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Stereoselective *O*-Glycosylation of *Trans*-4-Hydroxy-L-Proline Derivatives Promoted by Silver Zeolite

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Trans-4-hydroxy-L-proline has been converted to four imino- and carboxyl-blocked derivatives which are suitable for the synthesis of 4-*O*-glycosyl conjugates. Reaction of these derivatives with 2,3,5-tri-*O*-benzyl-α-L-arabinofuranosyl chloride in the presence of a silver zeolite promoter yielded the blocked β-furanosyl amino-acid conjugates. Deprotection gave _trans_-4-(β-L-arabinofuranosyloxy)-L-proline which was characterised as its crystalline isopropyl ester. ^{13}C-NMR Data are presented for the compounds described.

The crucial role which glycoproteins play in the maintenance and regulation of a plethora of biological processes [1, 2] is reflected in the amount of research directed towards the chemical synthesis of glycopeptides [3, 4].

We have been engaged in designing stereoselective glycosylation methods for the synthesis of β-arabinofuranosides such as the glycopeptide fragment *trans*-4-(β-L-arabinofuranosyloxy)-L-proline (**1**). This unit has been identified as a constituent of various plant glycoproteins and its structure elucidated using optical rotation, ^{1}H- and ^{13}C-NMR spectroscopy [5-7].

The majority of previous syntheses of *O*-arabinofuranosides has been non-stereoselective or led preferentially to the α-anomers. Results from our laboratory [8] have shown that the reaction of 2,3,5-tri-*O*-benzyl-α-L-arabinofuranosyl chloride **2** with various model alcohols proceeds under mild conditions with high stereoselectivity and in good yields, in the presence of various zeolite-based promoters. We envisaged that this method might be usefully applied to a stereoselective synthesis of the β-arabinofuranoside **1**.

A previous synthesis [9] *via* trifluoromethanesulphonic acid anhydride-promoted coupling of 2,3,5-tri-*O*-benzyl-L-arabinofuranose with a three-fold excess of *N*-(benzyloxycarbonyl)-*trans*-4-hydroxy-L-proline benzyl ester gave a 1:1 mixture of anomers with an 84% yield in the coupling step.

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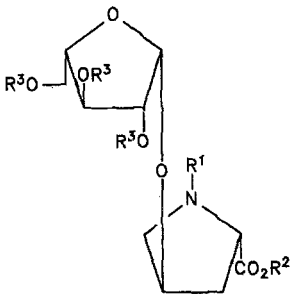

1	$R^1=H_2^+$	$R^2=R^3=H$	
10	$R^1=CO_2CH_2C_6H_5$	$R^2=CH(C_6H_5)_2$	$R^3=CH_2C_6H_5$
11	$R^1=CO_2CH_2C_6H_5$	$R^2=CH_2COC_6H_5$	$R^3=CH_2C_6H_5$
12	$R^1=CO_2CH_2C_6H_5NO_2p$	$R^2=CH(C_6H_5)_2$	$R^3=CH_2C_6H_5$
13	$R^1=CO_2CH_2C_6H_5NO_2p$	$R^2=CH_2COC_6H_5$	$R^3=CH_2C_6H_5$
14	$R^1=R^3=H$	$R^2=CH(CH_3)_2$	

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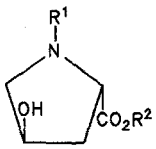
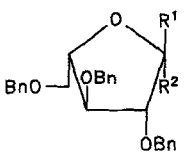


4	$R^1=CO_2CH_2C_6H_5$	$R^2=H$
5	$R^1=CO_2CH_2C_6H_5$	$R^2=CH(C_6H_5)_2$
6	$R^1=CO_2CH_2C_6H_5$	$R^2=CH_2COC_6H_5$
7	$R^1=CO_2CH_2C_6H_4pNO_2$	$R^2=H$
8	$R^1=CO_2CH_2C_6H_4pNO_2$	$R^2=CH(C_6H_5)_2$
9	$R^1=CO_2CH_2C_6H_4pNO_2$	$R^2=CH_2COC_6H_5$
15	$R^1=R^2=H$	
16	$R^1=CO_2CH_2C_6H_5$	$R^2=H.C_6H_{11}NH_2$



2	$R^1=Cl$	$R^2=H$
17	$R^1=H$	$R^2=OCH(CH_3)_2$

Results and Discussion

The *O*-glycosidic bond in the arabinoside **1** is known to be very acid labile [10], acidic conditions are also likely to lead to anomerisation. Furthermore, *trans*-4-hydroxyproline is prone to base-catalysed epimerisation at C-2 [6, 7, 11-13]. These facts impose certain limitations on the choice of methods that might serve for the temporary protection, and deprotection of intermediates in a synthesis of glycoside **1**.

A derivative of L-hydroxyproline of the general type **3** is needed. We considered that other advantageous features would be crystallinity and susceptibility of all blocking groups to a single set of conditions for their removal. None of the available derivatives [14-18] wholly meets these criteria. The synthesis of a number of alternatives was therefore undertaken, in which the imino function was protected by either the benzyloxycarbonyl or *p*-nitrobenzyloxycarbonyl group and the carboxyl function as either its diphenylmethyl or phenacyl ester. The successful synthesis of such derivatives **4-9** would depend on achieving selective reactions at the imino and carboxyl functions in the presence of the hydroxyl function at C4.

N-Benzyloxycarbonyl-*trans*-4-hydroxy-L-proline (**4**) crystallises [11, 19], but only with difficulty [20]. Compound **4** was therefore obtained pure *via* its crystalline cyclohexylammonium salt **16** as previously described [21] (80% yield). This derivative was converted into its crystalline diphenylmethyl ester **5** by reaction [22] with diphenyldiazomethane (79% yield). The crystalline phenacyl ester **6** was obtained from **4** by reaction [23] with 2-bromoacetophenone using potassium fluoride as base (73% yield). The procedure [22] employing triethylamine as base proved less efficient and gave pure **6** only after chromatography. The *p*-nitrobenzyloxycarbonyl derivative **7** was obtained in higher yield (89%) than previously reported [20] by adapting the method [21] described to make the benzyloxycarbonyl derivative **4** ; it crystallises readily and is therefore more easily purified and handled. Reaction [22] of the urethane **7** with diphenyldiazomethane gave the crystalline ester **8** (72% yield). The crystalline phenacyl ester **9** was obtained (68% yield) by the reaction [23] of **7** with 2-bromoacetophenone using potassium fluoride as base.

^{13}C-NMR Specroscopy provides a convenient method for elucidating the structures of the new imino-acid derivatives. For example, the proton-decoupled ^{13}C-NMR spectrum of phenacyl ester derivative **6** can be assigned by comparison with the spectra of its precursors, *N*-benzyloxycarbonyl derivative **4** and hydroxy-L-proline (**15**) (see Table 1).

Little change occurs in the chemical shifts of the imino-acid carbons upon derivatisation of hydroxy-L-proline. The analysis was simplified through the use of polarisation transfer experiments which allowed primary, secondary, tertiary and quaternary carbons to be distinguished from each other.

The majority of the resonances in the proton decoupled ^{13}C-NMR spectra of the imino-acid derivatives appears as closely separated pairs of equal intensity. It was considered that this spectral feature reflected the presence of two conformational isomers formed as a result of hindered rotation about the *N*-acyl carbon-nitrogen bond [24-26]. An alternative explanation involving hindered inversion of the proline nitrogen atom has also been proposed to account for this spectral feature in *N*-acyl derivatives of hydroxy-L-proline [26]. A ^{13}C-NMR

Table 1. ^{13}C Chemical shifts[a] of *trans*-4-hydroxy-L-proline (**15**) and derivatives[b].

	Imino-acid carbons					Diphenylmethyl group carbons		
	C2[c]	C3	C4	C5	$-CO_2-$	$-CHPh_2$	C(Ph)	CH(Ph)
4[d]	57.39	37.95	67.69	54.40	173.52			
	57.87	38.14	68.47	54.95	173.91			
5[d]	57.56	37.07	67.69	54.48	170.95	76.80	140.01	126.0-
	58.06	37.69	68.47	54.91	171.32		140.07	128.0
6[d]	57.36	38.01	67.65	54.38	171.64			
	57.76	38.50	68.42	54.80	171.97			
7[d]	57.52	38.00	67.87	54.61	173.68			
	58.00	38.96	68.65	55.12	174.20			
8[d]	57.67	37.75	67.80	54.57	170.90	76.87	140.0	123.0-
	58.16	38.73	68.56	55.07	171.43			128.0
9[e]	57.79	38.60	69.16	34.56	171.92			
	58.09	39.36	69.93	55.25	172.17			
16[d]	59.84	37.92	67.82	54.17	175.04			
	60.13	38.09	68.55	54.68	175.23			
15[f]	59.79	37.43	69.96	52.87	174.08			

	CBz group carbons					Phenacyl group carbons			
	CO-	$-OCH_2-$	ArC1	ArC2C3	ArC4	$-OCH_2-$	-CO-	ArC1	ArC2-C4
4[d]	153.89	65.93[g]	137.0	137.0[g]	137.0[g]				
	154.21								
5[d]	153.78	66.10[g]	136.36	126.0	-128.0[g]				
	154.29								
6[d]	153.69	66.56[gh]	136.70	127.0	-128.0[g]	66.11[h]	192.42	134.00	127.0[g]
	154.24						192.56		
7[d]	153.75	65.02[g]	144.92	123.0	147.04				
	154.11		144.97[h]	128.0[g]	147.13[h]				
8[d]	153.35	65.06[g]	144.19	123.0	146.70				
	154.01		144.60[h]	128.0[g]	146.92[h]				
9[e]	154.30	65.81	144.00[h]	123.0	-147.52[h]	66.23	191.51	134.19	123.0-
	154.76	65.92		133.0[gh]		66.42	192.13	134.27	133.0[gh]
16[d]	153.91	65.16	~137.0[g]	~137.0[g]	~137.0[g]				
	154.39								

[a] In ppm.

[b] The doubling of resonances is ascribed to hindered rotation in the urethane group.

[c] Hydroxyproline numbering according to Definitive Rules for Nomenclature of Organic Chemistry, IUPAC 1957.

[d] In DMSO-$^2H_6$ with reference to TMS.

[e] In C^2HCl_3 with reference to TMS.

[f] In ^2H_2O with reference to dioxan at 66.50 ppm.

[g] Broad signal.

[h] The assignment of these signals may be reversed.

experiment performed at various temperatures supported the presence of conformational isomers. Thus, all the doublets present in the spectrum of the *N*-benzyloxycarbonyl derivative **4** coalesced at 100°C and reappeared on cooling to 25°C .

2,3,5-Tri-*O*-benzyl-α-L-arabinofuranosyl chloride **2** was prepared from 2,3,5-tri-*O*-benzyl-L-arabinofuranose [27] *via* the anomeric 1-*O*-(*p*-nitrobenzoyl)-2,3,5-tri-*O*-benzyl-L-arabinofuranose esters [28-29] as first described [30] for the preparation of the enantiomeric α-D-chloride (44% yield from L-arabinose). In the presence of silver zeolite promoters (formed by exchange of silver for sodium cations in molecular sieves [31]) the chloride **2** has been shown [8] to react stereoselectively with model alcohols (e.g. isopropanol or cholesterol). Good yields of the corresponding β-glycosides were obtained using stoichiometric amounts of reactants in reaction times of 4 h at ambient temperature. Thus, each of the protected imino-acid derivatives **5** , **6**, **8** and **9** was reacted in turn with the α-chloride **2**. The reactions were stopped after 4 h at 25°C and the mixtures purified by flash chromatography to give the corresponding β-arabinofuranosides **10-13**. Examination of the crude reaction mixtures by thin layer chromatography showed the presence of only one new component in each experiment. The isolated yield of the glycoside product varied between different batches of the promoter. This might be due to the non-uniform nature of the heterogenous zeolite-based promoters. However, despite the small differences between experiments, yields always remained good and no sign was observed (by TLC or ^{1}H-NMR spectroscopy) of the corresponding α-arabinosides. No attempt was made to optimise the yield by varying for example, the reaction times or temperatures.

^{13}C-NMR Spectroscopy has been shown to provide a general and convenient means by which to determine the anomeric configurations of glycofuranosides [32-34]. α-Arabinofuranosides show a resonance in their proton-decoupled ^{13}C-NMR spectra at ≈107 ppm due to their anomeric carbon atoms, whereas the corresponding signal for the β-anomers lies at ≈100 ppm. Furthermore, both these signals appear well separated from other sugar carbon resonances and are easily identified [9, 32-34].

Assignment of the proton decoupled ^{13}C-NMR spectrum of the arabinofuranoside derivative **10** for example, follows from a comparison with that of its amino-acid precursor (**5**) and the related isopropyl 2,3,5-tri-*O*-benzyl-β-L-arabinofuranoside **17** (see Table 2). Of particular significance is the difference in chemical shift between the resonance due to the C4 carbon in the imino-acid derivatives (at ≈68 ppm) and the corresponding signal in the *O*-glycoside derivatives (at ≈74 ppm). This difference (≈6 ppm) confirms that the imino-acid derivatives (**5**, **6**, **8** and **9**) are covalently linked to the sugar moiety in the *O*-arabinosides (**10**, **11**, **12** and **13**, respectively). The doubling of peaks is a consequence of conformational isomers (see above).

Catalytic hydrogenolysis of the protected *O*-glycoside derivative **10** under neutral conditions (the use of acetic acid in the hydrogenolysis step complicates the purification of the product, see [9]) gave the *O*-glycoside **1** as a syrup (96% yield) upon removal of the catalyst and evaporation of the solvent. The product gave optical rotation and ^{13}C-NMR spectroscopic data similar to those previously reported [9] for the β-arabinofuranoside **1**. As expected, the doubling of peaks (apparent in the spectra of all the *N*-protected derivatives) is not a feature in the spectrum of the deprotected arabinoside **1**. Evaporation of the syrupy glycoside

Table 2. ^{13}C Chemical shifts of arabinofuranosides[a,b].

	Imino-acid carbons					Diphenylmethyl group carbons			
	C2[c]	C3	C4	C5	-CO_2	-C**H**Ph_2	C(Ph)	CH(Ph)	
1[f]	52.66	37.62	78.35	52.66	174.61				
10[e]	58.11	36.28	73.69	51.40	171.72	77.54	139.86	127.0-	
	58.40	37.33	75.19			77.85		128.0	
11[e]	57.62	38.40	73.22	51.36	171.83				
	58.01	39.25	75.52						
12[e]	58.16	37.37	75.21	51.61	171.42	77.47	139.58	126.0-	
	58.40		75.43			77.89		128.0	
13[e]	57.89	36.39	73.85	51.75	171.88				
	58.27	37.72	75.53		172.17				
14[f]	66.62	37.66	76.17	56.31	174.35				

	Arabinofuranosyl carbons						Benzyl group carbons		Other aglycone carbons
	C1'	C2'	C3'	C4'	C5'	-CH_2	CH(Ph)	C(Ph)	
1	101.81	78.12[h]	78.46[h]	83.68	64.92				
10	98.94	82.60	80.21	83.97	71.88[h]	72.37[h]	~138	127.0-	
	99.68				72.46	73.33		128.0	
11	98.78	82.43	80.21	83.91	72.15[h]	72.24[h]	~138	127.0-	
	99.79				72.56	72.62		128.0	
12	98.74	82.31	80.12	83.97	71.68[h]	72.24[h]	~138	127.0-	
	99.95				72.45	72.57		128.0	
13	99.20	82.66	80.32	84.18	72.09[h]	72.34[h]	~138	127.0-	
	99.95				72.45	72.57		128.0	
14	100.97	77.04	74.85	82.75	63.67				58.96(CH);
									18.06, 18.69 (2xCH_3)
17	98.95	83.89	80.07	84.14	72.35[h]	72.41[h]	~138	~128	68.85(CH);
					73.02	73.39			21.56, 23.51 (2xCH_3)

	CBz group carbons					Phenacyl group carbons			
	-NCO-	-OCH_2-	C(Ph)	*o,m*-CH(Ph)	*p*-CH or -CNO_2Ph)	CH_2	-CO-	C(Ph)	CH(Ph)
10	154.58	67.11	136.29	127.0–	128.0[g]				
	154.92	67.20	136.62						
11	154.01	67.20[h]	136.61	127.0 –	128.0[g]	67.03[h]	192.50	133.82	127.0-
									128.0
12	153.79	65.63	137.38	127.0-	143.30				
				128.0					
13	154.11	65.79[h]	144.05	127.0-	147.59	66.24[h]	191.39	~134[g]	127.0-
	154.52			128.0			191.76		128.0

For footnotes see Table 1.

1 from isopropanol gave a crystalline derivative (92% yield). Elemental analysis indicated it to be the isopropyl ester **14** and this is further supported by its ^{13}C- and ^{1}H-NMR spectral data. The assignment of resonances in the ^{13}C-spectrum of ester **14** was made with the aid of DEPT and homonuclear (^{1}H-^{1}H) and heteronuclear (^{13}C-^{1}H) scalar correlated (COSY) spectra. Thus, the hydroxyproline C=O, C3; the isopropyl CH and CH_3; and the arabinofuranosyl C1', C4' resonances could be assigned directly from the 1D, 100 MHz ^{13}C-NMR spectrum. The chemical shifts of all protons were located from a 400 MHz ^{1}H-^{1}H COSY spectrum; DEPT spectra identified two alternative resonances for the Araf-C5' and Hyp-C5 methylene carbons. These and all the remaining resonances could then be assigned from the ^{1}H-^{13}C correlated spectrum. (The details of the ^{1}H-NMR spectrum and a conformational analysis of ester **14** will be reported elsewhere).

Materials and Methods

General

Melting points were determined in capillary tubes with a Thomas-Hoover apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. NMR spectra were run either on a Jeol FX90Q spectrometer (^{1}H, 89.6 MHz; ^{13}C, 22.5 MHz), a Bruker WM-250 spectrometer [^{1}H, 250.13 MHz; ^{13}C, 62.9 MHz; University of London Intercollegiate Research Services (ULIRS) King's College] or a Bruker WH-400 spectrometer (^{1}H, 400.13 MHz; ^{13}C, 100.0 MHz; ULIRS, Queen Mary College). Mass spectra were recorded using a VG ZAB-1F spectrometer [fast atom bombardment (FAB) using a thioglycerol oxalic acid matrix; ULIRS, School of Pharmacy].

Microanalyses were performed by the microanalytical services of the Bourne Laboratory, Royal Holloway and Bedford New College. TLC was done on 'Polygram Sil G', pre-coated plastic sheets supplied by Machery-Nagel and Co., Duren, West Germany and the plates "developed" by spraying with a solution of sulphuric acid in ethanol (5% by vol) and heating at 100°C . Flash chromatography was conducted following the method described by Still *et al.* [35]; the silica gel used was kieselgel 60 (230-410 mesh ASTSM) supplied by Merck, Darmstadt, West Germany. Evaporations *in vacuo* were conducted at under 35°C (bath temperature). Experiments using a nitrogen atmosphere were conducted in glassware preheated at 200°C before being assembled (hot) under N_2; all subsequent manipulations were carried out with a positive N_2 pressure (N_2 was only passed through the reaction vessel when it was open to the atmosphere so as to minimise evaporation of solvent). Dichloromethane was distilled from CaH_2 immediately prior to use. Dry solids and syrups were prepared by keeping under vacuum (0.5 mm Hg) at 25°C for 6-24 h. All other dry reagents were prepared by standard methods [36, 37]. Chemicals were purchased from the Aldrich Chemical Co., Milwaukee, WI, USA, and used without purification unless otherwise stated.

*N-(Benzyloxycarbonyl)-trans-4-hydroxy-L-proline Cyclohexylammonium Salt (**16**)*

15 (6.65 g, 50.7 mmol) was treated with benzyl chloroformate and then cyclohexylamine following the method described by Baer and Stedman [21] to give **16** as a crystalline salt (16.6 g, 89%). A portion was recrystallised from ethanol-ether: m.p. 190-192°C (dec), $[\alpha]_D^{20}$

-43.2° (c 3.0, H_2O); Lit. [21], m.p. 191-192°C (dec) (from ethanol-ether), $[\alpha]_D^{25}$ 43.9° (c 5.0, water); ^{1}H-NMR (250.14 MHz; DMSO-$^2H_6$) δ = 7.31 (5H, m, Ph), 5.01 (2H, m, C**H**$_2$Ph), 4.23 (1H, m, C2-H), 4.03 (1H, m, C4-H), 3.45 (1H, m, C5-H_a), 3.25 (1H, m C5-H_b), 2.81 (1H, br s, C4-OH), 2.5-1.11 (15H, m, cyclohexylamine); ^{13}C-NMR, see Table 1.

*N-(Benzyloxycarbonyl)-trans-4-hydroxy-L-proline (**4**)*

16 (5.47 g, 15 mmol) was converted following the method of Baer and Stedman [21] into **4,** isolated as a clear syrup (3.75 g, 99% yield). $[\alpha]_D^{25}$ -77.4° (c 3, $CHCl_3$); Lit. [21], $[\alpha]_D^{20}$ -77.7° (c 3, $CHCl_3$); Lit. [11], m.p. 106-107°C , $[\alpha]_D^{20}$ -72° (c 1.0, $CHCl_3$); ^{1}H-NMR (250.13 MHz; DMSO-$^2H_6$) δ = 7.33 (5H, m, Ph), 5.06 (2H, m, CH_2Ph), 4.24 (1H, m, C4-H), 4.03 (1H, m, C2-H), 3.35 (2H, m, C5-H_a and C5-H_b), 2.17 (1H, m, C3-H_a), 1.94 (1H, m, C3-H_b); ^{13}C-NMR, see Table 1.

*N-(Benzyloxycarbonyl)-trans-4-hydroxy-L-proline Diphenylmethyl Ester (**5**)*

Diphenyldiazomethane [38] (2.6 g, 13.2 mmol) was added in small portions (over 30 min) to a vigorously stirred, occasionally cooled (ice-bath), solution of **4** (3.1 g, 12.0 mmol) in dry acetone (25 ml). The mixture was stirred for a further 4 h at 25°C , during which it turned from a deep violet to a yellow colour. The solvent was evaporated *in vacuo*, the residue dissolved in ethyl acetate (30 ml) and the mixture filtered. Addition of water (20 ml) to the filtrate caused the precipitation of a crystalline solid almost immediately (4.9 g). The solid was isolated by filtration, washed with water and recrystallised from ethanol to give **5** (4.1 g, 79%), m.p. 114-119°C , $[\alpha]_D^{20}$ -55.4° (c 1.25, $CHCl_3$); ^{1}H-NMR (250.13 MHz; DMSO-$^2H_6$) δ = 7.28 (15H, m, Ph), 5.08 (5H, m, C2-H, C**H**Ph$_2$ and C**H**$_2$Ph), 4.49 (1H, m, C4-H), 4.28 (1H, br s, OH), 3.3 (2H, m, C5-H_a and C5-H_b), 2.25, 1.94 (2H, m, C3-H_a and C3-H_b); ^{13}C-NMR, see Table 1. Found: C, 72.5; H 5.7. $C_{26}H_{25}O_5N$ requires C, 72.4; H 5.8%.

*N-(Benzyloxycarbonyl)-trans-4-hydroxy-L-proline Phenacyl Ester (**6**)*

Potassium fluoride (1.20 g, 22 mmol) and α-bromoacetophenone (1.99 g, 10 mmol) were stirred together in dimethylformamide (10 g) for 15 min at 25°C. **4** (2.65 g, 10 mmol) was added and the reaction mixture stirred for 4 h at 25°C, diluted with water and extracted with ether. The combined ethereal extracts were washed three times with water, dried ($MgSO_4$) and evaporated *in vacuo* to a syrup which gave **6** from ethanol as crystals (2.8 g, 73%) m.p. 71-73°C , $[\alpha]_D^{25}$ -76.9° (c 1.23, $CHCl_3$); ^{1}H-NMR (250.13 MHz; DMSO-$^2H_6$) δ = 7.9-7.6 (10H, m, Ph), 5.53 (3H, m, CH_2CO and C2-H), 5.19 (1H, br s, OH), 5.07 (2H, m, C**H**$_2$Ph); ^{13}C-NMR, see Table 1. Found: C, 65.5; H, 5.5. $C_{21}H_{21}O_6N$ requires C, 65.7; H, 5.5%.

*N-(p-Nitrobenzyloxycarbonyl)-trans-4-hydroxy-L-proline (**7**)*

A solution of *p*-nitrobenzyl chloroformate (12.4 g, 57.5 mmol) in cold acetone (50 ml) was added dropwise (0.5 h) to an ice-cooled, vigorously stirred suspension of **15** (6.7 g, 50.7 mmol), potassium bicarbonate (5.0 g, 50 mmol) and anhydrous potassium carbonate (17.3 g, 125 mmol) in water (50 ml). The reaction mixture was stirred for a further 4 h at 0°C , diluted with water (200 ml) and extracted with diethyl ether (300 ml total). The aqueous phase was ice-cooled, brought to pH <2 (universal indicator paper) with concentrated

hydrochloric acid and extracted with ethyl acetate. The organic phase was evaporated *in vacuo* to a syrup (14.2 g) which gave **7** from ethanol-ether as crystals (13.9 g, 89%), m.p. 133-136°C (from amyl acetate), $[\alpha]_D^{25}$ -40.5° (c 1.1, in N NaOH); Lit. [24], m.p. 136.5-139°C (from amyl acetate), $[\alpha]_D^{25}$ -41.6° (c 1, in N NaOH), yield 66%; ^{1}H-NMR (250.13 MHz; DMSO-$^2H_6$) δ = 8.22, 7.61 (4H, m, Ph), 5.22 (3H, m, CH_2Ph and C2-H), 4.29 (1H, m, C4-H), 3.35 (2H, m, C5-H_a and C5-H_b), 2.20, 1.95 (2H, m, C3-H_a and C3-H_b); ^{13}C-NMR, see Table 1.

*N-(p-Nitrobenzyloxycarbonyl)-trans-4-hydroxy-L-proline Diphenylmethyl Ester (**8**)*

A solution of **7** (2.3 g, 7.5 mmol) in dry acetone was treated with diphenyldiazomethane as described for the preparation of **5** to give **8** from ethanol as crystals (2.6 g, 72%), m.p. 160-161°C , $[\alpha]_D^{25}$ -36.0° (c 1.4, $CHCl_3$); ^{1}H-NMR (250.13 MHz; DMSO-$^2H_6$) δ = 8.2-6.8 (14H, m, Ph), 5.22 3H, m, C**H**Ph and C**H**$_2$Ph), 5.05 (1H, m, C2-H), 4.5 (1H, m C4-H), 4.3 (1H, br s, C4-OH), 3.35 (2H, m, C5-H_a and C5-H_b) 2.3-2.0 (2H, m, C3-H_a and C3-H_b); ^{13}C-NMR, see Table 1. Found: C, 65.1; H, 5.1. $C_{26}H_{24}O_7N_2$ requires C, 64.6; H, 5.0%.

*N-(p-Nitrobenzyloxycarbonyl)-trans-4-hydroxy-L-proline Phenacyl Ester (**9**)*

7 (3.1 g, 10 mmol) was treated with potassium fluoride and bromoacetophenone in dimethylformamide as described for the preparation of **6** to give **9** from ethanol as crystals (2.9 g, 68%), m.p. 79-82°C , $[\alpha]_D^{25}$ -68.2° (c 1, $CHCl_3$); ^{1}H-NMR (250.13 MHz; C^2HCl_3) δ = 8.22-7.28 (9H, m, Ph), 5.60 (2H, m, CH_2C=O), 5.25 (3H, m, C2-H and C**H**$_2$Ph), 4.72 (2H, m, C4-H), 3.72 (2H, m, C5-H_a and C5-H_b), 2.52 (2H, m, C3-H_a and C3-H_b), 1.7 (br s, OH); ^{13}C-NMR, see Table 1. Found: C, 59.0, H, 4.7. $C_{21}H_{20}O_8N_2$ requires C, 58.9; H, 4.7%.

*N-(Benzyloxycarbonyl)-trans-4-(2,3,5-tri-O-benzyl-β-L-arabinofuranosyloxy)-L-proline Diphenylmethyl Ester (**10**)*

A solution of freshly prepared dry **2** [29, 30] (0.14 g, 0.319 mmol) in dry dichloromethane (2.5 ml) was added (in one batch) to a stirred suspension of silver zeolite [31] (0.4 g), powdered 4A molecular sieves (0.3 g) and dry **5** (0.138 g, 0.319 mmol) in dry dichloromethane (2.5 ml). The reaction mixture was stirred at 25°C with exclusion of moisture (N_2 atmosphere) and light. After 4 h, the mixture was filtered through a thin bed of celite, the filtrate concentrated *in vacuo* and purified by flash chromatography (ethyl acetate/petroleum ether, 1/2 by vol) to give **10** which crystallised on standing (0.22 g, 83%), R_F 0.47, m.p. 79-80°C , $[\alpha]_D^{25}$ +11.4° (c 1, in $CHCl_3$); ^{13}C-NMR, see Table 2, MS: m/z FAB 855 (M + Na^+), $C_{52}H_{51}O_9N$ requires M 832.

*N-(Benzyloxycarbonyl)-trans-4-(2,3,5-tri-O-benzyl-β-L-arabinofuranosyloxy)-L-proline Phenacyl Ester (**11**)*

Freshly prepared **2** (0.14 g, 0.319 mmol) and dry **6** (0.122 g, 0.319 mmol) were reacted together as described for the preparation of **10**. Flash chromatography (ethyl acetate/petroleum ether, 1/1 by vol) gave **11** as a syrup (0.16 g, 64%), R_F 0.71, $[\alpha]_D^{25}$ +9.29° (c 1.1, in $CHCl_3$); ^{13}C-NMR, see Table 2, MS: m/z FAB 808 (M + Na^+), $C_{47}H_{47}O_{10}N$ requires M 785.

*N-(p-Nitrobenzyloxycarbonyl)-trans-4-(2,3,5-tri-O-benzyl-β-L-arabinofuranosyloxy)-L-proline Diphenylmethyl Ester (**12**)*

Freshly prepared **2** (0.14 g, 0.319 mmol) and dry **8** (0.152 g, 0.319 mmol) were reacted together as described for the preparation of **1**. Flash chromatography (ethyl acetate/petroleum ether, 1/1 by vol), gave **12** as a syrup which crystallised on standing (0.25 g, 90%). R_F 0.24, m.p. 132-133°C , $[\alpha]_D$ -16.6° (c 1.1, $CHCl_3$); ^{13}C-NMR, see Table 2, MS: m/z FAB 901 (M + Na^+), $C_{52}H_{50}O_{11}N_2$ requires M 878.

*N-(p-Nitrobenzyloxycarbonyl)-trans-4-(2,3,5-tri-O-benzyl-β-L-arabinofuranosyloxy)-L-proline Phenacyl Ester (**13**)*

Freshly prepared **2** (0.14 g, 0.319 mmol) and dry **9** (0.13 g, 0.319 mmol) were reacted together as described for the preparation of **10**. Flash chromatography (ethyl acetate/petroleum ether, 1/1 by vol) gave **13** as a syrup (0.19 g, 72%), R_F 0.26, $[\alpha]_D^{25}$ +14.35° (c 1.1, CH_2Cl_2); ^{13}C-NMR, see Table 2, MS: m/z FAB 853 (M + Na^+), $C_{47}H_{46}O_{12}N_2$ requires M 830.

*Trans-4-(β-L-arabinofuranosyloxy)-L-proline (**1**)*

A suspension of **10** (0.15 g, 0.18 mmol) in aqueous methanol (80% by vol; 5 ml) was hydrogenated over a 10% palladium on carbon catalyst (200 mg) for 24 h at 25°C by which time hydrogen uptake had ceased and TLC (ethyl acetate/petroleum ether, 1/1 by vol) revealed the absence of any starting material. The reaction mixture was filtered through a thin bed of celite, the catalyst washed thoroughly with hot water and the filtrate and washings evaporated *in vacuo* to give **1** as a clear syrup (45 mg, 96%), $[\alpha]_D^{25}$ +16.2° (c 1.0, H_2O); Lit. [9] $[\alpha]_D^{22}$ +14.4° (c 1.2, in water) as a crystalline hygroscopic solid; ^{13}C-NMR, see Table 2.

*Trans-4-(β-L-arabinofuranosyloxy)-L-proline Isopropyl Ester (**14**)*

Syrup **1** (50 mg, 19 mmol) was diluted with isopropanol and evaporated *in vacuo* several times to give **14** as crystals (53 mg, 92%), m.p. 205-210°C (dec.), $[\alpha]_D^{25}$ +40.1° (c 1.1, water); ^{13}C-NMR, see Table 2; MS: m/z FAB 328 (M + Na^+). Found: C, 51.4, H 7.4; $C_{13}H_{23}O_7N$ requires C, 51.1; H 7.6%.

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