Stereoselective Synthesis of α-*C*-Glycopyranosyl Isoprenoid Compounds

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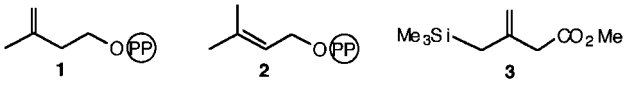
Abstract: Addition of the allylsilane $Me_3SiCH_2C{:}CH_2CH_2CO_2Me$ (**3**) to D-gluco and D-galactopyranosyl derivatives gives in good yields 3-(α-*C*-glycopyranosylmethyl)-but-3-enoates which can undergo oxidation to β-ketoesters, electrophile-promoted cyclizations or double bond migration.

Isopentenyl pyrophosphate (**1**) and its isomerization product, dimethylallyl pyrophosphate (**2**), are well-known[1] five-carbon building blocks involved in the terpenoid biosynthesis. These activated forms of isoprene can be chemically mimicked[2,3] by the allylsilane **3** which is easily obtained[2,4] by reaction of diketene with the Grignard reagent of chloromethyltrimethylsilane, followed by diazomethane esterification.

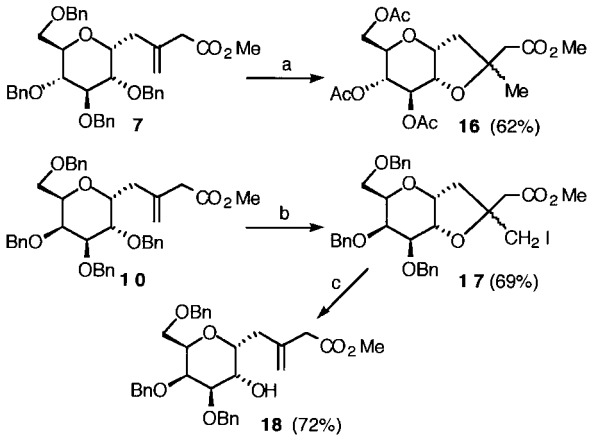


1 **2** **3**

Addition of **3** to carbonyl compounds[2] or iminium ions[5] occurs in high yields, the presence of a carboxylate function then allowing an easy double bond migration to yield a conjugated product.

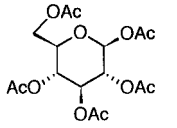
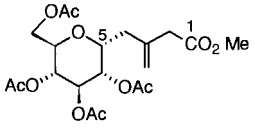
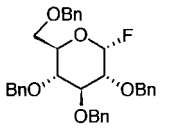
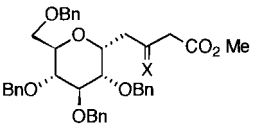
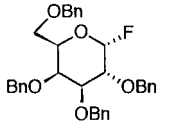
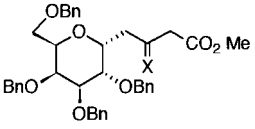
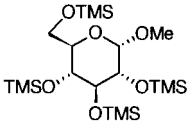
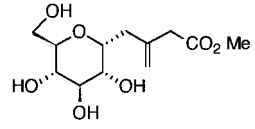
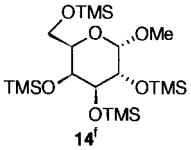
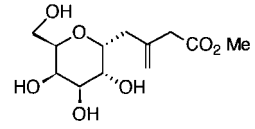
Herein we report the stereoselective addition of **3** to oxocarbenium species[6] generated from pyrano sugars (Table 1) and various transformations of the resulting *C*-glycosides.[7]

The stereoselective synthesis of α-*C*-allyl glycopyranosides from peracyl hexopyranoses has been described.[8] However, β-D-glucopyranose pentaacetate (**4**) reacted sluggishly with **3** and $BF_3{\cdot}OEt_2$ in acetonitrile to give a 6:1 mixture of α- and β-*C*-glycosides **5** in only 24% yield. More reactive perbenzylated fluorides[9,10] **6** and **9** gave *C*-glycosides **7** and **10**, respectively in much higher yields and stereoselectivities. ^1H NMR analysis of **7**α and **10**α in $CDCl_3$ at room temperature showed complex mixtures of conformers at the pyranose ring. The expected multiplicity of anomeric H-5 (ddd, $J_{4a,5}$ 11, $J_{4b,5}$ 3.3 and $J_{5,6}$ 5.6 Hz) was however observed in DMSO-d_6 at 80°C.[11] Pertrimethylsilylated sugars have been rarely used[12,13] for *C*- and *O*-glycoside synthesis. Silylation of methyl α-D-gluco and galactopyranosides gave **12** and **14** which reacted with silane **3** and trimethylsilyl trifluoromethanesulfonate



Scheme 1. a) $FeCl_3$ (12 eq), CH_2Cl_2, rt, 5h, then Ac_2O, pyridine, rt, 16h. b) I_2 (3 eq), CH_3CN, 0→20°C, 16h. c) Zn (10 eq), 10:10:1 MeOH-THF- AcOH, rt, 16h

Table 1. Addition of allylsilane **3** (3-5 eq) to D-gluco-(**4**, **6**, **12**) and D-galacto-(**9**, **14**)-pyranose derivatives

Starting material	Product	Method[a]	Yield[b] (%)	dr[c] α:β
 **4**	 **5**	A	24%	6 : 1
 **6**[d]	 e → **7** X = CH_2, **8** X = O (64%)	B	86%	95 : 5
 **9**[d]	 e → **10** X = CH_2, **11** X = O (65%)	B	90%	1 : 0
 **12**[f]	 **13**	C	74%	9 : 1
 **14**[f]	 **15**	C	75%	1 : 0

[a]Method A: $BF_3{\cdot}OEt_2$ (5 eq), CH_3CN, rt, 45h. Method B: $BF_3{\cdot}OEt_2$ (1.2 eq), CH_3CN, -30→0°C, 1h. Method C: i)TMSOTf (3 eq), CH_3CN, 0°C, 6h; ii)MeOH, 0°C, then Dowex 1 (OH^-), rt. [b]After column chromatography. [c]Diastereomeric ratios (dr) were determined by ^1H NMR analysis of chromatographed mixtures. [d]Ref 9. [e] i) O_3, CH_2Cl_2, -78°C, 5 min; ii) PPh_3 (3 eq), -78→20°C, 4h. [f]Methyl α-D-gluco and D-galactopyranosides were silylated by Me_3SiCl (5.2 eq) and NEt_3 (5.2 eq) in DMF, 0→20°C, 4h, according to ref 13

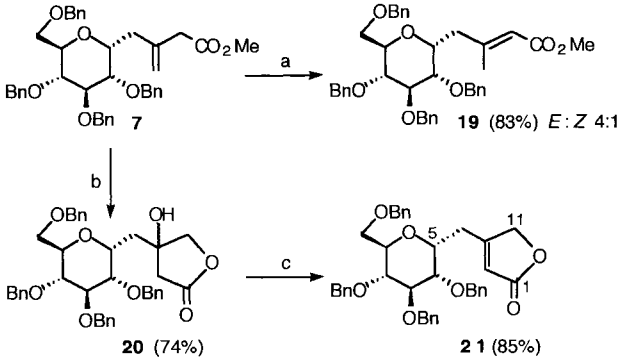
(TMSOTf) to give after desilylation unprotected *C*-glycosides **13** and **15**[14] respectively in good yields and selectivities.

Brief treatment of methylene compounds **7** and **10** by ozone at -78°C, followed by reaction with triphenylphosphine gave β-ketoesters **8**[15] and **11** respectively. A minor product resulting from regioselective oxidation of the 7-*O*-benzyl group into a benzoate was isolated in 6% yield after ozonolysis of the D-gluco compound **7**. γ-Furanosyl and pyranosyl-β-ketoesters have been previously prepared[16] by a non stereoselective Wittig reaction of phosphorane $Ph_3P{=}CHC{:}OCH_2CO_2R$ with a sugar hemiacetal.

Attempted debenzylation of **7** by anhydrous ferric chloride in dichloromethane[17], followed by acetylation, led to the bicyclic product **16** in 62% yield (Scheme 1). Activation of the double bond of **10** with iodine also led to the addition of *O*-6 with loss of the benzyl group. Treatment

of iodoether **17** (3:2 mixture of *C*-2 epimers) by zinc and acetic acid gave the *C*-glycoside **18** selectively debenzylated at *O*-6 (Scheme 1).[18] A stereoselective access to α-*C*-glycoside of D-galactosamine from **18** should then be possible.[19]

Conjugation of the double bond in **7** was accomplished by treatment with piperidine in refluxing tetrahydrofuran[20] (Scheme 2). A 4:1 mixture of *E* and *Z* isomers **19** was obtained in 83% yield.



Scheme 2. a) piperidine (2 eq), THF, reflux, 120h. b) OsO_4 cat, NMO (1.1 eq), pyridine (1 eq), 2:1:3 THF- H_2O - tBuOH, reflux, 24h. c) MsCl (4 eq), NEt_3 (8 eq), CH_2Cl_2, rt, 3h

Assignment of the stereochemistry[21] was made on the basis of ^1H and ^{13}C chemical shifts of Me and CH_2-4 groups.[22] In the *E* isomer these signals occur respectively at δ_H 2.16, δ_C 18.56 and $\delta_{H\text{-}4a}$ 2.58, $\delta_{H\text{-}4b}$ 2.48, δ_C 36.18, whereas in the *Z* isomer the following values are found: δ_H 1.92, δ_C 25.55 and $\delta_{H\text{-}4a}$ 3.34, $\delta_{H\text{-}4b}$ 2.95, δ_C 28.69.

Finally, *C*-glycoside **7** was treated with a catalytic amount of osmium tetroxide and *N*-methylmorpholine oxide (NMO)[23] to give the lactonized diol **20** as a 7:3 mixture of epimers at *C*-3. Treatment of **20** with methanesulfonyl chloride and triethylamine gave the butenolide **21**[24] in a 63% overall yield from **7.**

References and Notes

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(11) **7**α: mp 42-45°C; $[\alpha]_D$ +20 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6, 80°C) δ 7.34-7.21 (m, 20H, 4 Ph), 5.03 and 4.94 (2 bd s, 2H, CH_2=), 4.83 and 4.73 (2 d, 2H, *J* 11.5 Hz, CH_2Ph), 4.73 and 4.55 (2 d, 2H, *J* 11.3 Hz, CH_2Ph), 4.63 (m, 2H, CH_2Ph), 4.51 and 4.46 (2 d, 2H, *J* 12.1 Hz, CH_2Ph), 4.23 (ddd, 1H, $J_{4a,5}$ 11, $J_{4b,5}$ 3.3, $J_{5,6}$ 5.6 Hz, H-5), 3.78 (dd, 1H, $J_{6,7}$ 8.8, $J_{7,8}$ 8.2 Hz, H-7), 3.70 (m, 1H, H-9), 3.65 (dd, 1H, H-6), 3.62-3.58 (m, 2H, H-10a,10b), 3.60 (s, 3H, CO_2Me), 3.46 (dd, 1H, $J_{8,9}$ 9.4 Hz, H-8), 3.14 (bd s, 2H, H-2a,2b), 2.60 (dd, 1H, $J_{4a,4b}$ 15.4 Hz, H-4a), 2.41 (dd, 1H, H-4b); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.90 (C-1), 139.37, 138.80, 138.24, 138.23 and 138.08 (C-3, 4 C quat. arom.), 128.51-127.69 (20 C arom.), 116.64 (CH_2=), 82.42, 79.96, 78.03, 72.68 and 71.26 (C-5,6,7,8,9), 75.60, 75.22, 73.54 and 73.05 (4 CH_2Ph), 68.85 (C-10), 51.92 (CO_2CH_3), 41.31 (C-2), 30.75 (C-4). Calcd for $C_{40}H_{44}O_7$: C, 75.45; H, 6.96. Found: C, 75.44; H, 7.13.

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(14) **15**α: mp 103-5°C; $[\alpha]_D$ +73 (*c* 1, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 5.05 and 4.96 (2 bd s, 2H, CH_2=), 4.14 (ddd, 1H, $J_{4a,5}$ 11.2, $J_{4b,5}$ 3.1, $J_{5,6}$ 5.6 Hz, H-5), 3.94 (m, 1H, H-8), 3.91 (dd, 1H, $J_{6,7}$ 9.2 Hz, H-6), 3.76-3.64 (m, 4H, H-7,9,10a,10b), 3.67 (s, 3H, CO_2Me), 3.18 (m, 2H, H-2a,2b), 2.55 (dd, 1H, $J_{4a,4b}$ 15.3 Hz, H-4a), 2.43 (dd, 1H, H-4b); ^{13}C NMR (100.6 MHz, CD_3OD) δ 174.00 (C-1), 141.60 (C-3), 116.75 (CH_2=), 74.79, 73.88, 71.82, 70.04 and 69.99 (C-5,6,7,8,9), 61.96 (C- 10), 52.36 (CO_2CH_3), 42.08 (C-2), 32.36 (C-4).

(15) **8**α: $[\alpha]_D$ +33 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (m, 20H, 4 Ph), 4.89 and 4.79 (2 d, 2H, *J* 11.2 Hz, CH_2Ph), 4.79 and 4.56 (2 d, 2H, *J* 11.7 Hz, CH_2Ph), 4.69 (m, 1H, H-5), 4.61 and 4.47 (2 d, 2H, *J* 11.2 Hz, CH_2Ph), 4.59 and 4.46 (2 d, 2H, *J* 12.2 Hz, CH_2Ph), 3.78-3.55 (m, 6H, H- 6,7,8,9,10a,10b), 3.68 (s, 3H, CO_2Me), 3.48 and 3.41 (2 d, 2H, $J_{2a,2b}$ 15.8 Hz, H-2a,2b), 3.01 (dd, 1H, $J_{4a,4b}$ 15.6, $J_{4a,5}$ 5.8 Hz, H-4a), 2.82 (dd, 1H, $J_{4b,5}$ 8.1 Hz, H-4b); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 200.15 (C-3), 167.42 (C-1), 138.47, 138.01, 137.87 and 137.67 (4 C quat. arom.), 128.52-127.68 (20 C arom.), 81.87, 79.06, 77.57, 72.55 and 70.83 (C- 5,6,7,8,9), 75.38, 75.00, 73.51 and 73.38 (4 CH_2Ph), 68.73 (C-10), 52.30 (CO_2CH_3), 49.61 (C-2), 40.24 (C-4). Calcd for $C_{39}H_{42}O_8$: C, 73.33; H, 6.63. Found: C, 73.25; H, 6.57.

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(17) Rodebaugh, R.; Debenham, J.S.; Fraser-Reid, B. *Tetrahedron Lett.* **1996**, *37*, 5477.

(18) **18**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.22 (m, 15H, 3 Ph), 5.02 and 4.97 (2 bd s, 2H, CH_2=), 4.73, 4.72, 4.56 and 4.54 (4 d, 4H, *J* 11.7 Hz, 2 CH_2Ph), 4.52 and 4.48 (2 d, 2H, *J* 11.7 Hz, CH_2Ph), 4.23 (ddd, 1H, $J_{4a,5}$ 9.7, $J_{4b,5} \sim J_{5,6} \sim$ 4.6 Hz, H-5), 4.13-4.01 (m, 3H, H-8,10a,10b), 3.82 (dd, 1H, $J_{6,7} \sim$ 10 Hz, H-6), 3.71-3.60 (m, 2H, H-7,9), 3.64 (s, 3H, CO_2Me), 3.16 and 3.11 (2 d, 2H, *J* 15.8

Hz, H-2a,2b), 2.47 (dd, 1H, $J_{4a,4b}$ 15.3 Hz, H-4a), 2.39 (dd, 1H, H-4b); ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_3CONCO) δ 8.67 (bd s, 1H, NH), 7.39-7.26 (m, 15H, 3 Ph), 5.17 (m, 1H, H-6), 5.00 and 4.98 (2 bd s, 2H, CH_2=), 4.76 and 4.64 (2 d, 2H, *J* 12 Hz, C*H*$_2$Ph), 4.66 and 4.54 (2 d, 2H, *J* 11.7 Hz, C*H*$_2$Ph), 4.55 (s, 2H, C*H*$_2$Ph), 4.31 (m, 1H, H-5), 4.20 (m, 1H, H-9), 4.01 (dd, 1H, $J_{9,10a}$ ~ 8, $J_{10a,10b}$ 11 Hz, H-10a), 3.94 (dd, 1H, $J_{7,8}$ 2.8, $J_{8,9}$ 4.7 Hz, H-8), 3.90 (dd, 1H, $J_{6,7}$ 5.7 Hz, H-7), 3.73 (dd, 1H, $J_{9,10b}$ 3.9 Hz, H-10b), 3.64 (s, 3H, CO_2Me), 3.14 and 3.08 (2 d, 2H, *J* 15.6 Hz, H-2a,2b), 2.46 (dd, 1H, $J_{4a,4b}$ 15.2, $J_{4a,5}$ 8.8 Hz, H-4a), 2.34 (dd, 1H, $J_{4b,5}$ 4.5 Hz, H-4b).

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(21) (*E*)-**19**: mp 76-8°C; $[\alpha]_D$ +49 (*c* 0.98, $CHCl_3$); R_f 0.16 (19:1 toluene-EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.11 (m, 20H, 4 Ph), 5.72 (bd s, 1H, H-2), 4.93, 4.81 and 4.46 (3d, 4H, *J* 11.2 Hz, 2 C*H*$_2$Ph), 4.73 and 4.60 (2 d, 2H, *J* 11.7 Hz, C*H*$_2$Ph), 4.62 and 4.43 (2 d, 2H, *J* 12.2 Hz, C*H*$_2$Ph), 4.24 (ddd, 1H, $J_{4a,5}$ 11.2, $J_{4b,5}$ 2.5, $J_{5,6}$ 5.6 Hz, H-5), 3.78-3.57 (m, 6H, H-6,7,8,9,10a,10b), 3.65 (s, 3H, CO_2Me), 2.58 (dd, 1H, $J_{4a,4b}$ 14.8 Hz, H-4a), 2.48 (dd, 1H, H-4b), 2.16 (d, 3H, $J_{2,Me}$ 1 Hz, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.99 (C- 1), 156.98 (C-3), 138.76, 138.23, 138.19 and 138.11 (4 C quat. arom.), 128.68-127.72 (20 C arom.), 117.60 (C-2), 82.46, 80.03, 78.04, 72.48 and 71.64 (C-5,6,7,8,9), 75.67, 75.26, 73.65 and 73.63 (4 *C*H$_2$Ph), 68.80 (C-10), 50.97 (CO_2CH_3), 36.18 (C-4), 18.56 (Me). (*Z*)-**19**: $[\alpha]_D$ +46 (*c* 0.99, $CHCl_3$); R_f 0.25 (19:1 toluene-EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.13 (m, 20H, 4 Ph), 5.76 (bd s, 1H, H-2), 4.95 and 4.47 (2 d, 2H, *J* 10.7 Hz, C*H*$_2$Ph), 4.81 (m, 2H, C*H*$_2$Ph), 4.79 and 4.69 (2 d, 2H, *J* 11.7 Hz, C*H*$_2$Ph), 4.57 and 4.43 (2 d, 2H, *J* 12.2 Hz, C*H*$_2$Ph), 4.40 (ddd, 1H, $J_{4a,5}$ 11.7, $J_{4b,5}$ 3.1, $J_{5,6}$ 5.6 Hz, H-5), 3.86-3.75 (m, 3H, H-6,7,9), 3.69-3.55 (m, 3H, H-8,10a,10b), 3.64 (s, 3H, CO_2Me), 3.34 (dd, 1H, $J_{4a,4b}$ 14.2 Hz, H-4a), 2.95 (dd, 1H, H-4b), 1.92 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.55 (C-1), 157.86 (C-3), 138.82, 138.42, 138.37 and 138.08 (4 C quat. arom.), 128.37- 127.55 (20 C arom.), 117.59 (C-2), 82.28, 80.29, 78.07, 73.70 and 71.80 (C-5,6,7,8,9), 75.53, 74.92, 73.40 and 73.23 (4 *C*H$_2$Ph), 69.00 (C-10), 50.88 (CO_2CH_3), 28.69 (C-4), 25.55 (Me).

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(24) **21**: mp 113-5°C; $[\alpha]_D$ +44 (*c* 0.99, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 7.10-6.75 (m, 20H, 4 Ph), 5.41 (bd s, 1H, H- 2), 4.63 and 4.26 (2 d, 2H, *J* 11.2 Hz, C*H*$_2$Ph), 4.57 (m, 2H, C*H*$_2$Ph), 4.16 and 3.91 (2 d, 2H, *J* 11.6 Hz, C*H*$_2$Ph), 4.06 and 3.98 (2 d, 2H, C*H*$_2$Ph), 3.93 and 3.81 (2 dd, 2H, $J_{2,11a}$ ~ $J_{2,11b}$ ~ 1, $J_{11a,11b}$ 17.5 Hz, H-11a,11b), 3.48 (dt, $J_{4,5}$ ~ 7.2, $J_{5,6}$ ~ 5.9 Hz, H-5), 3.38-3.13 (m, 6H, H-6,7,8,9,10a,10b), 1.91 (d, 2H, H-4a,4b); ^{13}C NMR (100.6 MHz, C_6D_6) δ 171.81 (C-1), 164.88 (C-3), 137.93, 137.66, 137.30 and 137.15 (4 C quat. arom.), 126.96-126.44 (20 C arom.), 116.18 (C-2), 80.76, 78.70, 77.11, 71.26 and 70.99 (C-5,6,7,8,9), 73.93, 73.72, 72.32, 72.29 and 71.43 (4 *C*H$_2$Ph, C-11), 23.39 (C-4).