Tetrahedron Vol. 45, No. 9, pp. 2869 to 2874, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

STEREOSELECTIVE ARYLATIONS USING METAL PHENOLATES. COMPLEMENTARY SYNTHESIS OF 5-C-ARYLXYLOFURANOSE DERIVATIVES OF EITHER L-IDO OR D-GLUCO CONFIGURATION

Mara Cornia[a]* and Giovanni Casiraghi[b]

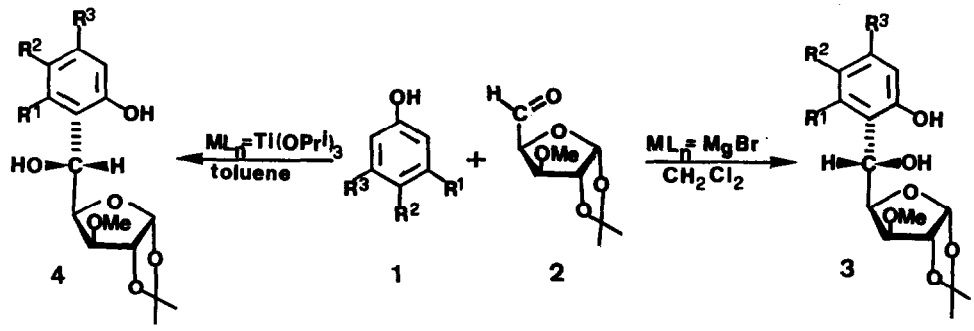
[a] Istituto di Chimica Organica dell'Universita', Viale delle Scienze, I-43100 Parma, Italy
[b] Istituto di Chimica dell'Universita', Via Vienna 2, I-07100 Sassari, Italy

(*Received in UK 7 February* 1989)

Abstract - The arylation of 3-O-methyl-1,2-O -isopropylidene-α -D-xylo-pentodialdofuranose (2) at the aldehyde centre by means of bromonagnesium or triisopropoxytitanium salts of phenols 1 provides a simple access to 5-C arylxylofuranoses 3 and 4 of either L-ido or D-gluco configuration.

As they contain both a nucleophilic aromatic ring and a Friedel-Crafts-type catalitic centre, the phenolates of co-ordinating metals are unique arylation reactants of potentially electrophilic carbons.[1] When applied to suitable carbohydrates a new route to C- glycosyl derivatives of phenols become feasible, often with high margins of diastereocontrol.[2] As a further study in this field, we now report an application of this procedure to 3-O-methyl-1,2-O-isopropylidene-α-D-xylo-pentodialdofuranose (2)[3] which, according to the metal involved, allows direct preparation of 5-C-(2-hydroxyaryl)-xylofuranose derivatives 3 and 4 in either L-ido or D-gluco form.

Scheme 1



The first employed phenolates were the bromomagnesium salts of phenol (**1a**), 4-tert-butylphenol (**1b**), 3,4-methylenedioxyphenol (**1c**), and 2-naphthol (**1d**). In all cases, using methylene chloride as solvent, L-ido isomers **3a-d** were produced in good yields either preferentially or exclusively (odd entries in Table 1).

Table 1. Synthesis of (5S)- and (5R)-1,2-O-isopropylidene- 3-O-methyl-5-(2-hydroxyaryl)-α -D-xylofuranoses 3 and 4.

Entry	Phenol	R^1	R^2	R^3	Counterion	Product	% Yield[a]	$[\alpha]_D$[b]	% D.e.	Confign.
1	**1a**	H	H	H	MgBr	**3a**	65	-23.9	95	L-ido
2	**1a**	H	H	H	$Ti(OPr^i)_3$	**4a**	58	-34.8	88	D-gluco
3	**1b**	H	$t\text{-}C_4H_9$	H	MgBr	**3b**	78	+10.8	95	L-ido
4	**1b**	H	$t\text{-}C_4H_9$	H	$Ti(OPr^i)_3$	**4b**	55	-57.6	85	D-gluco
5	**1c**	$O\text{-}CH_2\text{-}O$		H	MgBr	**3c**	64	-42.4	92	L-ido
6	**1c**	$O\text{-}CH_2\text{-}O$		H	Ti(OPri)3	**4c**	50	-18.0	94	D-gluco
7	**1d**	H	$-(CH{=}CH)_2-$		MgBr	**3d**	74	+60.9	92	L-ido
8	**1d**	H	$-(CH{=}CH)_2-$		$Ti(OPr^i)_3$	**4d**	94	-53.8	97	D-gluco

[a] Yields for pure isolated compounds, based on starting 2. [b] C 0.5 $CHCl_3$ at 20 ± 1°C. [c] Diastereomeric excess (d.e.) determined by ^1H NMR analysis of the crude reaction mixtures.

The reversal of stereochemistry was secured by the use of low Lewis acidic triisopropoxytitanium salts of phenols **1a-d**. Indeed, when reactions were carried out in toluene at room temperature, D-gluco derivatives **4a-d** predominated quite heavily as seen in even entries of Table 1.

The assignments of configurations to the various carbinols 3 and 4 were mainly based on ^1H NMR spectroscopy. The relevant parameters are presented in Table 2.

From these informations it appears that in the L-ido series, for a given epimeric pair, the vicinal coupling constants between H-4 and H-5 (threo relationship) are constantly larger than those of the corresponding D-gluco isomers (erythro relationship), in agreement with the literature data for related compounds.[1a,3a,3b] In addition, the chemical shift of the hydrogen at C-3 is extremely diagnostic in distinguishing L-ido derivatives (higher field) from D-gluco ones (lower field).

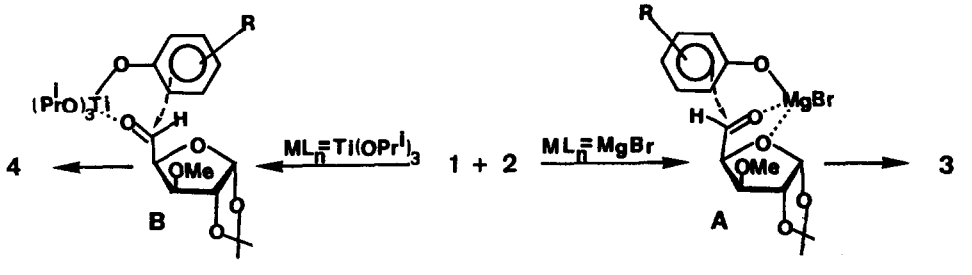
Table 2. Relevant ^{1}H NMR parameters for 5-C-Arylfuranoses 3 and 4.[a]

Compound	δ H-3	δ H-5	$J_{4,5}$	$J_{5\text{-OH}}$
3a	3.46	5.17	7.70	-
4a	3.86	5.26	6.87	2.21
3b	3.45	5.14	8.06	-
4b	3.86	5.24	6.73	3.78
3c	3.49	5.05	8.05	-
4c	3.90	5.12	7.53	3.51
3d	3.48	6.05	6.19	-
4d	3.73	6.10	5.91	2.22

[a] Chemical shifts in ppm vs. internal TMS in $CDCl_3$ at 20±1°C; coupling constants in Hz.

In conclusion, we have presented a high yielding regio- and diastereoselective arylation of a dialdose derivative which broaden the scope of our metal phenolate-based synthetic strategy. The sense of this arylation is very dependent on the nature of the metal species involved. Using either bromomagnesium or triisopropoxytitanium phenolates, aldehyde 2 exhibits striking and complementary stereselectivity during carbon-carbon bond formation. The use of a hyghly oxygenophilic metal promoter (MgBr) which would be chelated between the aldehyde function and pyran oxygen of 2 would favore a syn conformer (A) with the consequence that the aromatic ring attacks from the less hindered si-face of prochiral C-5.

Scheme 2.



On the other hand, recourse to a poorly oxygenophilic counterion $Ti(OPr^i)_3$ would favore the stable anti-conformer (B) and an arylation trajectory anti to the face containing the sugar fragment.[4]

EXPERIMENTAL

The ^1H NMR spectra were recorded with a Bruker CXP-200 (200 MHz) or a Bruker AC-100 (100 MHz) Spectrometer for $CDCl_3$ solutions (δ scale, TMS=0). The IR spectra were taken with a Perkin Elmer 298 Spectrofotometer as films on NaCl discs. Optical rotations were obtained on a Autopol III polarimeter with a 1-dm tube. Reagents and solvents were purified and dried using standard methods. Phenols and 1,2-O-isopropylidene-3-O-methyl-α-D-Xylo-pentodialdofuranose (1,4) (Fluka) were commercial products.

The reaction work-up involved quenching with a saturated aqueous ammonium chloride solution, extraction with CH_2Cl_2 or diethyl ether, drying of the combined extracts over Na_2SO_4, and concentration under reduced pressure. Preparative chromatography was performed on Merck Kieselgel (230-400 mesh) (hexane-acetone mixtures). TLC was performed on Merck DC-Fertigplatten Kieselgel 60F-254.

Reactions of Bromomagnesium Phenolates with Aldehyde 2. To a solution of EtMgBr (2 mmol) in diethyl ether (10 mL) the appropriate phenol 1 (2 mmol) was added; the ether was removed under vacuum and CH_2Cl_2 (10 mL) and then a solution of 2 (2.5 mL, 1 mmol) was added at 0°C. The reaction mixture was kept for 20 h at 0°C (at -30°C for 3c); worked up, and purified by chromatography (hexane-acetone 4:1). The following compounds were prepared in this manner. The yields and $[\alpha]_D$ values are collected in Table I.

(5S)-1,2-O-isopropylidene-3-O-methyl-5-(2-hydroxyphenyl)-α-D-xylofuranose (3a from 1a and 2). ^1H NMR data: δ 8.17 (bs, 1H, OH), 6.8-7.4 (m, 4H, H-3', H-4', H-6', and H-7'), 5.98 (d, 1H, $J_{1,2}$ 3.78 Hz, H-1), 5.17 (d, 1H, $J_{4,5}$ 7.70 Hz, H-5), 4.59 (d, 1H, $J_{1,2}$ 3.78 Hz, H-2), 4.41 (dd, 1H, $J_{4,5}$ 7.70, $J_{3,4}$ 3.23 Hz, H-4), 3.46 (d, 1H, $J_{3,4}$ 3.23 Hz, H-3), 3.37 (s, 3H, O-CH_3), 3.35 (s, 1H, OH), 1.46 and 1.30 (2s, each 3H, Me_2C); ν_{max} 3400, 2960, 1600, 1500, 1470, 1380, 1260, 1180, 1100, 1030, 910, and 660 cm^{-1}. Anal. Calc. for $C_{15}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.06; H, 7.11.

(5S)-1,2-O-isopropylidene-3-O-methyl-5-(2-hydroxy-5-tert-butylphenyl)-α-D-xylofuranose (3b from 1b and 2). ^1H NMR data: δ 8.00 (s, 1H, OH), 7.22 (dd, 1H, $J_{3',4'}$ 8.34, $J_{4',6'}$ 2.45 Hz, H-4'), 7.09 (d, 1H, $J_{4',6'}$ 2.45 Hz, H-6'), 6.82 (d, 1H, $J_{3',4'}$ 8.34 Hz, H-3'), 5.97 (d, 1H, $J_{1,2}$ 3.77 Hz, H-1), 5.14 (d, 1H, $J_{4,5}$, 8.06 Hz, H-5), 4.60 (d, 1H, $J_{1,2}$ 3.77 Hz, H-2), 4.44 (dd, 1H, $J_{3,4}$ 2.95, $J_{4,5}$ 8.06 Hz, H-4), 3.44 (s, 1H, OH), 3.45 (d, 1H, $H_{3,4}$ 2.95 Hz, H-3), 3.38 (s, 3H, OCH_3), 1.47 and 1.31 (2s, each 3H, Me_2C), 1.28 (s, 9H, ^tBu); ν_{max} 3340, 2900, 1500, 1370, 1210, 1080, 910, and 730 cm^{-1}. Anal. Calc. for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.71; H, 7.97.

(5S)-1,2-O-isopropylidene-3-O-methyl-5-(2-hydroxy-4,5-methylendioxyphenyl)-α-D-xylofuranose (3c from 1c and 2). ^1H NMR data: δ 7.92 (s, 1H, OH), 6.58 (s, 1H, H-6'), 6.45 (s, 1H, H-3'), 5.98 (d, 1H, $J_{1,2}$ 3.81 Hz, H-1), 5.90 (s, 2H, O-CH_2-O), 5.05 (d, 1H, $J_{4,5}$ 8.05 Hz, H-5), 4.61 (d, 1H, $J_{1,2}$, 3.81 Hz, H-2), 4.38 (dd, 1H, $J_{4,5}$ 8.05, $J_{3,4}$ 3.22

Hz, H-4), 3.49 (d, 1H, $J_{3,4}$ 3.22 Hz, H-3), 3.39 (s, 1H, O-CH_3), 3.32 (bs, 1H, OH), 1.49 and 1.32 (2s, each 3H, Me_2C); ν_{max} 3440, 2960, 1640, 1500, 1380, 1310, 1180, 1100, 1060, and 750 cm^{-1}. Anal. Calc. for $C_{16}H_{20}O_8$: C, 56.46; H, 5.92. Found: C, 56.51; H, 5.96.

(5S)-1,2-O-isopropylidene-3-O-methyl-5-(2-hydroxynaphtyl)-α-D-xylofuranose (3d from 1d and 2). ^{1}H NMR data: δ 8.99 (s, 1H, OH), 7.88, 7.80 and 7.74 (3d, each 1H, J = 8.88 Hz, H-4', H-5', and H-8'), 7.42 and 7.28 (2t, each 1H, J = 8.88, J = 2Hz, H-6' and H-7'), 7.14 (d, 1H, $J_{3',4'}$ 8.88 Hz, H-3'), 6.05 (d, 1H, $J_{4,5}$ 6.19 Hz, H-5), 6.01 (d, 1H, $J_{1,2}$ 3.76 Hz, H-1), 4.63 (dd, 1H, $J_{4,5}$ 6.19, $J_{3,4}$ 3.22 Hz, H-4), 4.57 (d, 1H, $J_{1,2}$ 3.76 Hz, H-2), 4.03 (s, 1H, OH), 3.48 (d, 1H, $J_{3,4}$ 3.22 Hz, H-3), 3.21 (s, 3H, O-CH_3), 1.28 and 1.42 (2s, each 3H, Me_2C); ν_{max} 3290, 2920, 1600, 1500, 1460, 1370, 1220, 1160, 1070, 1010, 820, and 740 cm^{-1}. Anal. Calc. for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.95; H, 6.43.

Reactions of Triisopropoxytitanium phenolates with Aldehyde 2. To a solution of $Ti(OPr^i)_4$ (2 mmol) in toluene (10 mL) the appropriate phenol (2 mmol) was added; the mixture was distilled to remove azeotropically the propan-2-ol formed and, after cooling at 20°C, toluene (10 mL) and then a solution of (2) (1 mmol) in toluene (2.5 mL) was added. The reaction mixture was kept at 20°C for 20 h, worked up, and purified by chromatography (hexane-acetone, 3:1). The following compounds are prepared in this manner. The yields and $[\alpha]_D$ values are collected in Table I.

(5R)-1,2-O-isopropylidene-3-O-methyl-5-(2-hydroxyphenyl)-α-D-xylofuranose (4a from 1a and 2). ^{1}H NMR data: δ 7.83 (s, 1H, OH), 7.2-6.6 (m, 4H, H-3', H-4', H-5', and H-6'), 5.98 (d, 1H, $J_{1,2}$ 3.81 Hz, H-1), 5.26 (d, 2H, $J_{4,5}$ 6.87 Hz, H-5), 4.62 (d, 1H, $J_{1,2}$ 3.82 Hz, H-2), 4.42 (dd, 1H, $J_{4,5}$ 6.87, $J_{3,4}$ 3.33 Hz, H-4), 3.86 (d, 1H, $J_{3,4}$ 3.33 Hz, H-3), 3.44 (s, 1H, O-CH_3), 3.37 (d, 1H, $J_{5\text{-OH}}$ 2.21, OH), 1.46 and 1.32 (2s, each 3H, Me_2C); ν_{max} 3400, 2960, 1600, 1470, 1380, 1230, 1090, 1030, and 770 cm^{-1}. Anal. Calc. for $C_{25}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.18; H, 7.08.

(5R)-1,2-O-isopropylidene-3-O-methyl-5-(2-hydroxy-5-tert-butylphenyl)-α-D-xylofuranose (4b from 1d and 2). ^{1}H NMR data: δ 7.41 (s, 1H, OH), 7.22 (dd, 1H, $J_{3',4'}$ 8.50, $J_{4',6'}$ 2.43 Hz, H-4'), 7.18 (d, 1H, $J_{4',6'}$ 2.43 Hz, H-6'), 6.79 (dd, 1H, $J_{3',4'}$ 8.50, $J_{3',6'}$ 1.88 Hz, H-3'), 5.98 (d, 1H, $J_{1,2}$ 4.03 Hz, H-1), 5.24 (dd, 1H, $J_{4,5}$ 6.73, $J_{5\text{-OH}}$ 3.78 Hz, H-5), 4.62 (d, 1H, $J_{1,2}$ 4.03 Hz, H-2), 4.41 (dd, 1H, $J_{4,5}$ 6.73, $J_{3,4}$ 3.50 Hz, H-4), 3.86 (d, 1H, $J_{3,4}$ 3.50 Hz, H-3), 3.45 (s, 3H, O-CH_3), 3.37 (d, 1H, $J_{5\text{-OH}}$ 3.78 Hz, OH), 1.46 and 1.32 (2s, each 3H, Me_2C), 1.28 (s, 9H, ^{t}Bu); ν_{max} 3360, 2920, 1580, 1380, 1220, 1080, 910, and 730 cm^{-1}. Anal. Calc. for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.78; H, 7.96.

(5R)-1,2-O-isopropylidene-3-O-methyl-5-(2-hydroxy-4,5-methylendioxyphenyl)-α-D-xylofuranose (4c from 1c and 2). ^{1}H NMR data: δ 7.51 (s, 1H, OH), 6.66 (s, 1H, H-6'), 6.44 (s, 1H, H-3'), 5.97 (d, 1H, $J_{1,2}$ 3.78 Hz, H-1), 5.12 (dd, 1H, $J_{4,5}$ 7.53, $J_{5\text{-OH}}$ 3.51 Hz, H-5), 4.62 (d, 1H, $J_{1,2}$ 3.78 Hz, H-2), 4.37 (dd, 1H, $J_{4,5}$ 7.53, $J_{3,4}$ 3.50 Hz, H-4),

3.90 (d, 1H, $J_{3,4}$ 3.50 Hz, H-3), 3.46 (s, 3H, O-CH_3), 3.22 (d, 1H, J_{5-OH} 3.51 Hz, OH), 1.33 and 1.47 (2s, each 3H, Me_2C); ν_{max} 3200, 2900, 1480, 1440, 1210, 1160, 1030, and 740 cm^{-1}. Anal. Calc. for $C_{16}H_{20}O_8$: C, 56.44; H, 5.92. Found: C, 56.49; H, 5.88.

(5R)-1,2-O-isopropylidene-3-O-methyl-5-(2-hydroxynapthyl)-α-D-xylofuranose (4d from 1d and 2). ^1H NMR data: δ 9.20 (s, 1H, OH), 7.88, 7.72 and 7.65 (3d, each 1H, J = 8.88 Hz, H-4', H-5', and H-8'), 7.40 and 7.27 (2t, each 1H, J = 8.88, J = 2 Hz, H-6' and H-7'), 7.18 (d, 1H, $J_{3',4'}$ 8.80 Hz, H-3'), 6.10 (dd, 1H, $J_{4,5}$ 5.91, J_{5-OH} 2.22 Hz, H-5), 5.92 (d, 1H, $J_{1,2}$ 3.76 Hz, H-1), 4.60 (dd, 1H, $J_{4,5}$ 5.91, $J_{3,4}$ 2.80 Hz, H-4), 4.57 (d, 1H, $J_{1,2}$ 3.76 Hz, H-2), 3.85 (d, 1H, J_{5-OH} 2.22 Hz, OH), 3.72 (d, 1H, $J_{3,4}$ 2.80 Hz, H-3), 3.39 (s, 3H, O-CH_3), 1.39 and 1.26 (2s, each 3H, Me_2C); ν_{max} 3260, 2920, 1590, 1370, 1215, 1060, 1020, 940, 815, and 750 cm^{-1}. Anal. Calc. for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.83; H, 6.33.

Acknowledgement - This work was supported by the Ministero della Pubblica Istruzione.

REFERENCES

1. (a) Casiraghi, G.; Cornia, M.; Rassu, G. J. Org. Chem., **1988**, 53, 4919-4922; (b) Casiraghi, G.; Bigi, F.; Casnati, G.; Sartori, G.; Soncini, P.; Gasparri Fava, G.; Ferrari Belicchi, M. J. Org. Chem., **1988**, 53, 1779-1785.
2. (a) Casiraghi, G.; Cornia, M.; Rassu, G.; Gasparri Fava, G.; Ferrari Belicchi, M. Tetrahedron Lett., **1988**, 29, 3323-3326; (b) Casiraghi, G.; Cornia, M.; Gasparri Fava, G.; Ferrari Belicchi, M.; Zetta, L. Carbohydr. Res., in press.
3. Reactions of protected dialdoses with carbon nucleophiles have been reported: (a) Mincher, D.J.; Shaw, G.J. J. Chem. Soc. Perkin Trans. I, **1984**, 1279-1282; (b) Danishefsky, S.J.; De Ninno, M.P.; Phillips, G.B.; Zelle, R.E.; Lartey, P.A. Tetrahedron, **1986**, 42, 2809-2819; (c) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. Tetrahedron, **1987**, 43, 3533-3539; (d) Hamana, H.; Ikota, N.; Ganem, B. J. Org. Chem., **1987**, 52, 5492-5494; (e) Mills, S.K.; Mincher, D.J.; Shaw, G.J. J. Chem. Soc., Chem. Commun., **1988**, 399-401; (f) Kim, K.S.; Sohng, J-K.; Ha, S.B. Tetrahedron Lett., **1988**, 29, 2847-2850; Coutrot, P.; Grison, C.; Tabyaoui, M.; Czernechi, S.; Valerly, J-M. J. Chem. Soc., Chem. Commun., **1988**, 1515-1516.
4. For related example of chelation vs non-chelation control in reactions of carbon nucleophiles with chiral carbonyl compounds, see: (a) Hanson, G.J.; Lindberg, T. J. Org. Chem., **1985**, 50, 5399-5401; (b) Kusakabe, M.; Sato, F. Chem. Lett., **1986**, 1473-1476; (c) Keck, G.E.; Castellino, S. J. Am. Chem. Soc., **1986**, 108, 3847-3849; (d) Bernardi, A.; Cardani, S.; Colombo, L.; Poli, G.; Schimperna, G.; Scolastico, C. J. Org. Chem., **1987**, 52, 888-891; (e) Reetz, M.T.; Drewes, M.W.; Schmitz, A. Angew. Chem. Int. Ed. Engl., **1987**, 26, 1141-1143; (f) Reetz, M.T. Organotitanium Reagents in Organic Synthesis: Springer, Berlin, **1986**.