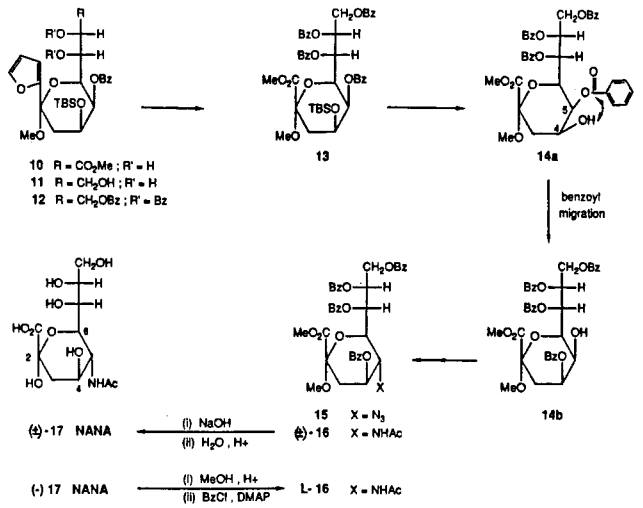

erties of (±)-16, thus obtained, were identical with those of L-16 prepared as shown.[18] Finally, (±)-16, upon saponification and acidic (Dowex) workup, afforded racemic NANA (17) whose ^{1}H NMR (490 MHz) and chromatographic properties were identical with those of authentic NANA (–)-17. The first total synthesis of NANA was thus complete.

During the course of these investigations, several other variations of C_7–C_9 functionalities were investigated with a view toward their suitability for hydroxylation. As a consequence of those studies, latitude in modifying the stereogenic centers at C_7 and C_8 is now possible. It was also found that masked furanoketosides (cf. **10–12**) are excellent substrates for simple acid catalyzed exchange reactions with other alcohols. Both of these findings augur well for the possibility of preparing novel stereoisomers and glycosides of NANA. These discoveries will be developed more fully in due course.

Acknowledgment. This work was supported by PHS Grant A116943. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

(18) Kuhn, R.; Lutz, P.; MacDonald, D. L. *Chem. Ber.* **1966**, *99*, 611.

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Reaction of Glycals with Trifluoroacetic Anhydride and Ammonium Nitrate: A Novel Cleavage Reaction of Glycals[1]

Summary: The reaction of 3-acetylated pyranoid glycals with trifluoroacetic anhydride and ammonium nitrate followed by aqueous pH >7 workup leads to chiral (*E*)-3-acetoxy-4-formoxy-1-nitro-1-pentenes via a Grob fragmentation of the 1-*O*-(trifluoroacetyl)-3-*O*-acetyl-2-deoxy-2-nitropyranoses.

Sir: The use of carbohydrates as chiral synthons for the asymmetric synthesis of natural products is well documented.[2] Because of such interest we wish to report in this paper a facile and novel cleavage reaction of glycals that leads to chiral nitroalkenes, potentially useful chiral synthons.

Table I. Chemical Shifts (δ) and Coupling Constants ($^3J_{1,2}$)[a] of the Anomeric Protons for the 1-*O*-(Trifluoroacetyl)-2-deoxy-2-nitropyranoses 2

	δ (*J*, Hz)			
2a	6.86 (4.0)	6.74 (2.5)	6.58 (3.0)	6.26 (8.5)
2b	6.99 (1.5)	6.87 (4.0)	6.84 (4.0)	6.20 (8.5)
2c	6.98 (3.0)	6.85 (4.0)	6.82 (2.0)	6.58 (8.5)
2d	6.81 (4.0)	6.69 (2.5)	6.50 (2.5)	6.22 (8.0)
2e	6.79 (5.0)	6.74 (4.0)	6.46 (3.5)	6.14 (8.5)

[a] Determined at 360 MHz in $CDCl_3$.

The reactions at the double bond in glycals can be classified into three types: 1,2-addition,[3] substitution with allylic rearrangement (Ferrier reaction),[4] and addition with subsequent ring cleavage between C-1 and the ring oxygen. The first two types of reactions are commonplace in carbohydrate chemistry but there are very few examples of the third type of reaction.[5] Now we have discovered another ring-cleavage reaction of glycals, this time between C-1 and C-2.

Treatment of 3,4,6-tri-*O*-acetyl-D-glucal (**1a**) with trifluoroacetic anhydride and ammonium nitrate (TFAA/AN) followed by aqueous, pH >7, workup[6] gave a 90% yield of nitroalkene (*E*)-3(*R*),5-diacetoxy-4(*R*)-(formyloxy)-1-nitro-1-pentene (**3a**), as a yellow viscous oil.[7] Similarly, 3,4,6-tri-*O*-acetyl-D-galactal (**1b**)[8] and 3,4-di-*O*-acetyl-L-rhamnal (**1d**)[9] gave (*E*)-3(*S*),5-diacetoxy-4(*R*)-(formyloxy)-1-nitro-1-pentene (**3b**) and (*E*)-3(*S*)-acetoxy-4(*S*)-(formyloxy)-1-nitro-1-pentene (**3d**) in 85% and 93% yields, respectively. However, 3,4,6-tri-*O*-acetyl-D-allal

(1) Abstracted in part from the M.S. thesis of D.D., Villanova University, 1983.

(2) Hanessian, S. *The Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: Oxford, 1983.

(3) Stanek, J.; Cerny, M.; Kocourek, J.; Pacak, J. *The Monosaccharides*; Academic: New York, 1963.

(4) Ferrier, R. J. In *The Carbohydrates: Chemistry and Biochemistry*; Pigman, W., Horton, D., Eds.; Academic: New York, 1980; Vol. 1B.

(5) Initially Fraser-Reid and Radatus, observed the formation of the α,β-unsaturated aldehyde, 4,6-di-*O*-acetyl-2,3-dideoxy-*aldehydo*-D-*erythro*-*trans*-hex-2-enose, in a 60% yield during the acid-catalyzed hydrolysis of 3,4,6-tri-*O*-acetyl-D-glucal; see: Fraser-Reid, B.; Radatus, B. *J. Am. Chem. Soc.* **1970**, *92*, 5288. Employing aqueous mercury(II) sulfate, Gonzalez et al. obtained a quantitative yield of the aldehyde; see: Gonzalez, F.; Lesage, S.; Perlin, A. *Carbohydr. Res.* **1975**, *42*, 267. During an attempted hydroxymercuration (aqueous mercury(II) acetate)–demercuration (sodium borohydride) a 60% yield of the aldehyde was obtained, see: Takiura, J.; Honda, S. *Carbohydr. Res.* **1973**, *29*, 477. However, oxidative cleavage of 3,4,6-tri-*O*-acetyl-D-glucal with palladium chloride in methanol with a catalytic amount of copper(II) nitrate gave a 60% yield of the saturated ester methyl 3,4,6-tri-*O*-acetyl-5-hydroxyhexanoate, see: Gouedard, M.; Gaudemer, F.; Gaudemer, A. *Bull. Soc. Chim. Fr.* **1973**, 577.

(6) A typical experimental procedure involves adding TFAA (5.0 mL, 35 mmol) to a mixture of 5 mmol of a glycal 1 and dry AN (0.48 g, 6.0 mmol). The mixture is stirred for 1 h. At this point the excess TFAA can be removed under reduced pressure and the ^{1}H NMR spectra run to demonstrate the formation of the intermediate addition products or the reaction mixture can be worked up in the following manner. The reaction mixture is diluted with 20 mL of water and extracted with dichloromethane (3 × 90 mL). The organic layer is then washed with 5% $NaHCO_3$ solution (3 × 90 mL) and saturated NaCl (30 mL), dried over $MgSO_4$, and concentrated. The resultant viscous oil can be purified by distillation under reduced pressure, (ca. 1–2 torr).

(7) Anal. Calcd for $C_{10}H_{13}NO_8$: C, 43.64; H, 4.73; N, 5.09. Found: C, 43.93; H, 4.75; N, 5.65. MS (EI), M^+ = 275; bp 181 °C (1.8 torr); ir (neat) 1735 (C=O), 1655 (C=C), 1532, 1450 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$) δ 8.10 (s, 1 H, CHO), 7.20 (dd, 1 H, $J_{1,2}$ = 13 Hz, $J_{1,3}$ = 6 Hz, CH), 7.18 (dd, 1 H, $J_{1,2}$ = 13 *Hz*, $J_{2,3}$ = 1 Hz, $CHNO_2$), 5.72–5.82 (s, 1 H, CHOAc), 5.35–5.55 (s, 1 H, $CHCH_2$), 4.22–4.35 (s, 2 H, CH_2), 2.15 (s, 3 H, CH_3CO_2), 2.10 (s, 3 H, CH_3CO_2); ^{13}C NMR ($CDCl_3$) δ 170.29 (CH_3CO_2), 169.14 (CH_3CO_2), 159.47 (HCO_2), 142.17 (HC=), 134.15 (=$CHNO_2$), 70.37 (CH), 67.97 (CH), 61.09 (CH_2), 20.55 (CH_3).

(8) Pigman, W.; Roth, W. *Methods Carbohydr. Chem.* **1962**, *1*, 405.

(9) Pfanstiehl Laboratories, Inc., Waukegan, IL 60085.

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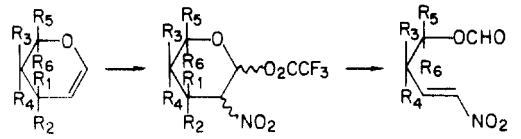
(**1c**)[10] gave only a 40% yield of the nitroalkene **3a** ≡ **3c** whereas 4,6-di-*O*-acetyl-3-*O*-methyl-D-glucal[11] (**1e**) and 3,4,6-tri-*O*-methyl-D-glucal (**1f**)[12] did not yield cleavage products **3e** and **3f**.[13]

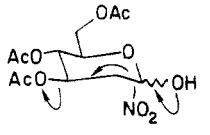


1 2 3

	R_1	R_2	R_3	R_4	% yield of 3
a[a]	OAc	H	H	OAc	90
b[a]	OAc	H	OAc	H	85
c[a]	H	OAc	H	OAc	40
d[b]	H	OAc	OAc	H	93
e[a]	OMe	H	H	OAc	0
f[a]	OMe	H	H	OMe	0

[a] $R_5 = CH_2OAc$, $R_6 = H$. [b] $R_5 = H$, $R_6 = CH_3$.

If aqueous workup was omitted[6] after the reaction of the glycal with TFAA/AN, the ^1H NMR spectra of the crude reaction mixture revealed the presence of four downfield doublets with chemical shifts characteristic of protons attached to an anomeric carbon (see Table I). As can be seen from ^1H NMR, the conversion of the glycals **1a–f** to **2a–f** is quantitative. If the reaction mixture is treated with aqueous bicarbonate, the cleavage products are obtained as described above. From the examination of ^1H NMR spectra of the reaction mixture and an analysis of the structure of the glycals that undergo cleavage, a mechanism for the fragmentation can be formulated. The initial reaction of each glycal is the regiospecific but nonstereospecific addition of trifluoroacetyl nitrate[14] to give four diastereomeric 1-*O*-(trifluoroacetyl)-2-deoxy-2-nitropyranoses **2a–f**[15] (see Table I). Under base-catalyzed hydrolytic conditions pyranoses having the appropriate stereoelectronic arrangement of functionalities undergo Grob-type fragmentation.[16,17] This can be illustrated by structure **4**. This mechanism accounts for the fact that



4

the 3-*O*-acetyl compounds **2a,b,d** undergo fragmentation whereas the 3-*O*-methyl compounds **2e,f** do not, since acetate is a better leaving group than methoxide. Furthermore, it is well-known that stereoelectronic effects are important in determining the rates of Grob fragmentation reactions.[18] Consistent with this is our observation that the glycals with an equatorial acetoxy group **1a,b,d** underwent a smooth fragmentation compared to the allal derivative **1c** in which the acetoxy group is axial. Also consistent with the mechanism is that the configurations at C-4 and C-6 are unimportant and that an acetoxy group at C-6 is not necessary for the fragmentation.[19]

Research is currently under way utilizing the enantiomerically pure nitroalkenes **3a,b,d**[20] as chiral synthons.

(10) Haga, M.; Tejima, S. *Carbohydr. Res.* **1962**, *34*, 408.
(11) Kugelman, M.; Mallams, A. K.; Vernay, H. F. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1113.
(12) Hirst, E. L.; Woolvin, C. S. *J. Chem. Soc.* **1931**, 1131.
(13) By ^1H NMR it appears that the reaction mixtures of **1c,e,f** contain a 2-deoxy-2-nitropyranose, its retro nitroaldol product, and a 2-nitroglycal.
(14) Crivello, J. V. *J. Org. Chem.* **1981**, *46*, 3056.
(15) α-Anomer with *R* or *S* configuration at C-2 and the β-anomer with the *R* or *S* configuration at C-2.
(16) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1.
(17) Although there are two examples of Grob fragmentations in carbohydrates which involve bond cleavage between C-1 and C-2, neither of these fragmentations has a glycal as the starting material. 3-*O*-(Methylsulfonyl)-D-glucose when treated wtih base yields 2-deoxy-D-ribose: Smith, D. C. *J. Chem. Soc.* **1957**, 2690. Attempted acetylation of methyl 4,6-*O*-benzylidene-2-deoxy-2-nitro-β-D-glucopyranoside with acetic anhydride and pyridine afforded a 1:1 mixture of the expected 3-*O*-acetate and (4*S*,5*R*)-4-(nitrovinyl)-2-phenyl-1,3-dioxan-5-yl formate: Sakakibara, T.; Sudok, R. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1263.
(18) Grob, C. A. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 535.
(19) A mechanism can be written which involves participation of the C-6 acetoxy group.
(20) Satisfactory elemental analysis was obtained.

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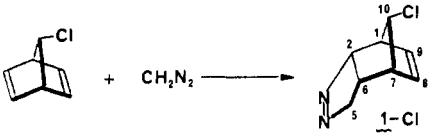
On the Addition of Diazomethane to 7-Chloronorbornadiene

Summary: The addition of diazomethane to 7-chloronorbornadiene is not stereospecifically endo,anti, as reported. The endo,syn isomer also forms. Nevertheless, the anti selectivity is high, ca. 9:1, and no exo adduct is observed. Discretion is advised on other reports of stereospecificity in related cycloadditions.

Sir: The addition of diazomethane to 7-chloronorbornadiene contrasts startlingly with the analogous addition of diphenyldiazomethane. The former is reported to form 1-Cl exclusively (eq 1).[1] The latter forms three



(1)

of the four possible monoadducts.[2] Although the specific addition in eq 1 has been cited frequently in several contexts,[3] we know of no confirmation of the result claimed.[4,5]

(1) Franck-Neumann, M.; Sedrati, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 606. No experimental details were given. The structure of 1-Cl was assigned by analogy to that of the corresponding diazoethane adduct.
(2) Wilt, J. W.; Roberts, W. N. *J. Org. Chem.* **1978**, *43*, 170. Only the exo,syn isomer was not detected.
(3) Astin, K. B.; Mackenzie, K. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1004. Battiste, M. A.; Timberlake, J. F.; Malkus, H. *Tetrahedron* **1976**, 2529. Alston, P. V.; Ottenbrite, R. M. *J. Heterocycl. Chem.* **1977**, *14*, 1443. DeMicheli, C.; Gandolfi, R.; Oberti, R. *J. Org. Chem.* **1980**, *45*, 1209.
(4) The earliest study of the title reaction in this laboratory was done by: Roberts, W. N.; Senior Research Report, Loyola University of Chicago, 1976. Only 1-Cl was detected at that time. The later acquisition of a Chromatotron made product analysis much more sensitive and allowed the present study.
(5) In ref 1 diazoethane was observed to give specific endo,anti addition to 7-bromo- and 7-iodonorbornadiene as well. Later these authors reported that diazomethane does likewise.[6] However, in this later paper the authors found that reaction of diazoethane with 7-fluoronorbornadiene gave three monoadducts, the two endo's and the exo,anti. Other results from these authors on reactions with other diazoalkanes are also reported, both in ref 6 and in: Franck-Neumann, M.; Sedrati, M. *Tetrahedron Lett.* **1983**, 1391. We have restricted our comments here to their reported results on additions of diazomethane and diazoethane to the norbornadienes mentioned in the text. These results to our knowledge have not been corrected. By our comments we do not wish in any way to detract from the importance of the Franck-Neumann and Sedrati discovery of preferred endo addition in certain of these additions.
(6) Franck-Neumann, M.; Sedrati, M. *Tetrahedron Lett.* **1983**, 1387.

0022-3263/86/1951-2618$01.50/0