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Cyclopropanation of Unsaturated Sugars with Ethyl Diazoacetate

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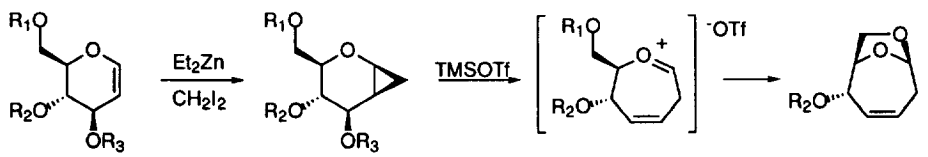
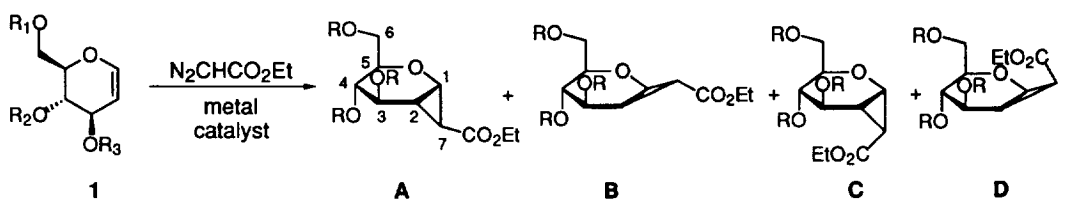
ABSTRACT: The cyclopropanation of unsaturated sugars with ethyl diazoacetate and a metal catalyst provides ester-substituted 1,2-*C*-methylene carbohydrates in good to excellent yields. Ring opening of the cyclopropane has also been achieved providing C-2 branched glycosyl bromides.

The importance of carbohydrate derivatives in the medicinal and agrochemical fields has stimulated the development of numerous new synthetic methods for their preparation.[1] In efforts to further develop this area, we recently reported a new carbohydrate transformation utilizing a cyclopropanation and ring-expansion of glycals (Scheme 1).[2] The cyclopropanation gave excellent yields and selectivities, and both intramolecular nucleophilic attack (as shown) and intermolecular attack on the oxonium ion were accomplished in the ring-expansion.



Scheme 1.

Our interest in developing this strategy has prompted us to investigate the functionalization of the cyclopropane moiety. Since the chemistry of ester-substituted cyclopropanes has been well established,[3] our choice for the functionalization involved reaction of glycals with diazoacetates and a metal catalyst as shown in Scheme 2.[4] The formation of cyclopropanes **A-D** should therefore enable us to further expand the use of carbohydrates in synthetic organic chemistry.

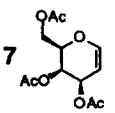
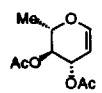


1 **A** **B** **C** **D**

Scheme 2.

The synthesis of the cyclopropanes was performed by dropwise addition of ethyl diazoacetate to a solution of glycal and 1 mol % catalyst in dichloromethane over 12 to 14 hours.[5] Accelerated addition of the diazoacetate resulted in decomposition of the diazoacetate to diethyl fumarate, maleate and recovery of the starting glycal. In most cases, the successful formation of the ester cyclopropane resulted in a mixture of isomers. The results are summarized in Table 1, and in all instances cyclopropane A was the major isomer. The stereochemistry of the major isomer was assigned using ^{1}H NMR coupling constants. Comparison of the coupling constants between H-2 and H-3 of A to those of the known unsubstituted cyclopropanes in Scheme 1 verified the *trans*- stereochemistry.[2,6] For example, coupling constants for H-2 and H-3 in **2A**, **3A**, **4A**, **5A** and **7A** are 1.5, 0, 1.8, 0 and 2.0 Hz, respectively, while literature values for the *cis* - H-2 and H-3 in Scheme 1 are between 6.8 to 7.4 Hz. This assignment agrees with approach of the metal-carbene from the side opposite to that of the protecting groups,[4c] as opposed to the hydroxy-directed Simmons-Smith cyclopropanation observed in Scheme 1.[7] In addition, as the size of the protecting group increases (TBS *vs.* Bn), increased selection of the less hindered cyclopropane A is observed (entry 2 *vs.* entry 4). The stereochemistry of the ester group was also established with NMR coupling constants and is in agreement with literature reports.[8,4c]

Table 1. Cyclopropanation of Glycals

Entry	substrate	% Isolated Yield[a] of A + B	% Isolated Yield[b] of C + D	Diastereoselectivity[c] A:B:C:D	Catalyst
1	**1** R_1=TBS; R_2,R_3=Ac	**2** (89) [d]	4 [e]	45:1:1:1	$Rh_2(OAc)_4$
2	**1** R_1,R_2,R_3 = TBS	**3** (81)	0	31:1:0:0[f]	$Rh_2(OAc)_4$
3	**1** R_1,R_2,R_3 = TIPS	**4** (61)	5	28:1:1:1[f]	$Rh_2(OAc)_4$
4	**1** R_1,R_2,R_3 = Bn	**5** (35)	9	9:1:1:1[f]	$Rh_2(OAc)_4$
5	**1** R_1,R_2,R_3 = Ac	**6** (62)	11	44:3:2:5	$Rh_2(OAc)_4$
6	**1** R_1,R_2,R_3 = Ac	**6** (4)	0	11:2:1:2	$Cu(acac)_2$
7	**1** R_1,R_2,R_3 = Ac	**6** (0)	0	-	$PdCl_2$
8	**1** R_1,R_2,R_3 = Ac	**6** (0)	0	-	$Pd(OAc)_2$
9	**1** R_1=TBS; R_2,R_3=H	0	0	-	$Rh_2(OAc)_4$
10	**7** 	**8** (67)	0	8:1:0:0	$Rh_2(OAc)_4$
11	**9** 	**10** (44) [g]	14	19:4:1:2	$Rh_2(OAc)_4$

[a] Isolated by flash chromatography as a mixture of the indicated products. [b] Isolated by flash chromatography as the second fraction and a mixture of the indicated products. [c] Determined on the crude reaction mixture by fused silica capillary gas chromatography. [d] Isolated as the single isomer **A**. [e] Isolated as a mixture of isomers **B**,**C** and **D**. [f] determined by ^{1}H NMR on the crude reaction mixture. [g] See ref. 8 for isomer assignments.

A limitation of the reaction is seen with entry 9. Attempted cyclopropanation of the 3,4-dihydroxy-D-glucal failed to produce a cyclopropanated sugar. However, reaction of the acetate-protected glycal gave an 89% yield of **2** (entry 1). Finally, several catalysts were compared using the commercially available triacetyl glycal (entries 5-8). As can be seen, catalysis with palladium complexes failed to generate cyclopropanes (entries 7 and

8), while use of copper acetylacetonate gave lower yields and selectivities (entry 6). Thus, it appears that rhodium is the more affective catalyst.[9]

Ring-expansion of the cyclopropanes according to Scheme 1 was examined next. However, all efforts failed to provide the desired ring-expanded oxacycle. We attribute this to a deactivation of the cyclopropane by the ester group. We therefore attempted opening of the cyclopropane moiety with hydrobromic acid as a method for the synthesis of C-2 branched glycosyl bromides (Scheme 3).[10] Treatment of **6** with HBr in acetic acid produced the glycosyl bromide **11** in 38% isolated yield with 13:1 β/α selectivity.[11] However, bromide substitution of the C-3 acetate also occurred.[12]

6 **11**

Scheme 3.

In conclusion, we have achieved the synthesis of ester-substituted cyclopropanes that uses readily available carbohydrates as stereospecific templates.[13] Furthermore, these cyclopropanes should offer access to numerous new carbohydrate derivatives using previously developed chemistry. Further research is currently underway to develop the chemistry of these cyclopropanes.

Acknowledgments. We thank the National Renewable Energy Laboratory Director's Development Fund for support of this research.

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4 a) For reviews see: Doyle, M. P. In *Catalytic Aymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 3. b) Doyle, M. P. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 305. c) Brookhart, M.; Studebaker, W. B. *Chem. Rev.* **1987**, *87*, 411.

5 Starting substrates were purchased from commercial suppliers and used as received or prepared according to literature procedures (see ref. 2). A representative procedure for the formation of **2** is as follows: A mixture of 3,4-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl-D-glucal (0.880 g, 2.56 mmol) and rhodium acetate dimer (0.0116 g, 0.0256 mmol) in dichloromethane (5 ml) was vigorously stirred under an argon atmosphere. Ethyl diazoacetate (0.584 g, 5.11 mmol) in dichloromethane (15 ml) was added dropwise to the mixture over the course of 14 hours via syringe pump, after which time TLC (hexanes/ethyl acetate 9:1) showed the reaction to be complete. The mixture was evaporated under reduced pressure to give a green syrup which was purified by flash chromatography. Elution with hexanes/ethyl acetate (9:1) gave 1.32 g of a colorless oil

(89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.01 (s, 6H), 0.81 (s, 9H), 1.16 (3, t, $CH_2\underline{CH_3}$), 1.62 (ddd, $J_{1,2}$=6.8, $J_{2,7}$=4.9, $J_{2,3}$=1.5 Hz, 1H, H-2), 1.95 (m, 1H, H-7), 1.96 (s, 3H, Ac), 2.00 (s, 3H, Ac), 3.58 (m, 1H, H-5), 3.72 (m, 2H, H-6), 3.84 (dd, $J_{1,2}$=6.8, $J_{1,7}$=4.4 Hz, 1H, H-1), 4.02 (q, 2H, $\underline{CH_2}CH_3$), 4.94 (dd, $J_{2,3}$=1.5, $J_{3,4}$=2.9 Hz, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.7, -5.7, 14.0, 18.0, 20.7, 20.7, 23.5, 25.4, 25.6, 56.4, 60.6, 62.1, 67.9, 68.4, 75.6, 169.2, 169.4, 170.6; IR (neat) 2967, 2940, 2860, 1755, 1721, 1370, 1130, 1044, 839, 787 cm^{-1}; MS *m/e* calc'd for $C_{20}H_{35}O_8Si$ (MH^+): 431.2101, found 431.2053.

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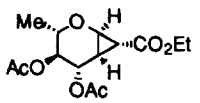
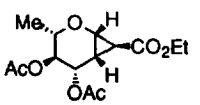
8 Coupling constants for cyclopropane systems range between 0-6 Hz for a *trans* -stereochemistry, while literature values for *cis* -protons range between 8-10 Hz. a) Kawabata, N.; Nakagawa, T.; Nakao, T.; Yamashita, S. *J. Org. Chem.* **1977**, *42*, 3031. b) Wiberg, K. B.; Barth, D. E.; Schertler, P. H. *J. Org. Chem.* **1973**, *38*, 378. c) Williamson, K. L.; Lanford, C. A.; Nicholson, C. R. *J. Am. Chem. Soc.* **1964**, *86*, 762. For example, the assignment of cyclopropane **9** was made using the following data:

Ring stereochemistry	ester stereochemistry
A - $J_{2,3}$=0Hz	$J_{2,7}$ = 5.9Hz (*trans*)
B - $J_{2,3}$=10.3Hz	
C - $J_{2,3}$=1.2Hz	
D - $J_{2,3}$= 3.9Hz	$J_{2,7}$ = 8.8Hz (*cis*)



9A



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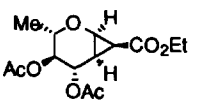
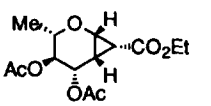


9C



9D

9 Similar results for the cyclopropanation of disubstituted olefins and vinyl ethers with ethyl diazoacetate have been observed, see reference 4c and a) Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssie, P. *J. Org. Chem.* **1980**, *45*, 695. Recently, Horton and Fraiser-Ried published the cyclopropanation using a 5 fold excess of copper powder. b) Horton, J. O.; Fraiser-Ried, B. *Tetrahedron Lett.* **1995**, *36*, 6831.

10 For a review on the use of glycosyl bromides in synthesis see: *C-Glycoside Synthesis*, Postema, M H. D.; CRC press, Boca Raton, 1995.

11 Isolated by flash chromotagraphy as an anomeric mixture of **11**: ^{1}H NMR (300 MHz, CDCl3) δ 6.70 (d, J=3.4Hz, 1H, H-1), 5.29 (t, J=10.0Hz, 1H, H-4), 4.30 - 4.06 (m, 4H, H-3, H-5, H-6), 4.15 (t, J=7.1Hz, 2H, $\underline{CH_2}CH_3$), 3.00 (dd, J=17.3, 3.3Hz, 1H, CH_2), 2.72 (m, 1H, H-2), 2.48 (dd, J=17.3, 10.0Hz, 1H, CH2), 2.12 (s, 3H, Ac), 2.09 (s, 3H, Ac), 1.28 (t, J=7.1Hz, $CH_2\underline{CH_3}$); ^{13}C NMR (75 MHz, CDCl3) δ 170.6, 170.5, 169.1, 92.7, 73.5, 70.0, 61.4, 61.1, 51.9, 46.5, 36.9, 20.7, 20.6, 14.1.

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