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Note

Rhodium(II)-catalyzed decomposition of 3-*O*-(2-diazo-2-phenylacetyl)-1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose: diastereoselective ether formation

Iulia A. Sacui, Matthias Zeller and Peter Norris*

Department of Chemistry, Youngstown State University, 1 University Plaza, Youngstown, OH 44555, USA

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Abstract—Standard diazo transfer to 3-*O*-(2-phenylacetyl)-1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose (**2**), using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA, **3**) and DBU as base, provides the expected 3-*O*-(2-diazo-2-phenylacetyl)-1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose (**4**) as an orange syrup in 49% isolated yield. Subsequent decomposition of **4** using $Rh_2(OAc)_4$ yields ether **5** in a highly diastereoselective manner and in 58% isolated yield. The X-ray crystal structure of **5** proves that both newly produced stereocenters have the (*S*) configuration; the conformation of the ester group at O-3 of the furanose ring of **5** is used to discuss the possible cause of the observed stereoselectivity.

Keywords: Allofuranose; Diazoester; Rhodium(II)-catalyzed decomposition; Diastereoselective insertion

Metal-stabilized carbenes have proven to be reliable and versatile reagents in organic chemistry, particularly for the formation of new carbon–carbon bonds by insertion into C–H bonds or addition to alkenes.[1] These species offer other interesting modes of reactivity that have scarcely been studied in the carbohydrate field. As such, we are exploring the possibilities of intramolecular carbenoid insertion chemistry for the synthesis of branched-chain sugars and C-glycosides and have been focusing on Rh(II)-catalyzed decomposition of stabilized diazo compounds derived from furanose platforms.[2] Others have found that decomposition of benzyl-protected pyranose-derived diazoesters does not lead to intramolecular insertion into the carbohydrate framework but to products formed by insertion into the protecting groups, into the solvent (benzene), or from dimerization of the carbenoid intermediate.[3] The choice of furanose-derived substrates, as well as careful selection of protecting groups, is seen as a way of increasing the chances of intramolecular insertion, however we are also finding that intermolecular processes are competing. Here we describe the diastereoselective intermolecular insertion of two sugar-derived carbenoids into the O–H bonds of a molecule of water to give a symmetrical ether as the major product.

Using 1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose (**1**) as the starting platform, esterification with phenylacetic acid was accomplished using standard conditions (DCC, 4-DMAP) to provide the 2-phenylacetyl ester **2** in 70% isolated yield (Scheme 1) as a colorless syrup. The ^{1}H NMR spectrum of **2** showed the expected 2H singlet at 3.70 ppm for the α-hydrogens of the phenylacetyl group and a 5H multiplet at 7.25–7.34 ppm for the protons on the phenyl ring. The ^{13}C NMR spectrum of this material featured a signal at 171.5 ppm, which corresponds to the ester carbonyl of **2**.

Diazo transfer to compound **2** was accomplished using commercially available *p*-acetamidobenzenesulfonyl azide (*p*-ABSA, **3**) and DBU as base. After aqueous workup and purification by silica gel chromatography, diazoester **4** was isolated as an orange syrup in 49% yield, and proved to be stable for months upon storing in the freezer. The ^{1}H NMR spectrum of **4**, when

* Corresponding author. Tel.: +1 330 941 1553; fax: +01 330 941 1579; e-mail: pnorris@ysu.edu

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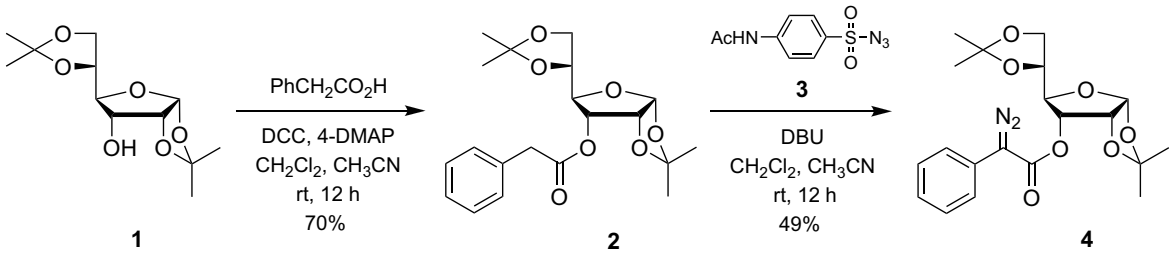
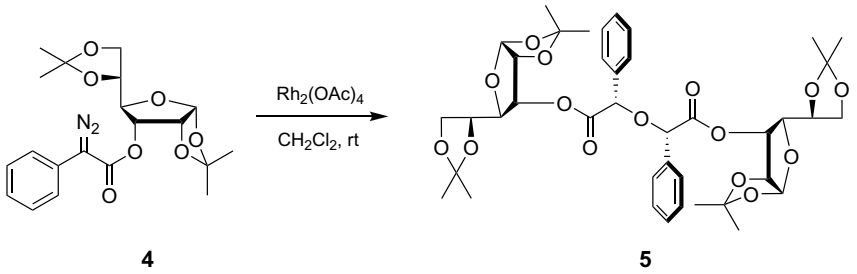


Scheme 1.

compared to that of precursor **2**, showed the loss of the 2H singlet at 3.70 ppm and the IR spectrum of **4** revealed the diagnostic diazo band at 2100 cm^{-1}. The diazoester was freely soluble in acetone, THF, $CHCl_3$, and CH_2Cl_2, and was homogenous by TLC (silica gel, $R_f = 0.45$, 2:1 hexanes–ethyl acetate).



(1)

Decomposition of diazoester **4** was achieved by addition of a dilute (0.04 g/mL) CH_2Cl_2 solution of the substrate by syringe pump over 1 h to a stirred suspension of $Rh_2(OAc)_4$ in CH_2Cl_2.[†] After stirring for a further 12 h, TLC showed that **4** had been consumed and that several very minor products had been formed along with a major component with $R_f = 0.08$ (2:1 hexanes–ethyl acetate). Analysis of the crude ^1H NMR spectrum confirmed that the bulk of the crude mixture was indeed one compound and careful column chromatography on silica gel yielded this material as a colorless syrup that could be crystallized from ethanol. The mass spectrum of the product showed a molecular ion at 793.6 $[M+Na]^+$ which suggested an intermolecular process involving the loss of N_2 from two molecules of the precursor diazoester and the introduction of the elements of a molecule of H_2O. That a symmetrical species had been formed was supported by the ^1H NMR spectrum; eight signals appear between 3.42 and 5.82 ppm corresponding to the seven protons on the sugar backbone plus a deshielded (5.13 ppm) singlet. The X-ray structure of **5** (Fig. 1, Tables 1 and 2) gave conclusive evidence that the major process occurring under these conditions was the insertion of 2 equiv of a carbenoid into one molecule of H_2O.

Insertion of metal-stabilized carbenoids into O–H bonds is a well-known process,[4] the intramolecular variant of which has been applied in several situations to the synthesis of carbohydrate analogs.[5] Related to the current work, the use of chiral auxiliaries to influence the stereochemical course of intermolecular O–H insertion processes in non-sugar examples has been studied by Moody and colleagues who observed differing levels of diastereoselectivity in insertions, using simple alcohols and water, with diazoesters based on enantiomerically pure alcohols such as (−)-borneol.[6] Although the mechanistic details of such insertions are still not fully understood, a model for diastereoselection was proposed that depends upon the preferred geometry of the carbenoid intermediate and involves the water (or alcohol) molecule attacking the highly electrophilic carbenoid carbon from the more accessible face.[6] The stereoselection observed upon the decomposition of diazoester **4** may be explained by a similar model.

The fact that we isolate an ether and not an alcohol product here is most likely due to only a limited amount of water being available in the reaction mixture thus allowing for sequential O–H insertions. With the known stereochemical identity of the allofuranose rings as reference, it can clearly be seen that both new stereocenters in **5** (which are identical) are of the (*S*) configuration (Fig. 1). It is reasonable to expect that **5** is formed by initial insertion of a molecule of carbenoid (**6**, Scheme 2) into H_2O to give alcohol **7**, which then serves as the substrate

[†] The catalyst and solvents employed in the decomposition experiments were used as received from the supplier without further drying.

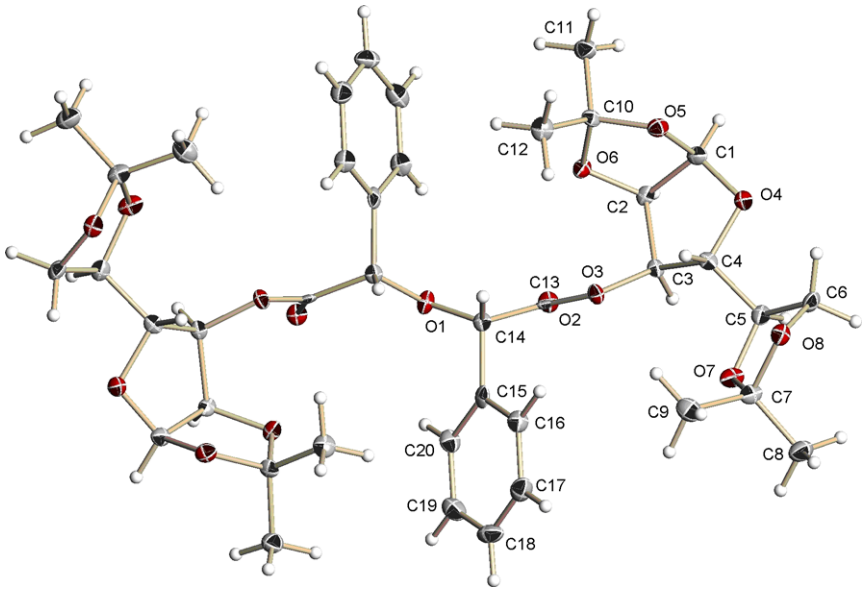


Figure 1. X-ray crystal structure with atom labeling scheme of ether **5**.

Table 1. Crystallographic data for ether **5**

Empirical formula	$C_{40}H_{50}O_{15}$
Formula weight	770.80
Crystal size (mm)	0.60 × 0.09 × 0.06
Crystal system	Monoclinic
Z	2
Space group	$C2$
a (Å)	28.638(3), $\alpha = 90°$
b (Å)	5.4002(5), $\beta = 907.249(2)°$
c (Å)	12.3306(12), $\gamma = 90°$
V (Å^3)	1891.7(3)
Density (calcd) (Mg/m^3)	1.353
$F(000)$	820
Absorption coefficient (mm^{-1})	0.103
Temperature (K)	90(2)
Wavelength (Å)	0.71073
Crystal shape, color	Needle, colorless
θ range for data collection	1.43–26.37°
Limiting indices	$-35 \leqslant h \leqslant 35$, $-6 \leqslant k \leqslant 6$, $-15 \leqslant l \leqslant 15$
Reflections collected	8530
Independent reflections	2160 (R(int) = 0.0453)
Completeness to $\theta = 26.37°$	100.0%
Absorption correction	Multi-scan
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2160/1/253
Goodness-of-fit on F^2	1.287
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0577$, $wR_2 = 0.1151$
R indices (all data)	$R_1 = 0.0621$, $wR_2 = 0.1167$
Largest difference in peak and hole (e Å^{-3})	0.378 and −0.219

Table 2. Selected bond lengths (Å) and bond angles (°) for ether **5**

Bond lengths			
C-1–C-2	1.530(5)	C-3–O-3	1.433(4)
C-2–C-3	1.566(5)	C-13–O-3	1.349(5)
C-3–C-4	1.540(5)	C-13–O-2	1.200(5)
C-1–O-4	1.396(4)	C-13–C-14	1.525(5)
C-4–O-4	1.444(4)	C-14–O-1	1.422(4)
Bond angles			
O-4–C-1–C-2	108.1(3)	C-2–C-3–O-3	111.4(3)
C-1–C-2–C-3	102.5(3)	C-3–O-3–C-13	115.6(3)
C-2–C-3–C-4	104.8(3)	C-14–C-13–O-3	108.7(3)
C-3–C-4–O-4	103.9(3)	C-14–O-1–C-14′	113.0(4)

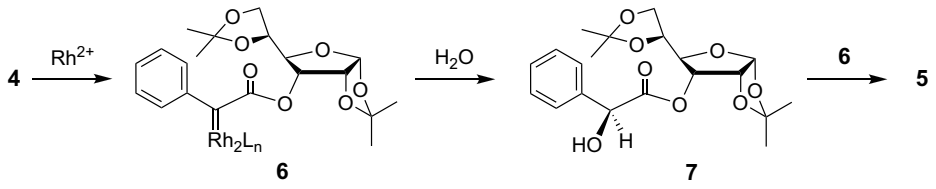
for a second insertion to give **5**. If carbenoid **6** adopts a conformation similar to that shown in Scheme 2 (cf. Ref. 6) this would favor attack at the 'front' face of the carbenoid by the incoming H_2O nucleophile with approach to the 'back' of the carbenoid being hindered by the presence of the O-5–O-6 isopropylidene acetal. This leads to the preferential creation of an (*S*) stereocenter. Once alcohol **7** is formed, insertion of a second equivalent of carbenoid (**6**) should occur in a similar manner to produce the same stereochemical outcome which is seen in **5**.

Isolation of ether **5** as the major product here suggests that the bulky acetal group at O-5–O-6 plays an important role not only in the stereochemical course of the intermolecular process, but that this large group might also preclude the possibility of intramolecular insertion. Once carbenoid **6** is formed (Scheme 2), the only intramolecular C–H insertion process that seems feasible is into the cis-aligned C-4–H-4 bond of the furanose ring. Unfavorable steric interactions between the bulky 'Rh$_2$L$_n$' group and the O-5–O-6 acetal in **6** likely prevents the intramolecular process from occurring.

1. Experimental

1.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 system, at 400 and 100 MHz, respectively, as solutions in $CDCl_3$; IR spectra were collected on a



Scheme 2.

Thermo Electron Corporation IR 200 spectrophotometer; low resolution mass spectra were obtained using a Bruker Esquire LC–MS instrument; high resolution mass spectra were carried out at the Campus Chemical Instrumentation Center at The Ohio State University; optical rotations were recorded on a Perkin Elmer model 343 automatic polarimeter as solutions in CH_2Cl_2.

Diffraction data for compound **5** was collected on a Bruker AXS SMART APEX CCD diffractometer at 90(2) K using monochromatic Mo Kα radiation with omega scan technique using the SMART software.[7] The unit cell was refined and the data were integrated using SAINT+.[8] The structure was solved by direct methods and refined by full matrix least squares against F^2 with all reflections using SHELXTL.[9] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions and refined with an isotropic displacement parameter 1.5 (CH_3) or 1.2 times (all others) that of the adjacent carbon atom. Friedel equivalents were merged prior to refinement and the absolute structure of the compounds was assigned based on the unchanged configuration of carbon atoms also present in the starting material. CCDC 675209 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

1.2. 3-*O*-(2-Phenylacetyl)-1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose (2)

1,2;5,6-Di-*O*-isopropylidene-α-D-allofuranose (**1**) (1.0 g, 3.9 mmol), phenylacetic acid (0.582 g, 4.3 mmol), and 4-dimethylaminopyridine (0.085 g, 0.69 mmol) were added to a flame-dried round-bottom flask under N_2 atmosphere and dissolved in anhydrous CH_2Cl_2 (10 mL) and anhydrous CH_3CN (10 mL). 1,3-Dicyclohexylcarbodiimide solution (4.3 mL, 1.0 M in CH_2Cl_2) was then added dropwise resulting in a white precipitate. The reaction mixture was stirred overnight at room temperature, gravity filtered, and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL) and the solution washed with 5% H_2SO_4 (3 × 10 mL) and H_2O (2 ×10 mL). After drying with $MgSO_4$, the filtrate was evaporated to give the crude product, which was then purified on a silica gel column (4:1 hexanes–EtOAc) to give 1.025 g (70% yield) of **2** as a colorless syrup: $[\alpha]_D$ +63.4 (*c* 5, CH_2Cl_2); ^{1}H NMR: δ 1.32 (s, 6H, 2 × –CH $_3$), 1.34 (s, 3H, –CH_3), 1.50 (s, 3H, –CH_3), 3.70 (s, 2H, –CH_2–), 3.75 (dd, 1H, H-4, $J = 6.0$, 8.6 Hz), 4.00 (dd, 1H, H-3, $J = 6.8$, 8.6 Hz), 4.13 (dd, 1H, H-2, $J = 4.4$, 8.1 Hz), 4.30 (ddd, 1H, H-5, $J = 4.2$, 6.0, 10.4 Hz), 4.80 (m, 2H, H-6 and H-6′), 5.85 (d, 1H, H-1, $J = 3.7$ Hz), 7.20–7.30 (m, 5H, Ar-H); ^{13}C NMR: δ 26.3, 27.4, 27.8, 28.0, 42.1, 66.7, 74.0, 76.0, 78.6, 78.7, 105.2, 110.9, 114.1, 128.2, 129.5 (2 × C), 130.4 (2 × C), 134.4, 171.5. HRMS *m*/*z* calcd for $C_{20}H_{26}O_7Na$: 401.1576. Found: 401.1551.

1.3. 3-*O*-(2-Diazo-2-phenylacetyl)-1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose (4)

2-Phenylacetyl derivative **2** (2.5 g, 6.6 mmol) and *p*-acetamidobenzenesulfonyl azide (**3**, 1.590 g, 6.6 mmol) were added to a flame-dried flask and dissolved in dry CH_2Cl_2 (25 mL) and dry CH_3CN (25 mL). While stirring at room temperature, 1,8-diazabicyclo [5,4,0]undec-7-ene (1.10 mL, 7.2 mmol) was added dropwise producing an orange solution. TLC showed the product at an R_f of 0.44 (3:1 hexanes–EtOAc) and, after stirring for 12 h, the reaction solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL) and washed with 5% H_2SO_4 (3 × 15 mL) and then H_2O (2 × 15 mL). After drying with $MgSO_4$ the solvent was evaporated to give the crude product which was then purified on silica gel (6:1 hexanes–EtOAc) to afford 1.31 g (49%) of **4** as an orange syrup: $[\alpha]_D$ +127.4 (*c* 0.5, CH_2Cl_2); IR (thin film): 2100 cm^{-1}; ^{1}H NMR: δ 1.35 (s, 6H, 2 × –CH_3), 1.43 (s, 3H, –CH_3), 1.56 (s, 3H, –CH_3), 3.90 (dd, 1H, H-4, $J = 5.3$, 8.6 Hz), 4.10 (dd, 1H, H-6, $J = 6.6$, 8.6 Hz), 4.20 (dd, 1H, H-6′, $J = 5.9$, 8.6 Hz), 4.30 (ddd, 1H, H-5, $J = 5.1$, 6.6, 10.3 Hz), 4.90 (t, 1H, H-3, $J = 4.8$ Hz), 5.00 (dd, 1H, H-2, $J = 4.9$, 8.7 Hz), 5.86 (d, 1H, H-1, $J = 4.0$ Hz), 7.20–7.50 (m, 5H, Ar-H); ^{13}C NMR: δ 26.2, 27.6, 27.9, 28.0, 67.1, 74.6, 76.4, 78.8, 79.0, 105.3, 111.1, 114.3, 125.0 (2 × C), 126.0, 127.1, 129.9 (2 × C), 165.0.

1.4. (2*S*,2′*S*)-Di-(3-*O*-1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose)-2,2′-oxybis(2-phenylacetate) (5)

$Rh_2(OAc)_4$ (0.025 g, 0.05 mmol) was suspended in anhydrous CH_2Cl_2 (10 mL) under N_2 atmosphere and a solu-

tion of diazoester **4** (0.400 g, 0.989 mmol) dissolved in anhydrous CH_2Cl_2(10 mL) was added dropwise over 1 h using a syringe pump. TLC showed a major product forming with an R_f value of 0.08 (3:1 hexanes–EtOAc) and, after stirring for 12 h at room temperature, the solvent was removed under reduced pressure and the residue was purified using a flash column eluted with 3:1 hexanes–EtOAc. Ether **5** was isolated as a colorless syrup (0.22 g, 58% yield), which was crystallized from ethanol: mp 168–170 °C; $[\alpha]_D$ +111.3 (*c* 1.3, CH_2Cl_2); ^1H NMR: 1.19 (s, 3H, $-CH_3$), 1.26 (s, 3H, $-CH_3$), 1.32 (s, 3H, $-CH_3$), 1.48 (s, 3H, $-CH_3$), 3.40 (dd, 1H, H-6, $J = 6.6$, 8.8 Hz), 3.70 (dd, 1H, H-6′, $J = 6.7$, 8.6 Hz), 4.10 (dd, 1H, H-2, $J = 3.7$, 8.4 Hz), 4.20 (ddd, 1H, H-5, $J = 3.8$, 6.8, 10.4 Hz), 4.80 (dd, 1H, H-3, $J = 5.1$, 8.4 Hz), 4.90 (dd, 1H, H-4, $J = 4.0$, 5.1 Hz), 5.13 (s, 1H, –CH–), 5.80 (d, 1H, H-1, $J = 3.7$ Hz), 7.30–7.50 (m, 5H, Ar-H); ^{13}C NMR: δ 26.3, 27.2, 27.9, 28.1, 66.2, 74.1, 75.6, 78.6, 78.7, 80.0, 105.2, 110.8, 114.1, 128.8 (2 × C), 129.6 (2 × C), 130.0, 136.1, 170.3. HRMS *m*/*z* calcd for $C_{40}H_{50}O_{15}Na$: 793.3047. Found: 793.2997.

Acknowledgments

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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.2008.04.005.

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