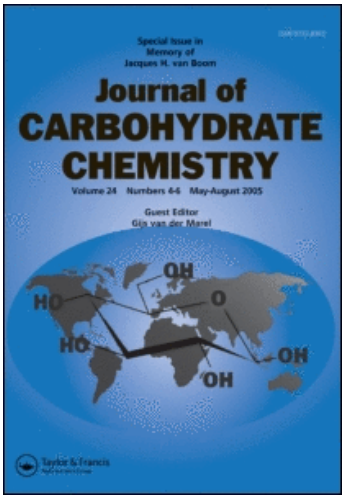


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Radical Addition to Levoglucosenone, Synthesis of Anhydrosugar Herbicide Analogues

Regine Blattner[a]; Dennis M. Page[a]
[a] Industrial Research Ltd, Lower Hutt, (New Zealand)

To cite this Article Blattner, Regine and Page, Dennis M.(1994) 'Radical Addition to Levoglucosenone, Synthesis of Anhydrosugar Herbicide Analogues', Journal of Carbohydrate Chemistry, 13: 1, 27 — 36
To link to this Article: DOI: 10.1080/07328309408009175
URL: http://dx.doi.org/10.1080/07328309408009175

J. CARBOHYDRATE CHEMISTRY, 13(1), 27-36 (1994)

RADICAL ADDITION TO LEVOGLUCOSENONE, SYNTHESIS OF ANHYDROSUGAR HERBICIDE ANALOGUES

Regine Blattner and Dennis M. Page

Industrial Research Ltd
P.O. Box 31-310
Lower Hutt (New Zealand)

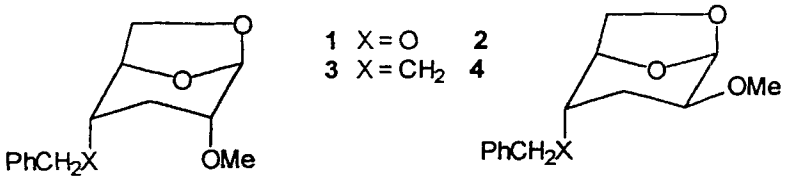
Received March 18, 1993 - Final Form August 13, 1993

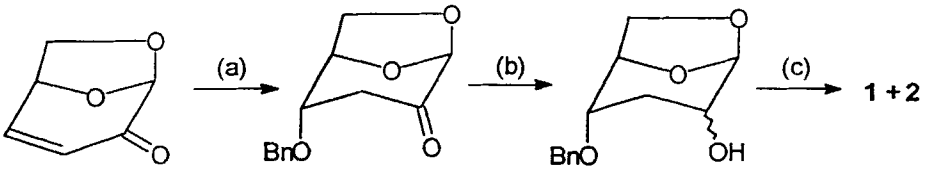
ABSTRACT

Addition of alkyl radicals to levoglucosenone (**5**) gave 4-*C*-alkyl-1,6-anhydro-3,4-dideoxy-β-D-*erythro*-hexopyranos-2-uloses **7** in moderate to good yields. The 4-*C*-phenyl ethyl derivative **7a** was converted by reduction and methylation to the methylene isoster **3** of the powerful herbicide **1**.

INTRODUCTION

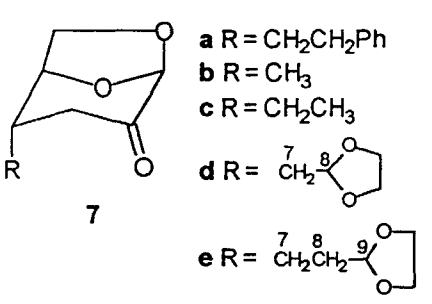
Several years ago, it was reported from this laboratory that certain anhydrosugar derivatives, and in particular 1,6-anhydro-4-*O*-benzyl-3-deoxy-2-*O*-methyl-β-D-*ribo*-hexopyranose (**1**), are potent herbicides.[1-4] During an investigation of the structural and functional requirements for herbicidal activity and selectivity, a sample of the 4-deoxy analogue **3** of the lead compound **1**, in which the oxygen atom at C-4 was replaced by a methylene group, was needed. A short and efficient synthesis of compound **1** and its *arabino*-isomer **2** (Scheme) starts with the conjugate addition of benzyl alcohol to levoglucosenone (**5**), readily available by pyrolysis of acid-treated cellulose, to give the 4-*O*-benzyl adduct **6**.[5] Access to the new compounds **3** and **4** by an analogous route *via* the 4-*C* analogue **7a** of **6** was envisaged.



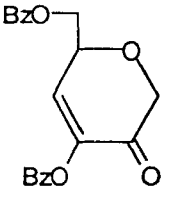


5 6

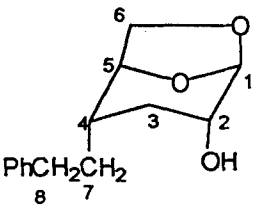
SCHEME : (a) BnOH, H^+. (b) $NaBH_4$ or DIBAL. (c) NaH, MeI, THF.



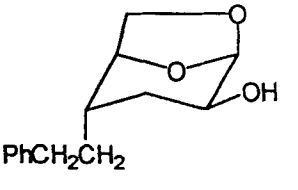
7



8



9



10

Levoglucosenone (**5**) is known to undergo highly stereoselective addition reactions, due to its rigid bicyclic framework and steric shielding of the "upper" face of the pyranose ring by the anhydro bridge. Thus, Michael addition of alcohols,[5] thiols,[6] organometallics[7,8] and other carbon nucleophiles[9] gave consistently products with axial substituents at C-4, and cycloadditions proceeded to furnished *exo* adducts almost exclusively.[9,10] The methyl-branched derivative **7b**, for example, has been prepared in good yield by stereoselective conjugate addition of lithium dimethylcuprate to **5**.[8]

For the introduction of larger and possibly functionalized side-chains however, radical methodology seemed more promising. Radical addition in the carbohydrate area involves, as a rule, monosaccharide-derived radicals and simple activated alkenes.[12] Only rarely have reactions been carried out between unsaturated sugars and simple alkyl radicals,[13-15] examples being addition of *n*-hexyl-, cyclohexyl-, and *t*-butyl-radicals to the enolone **8**.[14] In the following, we wish to describe the addition of a series of primary alkyl radicals to the carbohydrate enone **5**.

RESULTS AND DISCUSSION

When a solution of levoglucosenone (**5**) and iodomethane in 1,2-dimethoxyethane was heated over a 500W heat lamp in the presence of Bu_3SnH (3 molar equivalents, added in 3 portions at half hourly intervals), TLC showed that a single product was formed. In small scale experiments (10-100 mg of **5**) complete conversion was observed within approximately 2 h. On a preparatively useful scale (0.5-2 g of **5**), the reaction proceeded initially at a steady rate, and work-up after 2-3 h gave adduct **7b** in 50-70% yield with recovery of 20-30% of the starting material. On further heating, however, the reaction became sluggish, and although it could be driven to completion by use of a considerable excess of reagents and heating for up to 24 h, the yield was not significantly increased, nor was the efficiency of the reaction improved by changing the solvent (diethyl ether, toluene), by use of chemical initiation (AIBN) instead of light, or by slow, continuous rather than batchwise addition of hydride. Product **7b** was identified by its physical and especially its ^1H NMR spectral data, which were identical to those reported for this compound prepared by Michael addition of an organometallic reagent.[8]

Similar Bu_3SnH-mediated radical reactions of levoglucosenone (**5**) with iodoethane, 1-bromo-2-phenylethane, 2-bromomethyl-1,3-dioxolane, and 2-(2-bromoethyl)-1,3-

Table 1. ^{1}H and ^{13}C NMR Chemical Shifts (ppm) for Compounds **7**.

Compound	H-1 (C-1)	H-3a (C-3)	H-3e	H-4 (C-4)	H-5 (C-5)	H-6 (C-6)	H-6′	H-7 (C-7)	H-7′	H-8 (C-8)	H-9 (C-9)
7a[a]	5.08 (101.7)	2.88 (36.9)	2.21	2.03 (40.4)	4.55 (76.2)	← 3.96 - 3.99 → (68.0)		1.98 (33.9)	1.82	2.70 (33.0)	-
7b	5.08 (101.3)	2.84 (35.8)	2.06	2.34 (38.5)	4.44 (77.6)	4.04 (67.8)	3.97	1.19 (18.4)	-	-	-
7c	5.04 (101.6)	2.78 (36.9)	2.18	2.01 (42.9)	4.58 (75.8)	4.03 (68.0)	3.99	1.68 (25.4)	1.51	0.99 (11.7)	-
7d[b]	5.09 (101.3)	2.82 (36.1)[c]	2.25	2.43 (37.3)[c]	4.67 (76.6)	← 4.00 - 4.04 → (67.8)		2.05 (37.1)[c]	1.85	4.95 (102.8)	-
7e[b]	5.08 (101.6)	2.79 (37.0)	2.15	2.15 (36.0)	4.57 (75.9)	4.03 (68.0)	4.00	← 1.16 - 1.80 → (26.6) (31.1)			4.86 (104.1)

a. Aromatic resonances consistent with the given structure were also observed.

b. Resonances for O-CH_2-CH_2-O consistent with the given structures were also observed.

c. Not unambiguously assigned

Table 2. ^{1}H and ^{13}C NMR Chemical Shifts for Compounds **3**, **4**, **9** and **10**.

Compound	H-1 (C-1)	H-2 (C-2)	H-3a (C-3)	H-3e	H-4 (C-4)	H-5 (C-5)	H-6 (C-6)	H-6′	H-7 (C-7)	H-7′	H-8 (C-8)
3[a]	5.44 (100.7)	3.13 (75.8)[c]	1.89 (23.2)	1.70	1.48 (36.0)	4.44 (75.9)[c]	← 3.83 → (67.5)		2.15 (33.9)	2.05	2.72 (34.0)
4[a]	5.46 (100.6)	3.35 (75.4)	← 1.80 - 2.00 → (26.9)		(37.7)	4.40 (75.7)[c]	← 3.85 → (68.8)		← 1.90 → (33.6)		2.71 (33.6)
9[a,b]	5.35 (102.5)	3.60 (67.2)	← 1.60 - 2.00 → (27.4) (36.0)		1.50	4.44 (76.0)	← (67.8)	3.86	→ (33.8)[c]		2.73 (35.0)
10[a,b]	5.33 (103.1)	3.69 (68.6)	← 1.60 - 2.20 → (36.2)		(37.7)	4.42 (75.6)	3.87 (66.7)	3.81	← 2.00 → (33.3)		2.71 (33.9)[c]

. Aromatic resonances consistent with the given structure were also observed.

. CH_3O 3.38; CH_3O 56.2

. Not unambiguously assigned

dioxolane gave the adducts **7a** and **7c-e**, respectively. The stereochemistry of these new compounds was established from their ^{1}H NMR spectra (Tables 1 and 2), characteristic features of which were the well separated resonances at high field for H-3a (δ *ca.* 2.8 ppm) and H-3e (δ *ca.* 2.1 ppm). Values for $J_{3a,4}$ and $J_{3e,4}$ of 7.8-8.0 Hz and <1 Hz, respectively, and the lack of coupling between H-4 and H-5 indicated that the pyranose rings in these compounds are in the $^1C_4$ conformation, slightly distorted due to the presence of a carbonyl function at C-2, with an axial substituent at the 4-position. The complex multiplicity of the signals for H-3e due to long range couplings of 1-2 Hz, is consistent with a planar "W" arrangement of H-1, H-3, and H-5.

Thus, the addition of alkyl radicals to levoglucosenone (**5**) proceeded, not unexpectedly, with the same stereochemistry as conjugate addition.

Reduction of the 4-*C*-adduct **7a** with $NaBH_4$ gave a 1:2.5 mixture of the *ribo*- and *arabino*-alcohols **9** and **10**, respectively, whereas equal proportions of the two compounds were obtained by use of DIBAL at low temperature. They were readily separated by flash chromatography, and although the 200 MHz ^{1}H NMR spectra were not well resolved, their structures were unambiguously assigned on the basis of the width at half height of the well separated signals for H-2 (16 Hz for **9**, 28 Hz for **10**).

The synthesis of the target **3** and its D-*arabino*-isomer **4** was completed by conventional methylation of **9** and **10** (MeI, NaH, THF). Neither of the new compounds was herbicidal, leading to the hypothesis, that an oxygen atom attached to C-4 is essential for such activity.

EXPERIMENTAL

General Methods. Melting points were determined with a Reichert Jung Thermovar hot stage apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 automatic polarimeter on solutions in $CHCl_3$ (0.8-1.2g/100 mL). NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as internal standard on a Bruker AC 300E or a Varian XL 200 instrument. High resolution accurate mass determinations were performed on a VG 70-2505 mass spectrometer under chemical ionisation conditions using isobutane or ammonia as the ionising gas. Elemental analyses were performed by the Campbell Microanalytical Laboratory, Dunedin, New Zealand. Flash chromatography was carried out on Riedel de Haën Silica Gel 60 (0.63-0.04 mm) with light petroleum (boiling

Table 3. ^{1}H NMR Coupling Constants (Hz) for Compound **3** and Compounds **7**.[a,b]

Compound	$J_{3a,3e}$	$J_{3a,4}$	$J_{3e,4}$	$J_{5,6}$	$J_{5,6'}$	$J_{3,6'}$	$J_{1,3e}$	$J_{3e,5}$
3[c]	15.3	6.4	4.2					
7a	16.5	7.8	0.8	-	4.0	-	0.8	1.9
7b	16.3	7.8	0.9	1.0	5.1	7.5	0.9	1.9
7c	16.4	7.9	0.8	1.4	4.9	7.5	<1	1.5
7d	16.3	7.9	<1	0.9	-	7.3		
7e	16.5	7.9	<1	1.6	4.4	7.5		

a. For all compounds **7** $J_{4,5}$ was to small to be measured.

b. The spectra of **4**, **9**, and **10** were complex and only the following coupling constants could be determined: **4**: $J_{3e,3a}$ 10.1; **9**: $J_{5,6}$ 1.5, $J_{5,6'}$ 5.0, $J_{6,6'}$ 7.3.

c. Also $J_{2,3e}$ 1.6, $J_{2,3a}$ 4.6

range 60-80 °C)-ethyl acetate [(1-3):1] as eluant. Levoglucosenone (**5**) was obtained by pyrolysis of acid treated waste paper as described by Shafizadeh et *al.*[5] and purified by flash chromatography.

1,6-Anhydro-3,4-dideoxy-4-*C*-methyl-β-D-*erythro*-hexopyranos-2-ulose (7b). Method (a). To a solution of levoglucosenone (**5**) (0.945g, 7.5 mmol) and iodomethane (1.4 mL, 22.5 mmol) in 1,2-dimethoxyethane (30 mL) under argon, refluxing over a 500W heat lamp, Bu_3SnH (0.6 mL, 22.3 mmol) was added in several portions over a period of 3 h. The cooled solution was diluted with acetonitrile (150 mL) and extracted with light petroleum (5x30 mL). The residue obtained after removal of the acetonitrile was flash chromatographed to give the title compound **7b** (0.63 g, 59%) as a colourless oil. A Kugelrohr distilled (65-70 °C, 0.4 mbar) sample had $[\alpha]_D$ -290° (lit.[8] $[\alpha]_D$ -299.4°, diethyl ether). The NMR data (Tables 1 and 3) were identical to those reported.[8] By further elution of the column, unreacted starting material (0.29 g, 31%) was recovered.

Method (b). To a solution of **5** (0.945 g, 7.5 mmol) and iodomethane (1.4 mL, 22.5 mmol) in dry toluene (30 mL) stirred at 80 °C under argon, Bu_3SnH (6.0 mL, 22.3 mmol) and AIBN (50 mg) were added in portions over a period of 3 h. The reaction mixture was processed as described under method (a), to give product **7b** (0.61 g, 57%) and unreacted starting material (0.28 g, 30%).

1,6-Anhydro-3,4-dideoxy-4-*C*-(2-phenyl)ethyl-β-D-*erythro*-hexopyranos-2-ulose (7a). Preparation from **5** (1.96 g, 15 mmol) and 2-bromoethylbenzene (6.2 mL, 45 mmol) as described for **7b** *via* method (b) gave **7a** (2.0 g, 57%): bp 160-165 °C, 0.4 mbar; $[\alpha]_D$ -163 °C; ^1H and ^{13}C NMR data see Tables 1 and 3.

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.41; H, 6.90. Found: C, 72.28; H, 7.14.

1,6-Anhydro-3,4-dideoxy-4-*C*-ethyl-β-D-*erythro*-hexopyranos-2-ulose (7c). Preparation from **5** (0.945 g, 7.5 mmol) and iodoethane (1.8 mL, 22.5 mmol) as described for **7b** *via* method (b) gave product **7c** (0.760 g, 65%): bp 105-110 °C, 0.4 mbar; $[\alpha]_D$ -252°; ^1H and ^{13}C NMR data see Tables 1 and 3.

Anal. Calcd for $C_8H_{12}O_3$: C, 61.54; H, 7.69. Found: C, 61.64; H, 7.80.

1,6-Anhydro-3,4-dideoxy-4-*C*-(1,3-dioxolan-2-yl)methyl-β-D-*erythro*-hexopyranos-2-ulose (7d). Preparation from **5** (0.475 g, 3.75 mmol) and 2-bromomethyl-1,3-dioxolane (1.25 mL, 11.25 mmol) as described for **7b** *via* method (a) gave product **7d** (0.420 g, 52%): bp 125-130 °C, 0.4 mbar; $[\alpha]_D$ -190°; ^1H and ^{13}C NMR data see Tables 1 and 3.

Accurate Mass (M+H). Calcd for $C_{10}H_{15}O_5$: 215.0919. Found: 215.0910.

1,6-Anydro-3,4-dideoxy-4-*C*-(1,3-dioxolan-2-yl)ethyl-β-D-*erythro*-hexopyranos-2-ulose (7e). Preparation from **5** (0.475 g, 3.75 mmol) and 2-(2-bromoethyl-1,3-dioxolane (1.3 mL, 11 mmol) as described for **7b** *via* method (a) gave product **7e** (0.4 g, 45%): bp 140-145 °C, 0.4 mbar; $[\alpha]_D$ -177°; ^1H and ^{13}C NMR data see Tables 1 and 3.

Accurate Mass (M+H). Calcd for $C_{11}H_{17}O_5$: 229.1076. Found: 229.1075.

1,6-Anhydro-3,4-dideoxy-4-*C*-(2-phenyl)ethyl-β-D-*ribo*-hexopyranose (9) and 1,6-Anhydro-3,4-dideoxy-4-*C*-(2-phenyl)ethyl-β-D-*arabino*-hexopyranose (10). (a) By use of $NaBH_4$. To a stirred solution of ketone **7b** (0.080 g) in methanol (4 mL) at 0 °C, $NaBH_4$ (15 mg) was added. After 4 min the solution was acidified with glacial HOAc, concentrated to a small volume and partitioned between $CHCl_3$ and water. The organic extract was dried and concentrated. Fractionation of the residue by flash chromatography gave **9** (23 mg, 28%), $[\alpha]_D$ -51°, and **10** (53 mg, 66%): mp 100.0 - 100.5 °C; $[\alpha]_D$ -104°; ^1H and ^{13}C NMR data see Tables 2 and 3.

9: Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.79; H, 7.69. Found: C, 71.63; H, 7.58.

Accurate Mass (M+H). Calcd for $C_{14}H_{19}O_3$: 235.1334. Found: 235.1343.

10: Accurate Mass ($M+NH_4$). Calcd for $C_{14}H_{22}NO_3$: 252.1597. Found: 252.1600.

(b) By use of DIBAL. To a stirred solution of ketone **7b** (1.75 g, 7.5 mmol) in CH_2Cl_2

(30 mL) at -78 °C a solution of DIBAL (1M, 7.7 mL) in the same solvent was slowly added. After 30 min the reaction mixture was warmed to ambient tempeature, diluted with $CHCl_3$ (50 mL) and washed successively with HCl, water, saturated aqueous Na_2CO_3 and water, dried and concentrated to a yellow oil. Flash chromatography gave **9** (0.70 g, 40%) and **10** (0.70 g, 40%).

1,6-Anhydro-3,4-dideoxy-2-*O*-methyl-4-*C*-(2-phenyl)ethyl-β-D-*ribo*-hexoyranose (3). To a stirred solution of alcohol **9** (0.60 g, 2.6 mmol) in THF (10 mL) at 0 °C, sodium hydride (72 mg, 3.0 mmol) and iodomethane (0.19 mL, 3.0 mmol) were added. After 1 h at 0 °C, methanol (0.5 mL) and silica gel (0.063-0.2 mm, 1 g) were added and the mixture was concentrated to dryness. Flash chromatography gave **3** (0.57 g, 88%) mp 35-37 °C, $[\alpha]_D$ -66.1°. For ^1H and ^{13}C NMR data see Tables 2 and 3.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 72.58; H, 8.06. Found: C, 72.68; H, 8.08.

1,6-Anhydro-3,4-dideoxy-2-*O*-methyl-4-*C*-(2-phenyl)ethyl-β-D-*arabino*-hexopyranose (4). Methylation of alcohol **10** (0.170 g, 0.73 mmol) as described above gave **4** (0.173 g, 96%) mp 61-62 °C, $[\alpha]_D$ -92.0°. For ^1H and ^{13}C NMR data see Tables 2 and 3.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 72.58; H, 8.06. Found: C, 72.44; H, 7.88.

REFERENCES

1. R. F. Henzell, R. H. Furneaux and P. C. Tyler, *Pestic. Sci.*, **30**, 59 (1990).
2. R. Blattner, R. H. Furneaux, J. M. Mason and P. C. Tyler, *Pestic. Sci.*, **31**, 419 (1991).
3. DSIR, New Zealand, Eur. Patent 0229 034, 1987.
4. DSIR, New Zealand, Eur. Patent 0302 599, 1988.
5. F. Shafizadeh, R. H. Furneaux and T. T. Stevenson, *Carbohydr. Res.*, **71** 169 (1979).
6. M. G. Essig, *Carbohydr. Res.*, **156**, 225 (1986).
7. F. Shafizadeh and P. P. S. Chin, *Carbohydr. Res.*, **58**, 79 (1977).
8. M. Mori, T. Chuman and K. Kato, *Carbohydr. Res.*, **129**, 73 (1984).
9. D. D. Ward and F. Shafizadeh, *Carbohydr. Res.*, **95**, 155 (1981).
10. A. J. Blake, A. C. Forsyth and M. Paton, *J. Chem. Soc., Chem. Commun.*, 564 (1988).
11. F. Shafizadeh, D. D. Ward and D. Pang, *Carbohydr. Res.*, **102**, 217 (1982).

12. B. Giese, *Radicals in Organic Synthesis*, Pergamon, Oxford, 1986.

13. B. Giese and T. Witzel, *Angew. Chem., Int. Ed. Eng.*, **25**, 450 (1986).

14. B. Giese and T. Witzel, *Tetrahedron Lett.*, **28**, 2571 (1987).

15. B. Giese, M. Hoch, C. Lambert and R. R. Schmidt, *Tetrahedron Lett.*, **29**, 1375 (1988).