Tetrahedron Vol. 46, No. 8, pp. 3071-3076, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00
Pergamon Press plc

THE DIASTEREOSELECTIVE ARYLATION OF ARABINOFURANOSE DERIVATIVES USING BROMOMAGNESIUM PHENOLATES: SYNTHESIS OF β-D- and α-L-ARABINOFURANOSYL PHENOLS

Mara Cornia*
Istituto di Chimica Organica dell'Università, Viale delle Scienze I-43100 Parma, Italy

Giovanni Casiraghi
Dipartimento di Chimica dell'Università, Via Vienna 2, I-07100 Sassari, Italy

Lucia Zetta
Istituto di Chimica delle Macromolecole del CNR, Via Ampère 56, I-20133 Milano, Italy

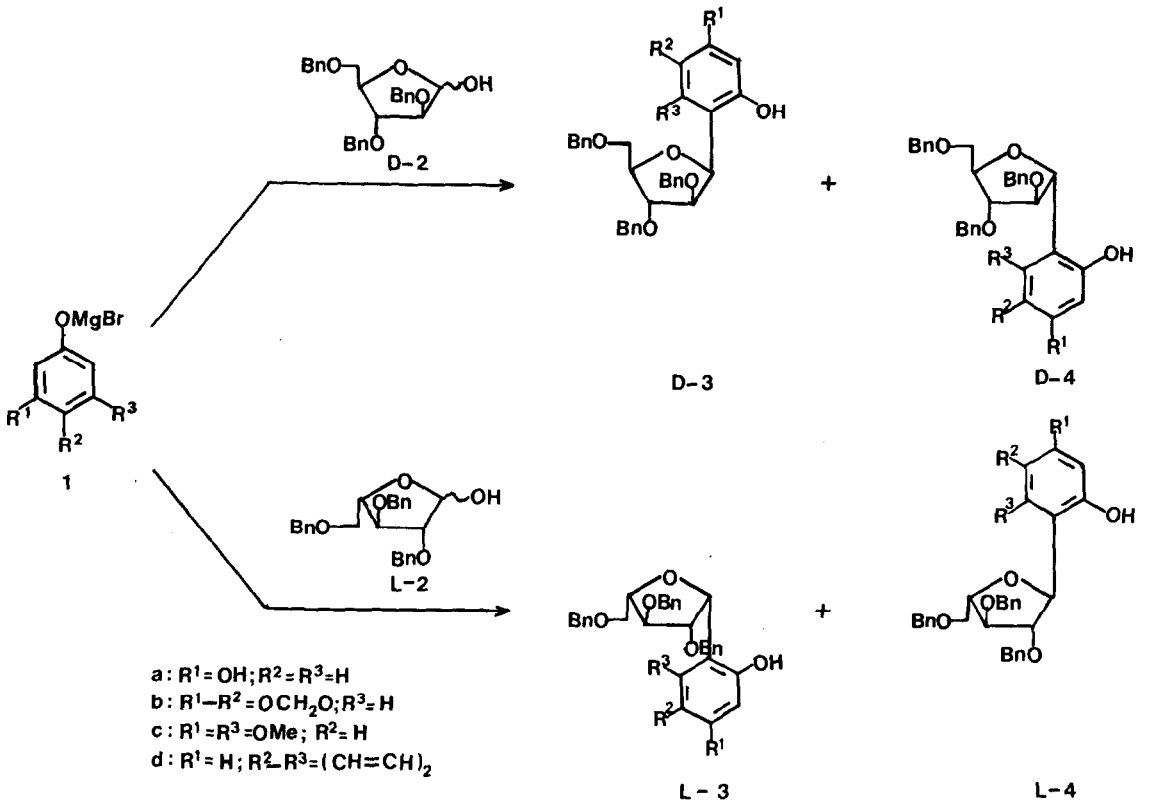
(*Received in UK* 19 *February* 1990)

Abstract - The direct arylation of either antipodes of 2,3,5-tri-O-benzyl arabinofuranose (D-2 and L-2) at the anomeric sites by means of bromomagnesium salts of activated phenols (1a-d) in 1,2-dichloroethane furnishes β-D- and α-L-arabinofuranosylphenols (D-3 and L-3) with very high margin of regio- and stereoselectivity.

There is current intense interest on the synthesis of C-glycosilated aromatic compounds, which emanates from their biological and synthetic relevance.[1] Among the existing routes to these substances,[2] the Lewis acid-promoted arylation of glycoside donors by means of activated aromatic species forms the basis of several synthetic procedures which often result in good stereocontrol and efficiency.[3] In the context of our studies about the use of co-ordinating metal phenolates as selective arylation reagents of sugar derived compounds,[4] we report here a new simple synthetic entry to arabinofuranosyl aromatics based on direct arylation of either antipodes of 2,3,5-tri-O-benzylarabinofuranose with bromomagnesium salts of certain phenols in an apolar solvent.

Attack by activated bromomagnesium phenolates 1a-d occur at the anomeric centre of arabinofuranoses D-2 and L-2 leading to the corresponding arabinofuranosylphenols 3 and 4 with very high level of regio- and stereocontrol. Scheme I illustrates the reactions and Table I lists the synthetic results.

SCHEME I



While conducting the reactions with **1a** and **1b** at room temperature under magnetic stirring resulted in acceptable yields of C-glycosylated compounds, reactions employing phenolates **1c** and **1d** required sonication and reaction temperatures of 40°C in order to obtain synthetically useful conversions. However, in all the cases, excess amounts of phenolates (4 *mol equiv.) were necessary to consume all of the sugars.*

The arylation proceeded regio- and stereoselectively being the phenol ortho-position solely sybstituted with β-D- and α-L-anomers **3** produced either predominantly or exclusively. It is noteworthy that the minor C-glycosides **4** undergo clean and quantitative epimerization into anomers **3** under the influence of EtMgBr in 1,2-dichloroethane at ambient temperature, suggesting that the epimeric composition of the final reaction mixtures might be the result of a thermodynamic control.[5]

Evidence for the structure and stereochemistry of **3** and **4** was provided by ^{1}H NMR studies. *Compounds 3 having 1',2'-cis stereodisposition (β-D and α-L-compounds) show a small* vicinal coupling constant ($J_{1',2'}$<4Hz), whilst anomers **4** (1',3'-trans; α-D and β-L compounds) have it larger ($J_{1',2'}$ > 6Hz). The assignments were corroborated by NOEDS experiments. Thus, irradiation of H-1' signal in compounds **3** resulted in strong enhancement of H-2' and H-4' signals, whereas these effects were absent in the minor anomers **4**.[6] Furthermore, compounds **4** show positive NOE's between H-1' and H-3', and between H-1' and H-5'.

Table I. Synthesis of Arabinofuranosyl Phenols 3 and 4. According to Scheme I.

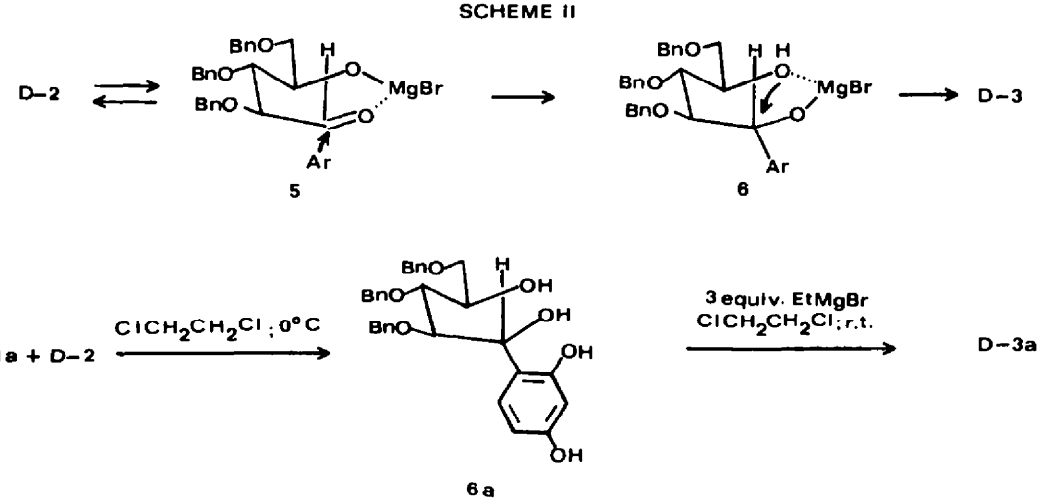
Phenol	Sugar	Conditions[a]	Products[b]	Yield[c]	β:α ratio[d]	$[\alpha]_D^{20e}$
1a	D-2	(A)	D-3a D-4a	67	85:15	+38.63 +16.00
1b	D-2	(B)	D-3b	75	<98:2	+42.68
1c	D-2	(A)	D-3c D-4c	86	88:12	+66.12 +16.60
1d	D-2	(A)	D-3d	69	<98:2	+ 6.77
1a	L-2	(A)	L-3a L-4a	65	85:15	-37.14 -25.71
1b	L-2	(B)	L-3b	73	<98:2	-40.23

[a] Conditions: (A), at 40°C under sonication for 48 h; (B), at 20°C, under magnetical stirring for 24 h. [b] Except for D-3d (m.p. 74-75°C) all compounds are oily substances. [c] Based on starting 2. [d] Determined by ^{1}H NMR. [e] For $CHCl_3$ solutions; c, see text.

Mechanistically, we postulate that this arylation process occurs via the sequence of reactions outlined in Scheme II (D-arabinose shown).

In the first step of the reaction, lactol ring opening occurs under the influence of bromomagnesium phenolate producing the complexed species 5.[7] Subsequent regio- and stereoselective arylation at the aldehyde centre of 5 results in formation of the arylalditol salt 6, which undergoes rapid dehydration-annelation to β-D-furanosylarene D-3 according to a mechanism which we have not be able to envision in detail.[8] Support for this sequence is

SCHEME II



derived from isolation of an appreciable amount of D-manno-arabinitol intermediate 6a[9] in the reaction between 1a and D-2 (0°C, one week) and its quantitative transformation into the corresponding β-furanoside D-3 by treatment with 3 mol equiv. of EtMgBr in dichloromethane at 25°C.

In conclusion, we have presented here examples of arylation of arabinofuranose derivatives by bromomagnesium phenolates, as a strategy for the rapid assembly of aryl C-glycosides, with considerable regio- and stereochemical control. We are currently extending this procedure to other furanose and pyranose derivatives, as well as appropriate heteroaromatic compounds.

EXPERIMENTAL

^{1}H NMR spectra were obtained on either a Bruker CXP-200 spectrometer at 200 MHz or a Bruker AM spectrometer at 270 MHz. NOE difference spectroscopy was performed on the latter instrument and ^{13}C NMR on a Bruker AC-100 spectrometer. Deuterochloroform was employed as the solvent and internal TMS as the standard. Optical rotations were obtained on a Autopol III polarimeter with a 1-dm tube. Mass spectra were recorded on a Finnigan 1020 GC/MS Quadrupole System Operating at 70 eV.

Reagents and solvents were purified and dried using standard methods. D- and L-2,3,5-tri-O-Benzylarabinofuranose (ca. 1:1 α/β anomers) were commercial products (SIGMA).

Chromatography was performed on Merck Kieselgel (230-400 mesh). TLC was performed on Merck DC-Fertigplatten Kieselgel 60F-254. All sonicated reactions were performed by using a ELMA TRANSONIC-460/H Model ultrasonic cleaner with the reaction vessel completely submerged.

Reaction of bromomagnesiumphenolates 1 with arabinofuranoses 2. To a solution of EtMgBr (6 mmol) in diethyl ether (20 mL) a solution of the appropriate phenol (6 mmol) in diethyl ether (20 mL) was added with stirring under nitrogen at room temperature. The ether was removed under vacuum, anhydrous 1,2-dichloromethane (50 mL), and then a solution of arabinofuranose (1 mmol) in 1,2-dichloroethane (5 mL) was added.

The reaction mixture was kept for 24 h at room temperature for 1b and 1c. For 1a and 1d the reaction vessel was sonicated for 48 h at 40°C. The mixture was quenched with saturated aqueous ammonium chloride and extracted with CH_2Cl_2 or diethyl ether (3x30 mL) and the combined extracts were dried, concentrated under reduced pressure, and purified by chromatography using the following solvent mixtures: 1a:CH_2Cl_2/MeOH, 20:1; 1b:hexane/acetone, 8:2; 1c:$CHCl_3$; 1d hexane/ethylether, 2:1. The following compounds were prepared in this manner.

2-(1',3',5'-tri-O-Benzyl-β-D-arabinofuranosil)-5-hydroxyphenol (D-3a). Colorless oil, $[\alpha]_D^{20}$ = +38.63 (c 3.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.24 (1H, s, OH), 7.4-6.9 (16H, m, O-CH_2-Ph + OH), 6.83 (1H, d, $J_{3,4}$ = 8.34 Hz, H-3), 6.38 (1H, d, $J_{4,6}$ = 2.69 Hz, H-6), 6.31 (1H, dd, $J_{3,4}$ = 8.34, $J_{4,6}$ = 2.69 Hz, H-4), 5.06 (1H, d, $J_{1',2'}$ = 3.50 Hz, H-1'), 4.57, 4.46, 4.21 (each 2H, 3s, O-CH_2-Ph), 4.16 (1H, m, H-4'), 4.02 (1H, d, $J_{3',2'}$ = 3.23, H-3'), 3.95 (1H, d, $J_{2',1'}$ = 3.50, H-2'), 3.67 (2H, m, H-5'); ^{13}C NMR δ 66.75, 70.38, 71.20, 72.61, 83.43, 83.43, 84.05, 84.70, 87.80, 105.67, 103.46, 126.36, 127.17, 127.70, 150.00, 155.11, 158.38; MS, m/e 512. Anal. Calcd for $C_{32}H_{32}O_6$: C, 79.98; H, 6.29. Found: C, 79.62; H, 6.37.

2-(2',3',5'-tri-O-Benzyl-α-D-arabinofuranosyl)-5-hydroxyphenol (D-4a). Colorless oil, $[\alpha]_D^{20}$ = +16.00 (c 0.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75 and 7.48 (each 1H, bs, OH), 7.4-7.1 (15H, m, O-CH_2-Ph), 6.99 (1H, d, $J_{3,4}$ = 8.34 Hz, H-3), 6.3-6.4 (2H, m, H-3+H-5), 4.96 (1H, d, $J_{1',2'}$ = 6.38 Hz, H-1'), 4.6-4.4 (6H, m, O-CH_2Ph), 4.10-4.30 (3H, m, H-4', H-3', H-2'), 3.65 (2H, m, H-5'); MS, m/e 512. Anal. Calcd for $C_{32}H_{32}O_6$: C, 79.98; H, 6.29. Found: C, 79.45; H, 6.35.

2-(2',3',5'-tri-O-Benzyl-β-D-arabinofuranosyl)-4,5-methylenedioxyphenol (D-3b). Colorless oil, $[\alpha]_D^{20}$ = +42.68 (c 9.6, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (1H, bs, OH), 7.4-7.0 (15H, m, O-CH_2-Ph), 6.46 (2H, 2s, H-3 and H-6), 5.92 (2H, s, O-CH_2-O), 5.02 (1H, d,

$J_{1',2'}$ = 3.37 Hz, H-1'), 4.61, 4.49, 4.28 (each 2H, 3s, O-$\underline{CH_2}$-Ph), 4.15 (1H, ddd, $J_{3',4'}$ = 3.07, $J_{4',5a}$ = 5.42, $J_{4',5b}$ = 5.12 Hz, H-4'), 4.01 (1H, dd, $J_{3',4'}$ = 3.07, $J_{2',3'}$ = 0.88 Hz, H-3'), 3.95 (1H, dd, $J_{1',2'}$ = 3.37, $J_{2',3'}$ = 0.88 Hz, H-2'), 3.67 (2H, dd, $J_{4',5a}$ = 5.42, $J_{4',5b}$ = 5.12 Hz, H-5'); ^{13}C NMR δ 68.8, 72.10, 72.32, 73.50, 83.22, 96.76, 102.61, 107.54, 111.51, 127.70-129.00, 138.70, 140.81, 152.57; MS, m/e 540. Anal. Calcd for $C_{33}H_{32}O_7$: C, 73.31; H, 5.97. Found: C, 73.58; H, 5.71.

2-(2',3',5'-tri-O-Benzyl-β-D-arabinofuranosyl)-4,6-dimethoxyphenol (D-3c). Colorless oil, $[\alpha]_D^{20}$ = +66.12 (c 2.7, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.92 (1H, s, OH), 6.9-7.4 (15H, m, O-CH_2-$\underline{Ph}$), 6.10 (1H, d, $J_{4,6}$ = 2.34 Hz, H-4), 5.79 (1H, d, $J_{4,6}$ = 2.34 Hz, H-6), 5.48 (1H, d, $J_{1',2'}$ = 3.37 Hz, H-1'); 4.57, 4.46, 4.29 (each 2H, 3s, O-$\underline{CH_2}$-Ph), 4.18 (1H, m, H-4'), 4.07 (1H, dd, $J_{1',2'}$ = 3.37, $J_{2',3'}$ = 0.88 Hz, H-2'), 3.97 (1H, dd, $J_{2',3'}$ = 0.88, $J_{3',4'}$ = 3.51 Hz, H-3'); 3.72 (2H, m, H-5'); ^{13}C NMR δ 55.12, 55.25, 59.55, 71.18, 71.35, 73.27, 80.55, 82.88, 84.45, 90.07, 94.55, 100.02, 127-129, 130.37, 133.78, 157.31, 159.62, 161.18; MS, m/e 556. Anal. Calcd for $C_{34}H_{36}O_7$: C, 73.36; H, 6.52. Found: C, 73.11; H, 6.47.

2-(2',3',5'-tri-O-Benzyl-α-D-arabinofuranosyl)-4,6-dimethoxyphenol (D-4c). Colorless oil, $[\alpha]_D^{20}$ = +16.60 (c 0.33, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.33 (1H, s, OH), 7.4-7.1 (15H, m, O-CH_2-$\underline{Ph}$), 6.09 (1H, d, J = 2.34 Hz, H-3), 6.02 (1H, d, J = 2.34 Hz, H-6), 5.52 (1H, d, $J_{1',2'}$ = 6.18 Hz, H-1'), 4.6, 4.4 (6H, m, O-$\underline{CH_2}$-Ph), 4.07-4.22 (3H, m, H-2', H-3' and H-4'), 3.75 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.65 (2H, m, H-5'); MS, m/e 556. Anal. Calcd for $C_{34}H_{36}O_7$: C, 73.36; H, 6.52. Found: C, 73.27; H, 6.19.

1-(2',3',5'-tri-O-Benzyl-β-D-arabinofuranosyl)-2-naphthol (D-3d). White crystals, m.p. 74-75°C, $[\alpha]_D^{21}$ = +6.77 (c 0.52 $CHCl_3$), ^{1}H NMR δ 9.44 (1H, s, OH), 7.9-6.6 (6H, m, H-Ar), 7.34-7.26 (15H, m, OCH_2-$\underline{Ph}$), 5.96 (1H, d, $J_{1',2'}$ = 3.37 Hz, H-1'), 4.62 (2H, s, $O\underline{CH_2}$Ph), 4.51 (2H, m, $O\underline{CH_2}$Ph), 4.34 (1H, m, H-4'), 4.24 (1H, dd, $J_{1',2'}$ = 3.37, $J_{2',3'}$ = 0.88 Hz, H-2'), 4.06 (1H, dd, $J_{2',3'}$ = 0.88, $J_{3',4'}$ = 3.07 Hz, H-3'), 3.94 (2H, s, $O\underline{CH_2}$Ph), 3.75 (2H, m, H-5'); MS, m/e 546. Anal. Calcd for $C_{36}H_{34}O_5$: C, 79.10; H, 6.27. Found: C, 79.27; H, 6.49.

2-(2',3',5'-tri-O-Benzyl-α-L-arabinofuranosyl)-5-hydroxyphenol (L-3a). Colorless oil. $[\alpha]_D^{20}$ = -37.14 (c 0.3, $CHCl_3$); spectral data are identical to D-3a. Anal. Calcd for $C_{32}H_{32}O_6$: C, 79.98; H, 6.29. Found: C, 79.50; H, 6.15.

2-(2',3',5'-tri-O-Benzyl-β-L-arabinofuranosyl)-5-hydroxyphenol (L-4a). Colorless oil, $[\alpha]_D^{20}$ = -25.71 (c 0.2, $CHCl_3$); spectral data are identical to D-4a. Anal. Calcd for $C_{32}H_{32}O_6$: C, 79.98; H, 6.29. Found: C, 79.31; H, 6.20.

2-(2',3',5'-tri-O-Benzyl-α-L-arabinofuranosyl)-4,5-methylenedioxyphenol (L-3b). Colorless oil. $[\alpha]_D^{20}$ = -40.23 (c 1.6, $CHCl_3$); spectral data are identical to D-3b. Anal. Calcd for $C_{33}H_{32}O_7$: C, 73.31; H, 5.97. Found: C, 73.18; H, 5.55.

1-(2'-4'-dihydroxyphenyl)-2,3,5-tri-O-benzyl-D-manno-arabinitol (D-6a). To a solution of EtMgBr (6 mmol) in diethyl ether (20 mL) a solution of resorcin (1a) (6 mmol) in diethyl ether (20 mL) was added with stirring at 0°C for one week. Usual work-up affords 6a in 45% yield. Colorless oil, $[\alpha]_D^{20}$ = +8.9 (c 2.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.60 (1H, s, OH), 7.5-7.1 (16H, m, O-CH_2-$\underline{Ph}$+OH), 6.71 (1H, d, $J_{6',5'}$ = 8.21 Hz, H-6'), 6.32 (1H, d, $J_{3',5'}$ = 2.31 Hz, H-3'), 6.24 (1H, dd, $J_{5',6'}$ = 8.21, $J_{3',5'}$ = 2.31 Hz, H-5'), 4.99 (1H, d, $J_{1,2}$ = 2.98 Hz, H-1), 4.46, 4.43, 4.39 (each 2H, 3s, O-$\underline{CH_2}$Ph), 4.05 (1H, m, H-4), 3.86 (1H, dd, $J_{1,2}$ = 2.98, $J_{2,3}$ = 6.92 Hz, H-3), 3.71 (1H, bs, OH), 3.61 (2H, m, $H_{5a'}$, H_{5b}).

Reaction of D-6a with EtMgBr to D-3a. To a solution of EtMgBr (3 mmol) in diethyl ether (10 mL) a solution of D-6a (1 mmol) (5 mL) was added dropwise under nitrogen at room temperature under stirring. The reaction mixture was kept at room temperature for 4 h, then worked up as described before. The crude mixture was directly examined by ^{1}H NMR. The unique product results D-3a.

ACKNOWLEDGEMENT

This work was supported by the Ministero della Pubblica Istruzione. The NMR spectra at 200 and 100 MHz and Mass Spectra were performed by using the instruments of the Centro Interfacoltà Misure, University of Parma.

REFERENCES AND NOTES

1.- Buchanan, J.G. Prog. Chem. Org. Nat. Prod. 1983, 44, 243; Hacksell, V.; Daves, G.D. Prog. Med. Chem., 1985, 22, 1.

2.- Arylation via metalated aromatics: Joyce, R.P.; Parvez, M.; Weinreb, S.M. Tetrahedron Lett. 1986, 27, 4885; Krans, G.A.; Molina, M.T. J. Org. Chem., 1988, 53, 752; Czernecki, S.; Ville, G. J. Org. Chem. 1989, 54, 610; Frick, W.; Schmidt, R.R. Liebigs Ann. Chem. 1989, 565; Arylation via Pd-mediated reactions: Czernecki, S.; Dechavanne, V. Can. J. Chem., 1983, 61, 533; Outten, R.A.; Daves, G.D. J. Org. Chem., 1987, 52, 5064; Outten, R.A.; Daves, G.D. J. Org. Chem., 1989, 54, 29. Arylation via intramolecular reactions: Martin, O.R.; Mahnken, R.E. J. Chem. Soc., Chem. Commun., 1986, 497; Martin, O.R.; Rao, S.P.; Kurz, K.G.; El-Shenawy H.A. J. Am. Chem. Soc. 1988, 110, 8698; Martin, O.R.; Rao, S.P.; El-Shenawy, H.A.; Kurz, K.G.; Cutler, A.B.; Araki, Y.; Mokubo, E.; Kobayashi, N.; Nagasawa, J.; Ishido, Y. Tetrahedron Lett. 1989, 30, 1115. Arylation via O--C rearrangement: Kometani, T.; Kondo, H.; Fujimori, Y. Synthesis 1988 1005. Arylation via cycloaddition reactions: Kozikowski, A.P.; Cheng, X-M. J. Chem. Soc., Chem. Commun. 1987, 680; Schimidt, R.R.; Frick, W.; Haag-Zeino, B.; Apparao, S. Tetrahedron Lett. 1987, 28, 4045.

3.- Arylation via Lewis acid-assisted reactions: Grynkiewicz, G.; Be Miller, J.N. Carbohydr. Res. 1984, 131, 273; Allevi, P.; Anastasia, M.; Ciuffreda, P.; Fiecchi, A.; Scala, A. J. Chem. Soc., Chem. Commun. 1987, 1245; Kwok, D-I; Outten, R.A.; Huhn, R.; Daves, G.D. J. Org. Chem. 1988, 5359; Mutsumoto, T.; Katsuki, M.; Suzuki, K. Tetrahedron Lett. 1988, 29, 6935; Matsumoto, T.; Katsuki, M.; Suzuki, K. Tetrahedron Lett. 1989, 30, 833; Kwok, D-I; Daves, G.D. J. Org. Chem. 1989, 4496; Cai, M.S.; Qin, D-X. Synth. Commun. 1989, 19, 851.

4.- Casiraghi, G.; Cornia, M.; Rassu, G. J Org. Chem. 1988, 53, 4919; Casiraghi, G.; Cornia, M.; Gasparri Fava, G.; Ferrari Belicchi, M.; Zetta, L. Carbohydr. Res., 1989, 207; Cornia, M.; Casiraghi, G. Tetrahedron, 1989, 45, 2869; Casiraghi, G.; Cornia, M.; Rassu, G.; Zetta, L.; Gasparri Fava, G.; Ferrari Belicchi, M. Carbohydr. Res. 1989, 243.

5.- Equilibration between D-3b and D-4b also occurs in acidic conditions (TFAA-$CDCl_3$, room temperature); however a 56:44 β/α anomeric mixture is produced in the event.

6.- Structural assignment of ribofuranosyl aromatics and heteroaromatics via NOE difference spectroscopy is reported: Matsumoto, T.; Katsuki, M.; Suzuki, K. Tetrahedron Lett. 1988, 29, 6935; Macdonald, S.J.F.; Huizinga, W.B.; McKenzie, T.C. J. Org. Chem. 1988, 53, 3373.

7.- An alternative pathway via formal substitution of the hydroxyl group at C-1 to give C-arylated furanosides can not be excluded a priori. See for example: Tomooka, K.; Okinaga, T.; Suzuki, K.; Tsuchihashi, G. Tetrahedron Lett. 1987, 28, 6335; Tomooka, K.; Matsuzawa, K.; Suzuki, K.; Tsuchihashi, G. Tetrahedron Lett. 1987, 28, 6339.

8.- The mechanism could proceed via SN_1-type annelation with the production of thermodynamically more stable anomer 3.

9.- The D-manno configuration in 6a ($J_{1',2'}$ = 2.98 Hz) is the one expected from an anti (erythro) selective nucleophilic arylation of D-2 in the chelate from 5. See for example: Tomooka, K.; Okinaga, T.; Suzuki, K.; Tsuchihashi, G. Tetrahedron Lett. 1989, 30, 1563.