# Synthesis of a (2*R*,6*R*)-2-(Hydroxymethyl)-6-propa-1,2-dienyl-2*H*-pyran-3(6*H*)-one Derivative, a New Enone for the Convergent Construction of C-Glycosides of C-Disaccharides

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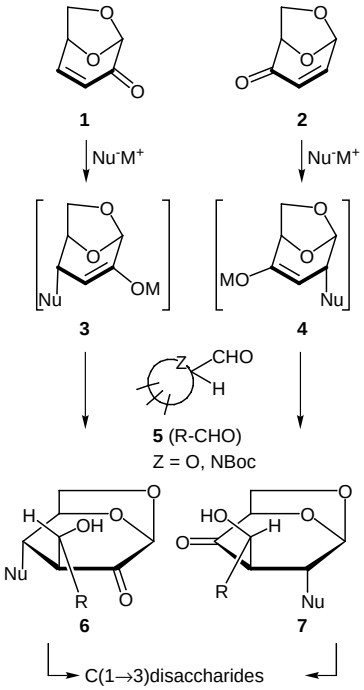
**Abstract:** The previously unknown (2*R*,6*R*)-2[(*tert*-butyl)diphenylsilyloxy]-6-propa-1,2-dienyl-2*H*-pyran-3(6*H*)-one (**16**) was derived from tri-O-acetylglucal. Conjugate addition of $PhSAlMe_2$ to **16** followed by enolate trapping with 1,2-O-isopropylidene-3-O-methyl-α-D-*xylo*-pentodialdo-1,4-furanose and $NaBH_4$ reduction of the intermediate aldol furnished a new C-glycoside of a C-disaccharide: 4,8-anhydro-9-O-[(*tert*-butyl)diphenylsilyl]-6-[(5*R*)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-furanos-5-*C*-yl]-5-*S*-phenyl-1,2,3,6-tetradeoxy-5-thio-D-*glycero*-L-*gulo*-nona-1,2-dienitol (**24**). Similarly, conjugate addition of $PhMe_2SiZnMe_2Li$ to **16**, followed by cross-aldol reaction with 2,6-anhydro-1,3,4,5-tetra-*O*-[(*tert*-butyl)dimethylsilyl]-D-glycero-L-manno-heptose (**27**), and reduction gave either 4,8-anhydro-6-{(1*S*)-2,6-anhydro-3,4,5,7-tetra-*O*-[(*tert*-butyl)dimethylsilyl-D-*glycero*-L-*manno*-heptitol-1-*C*-yl}-9-*O*-[*tert*-butyl)diphenylsilyl]-1,2,3,5,6-pentadeoxy-5-phenyldimethylsilyl-D-*glycero*-D-*manno*-(**29**) or L-*gulo*-nona-1,2-dienitol (**30**).

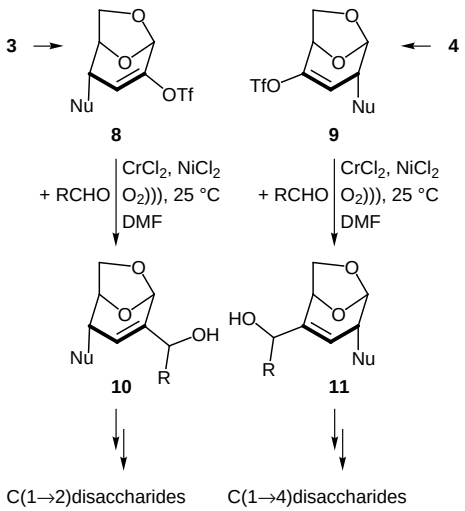
**Key words:** aldol reaction, carbohydrate-derived enone, conjugate addition, C-disaccharides, C-glycosides, glycal, C-silyl substituted carbohydrate

Because of their bicyclic structure levoglucosenone (**1**)[1] and isolevoglucosenone (**2**)[2] are attractive templates for the convergent and stereoselective construction of disaccharide mimetics,[3] including C-disaccharides.[4-8] For instance, the conjugate addition of a nucleophile $Nu^-M^+$ to enones **1** and **2** occurs on their less sterically hindered face[9] leading to enolate intermediates **3** and **4**, respectively. These species can add to sugar-derived carbaldehydes of type **5** to generate aldols **6**[10] and **7**,[5,8] respectively, that are precursors of C(1→3)-disaccharides (Scheme 1). Alternatively, enolates **3** and **4** can be trapped as their trifluoromethanesulfonates **8** and **9,** respectively that undergo Nozaki-Kishi couplings[6] with aldehydes **5** giving adducts **10** and **11** that can be transformed into the corresponding C(1→2) and C(1→4)-disaccharides, respectively (Scheme 2).[7]

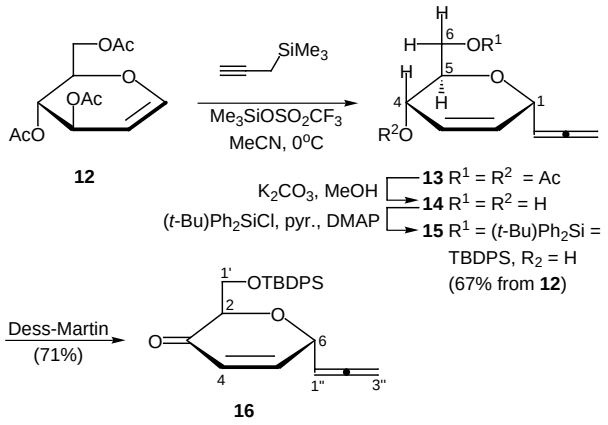
During the development of this chemistry we encountered some difficulties in the conversion of 1,6-anhydropyranose moieties into the corresponding C-pyranosides. To circumvent this problem, we proposed the substitution of templates **1** and **2** by monocyclic enones. We set out to synthesize enone **16** and explore its potential as a precursor to C-disaccharides.[11,12] We view the allenyl group as a masked carbaldehyde, which opens up the possibility of an iterative method for the assembly of oligomers containing C-glycosidic linkages.




**Scheme 1**




**Scheme 2**

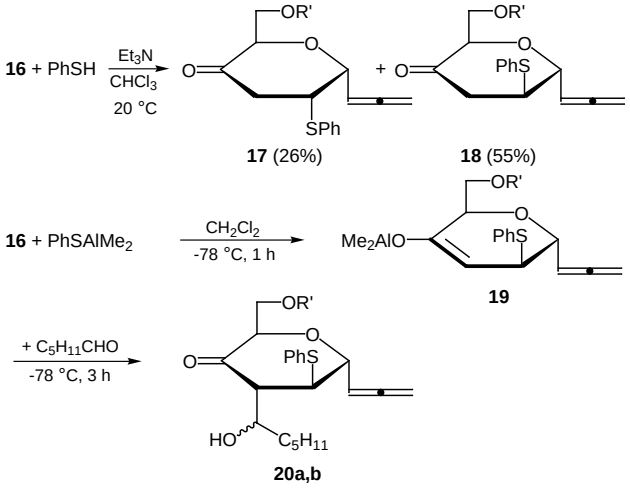



**Scheme 3**

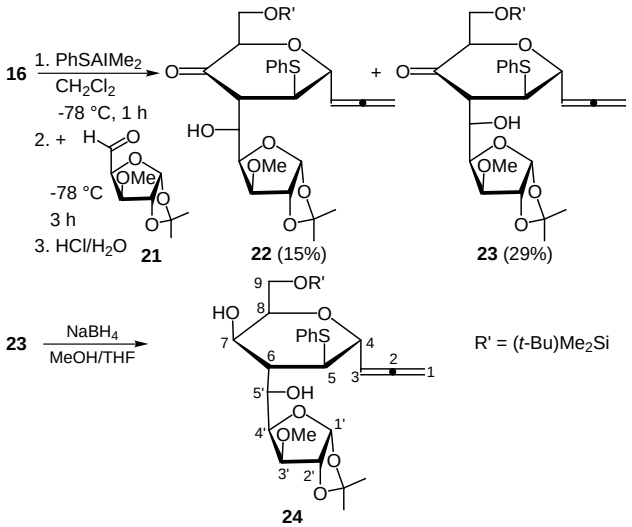
C-Glycosidation of tri-O-acetyl glucal (**12**) with allylsilane[13] and trimethylsilylmethylacetylenes[14] are well known processes.[15,16] We have found that the dropwise addition of $Me_3SiOSO_2CF_3$ to a 1:1.5 mixture of **12** and propargyltrimethylsilane in $CH_3CN$ at 0 °C gives the α-C-allenyl derivative **13**. This α-C-allenation of glucal **12** was well precedented[13,15] and the outcome supported by the absence of a NOE between the anomeric proton H-1 ($\delta_H$ = 4.82 ppm) and H-5 ($\delta_H$ = 3.78 ppm) and the observation of weak NOE's between the signals of H-1 ($\delta_H$ = 4.82 ppm), H-4 ($\delta_H$ = 5.25 ppm) and H-6 ($\delta_H$ = 4.16, 3.78 ppm). Methanolysis of the acetates (MeOH, $K_2CO_3$) provided diol **14** in 83% yield. Subsequent selective silylation of its primary alcohol with (*t*-Bu)$(Ph)_2$SiCl/pyridine/4-dimethylaminopyridine furnished **15** (64%), an unstable compound that was decomposed with silica gel. Hence, the above three successive reactions were performed without purification providing **15** in 67% based on glucal **12**. Dess-Martin periodinane oxidation[17] of **15** gave enone **16**[18] in 71% yield (Scheme 3).

Our goal being to generate C-pyranosides and C-disaccharides by conjugate additions to enone **16**, we examined first the possibility to introduce a protected hydroxy group following the method we had used with the bicyclic enones **1** and **2** (Scheme 1, 2). Contrary to levoglucosenone (**1**)[10] and isolevoglucosenone (**2**)[5] that underwent smooth addition of all kind of alcohols (including benzyl alcohol) giving the corresponding β-alkoxyketones with high *exo*-stereoselectivity, the treatment of monocyclic enone **16** with benzyl alcohol ($Et_3N$, 20 °C, no solvent) did not lead to any detectable adduct. With sodium benzylate (THF, DMF, −50 to −20 °C) **16** was transformed into an untractable mixture. Since phenylthio ethers can be converted into ketones by oxidation first into the corresponding sulfoxides, followed by Pummerer rearrangements,[19] we studied the conjugate additions of thiophenol and thiophenolates to enone **16**.

In the presence of an excess of thiophenol and one equivalent of $Et_3N$ ($CHCl_3$, 20 °C) **16** gave a 1:2 mixture of adducts **17** and **18**. With $Me_2AlSPh$ in $CH_2Cl_2$ **16** (−78 °C) generated a single aluminum enolate **19** that reacted with *n*-hexanal to give a 1:1 mixture of aldols **20a** and **20b** (Oshima's reaction,[20] Scheme 4) in 50-60% yield. Trapping enolate **19** with aldehyde **21** led to a mixture of aldols **22** and **23** that were separated by column chromatography on silica gel and isolated in 15% and 29% yield, respectively (Scheme 5). Reduction of the major aldol **23** with $NaBH_4$ in MeOH/THF was highly stereoselective and provided the C-disaccharide **24** in 77% yield.[21]



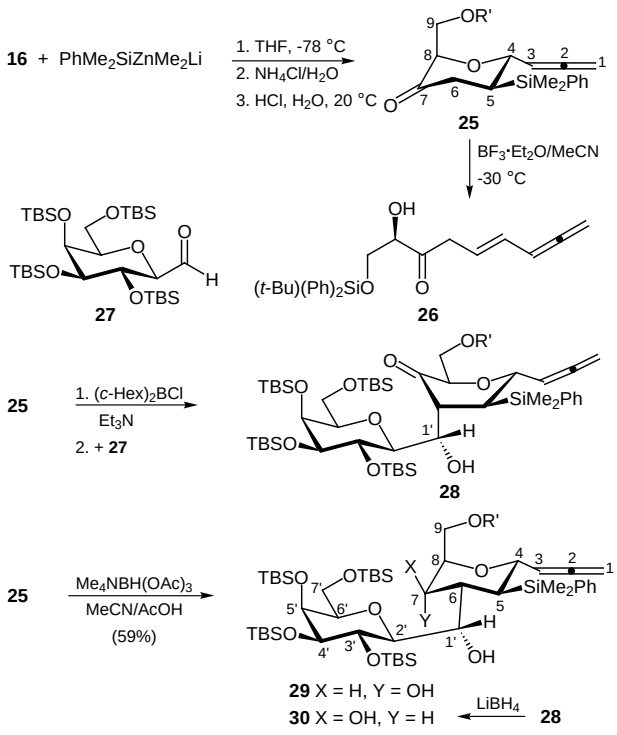

**Scheme 4**




**Scheme 5**

Coupling constants between vicinal protons and the 2-D-NOESY $^1H$ NMR spectrum of **24** established the α-configuration of the C-glycoside linkage. The *trans* diaxial relationship between H-4/H-5, H-5/H-6 and H-6/H-7 proton pairs was established by the vicinal coupling constants $^3J$(H-4,H-5) = 10.2 Hz, $^3J$(H-5,H-6) = $^3J$(H-6,H-7) = 9.5 Hz.

It is well known that trialkylsilyl groups can be considered as masked hydroxy groups (Tamao oxidation).[22] Fleming and co-workers[23,24] have developed efficient nucleophilic silyl reagents for their conjugate additions to enones. When reacted with $PhMe_2SiZnMe_2Li$[24] in THF at −78 °C **16** gave a single adduct **25** in 87% yield. The *trans* relative configuration of the 4-allenyl and 5-(dimethyl)phenylsilyl substituents, as well as the conformation proposed for **25** (Scheme 6) were given by its $^1$H NMR data ($^3J$(Haxial-5,Haxial-6) = 9.5 Hz). With the hope to equilibrate **25** with a diastereomer we attempted a Lewis acid promoted heterolysis of its tetrahydropyranosyl moiety. Because of the assistance by the 4-allenyl (π-conjugation) and the 5-silyl substituent (β-silyl effect[25]) the O-C(4) σ-bond of **25** is likely to undergo $S_N1$ heterolysis. We thus treated **25** with $BF_3{\cdot}Et_2O$ in MeCN at −30 °C. A quick reaction occurred with β-elimination of the (dimethyl)phenylsilyl group giving trienone **26**[26] in 59% yield (Scheme 6). The heterolytical process, apparently, does not allow for σ-bond rotations and internal return: the elimination is too easy (β-silyl electrofugal group).




**Scheme 6**

Treatment of ketone **25** with $(Me_3Si)_2NLi$(THF,−78°C) gave an enolate that did not react with β-C-galactopyranosylformaldehyde derivative **27**.[27] Zincation of the lithium enolate of **25** with $ZnCl_2$ followed by addition of aldehyde **27** failed to give the expected aldol. Better results were obtained with the boron enolate[28] prepared by treatment of **25** with dicyclohexylboron chloride and $Et_3N$ at −15 °C.[29] After the addition of **27** to the boron enolate of **25** (−15 °C, 4 h), the resulting aldol-borate was oxidized with 35% $H_2O_2$ (pH 7, phosphate buffer) giving adduct **28** isolated in 24%, together with 30% of recovered **25** (Scheme 6). The retro-aldol reaction appears to be a problem during the work-up of these reactions. Stereoselective reduction of aldol **28** with $Me_4NBH(AcO)_3$[30] afforded diol **29** in 59% yield.[31] The D-*altro*-configuration of its C-pyranosyl unit was established by its $^1$H NMR spectrum that showed $^3J$(H-4, H-5) = 10.8 Hz, $^3J$(H-5, H-6) = 12.1 Hz, $^3J$(H-6, H-7) = 5.0 Hz, $^3J$(H-7, H-8) = 5.2 Hz. Reduction of the boron-aldolate obtained from **25**+**27**+$(c\text{-Hex})_2BCl/Et_3N$ with $LiBH_4$ (−30°C)[32] provided **30** as major product the structure of which was given by its $^1$H NMR and 2D-NOESY-$^1$H NMR spectra ($^3J$(H-4, H-5) = 9.2 Hz, $^3J$(H-5, H-6) = 12.2 Hz, $^3J$(H-6, H-7) = 9.2 Hz,$^3J$(H-7, H-8) = 2.2 Hz). The 1'*S* configuration of aldol **28** was not established unambigously. It is proposed to be as such by analogy with other cross-adol reactions of boron enolates known to adopt closed transition structures (Zimmerman-Traxler model).[33]

The new enone template **16** has been derived readily from tri-O-acetylglucal. Conjugate addition to **16** followed by cross-aldol reaction with sugar-derived carbaldehydes generate C-disaccharide precursors with high diastereoselectivity. The systems so obtained are expected to be useful for the construction of C-glycosides of C-disaccharides and of C,C-trisaccharides.

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(18) Data for **16**: colorless oil; $^1$H NMR (400MHz, $CDCl_3$) $\delta_H$ 7.70 (m, 4H), 7.41 (m, 6H), 7.04 (dd, 1H, $^3J$(H-4,H-5) = 10.3 Hz, $^3J$(H-5,H-6) = 3.0 Hz, H-5), 6.18 (dd, 1H, $^3J$(H-4,H-5) = 10.3 Hz, $^4J$(H-4,H-6) = 1.8 Hz, H-4), 5.36 (q, 1H, $^3J$(H-6,H-1") = $^4J$(H-1",H-3a") = $^4J$(H-1",H-3"b) = 6.4 Hz, H-1'), 5.46 (m, 1H, H-6), 4.94 (ddd, 1H, $^2J$ = 11.5 Hz, $^4J$(H-1",H-3"a) = 6.4 Hz, $^5J$(H-6,H-3"a) = 2.7 Hz, H-3"a), 4.89 (ddd, 1H, $^2J$ = 11.5 Hz, $^4J$(H-1",H-3"b) = 6.4 Hz, $^5J$(H-6,H-3"b) = 2.7 Hz, H-3"b), 4.34 (dd, 1H, $^3J$(H-1'a,H-2) = 4.5 Hz, $^3J$(H-1'b,H-2) = 3.0 Hz, H-2), 4.10 (dd, 1H, $^2J$ = 11.2 Hz, $^3J$(H-1'a,H-2) = 4.5 Hz, H-1'a), 4.06 (dd, 1H, $^2J$ = 11.2 Hz, $^3J$(H-1'b,H-2) = 3.0 Hz, H-1'b), 1.09 (s, 3H, Me), 1.03 (s, 6H, 2Me); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta_C$ 209.1, 194.6, 135.7, 135.6, 134.8, 129.7, 129.6, 127.7, 126.9, 88.8, 78.5, 77.7, 69.8, 64.5, 26.7, 19.2.

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(21) Data for **24**: colorless oil; $^1$H NMR (400MHz, $CDCl_3$): $\delta_H$ 7.68-7.63 (m,4H), 7.51-7.37 (m, 8H), 7.26-7.20 (m, 3H), 5.81 (d, 1H, $^3J$(H-1',H-2') = 3.8 Hz, H-1'), 5.13 (q, 1H, $^4J$(H-3,H-1a) = $^4J$(H-3,H-1b) = $^3J$ (H-3,H-4) = 6.7 Hz, H-3), 4.85 (td, 1H, $^3J$(H-4',H-5') = $^3J$(H-5',OH) = 9.2 Hz,$^3J$(H-3,H-5') = 3.5 Hz, H-5'), 4.78 (ddd, 1H, $^2J$ = 11.1 Hz, $^4J$(H-3,H-1a) = 6.7 Hz, $^5J$(H-4,H-1a) = 2.2 Hz, H-1a), 4.73 (ddd, 1H, $^2J$ = 11.1 Hz, $^4J$(H-3,H-1b) = 6.7 Hz, $^5J$(H-4,H-1b) = 2.2 Hz, H-1b), 4.56 (d, 1H, $^3J$(H-1',H-2') = 3.8 Hz, H-2'), 4.46 (dd, 1H, $^3J$(H-4',H-5') = 8.9 Hz, $^3J$(H-3',H-4') = 3.2 Hz, H-4'), 4.36 (ddd, 1H, $^3J$(H-6,H-7) = 9.5 Hz, $^3J$(H-7,H-8) = 4.8 Hz, $^4J$(H-7,H-9) = 1.6 Hz, H-7), 4.13-4.06 (m, 3H, H-4,8,9), 3.95 (d, 1H, $^3J$(H-3',H-4') = 3.2 Hz, H-3'), 3.83 (m, 1H, H-9), 3.52 (d, 1H, $^3J$(H-5',OH) = 9.2 Hz, OH), 3.46 (s, 3H, OMe), 3.45 (dd, 1H, $^3J$(H-4,H-5) = 10.2 Hz, $^3J$(H-5,H-6) = 9.5 Hz, H-5), 2.34 (td, 1H, $^3J$(H-5,H-6) = $^3J$(H-6,H-7) = 9.5 Hz, $^3J$(H-6,H-5') = 3.5 Hz, H-6), 1.51, 1.34 (2s, 6H, $Me_2Si$), 1.04 (s, 9H, *t*-Bu); $^{13}$C NMR (100.6 Hz, $CDCl_3$): $\delta_c$ 209.1, 171.1, 135.5, 133.8, 134.4, 132.2, 130.0, 128.6, 127.4, 111.7, 105.4, 91.1, 84.7, 80.9, 80.6, 74.3, 72.2, 70.3, 68.2, 62.3, 60.3, 58.0, 49.1, 46.5, 27.0, 26.7, 26.3, 21.0, 19.0, 14.1.

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(26) Data for **26**: colorless oil; $^1$H NMR (400MHz, $CDCl_3$): $\delta_H$ 7.70-7.59 (m, 4H), 7.49-7.34 (m, 6H), 5.94 (dd, 1H, $^3J$(H-5,H-6) = 15.4 Hz, $^3J$(H-6,H-7) = 10.2 Hz, H-6), 5.84 (dt, 1H, $^3J$(H-6,H-7) = 10.2 Hz, $^4J$(H-7,H-9) = 6.6 Hz, H-7), 5.73 (dt, 1H, $^3J$(H-5,H-6) = 15.4 Hz, $^3J$(H-4,H-5) = 6.9 Hz, H-5), 4.93 (br.d, 2H, $^4J$(H-7,H-9) = 6.6 Hz, H-9), 4.27 (dt, 1H, $^3J$(H-2,OH) = 6.0 Hz, $^3J$(H-1a,H-2) = $^3J$(H-1b,H-2) = 3.3 Hz, H-2), 4.03 (dd, 1H, $^2J$ = 11.0 Hz, $^3J$(H-1a,H-2) = 3.3 Hz, H-1a), 3.92 (dd, 1H, $^2J$ = 11.0 Hz, $^3J$(H-1b,H-2) = 3.3 Hz, H-1b), 3.65 (d, 1H, $^3J$(H-2,OH) = 6.0 Hz, OH), 3.43 (dd, 1H, $^2J$ = 17.6 Hz, $^3J$(H-4a,H-5) = 6.9 Hz, H-4a), 3.31 (dd, 1H, $^2J$ = 17.6 Hz, $^3J$(H-4b,H-5) = 6.9 Hz, H-4b), 1.05 (s, 9H, *t*-Bu).

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(31) Data for **29**: colorless oil; $^1$H NMR (400MHz, $CDCl_3$): $\delta_H$ 7.75-7.65 (m, 4H), 7.59-7.53 (m, 2H), 7.40-7.28 (m, 9H), 5.31 (td, 1H, $^4J$(H-1a,H-3) = $^4J$(H-1b,H-3) = 6.6 Hz, $^3J$(H-3,H-4) = 5.8 Hz, H-3), 4.83, 4.76 (2ddd, 2H, $^2J$ = 10.6 Hz, $^4J$(H-1,H-3) = 6.6 Hz, $^5J$(H-1,H-4) = 2.2 Hz, H-1), 4.72 (m, 1H, H-4), 4.28 (m, 1H, H-7), 4.14 (dd, 1H, $^3J$(H-5',H-6') = 6.6 Hz, $^3J$(H-6',H-7') = 2.5 Hz, H-6'), 4.12 (dd, 1H, $^3J$(H-2',H-3') = 12.4 Hz, $^3J$(H-3',H-4') = 9.5 Hz, H-3'), 3.94 (m, 1H, H-5'), 3.92 (dd, 1H, $^2J$ = 11.7 Hz, $^3J$(H-8,H-9a) = 7.7 Hz, H-9a), 3.82 (m, 1H, H-8), 3.81 (dd, 1H, $^2J$ = 11.7 Hz, $^3J$(H-8,H-9b) = 2.6 Hz, H-9b), 3.80 (m, 1H, H-4'), 3.71 (m, 1H, H-1'), 3.66 (d, 1H, $^3J$(H-2',H-3') = 12.4 Hz, H-2'), 3.65 (dd, 1H,

$^{2}J$ = 4.1 Hz, $^{3}J$(H-6',H-7'a) = 2.5 Hz, H-7'a), 3.33 (d, 1H, $^{2}J$ = 4.1 Hz, H-7'b), 1.92 (dd, 1H, $^{3}J$(H-5,H-6) = 12.1 Hz, $^{3}J$(H-6,H-7)) = 5.0 Hz, H-6), 1.68 (dd, 1H, $^{3}J$(H-5,H-6) = 12.1 Hz, $^{3}J$(H-4,H-5) = 10.6 Hz, H-5), 1.04, 0.92, 0.88, 0.83, 0.70 (5s, 45H), 0.39, 0.29, 0.08, 0.06, 0.05, 0.03, 0.00, -0.01, -0.09, -0.10 (10s, 30H, 5 $Me_2Si$); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta_C$ 209.2, 138.9, 135.7, 135.6, 133.9, 129.3, 129.2, 127.7, 127.5, 94.1, 79.6, 73.7, 72.8, 72.3, 72.2, 67.1, 66.6, 66.3, 64.8, 58.6, 48.4, 26.8, 26.0, 25.9, 25.8, 25.7, 23.6, 19.3, 18.1, 18.0, 17.9, -1.2, -1.8, -3.4, -4.4, -4.6, -4.7, -4.8, -5.1, -5.3, -5.4.

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