Carbohydrate Research, 141 (1985) 153–158
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Stereospecific formation of carbon–carbon bonds in ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*ribo*-hex-3-enopyranoside

YVES CHAPLEUR AND YOANNIS GRAPSAS
Laboratoire de Chimie Organique III, ERA CNRS 558, Université de Nancy I B.P. 239, 54506 VANDOEUVRE-les-NANCY Cédex (France)
(Received July 9th, 1984; accepted for publication, September 21st, 1984)

The stereospecific formation of carbon–carbon bonds, and especially the creation of chiral centres, are currently subjects of intense research. The use of carbohydrates in the total synthesis of elaborate chiral structures found in other natural products is now well developed[1].

In this context, it is of interest to create C–C bonds on carbohydrate templates. We have demonstrated recently that the alkylation of a carbohydrate enolate provides a new short route to 2-*C*-alkyl-2-deoxy sugars[2]. In connection with this program, we have studied an alternative route to such compounds.

It is well established that allylic acetates react with organocopper species to yield alkylated alkenes[3]. This reaction is highly stereoselective, and applications to chiral allylic esters[4–8] have recently been reported. Such a reaction has not been exploited in the carbohydrate field, although organocopper species have been used in the opening of carbohydrate epoxides[9] and in the 1,4 additions to α,β unsaturated carbonyl systems[10]. Trost and Klun[11] reported the reaction of an organocopper reagent with allylic γ-lactones derived from sugars, and Ogihara and Mitsunobu[12] reported on the reaction of 4,6-*O*-benzylidene 3-*O*-mesyl-D-allal with organometallics to give mixtures of alkylated products. We present here our preliminary findings in this area.

When the allylic acetate[13] **1** was allowed to react with lithium dimethyl cuprate in ether at 0°, a mixture of products was isolated that consisted mainly of alkene **2** and some of the deacetylated analogue **3**, together with some unreacted starting-material. Reacetylation of the crude mixture permitted the isolation of **2** in 52% yield. The use of methylmagnesium chloride in the presence of copper iodide gave identical results.

A rapid study of the different organocopper reagents available from methyllithium showed that the best results were obtained by using an equimolecular amount of methyllithium and copper cyanide[14]. The reaction was then performed

0008-6215/85/$ 03.30

TABLE I

REACTION OF ORGANOMETALLICS WITH ALLYLIC ACETATE **1**

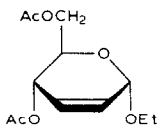
Product	*Reagent*	*Reaction temp. (°)*	*Conditions time (h)*	*Yield[a] (%)*
2	Me_2CuLi	[b]	4	52[c]
2	MeCuCNLi	0	4	72
2	MeMgCl, CuI	[b]	1	48[c]
4	BuCuCNLi	0	2	85
5	tBuCuCNLi	0	2	86
6	PhCuCNLi	[b]	4	61
9	MeCuCNLi	0	0.5	70

[a]Yields are unoptimized and are based on pure, isolated materials. [b]Room temperature. [c]After reacetylation.

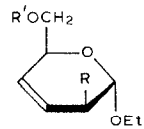
by slow addition of the organometallic reagent to a solution of **1** in diethyl ether, with vigorous stirring at $-10°$ to $0°$. The various reaction conditions are summarized in Table I. The reaction was extended to several organolithium derivatives, including *tert*-butyllithium, which gave excellent results.

The structures of compounds **2–6** were deduced from spectral analysis. The high-field ^{1}H-n.m.r. spectra exhibited a singlet for the H-1 signal, indicating alkylation at C-2, the substituent being axial. Furthermore, the presence of a 3,4-double bond was supported by the observation of allylic coupling between H-3 and H-5. Finally, catalytic hydrogenation of the double bond of **2** gave the saturated analog **7**. In the ^{1}H-n.m.r. spectrum of **7**, the H-1 pattern appeared as a singlet, whereas the H-5 signal was complicated because of the presence of a vicinal methylene group at C-4.

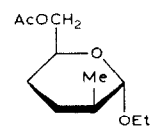
These data indicate alkylation at the γ position of the acetate with net *anti*



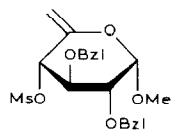
1



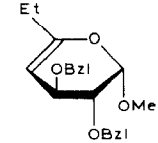
	R	R'
2	Me	Ac
3	Me	H
4	Bu	Ac
5	Bu^t	Ac
6	Ph	Ac



7



8



9

stereochemistry, in agreement with the generally postulated stereochemical course of such reaction in cyclohexenyl systems[15]. Further confirmation of the proposed structure was obtained by studying the reaction of the methanesulfonate* **8** with methylcyanocuprate. In this case, the α or γ alkylation mechanisms would lead to completely different and readily identifiable products. In this instance, only the alkene **9** was isolated, in 70% yield; its structure was evident from spectroscopic data.

The present work demonstrates the utility of readily available sugar allylic acetates and methanesulfonates for the creation of C–C bonds with complete stereocontrol. Subsequent transformation of the alkenes obtained and the use of more-functionalized organometallic reagents are now under investigation.

EXPERIMENTAL

General methods. — T.l.c. was performed on Merck precoated plates of silica gel 60, and detection was effected by spraying the plates with sulfuric acid and heating under an i.r. lamp. I.r. spectra were recorded for thin films with a Perkin–Elmer 580 B spectrometer and ^{1}H-n.m.r. spectra were recorded for solutions in chloroform-*d* with tetramethylsilane as the internal standard on a Cameca 250 spectrometer (250 MHz). Optical rotations were measured with a Perkin–Elmer 141 polarimeter. Alkyllithiums were purchased from Fluka.

*Ethyl 6-O-acetyl-2,3,4-trideoxy-2-C-methyl-α-*D-threo*-hex-3-enopyranoside* (**2**). — *(a) Reaction with lithium dimethyl cuprate.* To a suspension of dry copper iodide (570 mg, 3 mmol), in anhydrous diethyl ether (10 mL) under argon, was added 3 mL of an ethereal solution of methyllithium (2M, 6 mmol) at 0°. This clear solution of lithium dimethyl cuprate was transferred *via* a syringe needle into a vigorously stirred solution of the allylic acetate **1** (258 mg, 1 mmol) in diethyl ether (10 mL). A yellow precipitate appeared immediately. Stirring was continued for 1 h at 0°. The reaction was then quenched with saturated aqueous ammonium chloride (20 mL) and the product extracted with diethyl ether (3 × 100 mL). The organic layer was washed with ammonium chloride solution (20 mL) and water (2 × 20 mL), dried (Na_2SO_4), and evaporated. The residue was directly acetylated with acetic anhydride (1 mL) in pyridine (10 mL). After 4 h at room temperature, the mixture was evaporated *in vacuo* and the residue was taken up in diethyl ether (100 mL). After washing with 15% hydrochloric acid (10 mL), water, 15% aqueous sodium hydroxide (10 mL) and water, the organic layer was dried ($MgSO_4$) and evaporated. Column chromatography of the residue (with 4:1 hexane–ethyl acetate) afforded **2** (112 mg, 52%) and **1** (75 mg, 29%).

Compound **2** had $[\alpha]_D^{20}$ +112° (*c* 0.8, chloroform); R_F 0.65 (7:3 hexane–ethyl acetate, ν_{max} 1740 cm^{-1} (ester); n.m.r. data: δ 1.08 (d, 3 H, *J* 7 Hz, CH_3), 1.25 (t, 3 H, *J* 7 Hz, CH_3-CH_2O), 2.08 (s, 3 H, CH_3CO), 2.1 (m, 1 H, H-2), 3.56 (dq, 1 H,

*Prepared[16] by F. Chrétien from D-glucose by standard procedures; $[\alpha]_D$ −9.0° (*c* 1.55, $CHCl_3$).

OCH_2CH_3), 3.84 (dq, 1 H, OCH_2CH_3), 4.18 (d, 2 H, $J_{6,5}$ 5 Hz, H-6), 4.4 (m, 1 H, H-5), 4.67 (s, 1 H, H-1), 5.59 (dt, 1 H, $J_{4,3}$ 10, $J_{4,5}$ 1, $J_{4,2}$ 1 Hz, H-4), and 5.82 (m, 1 H, $J_{3,5}$ 1 Hz, H-3).

Anal. Calc. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.71; H, 8.50.

(b) Reaction with methylmagnesium chloride–copper iodide. To a suspension of dry copper iodide (57 mg, 0.3 mmol) in anhydrous ether (10 mL) under argon was added 1.5 mL of a solution of methylmagnesium chloride (Alfa) in tetrahydrofuran (3 mmol) at 0°. This solution was transferred into the solution of **1** in diethyl ether *via* a syringe needle. After stirring for 1 h at room temperature, the mixture was processed as already described. Reacetylation and column chromatography gave pure **2** (102 mg, 48%).

(c) Reaction with methyllithium–copper cyanide. To a suspension of dry copper cyanide (268 mg, 3 mmol) in anhydrous diethyl ether (10 mL) under argon was added slowly a 2M solution of methyllithium (1.5 mL, 3 mmol) at 0°. After stirring at this temperature for 10 min, the suspension was transferred *via* a syringe needle into a vigorously stirred solution of **1** (258 mg, 1 mmol) in ether (10 mL) at −10°. A yellow precipitate appeared immediately. The suspension was stirred for 4 h at 0° and processed as described for the reaction with lithium cuprate. Column chromatography yielded pure **2** (155 mg, 72%).

Products **4, 5,** and **6** were obtained by the same procedure, using the appropriate alkyllithium derivatives. Analytical data are given next.

Ethyl 6-O-acetyl-2-C-butyl-2,3,4-trideoxy-α-D-threo-hex-3-enopyranoside (**4**). — Yield 218 mg (85%), $[\alpha]_D^{20}$ +124° (*c* 0.8, $CHCl_3$); R_F 0.56 (4:1 hexane–ethyl acetate); ν_{max} 1740 cm^{-1}; n.m.r. data: δ 0.66–0.78 (m, 12 H, Bu, CH_3-CH_2O), 2.04 (m, 1 H, H-2), 2.08 (s, 3 H, CH_3CO), 3.57 (dq, 1 H, *J* 7 Hz, OCH_2CH_3), 3.84 (dq, 1 H, J_{gem} 10 Hz, OCH_2CH_3), 4.18 (d, 2 H, H-6), 4.38 (m, 1 H, H-5), 4.76 (s, 1 H, H-1), 5.63 (broad d, 1 H, *J* 10 Hz, H-4), and 5.87 (m, 1 H, H-3).

Anal. Calc. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.68; H, 9.50.

Ethyl 6-O-acetyl-2-C-tert-butyl-2,3,4-trideoxy-α-D-threo-hex-3-enopyranoside (**5**). — The product was an oil (220 mg, 86%), $[\alpha]_D^{20}$ +110° (*c* 0.8, $CHCl_3$); R_F 0.54 (4:1 hexane–ethyl acetate); ν_{max} 1740 cm^{-1} (ester); n.m.r. data: δ 0.95 (s, 9 H, Bu^t), 1.23 (t, 3 H, *J* 7 Hz, CH_3-CH_2O), 1.85 (dq, 1 H, $J_{2,3}$ 4.5, $J_{2,4}$ 1.5, $J_{2,5}$ 1.5 Hz, H-2), 2.08 (s, 3 H, CH_3CO), 3.55 (dq, 1 H, *J* 7, J_{gem} 10 Hz, OCH_2CH_3), 3.8 (dq, 1 H, OCH_2CH_3), 4.09 (dd, 1 H, J_{gem} 11, $J_{5,6}$ 6.5 Hz, H-6), 4.22 (dd, 1 H, $J_{5,6'}$ 3.5 Hz, H-6′), 4.31 (m, 1 H, H-5), 5.00 (s, 1 H, H-1), 5.75 (dt, 1 H, $J_{3,4}$ 10, $J_{4,5}$ 1.5 Hz, H-4), and 5.90 (m, 1 H, H-3).

Anal. Calc. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.51; H, 9.40.

Ethyl 6-O-acetyl-2,3,4-trideoxy-2-C-phenyl-α-D-threo-hex-3-enopyranoside (**6**). — The product was an oil (169 mg, 61%), $[\alpha]_D^{20}$ +194° (*c* 0.5, $CHCl_3$); R_F 0.4 (4:1 hexane–ethyl acetate); ν_{max} 1740 cm^{-1} (ester); n.m.r. data: δ 1.25 (t, 3 H, *J* 7 Hz, CH_3-CH_2O), 2.12 (s, 3 H, CH_3CO), 3.35 (t, 1 H, $J_{2,3}$ 4, $J_{2,5}$ Hz, H-2), 3.53 (dq, 1 H, *J* 7, J_{gem} 10 Hz, OCH_2CH_3), 3.82 (dq, 1 H, OCH_2CH_3), 4.3 (m, 2 H, H-6), 4.46 (m, 1 H, H-5), 4.85 (s, 1 H, H-1), 5.83 (d, 1 H, $J_{3,4}$ 10 Hz, H-4), and 5.9 (m, 1 H, H-3).

Anal. Calc. for $C_{16}H_{20}O_4$: C, 69.56; H, 7.24. Found: C, 69.34; H, 7.25.

*Ethyl 6-O-acetyl-2,3,4-trideoxy-2-C-methyl-α-*D-threo*-hexopyranoside* (**7**). — Compound **2** (214 mg, 1 mmol) was dissolved in ethyl acetate, the flask was purged with nitrogen, and palladium-on-charcoal (5%, 100 mg) was added. The flask was placed under a hydrogen atmosphere. After stirring for 4 h, t.l.c. (4:1 hexane–ethyl acetate) showed no starting material and the presence of a fast-moving product, R_F 0.57. After filtration from the catalyst through a pad of Celite, the solvent was removed under vacuum. Purification by rapid column-chromatography yielded pure **7** as an oil (190 mg, 88%), $[\alpha]_D^{20}$ +91° (*c* 0.3, chloroform); ν_{max} 1740 cm^{-1} (ester); n.m.r. data: δ 1.05 (d, 3 H, Me), 1.25 (t, 3 H, CH_3CH_2O), 1.34 (m, 1 H, H-4), 1.40 (m, 1 H, H-4′), 1.55 (m, 1 H, H-3), 1.77 (m, 1 H, H-2), 2.03 (m, 1 H, H-3′), 2.08 (s, 3 H, CH_3-CO), 3.49 (dq, 1 H, *J* 7, *J* 10 Hz, CH_3CH_2-O), 3.54 (dq, 1 H, CH_3CH_2-O), 3.9–4.1 (m, 3 H, H-6, H-6′, H-5), and 4.54 (s, 1 H, H-1).

Anal. Calc. for $C_{11}H_{20}O_4$: C, 61.1; H, 9.25. Found: C, 61.5; H, 9.38.

*Methyl 2,3-di-O-benzyl-4,6,7-trideoxy-α-*D-xylo*-hept-4-enopyranoside* (**9**). — A solution of lithium methyl copper cyanide was prepared as already described at 0° and transferred into a cooled solution of the methanesulfonate **8** (435 mg, 1 mmol) *via* a syringe needle. The mixture was stirred for 30 min at 0°. At this time t.l.c. (4:1 hexane–ethyl acetate) showed only one product, R_F 0.57, which was isolated by the aforementioned procedure. Column chromatography afforded pure **8** as an oil (248 mg, 70%), $[\alpha]_D^{20}$ +131° (*c* 0.7, chloroform); n.m.r. data: δ 1.05 (t, 3 H, *J* 7 Hz, CH_3CH_2), 2.08 (q, 2 H, H-6), 3.49 (s, 3 H, OCH_3), 3.72 (dd, 1 H, $J_{1,2}$ 2.5, $J_{2,3}$ 6 Hz, H-2), 4.13 (m, 1 H, H-3), 4.58 (2 s, 2 H, CH_2Ph), 4.69 (d, 1 H, $J_{3,4}$ 3 Hz, H-4), 4.77 (s, 2 H, CH_2Ph), 4.78 (d, 1 H, H-1), and 7.3 (m, 10 H, Ph).

Anal. Calc. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.60; H, 7.42.

ACKNOWLEDGMENTS

We gratefully thank Prof. B. Gross for his constant encouragement and Dr. F. Chrétien for a generous gift of compound **8**.

REFERENCES

1 For a recent account see: S. Hanessian, in J. E. Baldwin (Ed.), *Total Synthesis of Natural Products. The "Chiron" Approach*, Pergamon Press, Oxford, 1983.
2 Y. Chapleur, *J. Chem. Soc. Chem. Comm.*, (1983) 141–142.
3 For a review see: G. Posner, *Organic Reactions*, J. Wiley, New York, 1975, pp. 253–400.
4 R. Rona, L. Tokes, J. Tremble, and P. Crabbé, *Chem. Comm.*, (1969) 43–44.
5 R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Am. Chem. Soc.*, 92 (1970) 735.
6 J. Levisalles, M. Rudler-Chauvin, and H. Rudler, *J. Organomet. Chem.*, 136 (1977) 103–110.
7 C. Gallina and P. G. Ciattini, *J. Am. Chem. Soc.*, 101 (1979) 1035–1036.
8 H. L. Goering and C. Chyi-Tseng, *J. Org. Chem.*, 48 (1983) 3986–3990.
9 D. R. Hicks and B. Fraser-Reid, *Can. J. Chem.*, 53 (1975) 2017–2023; M. B. Yunker, D. E. Plaumann, and B. Fraser-Reid, *ibid*, 55 (1977) 4002–4004; A. Lagrange, A. Olesker, S. Soares-Costa, G. Lukacs, and T. That Thang, *Carbohydr. Res.*, 110 (1982) 159–164.
10 S. Hanessian, P. C. Tyler, and Y. Chapleur, *Tetrahedron Lett.*, 22 (1981) 4583–4586; W. R. Roush and B. M. Lesur, *Tetrahedron Lett.*, 24 (1983) 2231–2234; T. E. Goodwin, C. M.

CROWDER, R. B. WHITE, J. S. SWANSON, F. E. EVANS, AND W. L. MEYER, *J. Org. Chem.*, 48 (1983) 376–380.
11 B. TROST AND T. P. KLUN, *J. Org. Chem.*, 45 (1980) 4257–4259.
12 T. OGIHARA AND O. MITSUNOBU, *Tetrahedron Lett.*, 24 (1983) 3505–3508.
13 R. J. FERRIER AND N. PRASAD, *J. Chem. Soc., C*, (1969) 581–586.
14 J. P. GORLIER, L. HAMON, J. LEVISALLES, AND J. WAGNON, *J. Chem. Soc. Chem. Comm.*, (1973) 88.
15 H. L. GOERING AND V. D. SINGLETON, JR., *J. Org. Chem.*, 48 (1983) 1531–1533.
16 F. CHRÉTIEN, unpublished results.