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Note

Synthesis of branched-chain nitro sugars by use of organocopper reagents*

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The synthesis of branched-chain nitro sugars has been achieved by cyclization of sugar dialdehydes with nitroalkanes[2–5], by Michael addition of carbanions to nitro-olefinic sugars[6–9], by nitroalkane additions to glycosulose derivatives[5,10–12], by pyrolysis of nitro sugars bearing a fused pyrazolino ring[13], and by peroxy acid oxidation of branched-chain amino sugars[14]. Although only one branched-chain nitro sugar, evernitrose, has thus far been reported[15] to occur in Nature (as a component of the everninomycin group of oligosaccharide antibiotics), the synthesis of analogs commands obvious interest, as such compounds may serve as preparative precursors for branched-chain amino sugars. Several compounds of the latter category are known to be constituents of important antibiotics.

In continuation of our exploratory work[16] on the utility of organometallic reagents for carbohydrate functionalization, we decided to examine the possible use of organocopper reagents as a means of introducing chain-branching into nitrogenous sugars. To effect *C*-alkylation, lithium dialkylcuprates** have been widely employed in recent years both by way of conjugate addition to unsaturated systems[17,18] and by nucleophilic substitution[19]. In this Note, we report on addition reactions of lithium dimethylcuprate and lithium divinylcuprate with some nitro hexenopyranosides. Although a large variety of reactive, unsaturated structures had served previously as substrates in similar conjugate additions[17], we have found only one brief report[20] referring specifically to nitroalkenes, namely, to some β-arylnitroethylenes. The reaction mechanism still appears to be a contentious issue[17c].

Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside (**1**) was treated with 2 molar equivalents of $LiMe_2Cu$ in a mixture of diethyl ether and oxolane, initially at −50°, and then for 1 h at 0°. A single product resulted; this was isolated crystalline in 91% yield, and proved to be methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-methyl-3-*C*-nitro-β-D-glucopyranoside (**2**). With $Li(CH_2=CH)_2Cu$, the enopyranoside **1** afforded in like fashion the crystalline 2-*C*-vinyl analog **3** in

*Reactions of Nitro Sugars, Part XLIII. For Part XLII, see ref. 1. Financial support of this work by the Natural Sciences and Engineering Research Council of Canada is acknowledged.
**These reagents are often represented by their stoichiometric composition, LiR_2Cu, although they are known to exist as dimers in solution[17–19].

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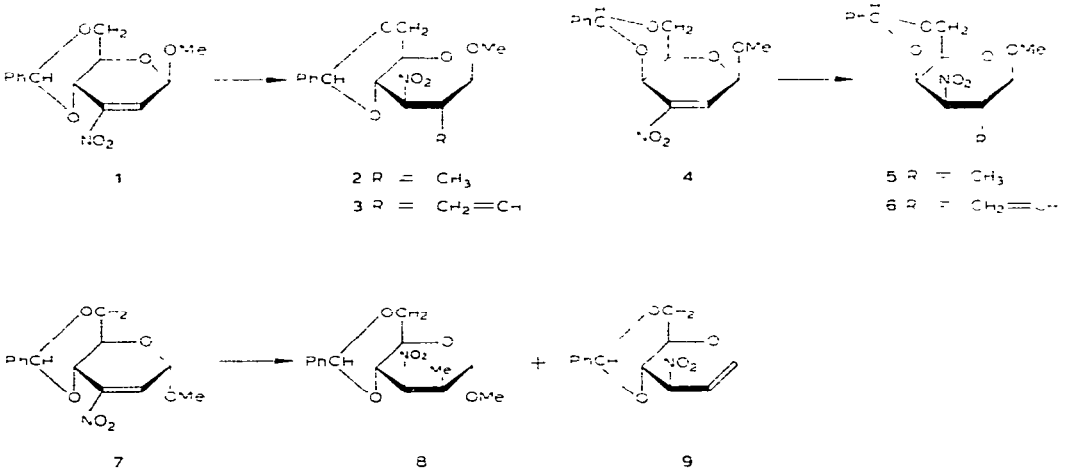


68% yield. Similarly, the β-D-*threo* enopyranoside **4** gave the β-D-galactopyranoside derivatives **5** and **6**, respectively, also in crystalline form. Whereas the yield of **5** was 72%, that of isolated **6** was only 35–40%. These lower yields were due to the formation of a second, major product that was detected in chromatography, but could not be isolated as it tended to decompose rapidly.

The reactions of the α-D-*erythro* hexenopyranoside **7** were also found to be less straightforward than those of the β anomer **1**. With the methylcopper reagent, **7** gave a mixture showing two spots in t.l.c. (R_F 0.7 and 0.6). During processing and preparative t.l.c., partial decomposition occurred, and several additional spots appeared. Nevertheless, the two original products could be separated, and isolated crystalline in yields of 42 and 38%. The compound of R_F 0.6 proved to be the 2-*C*-methyl glycoside **8**, having the α-D-*manno* configuration. Interestingly, in all of the alkylated products encountered and characterized thus far in this study, the 2-*C* substituent was *trans* to the anomeric methoxyl group. This stereochemical result was in accord with earlier observations showing the same directive effect of the anomeric configuration in various, kinetically controlled, nucleophilic-addition reactions of the same and similar substrates[7,8,21,22]. (By contrast, the stereochemistry of the addition of diazomethane to **1**, **4**, and **7** appears to be governed[13] by the configuration of C-4.)

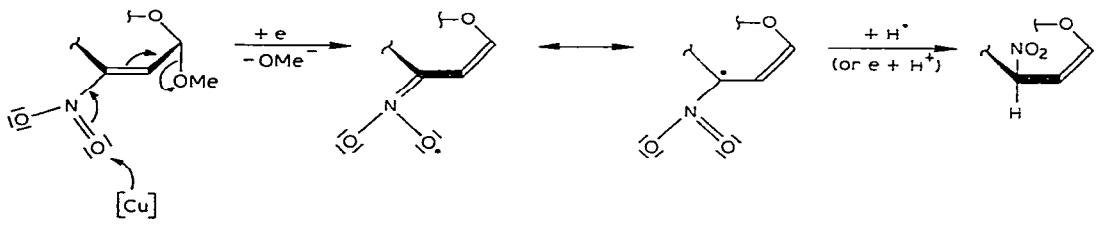
The other product (R_F 0.7) obtained from **7** with $LiMe_2Cu$ was revealed by spectral and elemental analysis to be the nitro glycal **9**. It evidently arose from a competing, reductive elimination. This process might be initiated by electron transfer[18] from the cuprate to an oxygen atom of the nitro group, with concomitant bond-shift and departure of methoxide ion; the intermediary, nitronic radical[1] would, upon further reduction, yield the nitro compound **9** (see Scheme 1). At least one precedent for such an event could be seen in the conversion[23], by $LiMe_2Cu$, of 4,4-dimethoxy-2,5-cyclohexadien-1-one into *p*-methoxyphenol. The reaction also recalls the genera-

TABLE I

PROTON CHEMICAL-SHIFT DATA[a]

Compound	*Chemical shifts (δ)* *H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6a*	*H-6e*	*PhCH*	*OMe*	*C-Me*	*-CH=C*	*-C=CH₂*
2	4.17d	2.31m	4.48dd	4.14dd	3.46o[b]	3.84t	4.36dd	5.54s	3.51s	1.06d	—	—
3	4.35d	2.93sx	4.69dd	4.16dd	3.52m[b]	3.86t	4.39dd	5.57s	3.51s	—	5.68o	~5.26m (2 H)
5	4.03d	2.68m	4.34dd	4.48dd	3.45m[c]	4.07dd	4.35dd	5.51s	3.50s	1.06d	—	—
6	4.15d	3.32m	4.65dd	4.52dd	3.48m[c]	4.08dd	4.35dd	5.51s	3.48s	—	5.73o	~5.26m (2 H)
8	4.58d	2.76[d]	5.01dd	← ~4.3m (2 H), ~3.9m (2 H) →				5.66s	3.36s	1.06d	—	—
9	6.52dd	4.90dd	5.26dt	← ~4.5m (2 H), ~3.9m (2 H) →				5.62	—	—	—	—

[a]From 100-MHz spectra, measured at 250-Hz sweep-width, of solutions in $CDCl_3$ containing tetramethylsilane as the internal standard. All spectra showed 5 H-signals for the phenyl group, near δ 7.4. Signal multiplicities: d, doublet; m, multiplet; o, octet; s, singlet; sx, sextet; and t, triplet. [b]Partially overlapped by OMe signal. [c]Very narrow. [d]Quintet, with lines broadened by a very small splitting with H-1; total width, 29 Hz.



Scheme 1

TABLE II

PROTON–PROTON SPIN-COUPLING DATA

Compound	*Splittings[a] (Hz)* $J_{1,2}$	$J_{2,Me}$	$J_{2,Vi}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6e}$	$J_{6a,6e}$	*Others*
2	8.5	6.5	—	11.2	10	9	10	5	10.5	
3	8.3	—	8.3	11.2	10	9	10	5	10.5	J^b 16.5, 11.5, ~2
5	8.7	6.3	—	11.5	3.7	1.3	1.7	1.5	13	
6	8.5	—	7.5	11.7	3.8	1.3	1.8	1.6	12.7	J^b 18, 9.5, 1.5–2
8	<1	7.5	—	5.5	10.5					
9	6	—	—	2	8.5					$J_{1,3}$ 2

[a]See footnote *a* in Table I. [b]*trans*- and *cis*-vicinal, and geminal coupling, respectively, of the vinylic protons.

tion of a glycal as a by-product, by the action of LiMeCu upon a methyl 2,3-anhydroglycoside[24].

Reaction of **7** with $Li(CH_2{-}CH)_2Cu$ also gave a mixture of two products (one of which was possibly identical with **9**, according to t.l.c.), but the formation of secondary decomposition-products during processing frustrated all attempts at separation.

The ^{1}H-n.m.r. spectra of the new compounds exhibited substituent resonances as required for the structures shown, and configurations were assigned on the basis of ring-proton coupling-patterns (see Tables I and II).

EXPERIMENTAL

General procedures. — Thin-layer chromatography was performed on plates precoated with silica gel SIL G-25 UV_{254} (Macherey–Nagel & Co.) and irrigated with 1:2 (solvent *A*) or 1:1 (solvent *B*) ethyl acetate–petroleum ether (b.p. 30–60°); the spots were detected by heating the plates after spraying with 5% sulfuric acid in ethanol. Optical rotations were determined in chloroform solutions at ~25°. The unsaturated nitro glycosides **1**, **4**, and **7** were prepared as described previously[25]. The lithium dialkylcuprates were prepared, and allowed to react with the glycosides,

under nitrogen and with careful exclusion of moisture, following general prescriptions[17a,19]. The solvents, ether and oxolane, were respectively dried over, and distilled from, sodium and lithium aluminum hydride. The preparation of **2** will be described in detail; all other products were obtained in complete analogy, unless specified otherwise.

Methyl 4,6-O-benzylidene-2,3-dideoxy-2-C-methyl-3-nitro-β-D-glucopyranoside (**2**). — The reaction vessel consisted of a 50-mL flask equipped with an inlet for nitrogen and a side-arm capped with a rubber septum. Solid cuprous iodide (380 mg, 2 mmol) was introduced, and the flask was gently heated over a Bunsen burner while being purged with nitrogen, to ensure complete drying. The buff color of the iodide changed to a light green. The apparatus was allowed to cool to room temperature, ether (10 mL) was added, and the suspension was then cooled to −50° and stirred magnetically. A 1.6M solution of methyllithium in ether (2.5 mL, 4 mmol) was added dropwise through the septum by means of a syringe. A yellow precipitate that formed dissolved gradually, and, after the end of the addition, the mixture was allowed to warm to 0°. The resulting, colorless solution was again cooled to, and kept for 15 min at, −50°. Compound **1** (293 mg, 1 mmol) in oxolane (3 mL) was then added dropwise, producing a yellow precipitate, and the mixture was warmed to 0° and stirred for 1 h. The reaction was then quenched by the addition of a saturated, aqueous solution of ammonium chloride (~15 mL). The phases were separated, and the blue, aqueous phase was extracted with dichloromethane (3 × 10 mL). The extracts and ethereal phase were combined, dried ($MgSO_4$), and evaporated, to give 280 mg (91%) of a white solid that was homogeneous in t.l.c., migrating slightly faster than **1** (solvent *A*). Recrystallized from chloroform–petroleum ether, it showed m.p. 198–199°, $[\alpha]_D$ −87.7° (*c* 1.1), and ν_{max}^{Nujol} 1565 cm^{-1} (NO_2).

Anal. Calc. for $C_{15}H_{19}NO_6$ (309.3): C, 58.24; H, 6.19; N, 4.53. Found: C, 58.09; H, 6.14; N, 4.43.

Methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-C-vinyl-β-D-glucopyranoside (**3**). — The organocuprate reagent was prepared from cuprous iodide (1.14 g, 6 mmol) suspended in ether (30 mL), and 2.05M vinyllithium in ether (6 mL, 12.3 mmol), at an initial temperature of −70°. The precipitate appearing in this case was black, and did not dissolve completely in the pale-yellow solution that resulted on warming the mixture to 0°. The reaction with **1** (880 mg, 3 mmol) was performed as described before. The crude product was a white solid (1.17 g) that showed one major spot in t.l.c. (solvent *A*), with a mobility slightly greater than that of **1**, together with one still-faster and two slow-moving, trace spots. Pure **3** was obtained as beautiful, cube-like crystals (0.65 g, 68%) by crystallization from ether–petroleum ether; m.p. 198–199°, $[\alpha]_D$ −90.0° (*c* 1.2); ν_{max}^{Nujol} 1640 (weak, C=C) and 1560 cm^{-1} (strong, NO_2). The similarity of the physical properties to those of **2** is noteworthy.

Anal. Calc. for $C_{16}H_{19}NO_6$ (321.3): C, 59.80; H, 5.96; N, 4.36. Found: C, 59.90; H, 5.85; N, 4.31.

Methyl 4,6-O-benzylidene-2,3-dideoxy-2-C-methyl-3-nitro-β-D-galactopyranoside (**5**). — The reaction of nitro glycoside **4** (293 mg, 1 mmol) with lithium dimethyl-

cuprate was performed exactly like that of **1**. T.l.c. of the crude product with solvent *A* showed one major spot which was due to **5**, although the R_F value (0.25) happened to be the same as that of **4**. There were traces of slow-moving impurities; these were removed by purification of the material by preparative t.l.c. on silica gel, with 1:4 ethyl acetate–petroleum ether as the irrigant. The product was then crystallized from dichloromethane–ether, to give 210 mg (72%) of pure **5** as colorless crystals, m.p. 200–202°, $[\alpha]_D$ +63.6° (*c* 0.5); ν_{max}^{Nujol} 1555 cm^{-1} (NO_2).

Anal. Calc. for $C_{15}H_{19}NO_6$ (309.3): C, 58.24; H, 6.19; N, 4.53. Found: C, 58.13; H, 6.19; N, 4.29.

*Methyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-2-C-vinyl-β-*D*-galactopyranoside* (**6**). — Reactions of the nitro glycoside **4** with lithium divinylcuprate were performed as described for **1**, although usually on a scale using 1 mmol of **4** and correspondingly smaller amounts of the reagents and solvents. Five minutes after completion of the addition of the glycoside solution at −70° (or, in some experiments, at −50°), t.l.c. (solvent *B*) indicated that all of the **4** (R_F ~0.6) had been consumed, and stirring at 0° was, therefore, omitted. Two spots of comparable intensity were seen, one moving just slightly more slowly than **4**, and the other having R_F ~0.5. The product corresponding to the former was **6**, and was obtained pure by recrystallization of the crude mixture from warm, anhydrous ether. The yields were 35–40% in several experiments; m.p. 180.5–181.5°, $[\alpha]_D$ +64.3° (*c* 3.1); ν_{max}^{Nujol} 1650 (weak, C=C) and 1560 cm^{-1} (strong, NO_2).

Anal. Calc. for $C_{16}H_{19}NO_6$ (321.3): C, 59.80; H, 5.96; N, 4.36. Found: C, 59.66; H, 5.90; N, 4.28.

All attempts to isolate and characterize the second product (R_F 0.5), whether by processing of the ethereal mother liquor of **6**, or by preparative t.l.c., were unsuccessful. Invariably, decomposition, to give a large number of t.l.c. spots, occurred.

*Methyl 4,6-O-benzylidene-2,3-dideoxy-2-C-methyl-3-nitro-α-*D*-mannopyranoside* (**8**) *and 1,5-anhydro-4,6-O-benzylidene-2,3-dideoxy-3-nitro-*D*-arabino-hex-1-enitol* (**9**). — The procedure for the preparation of **2** was applied to the nitro glycoside **7** (293 mg, 1 mmol). Immediately after reaction for 1 h at 0°, t.l.c. (solvent *A*) indicated absence of **7** (R_F 0.5) and the presence of only two products (R_F 0.6 and 0.7). However, the crude product isolated was shown to contain small proportions of several, more-slowly moving contaminants that apparently arose during the processing. Preparative t.l.c. on plates of silica gel, with 10:1 petroleum ether–ethyl acetate as the irrigant, resulted in the separation of 4 bands (A–D, in order of decreasing mobility). Elution of band A gave **9** (R_F 0.7) contaminated by a small proportion of **8** (R_F 0.6), and elution of band B gave **8** contaminated by a trace of **9**. Elution of bands C and D gave by-products (20 and 40 mg) that were not investigated further.

Recrystallization of the material in eluate B from ether–petroleum ether yielded pure **8** (118 mg, 38%), m.p. 124–125°, $[\alpha]_D$ +55.0° (*c* 1.7); ν_{max}^{Nujol} 1560 cm^{-1} (NO_2).

Anal. Calc. for $C_{15}H_{19}NO_6$ (309.3): C, 58.24; H, 6.19; N, 4.53. Found: C, 58.44; H, 6.37; N, 4.30.

Recrystallization of the material in eluate A from ether–petroleum ether furnished pure **9** (111 mg, 42%), m.p. 92–93°, $[\alpha]_D$ −152.1° (*c* 3); ν_{max}^{Nujol} 1640 (medium strong, C=C) and 1560 cm^{-1} (strong, NO_2).

Anal. Calc. for $C_{13}H_{13}NO_5$ (263.2): C, 59.31; H, 4.98; N, 5.32. Found: C, 59.22; H, 4.93; N, 5.19.

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