Notes

The Configuration of *trans*-5-Nitro-6-glyconorbornenes. Synthesis of the Enantiomerically Pure *trans*-5-Nitronorbornene-6-carboxaldehydes†

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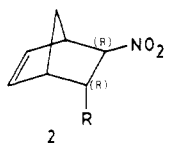
The use of carbohydrates as chiral auxiliaries in asymmetric Diels–Alder reactions constitutes an area of recent interest,[1-5] the products serving as starting materials for the synthesis of non-carbohydrate species of defined stereochemistry.[6-8]

In a previous paper,[9] we have described the reaction between (*E*)-1-deoxy-1-nitroalkenes derived from sugars and cyclopentadiene, yielding, in each case, a mixture of the four possible stereoisomeric adducts (**2–5a–c**). One problem in this synthesis is the determination of the absolute configurations at the newly generated chiral centers C-5 and C-6. In the case of the D-*manno* adducts **3a** and **5a**, the configurations were determined unambiguously by X-ray crystallographic structure analysis[9] as 5*S*,6*S* in both cases. Hence, by default, **2a** and **4a** must be 5*R*,6*R*. In the present paper, by chemical correlation, we confirm our configurational assignments of the corresponding D-*galacto* (**b**) and D-*gluco* (**c**) compounds, previously made tentatively, on the basis of NMR spectral comparisons.[9]



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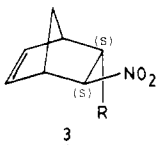

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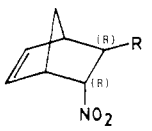

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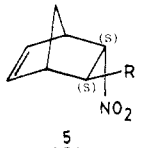

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R = CHO or R = $(CHOR^1)_4$–CH_2OR^1

Chain configurations:	R^1 = Ac	R^1 = H
	a) D-manno	d) D-manno
	b) D-galacto	e) D-galacto
	c) D-gluco	f) D-gluco

Results and Discussion

Treatment of crude mixtures of *trans*-5-nitro-6-(penta-*O*-acetylpentitol-1-yl)norbornenes[9] (**2–5a–c**) with sodium methoxide in methanol yielded the corresponding deacetylated mixtures,[10] from which we isolated the pure pentitols **4d**, **5d**, **3e**, **5e**, **3f**, and **5f** by fractional crystallizations, and **2d** by preparative TLC. The structure of each compound was established by reacetylation (leading back to the corresponding known[9] pentaacetate), elemental analysis, and spectral analysis (IR and ^1H and ^{13}C NMR). The chemical shifts and coupling constants of the norbornene moieties were similar to those in the corresponding pentaacetates, the major differences being in the shifts of H-4, H-6, H-7syn (at higher field in the pentitols), H-5, and H-7anti (at lower field). The sugar chain and hydroxyl protons appear as complex multiplets at 4.9–3.1 ppm. In the ^{13}C NMR spectra, C-2 is shifted to lower field for the 5-*endo*-nitro compounds, but to higher field for the 5-*exo*-nitro compounds, relative to the same carbon in the respective pentaacetate; the reverse is true for C-3.

Oxidative cleavage of the pentitols with sodium metaperiodate gave the nitroaldehydes **2–5** (R = CHO), which were characterized by optical rotations and spectral data. Compounds **2**[11] ($[\alpha]_D$ −83°, 5-*exo*-nitro) and **4** ($[\alpha]_D$ −88°, 5-*endo*-nitro) present opposite configurations at C-5 and C-6 to the dextrorotatory **3** and **5** (R = CHO). Moreover, the configuration of **2** and **4** (R = CHO) follows from their provenance from the corresponding known[9] pentaacetates of the D-*manno* series (**2a** and **4a**) [R = $(CHOAc)_4$–CH_2OAc] via the corresponding pentitols (**2d** and **4d**) [R = $(CHOH)_4$–CH_2OH] as being 5*R*,6*R*. Thus, **3** and **5** (R = CHO) must be 5*S*,6*S*. Hence, we may conclude that for adducts where deacetylation and degradation of the sugar chain leads to nitroaldehydes of negative optical rotation, the configurations at C-5 and C-6 must be 5*R*,6*R*. This is the case for the degradation products from **2a** or **4a**. On the other hand, for adducts that lead to dextrorotatory nitroaldehydes **3** or **5**, the configurations at C-5 and C-6 must be 5*S*,6*S*. This is the case for the degradation products from **3b**, **3c**, **5a**, **5b**, or **5c**. Therefore, through the preparation of nitroaldehydes **2–5** (R = CHO), we have unequivocally determined the configuration at C-5 and C-6 of the D-*galacto* and D-*gluco* adducts **3b**, **5b**, and **3c**, **5c** by correlating them with the known[9] D-*manno* analogues **2a**, **4a**, and **5a**, thereby confirming our previous assignments.[9] The correlation also discloses the absolute configuraton of the *trans*-nitro-aldehydes **2–5** (R = CHO).

Experimental Section

Solutions were evaporated in vacuo at temperatures below 40 °C. Melting points were determined with a Gallenkamp apparatus and are uncorrected. Optical rotations were measured at 20 ± 2 °C with a Perkin-Elmer 141 polarimeter. TLC was performed on silica gel GF_{254} (Merck) with 10:1:1 chloroform–methanol–acetic acid (solvent A) or 10:1 benzene–methanol (solvent B), and de-

† Dedicated to Professor Ernest L. Eliel.

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(10) Reacetylation of these led to the original mixture of acetates, thus establishing that no epimerization had occurred during the catalytic transesterification.
(11) The original numbering of compounds **2–5a–c** is maintained in the related nitroaldehydes in order to clarify the discussion.

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tection was with UV light or iodine vapor. IR spectra were recorded with a Perkin-Elmer 399 spectrophotometer. NMR spectra were recorded at ~25 °C with Perkin-Elmer R-32, Bruker WM-250, or Bruker AC-200 E instruments, for solutions in $CDCl_3$ or DMSO-d_6 with TMS as internal standard; assignments were supported by APT, DEPT, and heteronuclear double-resonance experiments. Elemental analyses were performed with a Perkin-Elmer 240 C apparatus.

5-Nitro-6-(1,2,3,4,5-penta-*O*-acetylpentitol-1-yl)bicyclo[2.2.1]hept-2-enes (2–5a–c). These compounds were prepared by Diels–Alder reaction between cyclopentadiene and (*E*)-3,4,5,6,7-pentaacetoxy-1-nitrohept-1-enes (**1a–c**), as previously described.[9]

(5*R*,6*R*)-1-*C*-(5-*endo*-Nitrobicyclo[2.2.1]hept-2-en-6-*exo*-yl)-D-*manno*-pentitol (4d), (5*S*,6*S*)-1-*C*-(5-*endo*-Nitrobicyclo[2.2.1]hept-2-en-6-*exo*-yl)-D-*manno*-pentitol (5d), and (5*R*,6*R*)-1-*C*-(5-*exo*-Nitrobicyclo[2.2.1]hept-2-en-6-*endo*-yl)-D-*manno*-pentitol (2d). The crude mixture of **2a–5a** (8.0 g) was crystallized from methanol, yielding several crops (4.4 g) of a solid that consisted preponderantly (^1H NMR) of **2a**, **3a**, and **5a**. The mother liquors (wherein **4a** was predominant) were diluted to 40 mL with methanol, and then a solution of sodium methoxide in methanol (1 N, 0.75 mL) was added. After 12 h at room temperature, the reaction mixture was neutralized with Amberlite IR-120 (H^+) resin and evaporated to a syrup that was crystallized from methanol. Two recrystallizations from methanol gave pure **4d** (0.4 g, 30% from **4a**): mp 167–169 °C; $[\alpha]_D$ −105° (*c* 0.65, Py); IR (KBr) ν 3600–3040, 1520, 1360 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 6.53 (br dd, 1 H, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 5.8 Hz, H-2), 5.92 (br dd, 1 H, $J_{3,4}$ = 2.3 Hz, H-3), 5.19 (dd, 1 H, $J_{4,5exo}$ = 4.2 Hz, $J_{5exo,6endo}$ = 3.8 Hz, H-5exo), 4.96 (d, 1 H, $J_{H,OH}$ = 6.0 Hz, OH), 4.6–4.0 (m, 4 OH), 3.8–3.2 (m, 6 H, H-1′,2′,3′,4′,5′,5″), 3.39 (m, 1 H, H-4), 2.89 (m, 1 H, H-1), 2.36 (m, 1 H, $J_{6endo,7syn}$ = 2.0 Hz, H-6endo), 1.92 (br d, 1 H, $J_{7syn,7anti}$ = 9.0 Hz, H-7anti), and 1.36 (br d, 1 H, H-7syn); ^{13}C NMR (50.31 MHz, DMSO-d_6) δ 141.3 (C-2), 131.9 (C-3), 86.6 (C-5), 72.1, 71.4 (2 C), 69.9 (C-1′,2′,3′,4′), 63.9 (C-5′), 50.9, 48.0, 47.8, and 47.1 (C-1,4,6,7). Anal. Calcd for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.62; N, 4.84. Found: C, 49.78; H, 6.80; N, 4.62.

The aforementioned solid mixture of **2a**, **3a**, and **5a** was dissolved in methanol (50 mL) and treated with a solution of sodium methoxide in methanol (1 N, 1 mL) as described above. After three recrystallizations from methanol and one from water, compound **5d** was obtained pure (0.31 g, 16% from **5a**): mp 141–143 °C; $[\alpha]_D$ +52° (*c* 0.75, Py); IR (KBr) ν 3640–3100, 1520, 1360 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 6.50 (br dd, 1 H, $J_{1,2}$ = 3.3 Hz, $J_{2,3}$ = 5.9 Hz, H-2), 5.97 (br dd, 1 H, $J_{3,4}$ = 2.9 Hz, H-3), 5.15 (t, 1 H, $J_{4,5exo}$ = $J_{5exo,6endo}$ = 4.1 Hz, H-5exo), 4.92 (d, 1 H, $J_{H,OH}$ = 6.2 Hz, OH), 4.7–3.9 (m, 4 OH), 3.8–3.3 (m, 6 H, H-1′,2′,3′,4′,5′,5″), 3.40 (m, 1 H, H-4), 3.02 (m, 1 H, H-1), 2.23 (m, 1 H, $J_{1',6endo}$ = 6.8 Hz, $J_{6endo,7syn}$ = 1.7 Hz, $J_{1,6endo}$ ~ 0 Hz, H-6endo), 1.83 (br d, 1 H, $J_{7syn,7anti}$ = 8.5 Hz, H-7anti), and 1.34 (dd, 1 H, H-7syn); ^{13}C NMR (62.89 MHz, DMSO-d_6) δ 140.8 (C-2), 131.8 (C-3), 87.9 (C-5), 72.0, 71.3, 69.8, 69.7 (C-1′,2′,3′,4′), 63.7 (C-5′), 47.9, 47.4, 45.3, and 43.2 (C-1,4,6,7). Anal. Calcd for $C_{12}H_{19}NO_7 \cdot H_2O$: C, 46.90; H, 6.89; N, 4.56. Found: C, 47.16; H, 7.05; N, 4.46.

The methanolic mother liquors of **5d** were concentrated and separated by silica gel TLC to afford a small sample of the more mobile product (**2d**, R_f 0.14, solvent A) as an amorphous solid: ^{13}C NMR (50.31 MHz, DMSO-d_6) δ 139.6 (C-2), 132.9 (C-3), 89.3 (C-5), 73.3, 71.4, 71.0, 69.7 (C-1′,2′,3′,4′), 63.5 (C-5′), 51.9, 49.7, 48.6, and 44.0 (C-1,4,6,7).

A part of **2d** was subjected to degradation of its sugar chain to yield **2**, and the other part was acetylated, giving a compound whose ^1H and ^{13}C NMR spectra were identical with those described[9] for **2a**.

(5*S*,6*S*)-1-*C*-(5-*exo*-Nitrobicyclo[2.2.1]hept-2-en-6-*endo*-yl)-D-*galacto*-pentitol (3e) and (5*S*,6*S*)-1-*C*-(5-*endo*-Nitrobicyclo[2.2.1]hept-2-en-6-*exo*-yl)-D-*galacto*-pentitol (5e). To a solution of the crude mixture **2b–5b** (8.0 g) in methanol (180 mL) was added a solution of sodium methoxide in methanol (1 N, 2.5 mL). After 24 h at room temperature, the reaction mixture was neutralized wtih Amberlite IR-120 (H^+) resin[10] and evaporated to half volume, giving a solid (0.45 g) with **3e** as the major product. Concentration of the mother liquors yielded several crops that were checked by ^1H NMR spectroscopy. The solids with **3e** prodominant (1.75 g) were combined and recrystallized from 80% ethanol (35 mL) and then from water (30 mL), yielding pure **3e** (0.15 g, 27% from **3b**): mp 225–227 °C; $[\alpha]_D$ +75° (*c* 0.70, Py); IR (KBr) ν 3530–3100, 1520, 1360 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 6.31 (br dd, 1 H, $J_{1,2}$ = 2.2 Hz, $J_{2,3}$ = 5.5 Hz, H-2), 6.22 (br dd, 1 H, $J_{3,4}$ = 3.1 Hz, H-3), 4.7–3.8 (m, 5 OH), 4.30 (br d, 1 H, H-5endo), 3.8–3.0 (m, 6 H, H-1′,2′,3′,4′,5′,5″), 3.27 (m, 1 H, H-4), 2.93 (dt, 1 H, $J_{1',6exo}$ = 11.0 Hz, $J_{1,6exo}$ = $J_{5endo,6exo}$ = 3.4 Hz, H-6exo), 2.88 (m, 1 H, H-1), 1.98 (br dd, 1 H, $J_{7syn,7anti}$ = 9.1 Hz, H-7anti), and 1.55 (br d, 1 H, H-7syn); ^{13}C NMR (62.89 MHz, DMSO-d_6) δ 138.8 (C-2), 133.4 (C-3), 89.8 (C-5), 72.0, 69.8, 69.7, 69.1 (C-1′,2′,3′,4′), 63.1 (C-5′), 50.3, 50.2, 46.2, and 42.8 (C-1,4,6,7). Anal. Calcd for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.62; N, 4.84. Found: C, 49,45; H, 6.73; N, 4.68.

Evaporation of the mother liquors of **3e** yielded compound **5e** that was obtained pure after two recrystallizations from water (0.35 g, 19% from **5b**): mp 169–171 °C; $[\alpha]_D$ +57° (*c* 0.57, Py); IR (KBr) ν 3600–3100, 1530, 1360 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 6.51 (br dd, 1 H, $J_{1,2}$ = 3.2 Hz, $J_{2,3}$ = 5.6 Hz, H-2), 5.91 (br dd, 1 H, $J_{3,4}$ = 2.6 Hz, H-3), 5.17 (t, 1 H, $J_{4,5exo}$ = $J_{5exo,6endo}$ = 3.8 Hz, H-5exo), 4.3–3.2 (m, 11 H, H-1′,2′,3′,4′,5′,5″, and 5 OH), 3.37 (m, 1 H, H-4), 2.75 (m, 1 H, H-1), 2.35 (ddd, 1 H, $J_{1',6endo}$ = 9.6 Hz, $J_{6endo,7syn}$ = 2.1 Hz, H-6endo), 1.75 (br d, 1 H, $J_{7syn,7anti}$ = 9.5 Hz, H-7anti), and 1.44 (dd, 1 H, H-7syn); ^{13}C NMR (62.89 MHz, DMSO-d_6) δ 140.6 (C-2), 131.3 (C-3), 88.2 (C-5), 72.0, 70.7, 69.8, 69.3 (C-1′,2′,3′,4′), 63.1 (C-5′), 48.1, 47.5, 45.9, and 45.1 (C-1,4,6,7). Anal. Calcd for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.62; N, 4.84. Found: C, 49.97; H, 6.77; N, 4.68.

(5*S*,6*S*)-1-*C*-(5-*endo*-Nitrobicyclo[2.2.1]hept-2-en-6-*exo*-yl)-D-*gluco*-pentitol (5f) and (5*S*,6*S*)-1-*C*-(5-*exo*-Nitrobicyclo[2.2.1]hept-2-en-6-*endo*-yl)-D-*gluco*-pentitol (3f). The crude mixture of **2c–5c** was dissolved in methanol (160 mL) and deacetylated with a solution of sodium methoxide in methanol (1 N, 2.5 mL). After 4 h at room temperature there appeared a solid (2.0 g) that was collected and showed to be chiefly **5f**. The filtrate was neutralized with Amberlite IR-120 (H^+) resin and then concentrated, yielding a second crop of crystals (2.3 g). The solids were combined and recrystallized twice from 90% ethanol and then twice from water to give pure **5f** (0.3 g, 17% from **5c**): mp 177–179 °C; $[\alpha]_D$ +76° (*c* 0.50, Py); IR (KBr) ν 3600–3100, 1530, 1360 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 6.49 (br dd, 1 H, $J_{1,2}$ = 2.8 Hz, $J_{2,3}$ = 5.8 Hz, H-2), 5.87 (br dd, 1 H, $J_{3,4}$ = 3.0 Hz, H-3), 5.16 (t, 1 H, $J_{4,5exo}$ = $J_{5exo,6endo}$ = 4.0 Hz, H-5), 4.74 (d, 1 H, $J_{H,OH}$ = 5.0 Hz, OH), 4.6–4.1 (m, 4 OH), 3.8–3.1 (m, 6 H, H-1′,2′,3′,4′,5′,5″), 3.38 (m, 1 H, H-4), 2.79 (m, 1 H, H-1), 2.34 (m, 1 H, H-6), 1.82 (br d, 1 H, $J_{7syn,7anti}$ = 9.5 Hz, H-7anti), and 1.36 (br d, 1 H, H-7syn); ^{13}C NMR (50.31 MHz, DMSO-d_6) δ 141.0 (C-2), 131.6 (C-3), 87.5 (C-5), 74.4, 73.3, 71.6, 70.3 (C-1′,2′,3′,4′), 63.2 (C-5′), 48.4, 47.4, 46.1, and 45.8 (C-1,4,6,7). Anal. Calcd for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.62; N, 4.84. Found: C, 49.77; H, 6.78; N, 4.64.

Evaporation of the mother liquors of **5f** yielded compound **3f**, obtained pure after two recrystallizations from water (0.14 g, 19% from **3e**): mp 206–208 °C; $[\alpha]_D$ +48° (*c* 0.62, Py); IR (KBr) ν 3520–3100, 1530, 1360 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 6.21 (m, 2 H, H-2,3), 4.70 (d, 1 H, $J_{H,OH}$ = 5.0 Hz, OH), 4.6–4.1 (m, 4 OH), 4.30 (br d, 1 H, $J_{5endo,6exo}$ = 3.4 Hz, H-5), 3.8–3.1 (m, 6 H, H-1′,2′,3′,4′,5′,5″), 3.30 (m, 1 H, H-4), 2.96 (m, 2 H, H-1,6), 1.95 (br d, 1 H, $J_{7syn,7anti}$ = 9.5 Hz, H-7anti), and 1.52 (br d, 1 H, H-7syn); ^{13}C NMR (50.31 MHz, DMSO-d_6) δ 139.1 (C-2), 133.9 (C-3), 89.6 (C-5), 75.7, 73.3, 71.7, 69.4 (C-1′,2′,3′,4′), 63.1 (C-5′), 50.5, 50.3, 46.5, and 43.2 (C-1,4,6,7). Anal. Calcd for $C_{12}H_{19}NO_7$: C, 49.82; H, 6.62; N, 4.84. Found: C, 49.70; H, 6.86; N, 4.64.

General Procedure for Degradation of the Pentahydroxypentyl Side Chains. To a solution of the deacetylated adduct (0.1 g, 0.35 mmol) in aqueous methanol (1:2, 8 mL) was added sodium metaperiodate (0.35 g, 1.61 mmol), and the mixture was stirred at room temperature. In all cases, there was immediate appearance of a voluminous precipitate. After 15 min, water was added, and the resulting solution was extracted with methylene chloride (3 × 15 mL). The extracts were washed with water, dried (sodium sulfate), and evaporated to a syrup (51–56 mg, 88–97%).

(5*R*,6*R*)-1-*C*-(5-*exo*-Nitrobicyclo[2.2.1]hept-2-en-6-*endo*-yl)carboxaldehyde (2). This compound was obtained by degradation of pentahydroxypentyl side chain of **2d**: $[\alpha]_D$ −83° (*c*

0.50, CH_2Cl_2); TLC R_f 0.48 (solvent B); IR (CCl_4) ν 2780, 2675, 1715, 1700, 1530, 1350 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.62 (s, 1 H, CHO), 6.23 (m, 2 H, H-2,3), 4.74 (dd, 1 H, $J_{4,5endo} \sim 0$ Hz, $J_{5endo,6exo} = 3.4$ Hz, $J_{5endo,7syn} = 1.1$ Hz, H-5endo), 3.74 (t, 1 H, $J_{1,6exo} = 3.5$ Hz, H-6exo), 3.56 (m, 1 H, H-4), 3.47 (m, 1 H, H-1), 1.95 (br d, 1 H, $J_{7syn,7anti} = 9.4$ Hz, H-7anti), and 1.79 (dd, 1 H, H-7syn); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 197.8 (CHO), 137.8 (C-2), 134.8 (C-3), 84.7 (C-5), 58.6 (C-6), 49.9 (C-4), 47.2 (C-7), and 43.4 (C-1).

(5*S*,6*S*)-1-*C*-(5-*exo*-Nitrobicyclo[2.2.1]hept-2-en-6-*endo*-yl)carboxaldehyde (3). Compound **3** (enantiomer of **2**) was prepared from **3e** or **3f** by the procedure above mentioned: $[\alpha]_D$ +86° (*c* 1.60, CH_2Cl_2).

(5*R*,6*R*)-1-*C*-(5-*endo*-Nitrobicyclo[2.2.1]hept-2-en-6-*exo*-yl)carboxaldehyde (4). Compound **4** was prepared from **4d**: $[\alpha]_D$ -88° (*c* 2.80, CH_2Cl_2); TLC R_f 0.58 (solvent B); IR (CCl_4) ν 2820, 2680, 1715, 1700, 1530, 1355 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.84 (s, 1 H, CHO), 6.53 (br dd, 1 H, $J_{1,2} = 3.1$ Hz, $J_{2,3} = 5.4$ Hz, H-2), 6.17 (br dd, 1 H, $J_{3,4} = 2.7$ Hz, H-3), 5.48 (t, 1 H, $J_{4,5exo} = J_{5exo,6endo} = 3.6$ Hz, H-5exo), 3.64 (m, 1 H, H-4), 3.33 (m, 1 H, H-1), 3.22 (dd, 1 H, $J_{6endo,7syn} = 2.1$ Hz, $J_{1,6endo} \sim 0$ Hz, H-6endo), 1.64 (br dd, 1 H, $J_{7syn,7anti} = 9.5$ Hz, H-7anti), and 1.42 (br dd, 1 H, H-7syn); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 197.8 (CHO), 138.7 (C-2), 134.4 (C-3), 84.2 (C-5), 57.0 (C-6), 47.0 (C-4), 45.5 (C-7), and 44.3 (C-1).

(5*S*,6*S*)-1-*C*-(5-*endo*-Nitrobicyclo[2.2.1]hept-2-en-6-*exo*-yl)carboxaldehyde (5). Compound **5** (enantiomer of **4**) was obtained from **5d**, **5e**, or **5f**: $[\alpha]_D$ +90° (*c* 2.50, CH_2Cl_2).

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Registry No. **2**, 123003-29-2; **2a**, 119448-02-1; **2b**, 119479-77-5; **2c**, 119479-80-0; **2d**, 123050-38-4; **3**, 123050-43-1; **3a**, 119479-74-2; **3b**, 119479-78-6; **3c**, 119479-81-1; **3e**, 123050-39-5; **3f**, 123050-42-0; **4**, 123050-44-2; **4a**, 119479-75-3; **4b**, 119479-79-7; **4c**, 119479-82-2; **4d**, 123003-28-1; **5**, 123050-45-3; **5a**, 119479-76-4; **5b**, 119565-81-0; **5c**, 119479-83-3; **5d**, 123050-37-3; **5e**, 123050-40-8; **5f**, 123050-41-9.

Coupling Reactions of *O*-(Trimethylsilyl) Glycosides and 6-*O*-(*tert*-Butyldiphenylsilyl)-Protected Galactosides in the Presence of Trimethylsilyl Triflate. A New Method of Forming β-(1→6)-Oligosaccharidic Linkages†

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Introduction

Our studies with monoclonal IgA's, having specificity for β-(1→6)-D-galactopyranans,[1] prompted a synthesis of β-(1→6)-linked oligosaccharides. Recently we reported[2] a method for the synthesis of (1→6)-β-D-galactopyranooligosaccharides. The method involves the selective protection of the 6-hydroxyl group of β-D-galactopyranosides with the *tert*-butyldiphenylsilyl group, followed by acylation of the remaining hydroxyls, selective de-*O*-silylation, and coupling of the resulting nucleophile with a suitable α-D-galactosyl halide. However, de-*O*-silylation with a solution of 3% hydrogen chloride proved[2] to be troublesome when acetyl groups or other, acid-sensitive functions were present.

Herein, a method for a stereospecific coupling of 6-*O*-*tert*-butyldiphenylsilyl-protected galactopyranosides with *O*-(trimethylsilyl) glycosides in the presence of trimethylsilyl trifluoromethanesulfonate[3] (abbreviated trimethylsilyl triflate, TMS triflate, TMSOTf) is presented. In this case, the silyl moiety allows the direct coupling, without a prior deprotection step.

Results and Discussion

Trimethylsilyl triflate, apart from being a powerful silylating agent, also catalyzes a wide variety of reactions. It has been used as a catalyst in reactions of acetals with trialkylallylsilanes to form new carbon–carbon bonds,[4] in reactions of acetals with trimethylsilyl glucosides to yield glucosides with 1,1′-diacetal structure[5] and has also been used in coupling reactions leading to the synthesis of nucleosides[6] as well as oligosaccharides.[7] In addition, TMSOTf has been used by Murata and Noyori[8] for the transetherification of silylated ethers and by Tietze et al.[9] for the synthesis of aryl glucosides from trimethylsilyl glucoside and silylated aromatic ethers. All this prompted us to examine the possibility of employing TMS triflate for oligosaccharide synthesis using two sugar units selectively protected at C-1 and C-6 with silyl groups.

Trimethylsilyl β-D-glycosides **1** (see Table I) reacted smoothly with 6-*O*-(*tert*-butyldiphenylsilyl)-protected mono- and trigalactopyranosides **2** in the presence of trimethylsilyl triflate to give β-linked di- and tetraoligosaccharides in good yields (entries a, b, c, e). The anomeric trimethylsilyl α-D-galactoside (entry c-α) and methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(*tert*-butyldiphenylsilyl)-β-D-galactopyranoside[2] also gave the β-linked disaccharide **3c** under the same conditions, but the yield was substantially lower.

To obtain the disaccharide ligand **3d** for photoaffinity labeling studies, the 6-*O*-(*tert*-butyldiphenylsilyl) derivative (**2d**) of 3-azi-1-methoxybutyl β-D-galactopyranoside[10] was prepared[2] and coupled with peracetylated trimethylsilyl β-D-galactopyranoside[10] in the presence of TMSOTf (entry d). In spite of some decomposition of the starting azimethoxybutyl galactoside, desired disaccharide **3d** was isolated in 54% yield.

The described coupling reactions occur under relatively mild conditions, in aprotic solvents, at -30 to -70 °C, and this allows the use of synthetic intermediates that are protected with acetyl, benzoyl, or *p*-phenylbenzoyl groups. The latter can be easily removed as we showed in the case of **3e**, yielding the unprotected tetrasaccharide **4e**.

In conclusion: the coupling of two silyl-protected saccharide units **1** and **2** in the presence of trimethylsilyl

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