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Rhodium(II) Catalyzed Asymmetric Cyclopropanation of Glycals with Ethyl Diazoacetate

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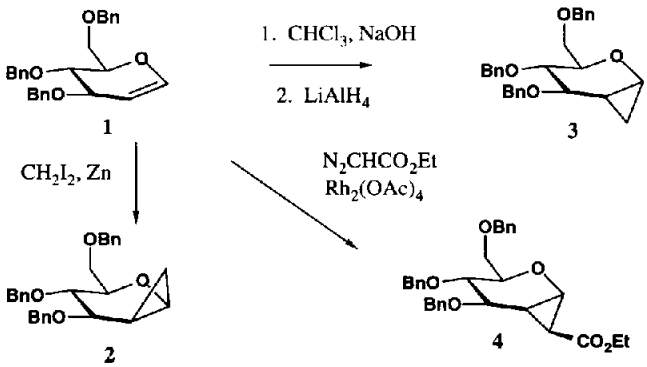
Abstract: Carbenoid species generated from ethyl diazoacetate and catalytic $Rh_2(OAc)_4$ react smoothly and with a high degree of stereoselectivity with glycals resulting in the predominant formation of doubly branched adducts containing an α-*exo*-orientated ethyl cyclopropanecarboxylate moiety.

Recently, Murali *et al.*[1] reported a route of synthesis to the individual diastereoisomers of 1,2-cyclopropanated sugars. For example, Simmons-Smith reaction (see Scheme 1) of fully benzylated D-glucal **1** gave the β-1,2-cyclopropyl adduct **2**. On the other hand, the corresponding α-1,2-derivative **3** was accessible from **1** by dichlorocarbene addition followed by reductive dehalogenation.

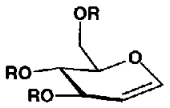
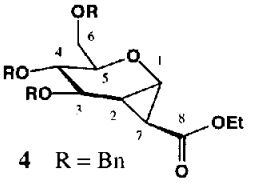
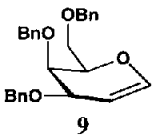
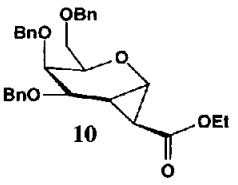
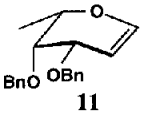
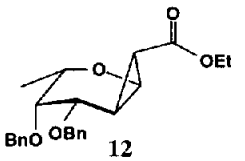
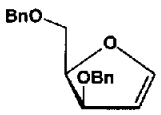
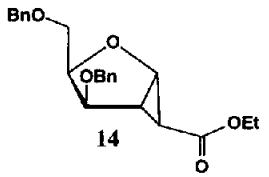
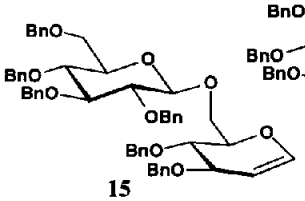
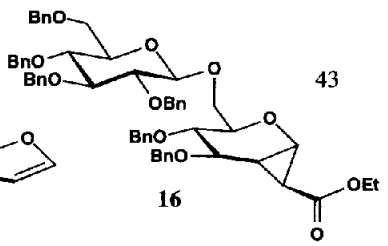


Scheme 1. Synthesis of cyclopropyl adducts **2-4** from glucal **1**.

As part of an ongoing study[2] on the use of glycals in sugar chemistry, we here report that glycals can be converted, according to the cyclopropanation method of Anciaux *et al.*[3], with a high degree of stereoselectivity into α-*exo*-carbethoxymethylene adducts (*e.g.*, conversion of **1** → **4** in Scheme 1).

In order to adapt the originally described cyclopropanation method, which implied dirhodium tetraacetate catalyzed cyclopropanation of neat olefins with ethyl diazoacetate (EDA), to our particular purpose we first explored the most economical and optimal conditions for the cyclopropanation of glucal **1**. Pilot studies revealed that the procedure involving dropwise addition of a moderate excess of EDA (3 mmol) to glucal **1** (1

Table 1. Rhodium(II) catalyzed cyclopropanation of glycals by ethyl diazoacetate.

entry	glycal	ethyl cyclopropanecarboxylate	yield (%)	$[\alpha]_D$[a]	NOE[b] (δ, ppm)	MS (m/z)[c]
1						
	1 R = Bn	**4** R = Bn	59	+21.6	H_7 (1.98), H_3 (3.77)	502
	5 R = TBDMS **7** R = Bz	**6** R = TBDMS **8** R = Bz	85 75	+17.4 -4.4		575 544
2	 **9**	 **10**	61	-19.2	H_7 (1.59), H_3 (3.67)	502
3	 **11**	 **12**	45[d]	-9.0	H_7 (1.58), H_3 (3.67), H_5 (3.49)	396
4	 **13**	 **14**	52[d]	-21.8	H_6 (1.88), H_3 (3.84)	382
5	 **15**	 **16**	43	-7.0	H_7 (2.03), H_3 (3.76)	935

[a] c 1, $CHCl_3$, 20 °C; [b] Obtained by 300 MHz ^1H NOESY NMR ($CDCl_3$, 25 °C) after irradiation at the cyclopropane *endo*-proton; [c] Electrospray; [d] Main product.

mmol) containing a catalytic amount of $Rh_2(OAc)_4$ (0.02 mmol) and using dichloromethane as the solvent proved to be satisfactory. Accordingly, cyclopropanation of **1** gave, after work-up and purification, the homogeneous adduct **4** in an acceptable yield (entry 1, Table 1). The α-*exo*-configuration of the ethyl cyclopropyl carboxylate moiety in **4** was firmly established by NMR-spectroscopy[4] (*i.e.* ^{13}C NMR, ^1H COSY NMR and NOE-experiments; see Table 1).

It was also demonstrated that silyl or benzoyl, instead of benzyl protective groups as in **1**, were fully compatible with the cyclopropanation conditions. Thus, cyclopropanation of 3,4,6-tri-*O*-(*tert*-butyldimethylsilyl)-D-glucal (**5**)[5] gave the α-*exo*-product **6** in 85% yield. A similar increase in yield, with respect to the fully benzylated glucal **1**, was observed in the conversion of the perbenzoylated substrate **7**[6] into **8** (see Table 1). In addition, desilylation of **6** with fluoride ion (*n*-Bu_4NF, THF) and debenzoylation (*cat.* KO*t*-Bu, EtOH) of **8** gave in each case partially deprotected **4** (R = H) in a near quantitative yield.

The general applicability of the cyclopropanation procedure was further illustrated using fully benzylated D-galactal **9**[7], L-fucal **11**[8] and D-xylal **13**[9] as the substrates. It can be seen in Table 1 (entries 2 - 4) that all three substrates can be transformed in an acceptable yield into the respective α-*exo*-adducts **10**, **12** and **14**. Finally, Rh(II) catalyzed cyclopropanation of dimeric glucal **15**[10] by EDA proceeded smoothly resulting in the exclusive formation of the expected α-*exo*-adduct **16** (see entry 5, Table 1).

In conclusion the highly stereoselective cyclopropanation approach presented in this paper gives access to a novel class of doubly branched sugar derivatives which may be of great value for the synthesis of branched-chain sugars and natural products.

General procedure for the cyclopropanation of glycals with ethyl diazoacetate in the presence of catalytic $Rh_2(OAc)_4$:

To a stirred suspension of glycal (1.0 mmol) and $Rh_2(OAc)_4$ (8.8 mg, 0.02 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise, over a period of 1 h, a solution of ethyl diazoacetate (0.32 mL, 3.0 mmol) in CH_2Cl_2 (10 mL). After cessation of the nitrogen evolution (5-10 min), the reaction mixture was concentrated *in vacuo* and the remaining residue was purified by silica gel column chromatography (eluent: 10-30% EtOAc in light petroleum) to give the desired 1,2-cyclopropyl adduct.

References and Notes

1. Murali, R.; Ramana, C.V.; Nagarajan, M.; *J. Chem. Soc., Chem. Comm.* **1995**, 217.
2. (a) Timmers, C.M.; Van der Marel, G.A.; Van Boom, J.H.; *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 609; (b) Timmers, C.M.; Van der Marel, G.A.; Van Boom, J.H.; *Chem. Eur. J.* **1995**, *1*, 161.
3. Anciaux, A.J.; Hubert, A.J.; Noels, A.F.; Petinot, N.; Teyssié, P.; *J. Org. Chem.* **1980**, *45*, 695.
4. Representative spectral data for 1,5-anhydro-2-deoxy-1,2-*C*-(*exo*-carbethoxymethylene)-3,4,6-tri-*O*-benzyl-α-D-glucitol (**4**): ^1H NMR (300 MHz, 2D-COSY, $CDCl_3$): δ (TMS) 7.38-7.19 (15 H, m, H_{arom}), 4.71 (2 H, AB, CH_2 Bn), 4.58 2 H, AB, CH_2 Bn), 4.53 (2 H, AB, CH_2 Bn), 4.12 (2 H, q, CH_2 Et), 3.94 (1 H, dd, H_1, $J_{1,7}$ = 2.2 Hz; $J_{1,2}$ = 7.4 Hz), 3.77 (1 H, dd, H_3, $J_{2,3}$ = 2.1 Hz; $J_{3,4}$ = 6.2 Hz), 3.70 (2 H, m, H_6/H_6'), 3.58 (2 H, m, H_4/H_5), 1.98 (1 H, dd, H_7, $J_{2,7}$ = 5.7 Hz), 1.78 (1 H, ddd, H_2), 1.26 (3 H, t, CH_3 Et). A strong NOE-DIFF resonance was observed after irradiation at H_7 (δ = 1.98

ppm) at δ = 3.77 ppm (H_3). ^{13}C NMR (50.1 MHz, $CDCl_3$): δ (TMS) 171.5 (C_8), 138.0, 137.9, 137.7 (3 x C_q Bn), 128.4-127.5 (C_{arom}), 76.5, 75.2, 74.3 ($C_3/C_4/C_5$), 73.3, 73.2, 71.4 (3 x CH_2 Bn), 69.1 (C_6), 60.6 (CH_2 Et), 57.6 (C_1), 24.4, 24.3 (C_2/C_7), 14.2 (CH_3 Et). $[\alpha]_D^{20}$ = +21.6 (c 1, $CHCl_3$). MS (E.I.): m/z = 502. All other cyclopropanated sugars were characterized by ^1H NMR (2D-COSY, NOESY), ^{13}C NMR and mass spectroscopy.

5. Lesimple, P.; Beau, J.-M.; Jaurand, G.; Sinaÿ, P.; *Tetrahedron Lett.* **1986**, *27*, 6201.
6. Guthrie, R.D.; Irvine, R.W.; *Aust. J. Chem.* **1980**, *33*, 1037.
7. Czernecki, S.; Randriamandimby, D.; *Tetrahedron Lett.* **1993**, *34*, 7915.
8. 3,4-Di-*O*-benzyl-L-fucal (**11**) was prepared from 3,4-di-*O*-acetyl-L-fucal (Elkhadem, H.S.; Schwartz, D.; Nelson, J.C.; Berry, L.A.; *Carbohydr. Res.* **1977**, *58*, 230) by deacetylation with NEt_3/MeOH/H_2O (1:10:10 v/v/v, 2 h, quantitative yield) and subsequent benzylation (BnBr, NaH, DMF, 2 h, 91%).
9. Kassou, M.; Castillón, S.; *Tetrahedron Lett.* **1994**, *35*, 5513.
10. Halcomb, R.L.; Danishefsky, S.J.; *J. Am. Chem. Soc.* **1989**, *111*, 6661.

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