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Useful Sialic Acid Modifications Catalyzed by Palladium

Chih-Wei Chang,[a] Stéphanie Norsikian,[a] and Jean-Marie Beau*[a, b]

The development of efficient synthetic methods for the preparation of *N*-acetylneuraminic acid (Neu5Ac) conjugates and modified structures for biological research or therapeutic intervention has been a major focus in carbohydrate chemistry, owing to its significant role in physiological processes and diseases.[1,2] This has led to intense research interest in sialic acid chemistry[3] comprising the design of potent chemotherapeutic agents against the influenza virus.[4] In the latter area, 2,3-unsaturated *N*-acetylneuraminic acid (**2**; 5-acetamido-2,6-anhydro-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-enoic acid, Neu5Ac2en), first discovered by Meindl and Tuppy in 1969 as a potent neuraminidase inhibitor,[5] was highly instrumental as it served as a structural basis for the discovery and development of two anti-influenza drugs currently used to treat infected patients, Zanamivir (**3**) (Relenza) and Oseltamivir phosphate (**4**) (Tamiflu), both very potent inhibitors of the influenza neuraminidase (Figure 1).[4,6] Recent reports on the emergence of drug resistance[7] make, however, the development of new anti-influenza molecules a priority, using fast and efficient procedures to access to new constructs.[8] Furthermore, the design and synthesis of selective human neuraminidase inhibitors is also highly desirable.[9]

Selective transformations at C-2 and C-4 are desirable goals and because of its broad scope and versatility, palladium(0)-catalyzed allylic substitution[10] would offer an efficient approach for these selective modifications of the allylic system in Neu5Ac2en derivatives **5** (Scheme 1). Also, a useful aspect would be the possibility of controlling the regio- and stereoselectivity of the reaction on the allylic system. This attractive solution was, however, largely discouraged by previous failures on substrate **5** (PG = Ac, R = Me, Scheme 1) equipped with an equatorial allylic substituent at C-4. This chemistry was rather exploited with the C-4 isomeric substrate **5** undergoing an easy formation of a π-allyl palladium complex because of the axially disposed leaving group, thus providing the C-4 products with overall retention of configuration with the azide ion.[11,12]

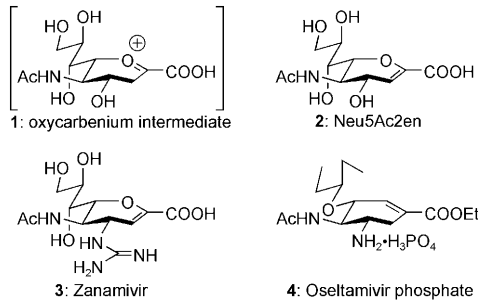
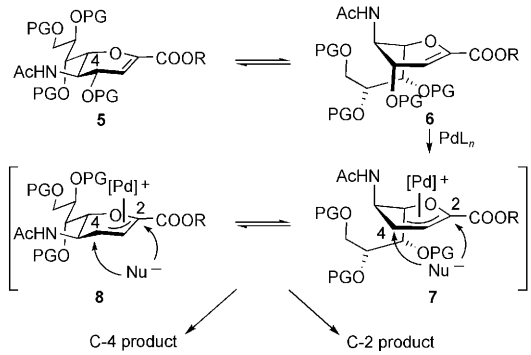


Figure 1. Potent neuraminidase inhibitors mimicking the putative high-energy oxycarbenium intermediate during the neuraminidase cleavage.



Scheme 1. Palladium-catalyzed substitution of 2,3-unsaturated sialic acid derivatives. Pg = protecting group. L = ligand.

The half-chair conformational flexibility in glycals[13] and the electronic effects in substrates such as **5** could, however, be modulated by a simple change of the protecting groups

[a] C.-W. Chang, Dr. S. Norsikian, Prof. J.-M. Beau
Institut de Chimie des Substances Naturelles du CNRS
Avenue de la Terrasse, 91198 Gif-sur-Yvette (France)

[b] Prof. J.-M. Beau
Université Paris-Sud 11, Institut de Chimie Moléculaire
et des Matériaux associé au CNRS, 91405 Orsay Cedex (France)
Fax: (+33) 1-6985-3715
E-mail: jmbeau@icmo.u-psud.fr

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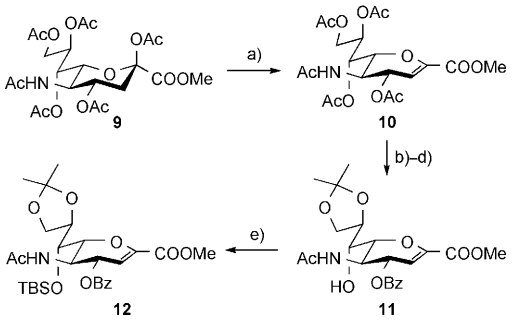
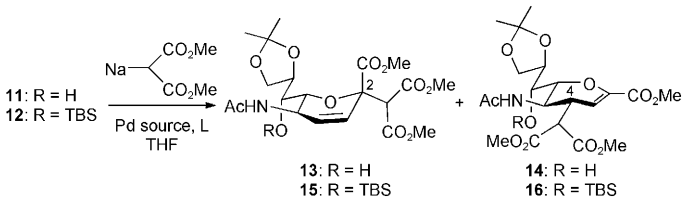
(PG). This would facilitate the initial oxidative addition on conformer $^5H_6$ **6**, with a pseudo-axial allylic group at C-4, to the π-allyl palladium complex **7**, eventually equilibrating to the inverted half-chair complex **8**. Further, it could be anticipated that the regioselectivity of the nucleophilic attack could be influenced by the nature of the nucleophile[14] as well as the ligands associated with the allylpalladium complex,[15] thus possibly providing a selective access to the C-2 or the C-4 products. We report here our preliminary results on the successful development of this approach on simple Neu5Ac2en derivatives, that ensure the control of the regio- and stereoselectivity and provide the C-2 or C-4 products with high efficiency.

For the purpose of this study, the Neu5Ac2en substrates were easily prepared from the peracetylated methyl ester **9** obtained by standard treatment (acetic anhydride, pyridine, cat. 4-(dimethylamino)pyridine, RT, overnight)[16] of the corresponding Neu5Ac methyl ester[17] (Scheme 2). Treatment of ester **9** by trimethylsilyl triflate in ethyl acetate readily induced the β-elimination to the unsaturated derivative **10**. Zemplén de-*O*-acetylation followed by a 8,9-isopropylidenation[18] furnished a diol which was selectively benzoylated to the allylic benzoate **11** and silylated to the 7-*O*TBS derivative **12** in 88% yield.[19]



Scheme 2. Preparation of Neu5Ac2en derivatives **11** and **12**. a) TMSOTf, AcOEt, 0°C to RT, 4 h; 89%; b) NaOMe, MeOH; c) CSA, 2,2-dimethoxypropane, acetone; d) BzCl, pyridine, CH_2Cl_2; 72% for the 3 steps; e) TBSOTf, CH_2Cl_2, lutidine, RT; 88%.

Treatment of acetate **10** under Pd^0-catalyzed allylic substitution conditions (see below) using sodium dimethylmalonate as a nucleophile failed to provide any alkylation product, an observation in agreement with previous work using similar conditions on this substrate.[11] In contrast, allylic benzoate **11** readily reacted with sodium dimethylmalonate in the presence of $Pd(OAc)_2$ (20 mol%) in combination with PPh_3 (40 mol%). The reaction, carried out at 50°C for 18 h provided regioselectively product **13**, alkylated at C-2 on the α face of the sugar (C-2/C-4 ratio of 81:19, 66% yield; Scheme 3). Different palladium sources {[Pd_2-$(dba)_3$]·$CHCl_3$, [(allylPdCl)$_2$], etc.} associated with different ligands (PPh_3, PBu_3, dppb, etc.) did not significantly improve this transformation. Surprisingly, silylated allylic benzoate **12** provided regioselectively, under similar conditions, the C-4 alkylated product **16** (palladium/PPh_3 ratio of 1, C-2/C-4 ratio of 25:75, 98%; Scheme 3 and Table 1, entry 1) after a notably shorter reaction time (0.5 vs. 18 h).



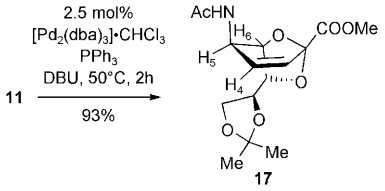
Scheme 3. Allylic substitution of Neu5Ac2en derivatives **11** and **12** with sodium dimethylmalonate.

Table 1. Regio- and stereoselective allylic substitution of Neu5Ac2en derivative **12** with sodium dimethylmalonate.

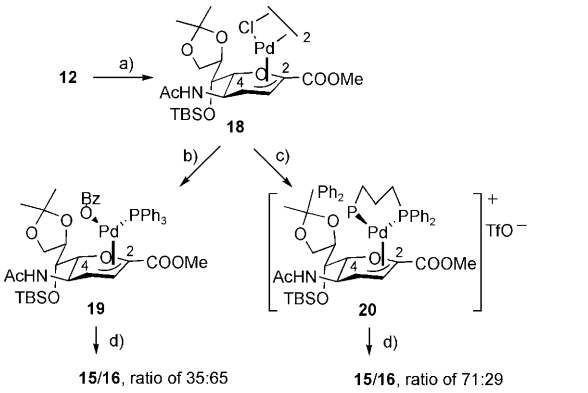
Entry	mol% of catalyst,[a] ligand (equiv)[b]	Yield[c] [%]	**15/16**[d]
1	10, PPh_3 (1)	98	25:75
2	10, PCy_3 (2)	91	9:91
3	10, PBu_3 (2)	95	5:95
4	5, PBu_3 (2)	95	13:87
5	10, dppb (2)	84	>95:5
6	10, dppb (1)	91	53:47
7	10, none	66	47:53
8	5, dppb (4)	92	>95:5
9	2.5, dppb (4)	87	93:7
10	10, dppe (2)	88	>95:5
11	10, dppf (2)	94	>95:5

[a] The reaction was carried out at 50°C for 0.5–3 h with [Pd_2-$(dba)_3$]·$CHCl_3$ and 2 equiv of sodium dimethylmalonate in degassed solvent at a concentration of 0.08 M in THF. [b] Equiv relative to the palladium catalyst. [c] Isolated yield following chromatography. [d] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. dppb = 1,4-bis-(diphenylphosphino)butane. dppe = 1,2-bis(diphenylphosphino)ethane. dppf = 1,1′-bis(diphenylphosphino)ferrocene.

The regioselectivity was largely improved to a synthetically useful level when using a more basic monophosphine ligand with a C-2/C-4 ratio of 9:91, (91% yield) with $P(Cy)_3$, or of 5:95, (95% yield) with $P(Bu)_3$ (Table 1, entries 2 and 3). Similar results were obtained with other palladium sources {[$Pd(OAc)_2$], [$PdCl_2(PhCN)_2$], [(allylPdCl)$_2$]} but [Pd_2-$(dba)_3$]·$CHCl_3$ was preferred. With tributylphosphine, a decrease in the catalyst loading to 5 mol% is possible (C-2/C-4 ratio of 13:87, 95% yield; Table 1, entry 4). Most unexpectedly, a complete reversal of the regioselectivity occurred when the reaction was performed in the presence of bidentate phosphines (dppe, dppb, dppf, entries 5, 8–11). With these ligands, the more substituted anomeric adduct **15** was largely favored independently of the palladium source tested, with the best results being obtained with [Pd_2-$(dba)_3$]·$CHCl_3$. The proportion of the ligand was crucial since at least two equivalents of the diphosphine dppb relative to palladium were needed to attain high regioselectivity (over 95:5). With only one equivalent of diphosphine per Pd atom, the reaction led unselectively to **15**/**16** in a 53:47 ratio (entry 6), a result very similar to the one obtained without added ligand (entry 7). The reaction was also performed in



Scheme 4. Formation of bicyclic acetal **17**.



Scheme 5. Preparation of the palladium complexes and their reaction with sodium dimethylmalonate. Reagents and conditions: a) $[Pd(dba)_2]$, LiCl, THF, RT, 72%; b) PPh_3 (2 equiv), $CDCl_3$ then AgOBz (2 equiv); c) dppb (3 equiv), $CDCl_3$ then AgOTf (2.2 equiv); d) sodium malonate anion, THF, 50°C. dppb = 1,4-bis(diphenylphosphino)butane.

other solvents such as dichloromethane, CH_3CN or toluene with similar trends.

The structures of **13**–**16** were assigned on the basis of ^1H NMR analysis.[20] Interestingly, bicyclic derivative **17** was formed in high yield by treating **11** with the palladium catalyst without an external nucleophile (Scheme 4). This revealed a probable transitory π-allyl palladium complex close in geometry to **17** and therefore to conformer **7** (Scheme 1). This explains logically the selective formation of the C-2 adduct based on steric grounds, with the bulky side chain at C-6 screening the C-4 attack of the incoming nucleophile.

The importance of the nature of the ligands and of the Pd/ligand ratio in obtaining high regioselectivities in the alkylation of the 7-*O*TBS derivative **12** suggests that different π-allyl palladium species could be involved. For this substrate, a 1:1 ratio of Pd/PPh_3 had to be used in order to obtain the selectivity at C-4, which led us to consider the involvement of a neutral complex with monophosphine ligands. In contrast, an excess of diphosphines is recommended for a selective C-2 alkylation. To better rationalize these results, the neutral complex **19** and the cationic complex **20** were prepared from the chloro-bridged dimer **18** (Scheme 5).[21] For the neutral complex **19**, detailed NMR analysis readily showed that C-4 is *trans* to the phosphine ligand, because of a shift of this carbon to higher frequency and the large value of the J(P,C4) coupling constant of 28 Hz (see Supporting Information for details).[15a,22]

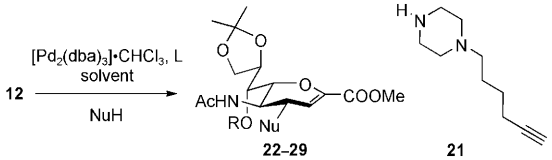
The two complexes **19** and **20** were then engaged in the stoichiometric reaction with sodium dimethylmalonate in THF at 50°C. The neutral complex **19** led to a 35:65 mixture of **15** and **16**, a selectivity in agreement with the catalytic reaction, with the favored attack of the nucleophile at C-4, *trans* to the best acceptor ligand.[23] The cationic complex **20** also gave a selectivity (a 71:29 mixture of **15** and **16**) consistent with the catalytic reaction, with the preferential formation of the 2-*C* alkylated compound. This is in line with a longer Pd–C-2 bond as detected by ^{13}C NMR spectroscopy in complex **20**.[24]

To complete these preliminary results, a short survey of the allylic substitution of **12** with other nucleophiles is presented in Table 2. In contrast with the reaction performed with sodium dimethylmalonate, the reaction led to the 4-*C* adduct as the major regioisomer whatever the ligand used.[25] For each nucleophile, various conditions were tested and the best ones are reported in Table 2.

Straightforward deprotection of these derivatives was possible as shown with the morpholine derivative **28** affording triol **30** (Scheme 6). The malonyl derivatives also offered an easy entry to a variety of transformations. Thus, hydrogenation of the C–C double bond in the unsaturated derivative **15** provided the corresponding 4-deoxy-*C*-glycosyl analogue **32** (Scheme 6).

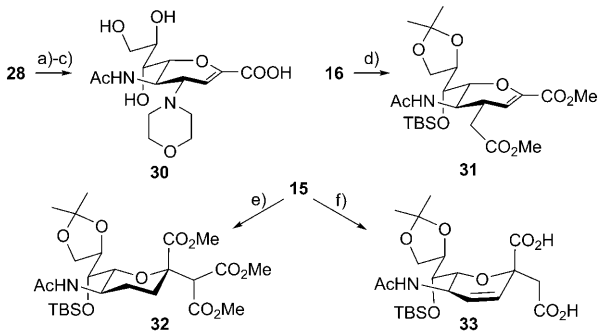
In addition, decarboxylation[26] of the methyl malonates **15** and **16** opened an efficient entry to the C-2 and C-4-branched modified sialo-acetic acids, under conditions that

Table 2. Conditions for the regioselective allylic substitution of **12** with various nucleophiles.



Entry	Nucleophile[a]	Solvent	Ligand (equiv)[b]	Additives (equiv)[c]	Product, Yield [%][d]
1	$NaCH(SO_2Ph)_2$	THF	PBu_3 (1)	–	**22**, 46
2	NaN_3	THF/H_2O[e]	dppb (1)	Bu_4NBr (0.1)	**23**, 65
3	aniline	CH_2Cl_2	dppb (2)	Et_3N (10)	**24**, 74
4	benzylamine	CH_2Cl_2	dppb (2)	Et_3N (10)	**25**, 89
5	*N*-methylbenzylamine	CH_2Cl_2	dppb (2)	Et_3N (10)	**26**, 82
6	**21**	CH_2Cl_2	dppb (2)	Et_3N (10)	**27**, 63
7	morpholine	CH_2Cl_2	dppb (2)	Et_3N (10)	**28**, 90
8	phenol	CH_2Cl_2	dppb (2)	Cs_2CO_3 (10)	**29**, 88

[a] The reactions were carried out in a degassed solvent at a concentration of 0.07 M with 20 mol% of $[Pd_2(dba)_3]\cdot CHCl_3$ and 3 equiv of the nucleophile at 60–80°C for 8–15 h, until TLC showed conversion of the starting material. [b] Equiv relative to the palladium catalyst. [c] Equiv relative to the substrate. [d] Isolated yield following chromatography. [e] As a 4:1 mixture.



Scheme 6. Selective transformations of the allylic substitution products. a) TBAF, THF, RT, 2 h; 91%; b) aq. NaOH, MeOH, RT, 19 h; c) 80% AcOH, 80 °C, 72% for the two steps; d) DMSO, H_2O, NaCl, 150 °C, 3 h, 62%; e) 10% Pd/C, H_2, AcOEt, RT, 24 h; 86%; f) aq. NaOH, MeOH, 140 °C, 3 h, 74%.

provided the di-acid **33** or maintained the ester groups as with di-ester **31** (Scheme 6). These derivatives represent suitable precursors for the elaboration of sialo clusters useful for biological studies.

In conclusion, we have developed a stereo- and regioselective allylic substitution on simple Neu5Ac2en derivatives that ensures the control of the regio- and stereoselectivity and affords the C-2 or C-4 products with high efficiency. Selective transformations of these products provide easy entry to a variety of modified sialic acid derivatives, which can serve as useful sialyl building blocks for biological research.

Experimental Section

Detailed experimental procedures have been provided in the Supporting Information.

Preparation of 15: In a Schlenk tube, a solution of $[Pd_2(dba)_3]\cdot CHCl_3$ (5.1 mg, 5 μmol) and dppb (8 mg, 20 μmol) in degassed THF (0.2 mL) was added to **12** (28.1 mg, 50 μmol). After stirring for 10 min, a solution of freshly-prepared sodium dimethyl malonate in THF (0.3 mL, 0.1 mmol) was added and the resulting mixture was heated at 50 °C for 3 h. After cooling, the solvents were removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH 1:0 to 49:1) to give **15** as a colorless solid (24 mg, 84%). M.p. 143 °C; $[\alpha]_D^{25} = -3.3$ ($c = 1.3$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 6.02$ (dd, ^3J(H-3,H-5) = 1.5, ^3J(H-3,H-4) = 10.4 Hz, 1H; H-3), 5.99 (dd, ^3J(H-4,H-5) = 1.5, ^3J(H-4,H-3) = 10.4 Hz, 1H; H-4), 5.48 (d, ^3J(NH,H-5) = 7.5 Hz, 1H; NH), 4.36 (ddt, ^3J(H-5,H-3) = ^3J(H-5,H-4) = 1.5, ^3J(H-5,NH) = 7.5, ^3J(H-5,H-6) = 9.3 Hz, 1H; H-5), 4.25 (td, ^3J(H-8,H-7) = 3.0, ^3J(H-8,H-9) = ^3J(H-8,H-9′) = 7.5 Hz, 1H; H-8), 4.15 (dd, ^3J(H-7,H-6) = 1.5, ^3J(H-7,H-8) = 3.0 Hz, 1H; H-7), 3.96 (t, J(H-9,H-9′) = ^3J(H-8,H-9′) = 7.5 Hz, 1H; H-9), 3.95 (s, 1H; H-malonyl), 3.88 (dd, ^3J(H-6,H-7) = 1.5, ^3J(H-6,H-5) = 9.3 Hz, 1H; H-6), 3.82 (t, ^3J(H-9′,H-8) = ^3J(H-9,H-9′) = 7.5 Hz, 1H; H-9′), 3.74 (s, 3H; OCH_3), 3.71 (s, 3H; OCH_3), 3.70 (s, 3H; OCH_3), 1.94 (s, 3H; NHCOCH_3), 1.40 (s, 3H; CH_3), 1.31 (s, 3H; CH_3), 0.89 (s, 9H; CH_3), 0.12 (s, 3H; CH_3), 0.11 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 170.1$ (*C*O), 169.8 (*C*O), 166.2 (*C*O), 166.0 (*C*O), 132.3 (C-4), 125.1 (C-3), 107.7 (Cq), 78.9 (C-2), 77.4 (C-8), 76.6 (C-6), 70.8 (C-7), 64.7(C-9), 59.0 (C-malonyl), 52.7 (O*C*H$_3$), 52.5 (O*C*H$_3$), 44.3 (C-5), 26.3 (*C*H$_3$), 26.0 (SiC(*C*H$_3$)$_3$), 24.8 (*C*H$_3$), 23.3 (CH$_3$ NHCO*C*H$_3$), 18.2 (Si*C*), −4.9 (Si*C*H$_3$), −3.9 ppm (q, Si*C*H$_3$); IR (neat): $\tilde{\nu} = 2951$, 1740, 1646, 1542, 1433, 1243, 1156, 1015, 835, 776, 714 cm^{-1}; ESI HRMS: *m/z*: calcd for $C_{26}H_{43}NO_{11}SiNa$ $[M+Na]^+$: 596.2503; found 596.2500; elemental analysis calcd (%) for $C_{26}H_{43}NO_{11}Si$: C 54.43, H 7.55, N 2.44; found: C 54.51, H 7.53, N 2.36.

Preparation of 16: In a Schlenk tube, a solution of $[Pd_2(dba)_3]\cdot CHCl_3$ (51 mg, 0.05 mmol) and PBu_3 (50 μL, 0.2 mmol) in degassed THF (2 mL) was added to **12** (281 mg, 0.5 mmol). After stirring for 10 min, a solution of freshly-prepared sodium dimethyl malonate in THF (3 mL, 1 mmol) was added and the resulting mixture was heated at 50 °C for 15 h. After cooling, the solvents were removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH 1:0 to 99:1) to give **16** as a colorless solid (261 mg, 92%). M.p. 78 °C; $[\alpha]_D^{25} = +30.2$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 6.02$ (d, ^3J(H-3,H-4) = 2.5 Hz, 1H; H-3), 5.62 (d, ^3J(NH,H-5) = 8.0 Hz, 1H; N*H*Ac), 4.38 (dd, ^3J(H-6,H-7) = 1.2, ^3J(H-6,H-5) = 10.0 Hz, 1H; H-6), 4.29 (td, ^3J(H-8,H-7) = 5.0, ^3J(H-8,H-9) = ^3J(H-8,H-9′) = 6.6 Hz, 1H; H-8), 4.14 (dd, ^3J(H-7,H-6) = 1.2, ^3J(H-7,H-8) = 5.0 Hz, 1H; H-7), 4.09 (dd, ^3J(H-9,H-8) = 6.6, ^3J(H-9,H-9′) = 8.1 Hz, 1H; H-9), 3.96 (dd, ^3J(H-9′,H-8) = 6.6, ^3J(H-9′,H-9) = 8.1 Hz, 1H; H-9′), 3.83 (td, ^3J(H-5,NH) = 8.0, ^3J(H-5,H-6) = ^3J(H-5,H-4) = 10.0 Hz, 1H; H-5), 3.78 (s, 3H; OCH_3), 3.77 (s, 3H; OCH_3), 3.75 (s, 3H; OCH_3), 3.72 (d, ^3J(H-malonyl,H-4) = 4.5 Hz,1H; H-malonyl), 3.54 (ddd, ^3J(H-4,H-3) = 2.5 Hz, ^3J(H-4, H-malonyl) = 4.5, ^3J(H-4,H-5) = 10.0 Hz, 1H; H-4), 1.96 (s, 3H; CH_3), 1.40 (s, 3H; CH_3), 1.30 (s, 3H, CH_3), 0.87 (s, 9H; 3×CH_3), 0.12 (s, 3H; CH_3), 0.11 ppm (s, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 170.2$ (CO), 168.7 (CO), 167.9 (CO), 162.3 (CO), 144.1 (C-2), 109.9.1 (C-3), 108.3 (Cq), 77.5 (C-6), 76.3 (C-8), 71.5 (C-7), 65.6 (C-9), 52.8 (O*C*H$_3$), 52.6 (O*C*H$_3$), 52.1 (C-malonyl, O*C*H$_3$), 47.7 (C-5), 38.2 (C-4), 26.6 (*C*H$_3$), 26.0 (SiC(*C*H$_3$)$_3$), 24.9 (*C*H$_3$), 23.6 (*C*H$_3$), 18.4 (Si*C*), −3.3 (Si*C*H$_3$), −4.3 ppm (Si*C*H$_3$); IR (neat): $\tilde{\nu} = 3476$ (br), 3267 (br), 2957, 2358, 1735, 1643, 1550, 1433, 1370, 1331, 1246, 1155, 1111, 1058, 1012, 890, 853, 757, 710 cm^{-1}; ESI HRMS: *m/z*: calcd for $C_{26}H_{43}NO_{11}SiNa$ $[M+Na]^+$: 596.2503; found 596.2503; elemental analysis calcd (%) for $C_{26}H_{43}NO_{11}Si$: C 54.43, H 7.55, N 2.44; found: C 54.31, H 7.54, N 2.38.

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Keywords: carbohydrates · palladium · regioselectivity · sialic acid · stereoselective catalysis

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