0 Hz, $J_{5',6'b}$ 2.1 Hz, 1H, H-6′b), 3.43 (s, 3H, –OCH_3).

β Isomer (**4b**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99–7.91 (m, 4H, Ph–*H*), 7.86–7.83 (m, 2H, Ph–*H*), 7.54–7.12 (m, 29H, Ph–*H*), 6.17 (t, $J_{2,3}$, $J_{3,4}$ 9.7 Hz, 1H, H-3), 5.47 (t, $J_{3,4}$, $J_{4,5}$ 9.7 Hz, 1H, H-4), 5.25 (dd, $J_{2,3}$ 9.7, $J_{1,2}$ 3.5 Hz, 1H, H-1), 5.20 (d, $J_{1,2}$ 3.5 Hz, 1H, H-1), 5.06 (d, *J* 10.8 Hz, 1H, –C*H*$_2$Ph), 4.91 (d, *J* 11.0 Hz, 1H, –C*H*$_2$Ph), 4.80 (d, *J* 11.0 Hz, 1H, –C*H*$_2$Ph), 4.76 (d, *J* 11.0 Hz, 1H, –C*H*$_2$Ph), 4.68 (d, *J* 10.8 Hz, 1H, –C*H*$_2$Ph), 4.53 (d, *J* 12.3 Hz, 1H, –C*H*$_2$Ph), 4.51 (d, *J* 11.0 Hz, 1H, –C*H*$_2$Ph), 4.47 (d, $J_{1',2'}$ 7.8 Hz, 1H, H-1′), 4.43 (d, *J* 12.3 Hz, 1H, –C*H*$_2$Ph), 4.41–4.34 (m, 1H, H-5′), 4.12 (dd, $J_{6a,6b}$ 11.0, $J_{5,6a}$ 2.1 Hz, H-6a), 3.81 (dd, $J_{6a,6b}$ 11.0, $J_{5,6ab}$ 7.5 Hz, H-6b), 3.67–3.56 (m, 4H, H-2′, H-3′, H-4′, H-5′), 3.48–3.43 (m, 2H, H-6′), 3.37 (s, 3H, –OCH_3).

4.3.2. One-pot dehydrative glycosylation

4.3.2.1. Procedure for the α-selective, one-pot dehydrative glycosylation with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (Table 4, entry 2). To a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1**) (20.3 mg, 37.5 μmol) in dry CH_2Cl_2 (0.25 mL) was added trichloroacetyl isocyanate (6.6 μL, 56.3 μmol) at room temperature. The reaction mixture was stirred at room temperature for 0.5 h. 5 Å MS (113 mg) and a solution of acceptor **3** (28.4 mg, 56.0 μmol) in dry Et_2O (1.25 mL) were added to the reaction mixture, followed by cooling to 0 °C. To the resulting suspension was added $TMSClO_4$ (37.0 μL, 0.2 M solution in Et_2O, 7.5 μmol). After the reaction mixture was stirred at 0 °C for 3 h, the reaction was quenched by adding satd $NaHCO_3$ solution, and the mixture was filtered through a Celite pad. The filtrate was extracted with AcOEt, and the combined organic extracts were washed with H_2O and brine, dried over anhyd Na_2SO_4. The crude product was purified by preparative TLC (silica gel, 10:1 benzene–AcOEt) to afford known disaccharide 4[10] (a colorless oil, 34.0 mg, 88%) as a mixture of anomers (α:β = 91:9), as determined by ^{1}H NMR spectroscopy (500 MHz).

4.3.2.2. Procedure for β-selective, one-pot dehydrative glycosylation with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (Table 4, entry 5). To the stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1**) (20.4 mg, 37.7 mmol) in dry CH_2Cl_2 (0.25 mL) was added trichloroacetyl isocyanate (6.6 mL, 56.3 mmol) at room temperature. The reaction mixture was stirred at room temperature for 0.5 h. 5 Å MS (114 mg) and a solution of acceptor **3** (28.3 mg, 55.9 mmol) in dry EtCN (1.25 mL) were added to the reaction mixture, followed by cooling to −40 °C. To the resulting suspension was added TMSOTf (1.3 mL, 7.5 mmol). After the reaction mixture was stirred at −40 °C for 1 h and −20 °C for 1 h, the reaction was quenched by adding satd $NaHCO_3$ solution and the mixture was filtered through a Celite pad. The filtrate was extracted with AcOEt, and the combined organic extracts were washed with H_2O and brine and dried over anhyd Na_2SO_4. The crude product was purified by preparative TLC (silica gel, 10:1 benzene–AcOEt) to afford known disaccharide 4[10] (a colorless oil, 32.9 mg, 85%) as a mixture of anomers (α:β = 12:88), as determined by ^{1}H NMR spectroscopy (500 MHz).

4.3.3. Scope of the stereoselective glycosylation with *N*-trichloroacetylcarbamate

4.3.3.1. Methyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (11a) (Table 5, entry 1). The glycosylation was performed according to the typical procedure employing carbamate donor **2** (34.5 mg, 47.3 μmol), acceptor **5** (18.5 mg, 39.8 μmol) and $TMSClO_4$ (80.0 μL, 0.2 M solution in Et_2O, 8.0 mmol) in Et_2O (3.0 mL) at 0 °C for 4 h. An anomeric mixture of the known disaccharide **11**[17] (38.8 mg, 99%, α:β = 94:6) was obtained as a colorless oil after the purification by preparative TLC (silica gel, 10:1 benzene–AcOEt). The NMR data for 11a matched those previously reported.[17] The anomeric ratio of **11** was determined by HPLC analysis [eluent, 4:1 hexanes–AcOEt; flow rate, 1.0 mL/min; t_R (**11b**, β disaccharide) = 14.8 min, t_R (**11a**, α disaccharide) 17.2 min].

4.3.3.2. Methyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (11b) (Table 5, entry 2). The glycosylation was performed according to the typical procedure employing carbamate donor **2** (34.9 mg, 47.6 μmol), acceptor **5** (18.5 mg, 39.6 μmol) and TMSOTf (1.4 μL, 7.7 μmol) in EtCN (3.0 mL) at −40 °C for 30 min then at −23 °C for 3 h. The anomeric mixture of the known disaccharide **11**[25] (38.0 mg, 97%, α:β = 7:93) was obtained as a colorless oil after purification by preparative TLC (silica gel, 10:1 benzene–AcOEt). The NMR data for 11b matched those previously reported.[17] The anomeric ratio of 11 was determined by HPLC analysis [eluent, 4:1 hexanes–AcOEt; flow rate, 1.0 mL/min; t_R (**11b**, β disaccharide) 14.8 min, t_R (**11a**, α disaccharide) 17.2 min].

4.3.3.3. Methyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-a-D-glucopyranoside (12a) (Table 5, entry 3). The glycosylation was performed according to the typical procedure employing carbamate donor **2** (35.2 mg, 48.2 mmol), acceptor **6**[27] (18.5 mg, 39.8 mmol) and $TMSClO_4$ (80.0 mL, 0.2 M solution in Et_2O, 8.0 mmol) in Et_2O (3.0 mL) at 0 °C for 5 h. The anomeric mixture of the known disaccharide **12**[28] (36.7 mg, 93%, α:β = 90:10) was obtained as a colorless oil after the purification by preparative TLC (silica gel, 10:1 benzene–AcOEt). The NMR data for 12a matched those previously reported.[28] The anomeric ratio of 12 was determined by HPLC analysis [eluent, 4:1 hexanes–AcOEt; flow rate, 1.0 mL/min; t_R (12b, β disaccharide) 12.0 min, t_R (12a, α disaccharide) 12.4 min].

4.3.3.4. Methyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl-(1→4)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (12b) (Table 5, entry 4). The glycosylation was performed according to the typical procedure employing carbamate donor **2** (35.7 mg, 49.0 μmol), acceptor **6**[27] (18.3 mg, 39.5 μmol) and TMSOTf (2.1 μL in toluene (0.15 mL), 11.6 mmol) in EtCN (3.0 mL) at 0 °C for 1.5 h. The anomeric mixture of the known disaccharide **12**[28] (32.3 mg, 83%, α:β = 15:85) was obtained as a colorless oil after purification by preparative TLC (silica gel, 10:1 benzene–AcOEt). The NMR data for 11 matched those previously reported.[28] The anomeric ratio of **12** was determined by HPLC analysis [eluent, 4:1 hexanes–AcOEt; flow rate, 1.0 mL/min; t_R (**12b**, β disaccharide) 12.0 min, t_R (**12a**, α disaccharide) 12.4 min].

4.3.3.5. Methyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (13a); (Table 5, entry 5). The glycosylation was performed according to the typical procedure employing carbamate donor **2** (35.2 mg, 48.2 μmol), acceptor **7**[29] (14.8 mg, 39.7 μmol) and $TMSClO_4$ (80.0 μL, 0.2 M solution in Et_2O, 8.0 μmol) in Et_2O (3.0 mL) at 0 °C for 3 h. An anomeric mixture of the known disaccharide **13**[30] (30.7 mg, 86%, α:β = 96:4) was obtained as a colorless oil after purification by preparative TLC (silica gel, 10:1 benzene–AcOEt). The NMR data for 13 matched those previously reported.[30] The anomeric ratio of **13** was determined by ^{1}H NMR spectroscopy (500 MHz).

4.3.3.6. Methyl 2,3,4,6-tetra-*O*-benzyl-D- glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (13b) (Table 5, entry 6). The glycosylation was performed according to the typical procedure employing carbamate donor **2** (34.5 mg, 47.3 μmol), acceptor **7**[29] (14.8 mg, 39.5 μmol) and TMSOTf (1.4 μL in toluene (0.1 mL), 7.7 μmol) in EtCN (3.0 mL) at 0 °C for 1.5 h. An anomeric mixture of the known disaccharide **13**[30] (26.1 mg, 74%, α:β = 17:83) was obtained as a colorless oil after purification by preparative TLC (silica gel, 10:1 benzene–AcOEt). The NMR data for **13** matched those previously reported.[30] The anomeric ratio of **13** was determined by ^{1}H NMR spectroscopy (500 MHz).

4.3.3.7. 3-*O*-(2,3,4,6-Tetra-*O*-benzyl-α,β-D-glucopyranosyl)cholesterol (14a) (Table 5, entry 7). The glycosylation was performed according to the typical procedure employing carbamate donor **2** (34.3 mg, 47.0 μmol), acceptor **8** (15.3 mg, 39.6 μmol) and $TMSClO_4$ (80.0 μL, 0.2 M solution in Et_2O, 8.0 μmol) in Et_2O (3.0 mL) at 0 °C for 4 h. An anomeric mixture of the known glycoside **14**[31] (33.8 mg, 93%, α:β = 94:6) was obtained as a colorless oil after the purification by preparative TLC (silica gel, 10:1 benzene–AcOEt). The NMR data for **14** matched those previously reported.[31] The anomeric ratio of **14** was determined by ^{1}H NMR spectroscopy (500 MHz).

4.3.3.8. 3-*O*-(2,3,4,6-Tetra-*O*-benzyl-α,β-D-glucopyraosyl)cholesterol (14b) (Table 5, entry 8). The glycosylation was performed according to the typical procedure employing carbamate donor **2** (34.3 mg, 47.3 μmol), acceptor **7** (15.3 mg, 39.6 μmol) and TMSOTf (1.4 μL in toluene (0.1 mL), 7.7 μmol) in EtCN (3.0 mL) at 0 °C for 2 h. The anomeric mixture of the known glycoside **14**[31] (31.7 mg, 88%, α:β = 21:79) as a colorless oil after the purification by preparative TLC (silica gel, 10:1 benzene–AcOEt). The NMR data for **14** matched those previously reported.[31] The anomeric ratio of **14** was determined by ^{1}H NMR spectroscopy (500 MHz).

4.3.3.9. Methyl (*S*)-2-((benzyloxycarbonyl)amino)-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosyl)propanoate (15a) (Table 5, entry 9). The glycosylation was performed according to the typical procedure employing carbamate donor **2** (36.6 mg, 50.2 μmol), acceptor **9** (10.5 mg, 41.5 μmol) and $TMSClO_4$ (80.0 μL, 0.2 M solution in Et_2O, 8.0 μmol) in Et_2O (3.0 mL) at 0 °C for 3 h. An anomeric mixture of the known disaccharide **15**[19] (29.0 mg, 90%, α:β = 92:8) as a colorless oil after the purification by preparative TLC (silica gel, 7:1 benzene–AcOEt). The NMR data for **15** matched those previously reported.[19] The anomeric ratio of **15** was determined by ^{1}H NMR spectroscopy (500 MHz).

4.3.3.10. Methyl (*S*)-2-((benzyloxycarbonyl)amino)-3-*O*-(2,3,4, 6-tetra-*O*-benzyl-α,β-D-glucopyranosyl)propanoate (15b) (Table 5, entry 10). The glycosylation was performed according to the typical procedure employing carbamate donor **2** (34.4 mg, 47.3 μmol), acceptor **9** (10.0 mg, 39.5 μmol) and TMSOTf (1.4 μL in toluene (0.1 mL), 7.7 μmol) in EtCN (3.0 mL) at −40 °C for 30 min then at −20 °C for 4.5 h. An anomeric mixture of the known disaccharide **15**[19] (27.0 mg, 88%, α:β = 20:80) was obtained as a colorless oil after the purification by preparative TLC (silica gel, 7:1 benzene–AcOEt). The NMR data for **15** matched those previously reported.[19] The anomeric ratio of **15** was determined by ^{1}H NMR spectroscopy (500 MHz).

4.3.3.11. *tert*-Butyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranoside (16a) (Table 5, entry 11). The glycosylation was performed according to the typical procedure employing carbamate donor **2** (34.8 mg, 47.9 μmol), acceptor **10** (7.0 mg, 95.7 μmol) and $TMSClO_4$ (80.0 μL, 0.2 M solution in Et_2O, 8.0 μmol) in Et_2O (3.0 mL) at 0 °C for 19 h. An anomeric mixture of the known glycoside **16**[17] (25.2 mg, 89%, α:β = 87:13) was obtained as a colorless oil after the purification by preparative TLC (silica gel, 10:1 hexanes–AcOEt). The NMR data for **16** matched those previously reported.[17a] The anomeric ratio of **16** was determined by HPLC analysis [eluent, 10:1 hexanes–AcOEt; flow rate, 1.0 mL/min; t_R (**16b**, β-saccharide) = 10.6 min, t_R (**16a**, α-saccharide) = 11.6 min].

4.3.3.12. *tert*-Butyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (16b) (Table 5, entry 12). The glycosylation was performed according to the typical procedure employing carbamate donor **2** (34.7 mg, 47.6 μmol), acceptor **10** (7.0 mg, 94.4 μmol) and TMSOTf (1.7 μL in toluene (0.1 mL), 9.5 μmol) in EtCN (3.0 mL) at −20 °C for 30 min, at 0 °C for 2.5 h, and then at room temperature for 96 h. An anomeric mixture of the known disaccharide **16**[17a] (10.8 mg, 38%, α:β = 39:61) was obtained as a colorless oil after the purification by preparative TLC (silica gel, 10:1 benzene–AcOEt). The NMR data for **16** matched those previously reported.[17a] The anomeric ratio of **16** was determined by ^{1}H NMR spectroscopy (500 MHz).

4.4. Glycosylation with various glycosyl *N*-trichloroacetylcarbamates

4.4.1. Preparation of various glycosyl carbamates

4.4.1.1. 2,3,4,6-Tetra-*O*-benzyl-α- and β-D-galactopyranosyl *N*-trichloroacetylcarbamate (18a and 18b). To a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (**17**) (1.06 g, 1.85 mmol) in dry CH_2Cl_2 (10 mL) was added trichloroacetyl isocyanate (0.23 mL, 1.91 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 0.25 h, and the solvent was evaporated in vacuo to give a mixture of **18a** and **18b** as colorless syrup (quant., α:β = 85:15, as determined by 500 MHz ^{1}H NMR spectroscopy). If necessary, the α isomer **18a** (R_f 0.40, 3:1 hexanes–AcOEt) and the β isomer **18b** (R_f 0.34, 3:1 hexanes–AcOEt) were separated by column chromatography on silica gel (7:1 hexanes–AcOEt). Data for the α isomer (**18a**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (s, 1H, –CONHCOCl$_3$), 7.38–7.25 (m, 20H, Ph–H), 6.42 (d, $J_{1,2}$ 3.7 Hz, 1H, H-1), 4.94 (d, J 11.5 Hz, 1H, –CH_2Ph), 4.81–4.73 (m, 4H, –CH_2Ph), 4.56 (d, J 11.5 Hz, 1H, –CH_2Ph), 4.47, 4.41 (d, J 11.9 Hz, 1H each, –CH_2Ph), 4.21 (dd, $J_{2,3}$ 10.1, $J_{3,4}$ 3.7 Hz,

1H, H-2), 4.11 (m, 1H, H-5), 4.06 (m, 1H, H-4), 3.97 (dd, $J_{2,3}$ 10.1, $J_{2,3}$ 2.3 Hz, 1H, H-3), 3.55 (m, 2H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.4 (–OCONHCOCCl$_3$), 148.9 (–OCONHCOCCl$_3$), 138.3, 138.3, 137.6, 137.6, 128.4, 128.4, 128.3, 128.1, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 95.0 (C-1), 91.8, 78.4 (C-3), 75.0 (–*C*H$_2$Ph), 75.0 (–*C*H$_2$Ph), 74.2 (C-2), 73.7 (C-4), 73.5 (–*C*H$_2$Ph), 73.0 (–*C*H$_2$Ph), 72.6 (C-5), 68.2 (C-6). Data for the β isomer (**18b**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (s, 1H, CON*H*COCl$_3$), 7.36–7.25 (m, 20H, Ph–H), 5.59 (d, $J_{1,2}$ 8.3 Hz, 1H, H-1), 4.93 (d, *J* 11.0 Hz, 1H, –C*H*$_2$Ph), 4.89 (d, *J* 11.5 Hz, 1H, –C*H*$_2$Ph), 4.76–4.69 (m, 3H, –C*H*$_2$Ph), 4.62 (d, *J* 11.0 Hz, 1H, –C*H*$_2$Ph), 4.44, 4.39 (d, *J* 11.9 Hz, 1H each, –C*H*$_2$Ph), 3.99 (m, 1H, H-4), 3.96 (dd, $J_{2,3}$ 9.6, $J_{1,2}$ 8.3 Hz, 1H, H-2), 3.71 (m, 1H, H-5), 3.65 (dd, $J_{2,3}$ 9.6, $J_{3,4}$ 2.3 Hz, 1H, H-3), 3.60–3.54 (m, 2H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.4 (–OCONH*C*OCCl$_3$), 147.7 (–OCONHCOCCl$_3$), 138.2, 138.1, 137.9, 137.5, 128.5, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 96.3 (C-1), 91.5, 82.4 (C-3), 77.6, 77.5, 77.1, 76.5, 75.2 (–*C*H$_2$Ph), 74.7 (–*C*H$_2$Ph), 74.2 (C-5), 73.5 (–*C*H$_2$Ph), 72.8 (–*C*H$_2$Ph), 72.7 (C-4), 67.7 (C-6).

4.4.1.2. 2,3,4,6-Tetra-*O*-benzyl-α- and β-D-mannopyranosyl *N*-trichloroacetylcarbamate (20a and 20b). To a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (**19**) (0.36 g, 0.67 mmol) in dry CH_2Cl_2 (3 mL) was added trichloroacetyl isocyanate (0.078 mL, 0.69 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 0.25 h, and the solvent was evaporated in vacuo to give a mixture of **20a** and **20b** as colorless syrup (quant., α:β = 85:15, determined by 500 MHz ^{1}H NMR spectroscopy). If necessary, the α isomer **20a** (R_f 0.40, 3:1 hexanes–AcOEt) and the β isomer **20b** (R_f 0.34, 3:1 hexanes–AcOEt) were separated by column chromatography on silica gel (7:1 hexanes–AcOEt). Data for α isomer (**20a**): ^{1}H NMR (300 MHz, C_6D_6): δ 8.59 (s, 1H, N–H), 7.44–6.98 (m, 20H, Ph–*H*), 5.56 (m, 1H, H-1), 4.82 (d, *J* 12.0 Hz, 1H, C*H*$_2$Ph), 4.80 (d, *J* 11.4 Hz, 1H, C*H*$_2$Ph), 4.74–4.71 (br m, 2H, C*H*$_2$Ph), 4.47 (d, *J* 11.6 Hz, 1H, C*H*$_2$Ph), 4.43–4.37 (br m, 2H, C*H*$_2$Ph), 4.28 (d, *J* 11.9 Hz, 1H, C*H*$_2$Ph), 4.17 (dd, $J_{3,4}$ 9.4, $J_{4,5}$ 8.8 Hz, 1H, H-4), 3.73- 3.61 (m, 3H, H-2, H-6), 3.44 (ddd, $J_{4,5}$ 8.8, $J_{5,6a}$ 4.4, $J_{5,6b}$ 2.3 Hz, 1H, H-5), 3.44 (m, 1H, H-3). ^{13}C NMR (75 MHz, C_6D_6): δ 157.9 (C=O), 148.6 (C=O), 139.2, 139.1, 138.8, 128.8, 128.6, 128.5, 128.08, 128.00, 127.97, 127.86, 127.8, 95.4 (C-1), 92.2 (CCl_3), 82.1 (C-3), 76.7 (C-5), 75.0, 74.8, 74.7 (C-2), 74.4 (C-4), 73.6, 72.4, 69.2 (C-6).

4.4.1.3. 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranosyl *N*-trichloroacetyl carbamate (22a and 22b). To a stirred solution of 2,3-di-*O*-benzyl-4,6-benzylidene- D-mannopyranose (**21**) (1.00 g, 2.23 mmol) in dry CH_2Cl_2 (10 mL) was added trichloroacetyl isocyanate (0.29 mL, 2.30 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 0.25 h, and the solvent was evaporated in vacuo to give a mixture of **22a** and **22b** as colorless syrup (quant., α:β = 85:15, determined by 500 MHz ^{1}H NMR spectroscopy). If necessary, the α isomer **22a** (R_f 0.40, 3:1 hexanes–AcOEt) and the β isomer **22b** (R_f 0.34, 3:1 hexanes–AcOEt) were separated by column chromatography on silica gel (7:1 hexanes–AcOEt): Data for α isomer (**22a**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (s, 1H, N–H), 7.44–6.98 (m, 15H, Ph–*H*), 6.19 (d, $J_{1,2}$ 1.4 Hz, 1H, H-1), 5.66 (s, 1H, PhC*H*–), 5.02–4.66 (m, 4H, C*H*$_2$Ph), 4.80 (d, *J* 11.4 Hz, 1H, CH$_2$Ph), 4.74–4.71(br m, 2H, CH$_2$Ph), 4.47 (d, *J* 11.6 Hz, 1H, CH$_2$Ph), 4.36–4.25 (m, 2H), 4.03–3.84 (m, 3H).

4.4.2. Glycosylation with various glycosyl carbamates

4.4.2.1. Methyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-galactopyranosyl)-(1→6)-2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside (23a) (Table 6, entry 1). The glycosylation was performed according to the typical procedure employing carbamate donor 18 (34.8 mg, 47.7 μmol), acceptor 3 (20.1 mg, 39.7 μmol) and $TMSClO_4$ (80.0 μL, 0.2 M solution in Et_2O, 8.0 mmol) in Et_2O at 0 °C for 3 h. An anomeric mixture of the known disaccharide **23**[32] (36.6 mg, 90%, α:β = 87:13) was obtained as a colorless oil after purification by preparative TLC (silica gel, 10:1 benzene–AcOEt). The NMR data for **23** matched those previously reported.[32]

4.4.2.2. Methyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-a-D-glucopyranoside (23b) (Table 6, entry 2). The glycosylation was performed according to the typical procedure employing carbamate donor **18** (30.6 mg, 41.2 mmol), acceptor **3** (17.5 mg, 34.3 mmol) and TMSOTf (2.0 mL, 8.0 mmol) in EtCN (1.5 mL) at −40 °C for 20 h. An anomeric mixture of the known disaccharide **23**[32] (33.8 mg, 96%, α:β = 19:81) was obtained as a colorless oil after purification by preparative TLC (silica gel, 10:1 benzene–AcOEt). The NMR data for **23** matched those previously reported.[32]

4.4.2.3. Methyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-mannopyraosyl)-(1→6)-2,3,6-tri-*O*-acetyl-α-D-glucopyranoside (25a) (Table 6, entry 3). The glycosylation was performed according to the typical procedure employing carbamate donor **20** (54.6 mg, 74.9 μmol), acceptor **24** (20.0 mg, 62.4 μmol) and TMSOTf (2.3 μL, 12.5 μmol) in Et_2O (1.5 mL) at rt for 15 min. The anomeric mixture of the known disaccharide **25**[24] (52.0 mg, 93%, α:β = 94:6) was obtained as a colorless oil after purification by preparative TLC (silica gel, 10:1 benzene–AcOEt). The NMR data for **25** matched those previously reported.[24]

4.4.2.4. Methyl 2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-acetyl-a-D-glucopyranoside (25b); (Table 5, entry 4). The glycosylation was performed according to the typical procedure employing carbamate donor **20** (54.6 mg, 74.9 mmol), acceptor **24** (20.0 mg, 62.4 mmol) and TMSOTf (13.6 μL, 74.9 μmol) in EtCN (3.0 mL) at −40 °C for 30 min. An anomeric mixture of the known disaccharide **25**[24] (52.2 mg, 99%, α:β = 76:24) was obtained as a colorless oil after purification by preparative TLC (silica gel, 10:1 benzene–AcOEt).

4.4.2.5. Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α,β-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (26) (Table 6, entry 5). The glycosylation was performed according to the typical procedure employing carbamate donor **22** (52.2 mg, 74.9 mmol), acceptor **24** (20.0 mg, 62.4 mmol) and TMSOTf (13.6 μL, 74.9 μmol) in CH_2Cl_2 (3.0 mL) at 0 °C for 1.5 h. An anomeric mixture of the known disaccharide **26**[24] (15.9 mg, 34%, α:β = 22:78) was obtained as a colorless oil after purification by preparative TLC (silica gel, 10:1 benzene–AcOEt). The NMR data for **26** matched those previously reported.[24]

4.5. Model study for the construction of a glycosyl bond in a natural product

4.5.1. Preparation of the glycosyl carbamate

4.5.1.1. 4-*O*-Acetyl-3-*O*-(*tert*-butyldimethylsilyl)-6-bromo-6-deoxy-2-*S*-phenyl-2-thio-α- and β-D-glucopyranosyl *N*-trichloroacetylcarbamates (29). To the stirred solution of 4-*O*-acetyl-3-*O*-(*tert*-butyldimethylsilyl)-6-bromo-6-deoxy-2-*S*-phenyl-2-thio-D-glucopyranose (**28**) (187.0 mg, 38.1 μmol) in dry CH_2Cl_2 (5 mL) was added trichloroacetyl isocyanate (68.0 μL, 57.2 μmol) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h, and the solvent was evaporated in vacuo to give a mixture of **29a** and **29b** as colorless syrup (quant., α:β = 90:10, anomeric ratio was determined by ^{1}H NMR spectroscopy (300 MHz)). If necessary, the α isomer **29a** (R_f 0.40, 3:1 hexanes–AcOEt) and the β isomer **29b** (R_f 0.34, 3:1 hexanes–AcOEt) were separated by column chromatography on silica gel (10:1 benzene–AcOEt). Data for α iso-

mer (**29a**): ^{1}H NMR (300 MHz,$CDCl_3$): δ 8.45 (s, 1H, N–*H*), 7.50–7.43 (m, 2H, SPh–*H*), 7.36–7.25 (m, 3H, SPh–*H*), 6.33 (d, $J_{1,2}$ 3.1 Hz, 1H, H-1), 5.02 (dd, $J_{4,5}$ 9.8, $J_{3,4}$ 8.6 Hz, 1H, 4-H), 4.14 (dd, $J_{2,3}$ 10.7, $J_{3,4}$ 8.6 Hz, 1H, H-3), 4.08 (ddd, $J_{4,5}$ 9.8, $J_{5,6a}$ 6.2 Hz, $J_{5,6b}$ 3.1 Hz, 1H, H-5), 3.42 (dd, $J_{6a,6b}$ 11.3, $J_{5,6b}$ 3.1 Hz, 1H, H-6b), 3.34 (dd, $J_{2,3}$ 10.7, $J_{1,2}$ 3.1 Hz, 1H, H-2), 3.30 (dd, $J_{6a,6b}$ 11.3, $J_{5,6a}$ 6.2 Hz, 1H, H-6a), 2.16 (s, 3H, –OCOC*H*$_3$), 0.90 (s, 9H, –SiC(C*H*$_3$)$_3$), 0.22 (s, 3H, –Si(C*H*$_3$)$_2$C–), 0.13 (s, 3H, –Si(C*H*$_3$)$_2$C–). ^{13}C NMR (75 MHz, C_6D_6): δ 169.6 (C=O), 157.4 (C=O), 148.8 (C=O), 136.6, 132.1 (2C), 129.3 (2C), 127.9, 127.5, 95.5 (C-1), 74.2 (C-4), 72.4 (C-3), 70.1 (C-5), 55.9 (C-2), 31.0 (C-6), 25.9 (3C, –SiC(*C*H$_3$)$_3$), 21.5 (–OCO*C*H$_3$), 18.1 (–Si*C*(CH$_3$)$_3$), –3.5 (–Si(*C*H$_3$)$_2$C–), –4.1 (–Si(*C*H$_3$)$_2$C–).

4.5.2. Glycosylation

4.5.2.1. Isopropyl 4-*O*-acetyl-3-*O*-(*tert*-butyldimethylsilyl)-6-bromo-6-deoxy-2-*S*-phenyl-2-thio-α,β-D-glucopyranose (31). The glycosylation was performed according to the typical procedure employing carbamate donor **29** (31.0 mg, 45.6 μmol), acceptor **30** (14.0 mL, 183.0 μmol) and TMSOTf (2.5 μL, 13.8 μmol) in 1,2-dichloroethane (1.0 mL) at 40 °C for 15 min. An anomeric mixture of the known glycoside **31**[26b] (17.0 mg, 70%, α:β = 19:81) was obtained as a colorless oil after purification by preparative TLC (silica gel, 70:1 benzene–AcOEt): ^{1}H NMR (300 MHz,$CDCl_3$) **31a**: δ 7.47–7.41 (m, 2H, SPh–*H*), 7.28–7.15 (m, 3H, SPh–*H*), 4.80 (dd, $J_{4,5}$ 9.4 Hz, $J_{3,4}$ 8.2 Hz 1H, H-4), 4.48 (d, $J_{1,2}$ 8.6 Hz, 1H, H-1), 3.93 (t, *J* 6.2 Hz, 1H, –OC*H*(CH$_3$)$_2$), 3.72 (dd, $J_{2,3}$ 10.1, $J_{3,4}$ 8.2 Hz 1H, H-3), 3.53 (ddd, $J_{4,5}$ 9.4, $J_{5,6a}$ 6.4, $J_{5,6b}$ 4.1 Hz 1H, H-5), 3.35 (m, 2H, H-6), 3.16 (dd, $J_{2,3}$ 10.1, $J_{1,2}$ 8.6 Hz, 1H, H-2), 2.13 (s, 3H, –OCOC*H*$_3$), 1.16 (d, *J* 6.2 Hz, 3H, –OCH(C*H*$_3$)$_2$), 1.01 (d, *J* 6.2 Hz, 3H, –OCH(C*H*$_3$)$_2$), 0.85 (s, 9H, –SiC(C*H*$_3$)$_3$), 0.19 (s, 3H, –Si(C*H*$_3$)$_2$C–), 0.07 (s, 3H, –Si(C*H*$_3$)$_2$C–).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2010.01.011.

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