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Synthesis of 1,2:5,6-di-O-Isopropylidene-D-Glucofuranos-3-yl and 1,2:3,4-di-O-Isopropylidene-D-Galactopyranos-6-yl-(N-Diphenylmethylene) glycinates.

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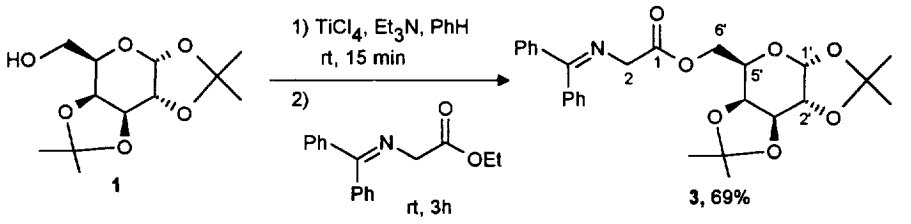
Abstract: 1,2:3,4-di-O-isopropylidene-D-galactopyranos-6-yl-(N-diphenylmethylene)-glycinate **3**, was prepared *via* a trans-esterification process from ethyl (N-diphenylmethylene)-glycinate and 1,2:5,6-di-O-isopropylidene-D-glucofuranos-3-yl-(N-diphenylmethylene) glycinate **9**, *via* a trans-imination reaction from 1,2:5,6-di-O-isopropylidene-D-glucofuranos-3-yl glycinate **6** and diphenyl-ketiminium chloride.

Carbohydrates are widespread chiral natural products and they have been transformed very often into interesting chiral intermediates in the so-called chiral pool syntheses of important biological active compounds. They were also used as chiral auxiliaries in stereoselective syntheses.[1] As a part of a program based on the development of new asymmetric syntheses, we had to prepare iminoglycinates of carbohydrates. We report in this paper the synthesis of two of theses glycinate derivatives from 1,2:3,4-di-O-isopropylidene-D-galactopyranose **1** and diacetone-D-glucose **2** , two commercially available carbohydrates.

The first one, 1,2:3,4-di-O-isopropylidene-D-galactopyranos-6-yl-(N-diphenylmethyl-ene)-glycinate **3** was prepared *via* a trans-esterification process, and the second molecule, 1,2:5,6-di-O-isopropylidene-D-glucofuranos-3-yl-(N-diphenylmethylene)-glycinate **9** *via* a trans-imination reaction.

In the first attempt to prepare the iminoglycinate **3**, we first made the alcoholate of **1** with sodium hydride and tried the trans-esterification of ethyl (N-diphenylmethylene)-glycinate under different experimental conditions. Yields were poor in THF as well as in DMF, at rt or under reflux, even in the presence of a large excess of carbohydrate.

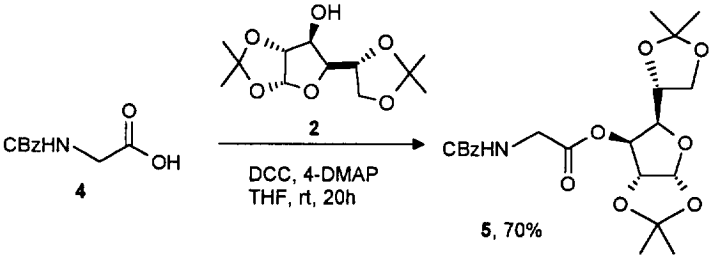


Scheme 1

However, the in presence of $TiCl_4$, the trans-esterification yield was drastically increased. The reaction was carried out in benzene from ethyl (N-diphenylmethylene)-glycinate in presence of 1 eq of $TiCl_4$, 4 eq of triethylamine and 5 eq of 1,2:3,4-di-O-isopropylidene-D-galactopyranose at rt for 3h. The reaction yield in purified iminoglycinate **3** was 69% (Scheme 1).

In the case of the iminoglycinate **9**, it was not possible to perform a trans-esterification from ethyl (N-diphenylmethylene)-glycinate and 1,2:5,6-di-O-isopropylidene-D-glucofuranose in presence of NaH or $TiCl_4$. We investigated then a trans-imination process : esterification of N-benzoyloxycarbonylglycine **4** with 1,2:5,6-di-O-isopropylidene-D-glucofuranose , hydrogenolysis of the Cbz protecting group followed by trans-imination with diphenyl-ketiminium chloride.

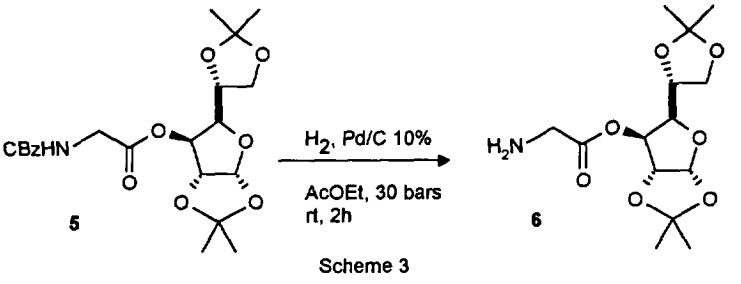
The protection of glycine was carried out with benzylchloroformate in presence of sodium bicarbonate in aqueous solution following a known procedure.[2] The esterification was first attempted from the mixed anhydride obtained from isobutyl chloroformate, N-methylpiperidine in CH_2Cl_2 . However the reaction of this mixed anhydride with **2** at rt in CH_2Cl_2 for 25h gave a 15% yield in protected 1,2:5,6-di-O-isopropylidene-D-glucofuranos-3-yl-(N-benzoyloxycarbonyl)-glycinate **5**. However, after activation of (N-benzoyloxycarbonyl)-glycine with DCC in presence of 4-dimethylamino-pyridine, esterification in THF with the carbohydrate gave the expected glycinate **5** in 70% yield (Scheme 2).



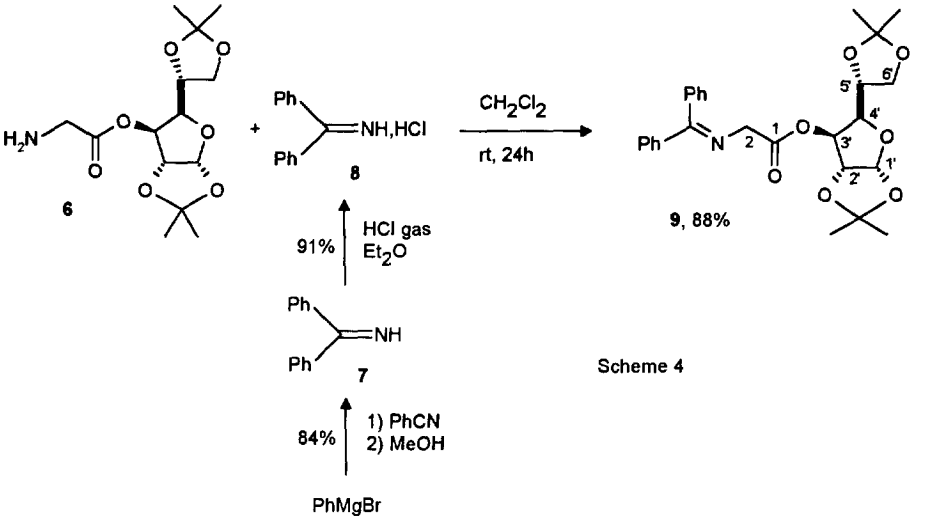
Scheme 2

Hydrogenolysis of the carbamate **5** was carried out in EtOAc, in presence of 10% Pd/C and 30 bars of hydrogen at rt for 2h (Scheme 3) to give glycinate **6** in quantitative yield. The choice of the solvent was crucial in this reaction. In ethanol, the product was trans-esterified giving a mixture of the carbohydrate and ethyl glycinate.

The imine **7** of benzophenone was prepared from benzenemagnesium bromide and benzonitrile in 84% yield. The corresponding hydrochloride **8** was prepared in 91% yield by adding HCl gas to the imine **7**. The trans-imination was carried out by adding the aminoester **6** to the hydrochloride **8** in CH_2Cl_2, at rt for 24h. The iminoglycinate **9** was obtained, after purification, in 88% yield (Scheme 4). The overall yield for this four step synthesis was 54%.

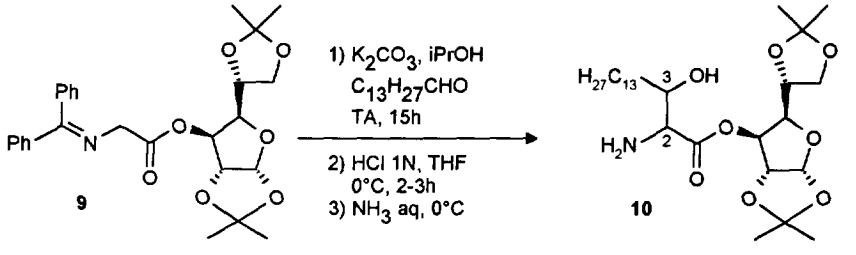


Scheme 3



Scheme 4

Iminoglycinates **3** and **9** were then used in asymmetric aldol type condensations with tetradecanal under phase transfer conditions (Scheme 5).



Scheme 5

For solid-liquid phase transfer condensations, we followed the experimental procedure reported by Yaozhong[4]. We observed a low diastereoselectivity (16%) for the formation of compound **10** as well as a low

enantioselectivity (19% for the minor diastereomer and 41% for the major diastereomer). Very similar results were obtained from the iminoglycinate **3**.

For liquid-liquid phase transfer experiments, we followed the experimental procedure described by Miller[5] . In both cases, **3** and **9**, in presence of an achiral catalyst (TEBAC) or a chiral catalyst (N-benzyl cinchoninium or cinchonidinium chloride), the diastereoselectivity was around 20% and the enantioselectivity was even lower. In liquid phase, when the enolate of **9** was prepared with LDA in THF , the diastereoselectivity was still low (16%) but the enantioselectivity was higher (45% for both diastereomers). Finally only one diastereomer was obtained when the enolate of **9** was prepared with $ClTi(OiPr)_3$ in CH_2Cl_2 but the enantioselectivity was only 6% and the chemical yield 11%.

These results in asymmetric aldol condensation with long chain aldehyde showed the poor effect of carbohydrates as chiral inducers.

Experimental Part.

1,2:3,4-di-O-Isopropylidene-D-galactopyranos-6-yl-(N-diphenylmethylene)-glycinate, 3.

To a mixture of 1,2:3,4-di-O-isopropylidene-D-galactopyranose **1** (19.4 g, 74.5 mmol, 5.2 eq) and triethylamine (dried on molecular sieves, 8.3 mL, 59.5 mmol, 4.1 eq) in benzene (dried over Na, 100 mL) was dropwise added $TiCl_4$ (2 mL, 18.2 mmol, 1.3 eq). The reaction mixture became orange-yellow and a precipitate of triethylammonium chloride was obtained. After stirring at rt for 15 min, ethyl (N-diphenylmethylene)-glycinate (4 g, 14.96 mmol, 1 eq) in benzene (15 mL) were dropwise added and stirring was maintained for 3h at rt. The dark red solution was filtrated and washed with ether. After evaporating the solvent, the residue was purified by chromatography on silica gel (treated with ether/triethylamine : 95/5, eluent: hexane/EtOAc: 90/10 and 80/20).A pure first fraction (4.05 g, 59%) was obtained. A second fraction containing the carbohydrate in excess and 14% of glycinate **3** was purified by chromatography in the same conditions to give 0.66 g of **3**. The overall yield was 69%. Rf = 0.22 (hexane/AcOEt: 80/20); $[\alpha]_D$ = -46 (c 1.32, $CHCl_3$). ^1H NMR ($CDCl_3$) : 1.31 ; 1.32 ; 1.44 and 1.46 (12H, 4s, 4 CH_3) ; 4.00- 4.08 (1H, m, H-5') ; 4.19- 4.37 (6H, m, H-2', H-4', H-6' et H-2) ; 4.60 (1H, dd, $J_{3',4'}$ = 7.9Hz, $J_{3',2'}$ = 2.5Hz, H-3') ; 5.53 (1H, d, $J_{1',2'}$ = 5.0Hz ; H-1') ; 7.17- 7.49 (8H, m, H arom.) ; 7.63- 7.68 (2H, m, H arom.). ^{13}C NMR ($CDCl_3$) : 24.4 ; 24.7 ; 25.7 and 25.9 (CH_3) ; 55.5 (CH_2-2) ; 63.6 (CH_2-6') ; 65.8 (CH-5') ; 70.3 ; 70.6 ; 70.9 (CH-2', 3', 4') ; 96.2 (CH-1') ; 108.6 and 109.5 (C acetonides); 127.6 to 130.3 (CH arom.) ; 135.6 and 139.2 (C arom.); 170.4 and 171.9 (C-1 and C=N). IR ($CHCl_3$) : 1740 (C=O), 1630 (C=N). Anal. calc. for $C_{27}H_{31}NO_7$: C, 67.35; H, 6.49; N, 2.91. Found: C, 67.32; H, 6.61; N, 2.68.

Diphenyl-ketiminium chloride, 8.

1) A solution of benzonitrile (distilled on P_2O_5, 21 mL, 0.21 mol) in anhydrous ether (50 mL) was added under reflux to benzenemagnesium bromide (prepared from 6.7 g of Mg, 28.8 mL of bromo-benzene and 100 mL of ether). After refluxing for 4.5h and stirring at rt for 11h, the reaction mixture was hydrolyzed with MeOH (60

mL) and stirring was maintained at rt for 2.5h. After filtration and washing with ether, the solvents were evaporated and the residue distilled to give diphenyl ketimine **7** in 84% yield (31.2 g, 0.172 mol), Eb = 115-116°C/0.5 mm.

2) Diphenyl ketimine **7** (10.1 g, 55.7 mmol) in anhydrous ether (200 mL) was treated by HCl gas at 0°C for 15 min. The excess of HCl was evaporated under a flow of argon. The white precipitate of diphenyl ketiminium chloride[3] **8** was dried overnight, yield 91% (11.1 g, 51.0 mmol).

1,2:5,6-Di-O-isopropylidene-D-glucofuranos-3-yl-(N-diphenylmethylene)-glycinate, 9.

1) 1,2:5,6-Di-O-isopropylidene-D-glucofuranos-3-yl-(N-benzyloxycarbonyl)-glycinate, 5.

To N-benzyloxycarbonyl-glycine[2] **4** (209 mg, 1 mmol) in THF (3 mL) were added, under argon, dicyclohexyl-carbodiimide (249 mg, 1.2 mmol) in THF (1.5 mL), diacetone-D-glucose (312 mg, 1.2 mmol) in THF (6 mL) and 4-dimethylaminopyridine (150 mg, 1.2 eq) in THF (1 mL). After stirring at room temperature for 15h, the reaction mixture was filtered on celite and washed with CH_2Cl_2. After evaporating the solvent, the residue was purified by silica gel chromatography (Φ = 3 cm, eluent: CH_2Cl_2/EtOAc : 90/10) to give the glycinate **5** (299 mg, 0.66 mmol, 66% yield) as a colorless oil, Rf = 0.35. ^{1}H NMR ($CDCl_3$) : 1.30 (6H, s, 2 CH_3) ; 1.39 and 1.51 (6H, 2s, 2 CH_3) ; 3.99-4.18 (6H, m, H-4', H-5', H-6' and H-2) ; 4.51 (1H, d, $J_{1'-2'}$ = 3.6Hz, H-2') ; 5.13 (2H, s, CH_2Ph) ; 5.25-5.38 (2H, m, H-3' and NH), 5.86 (1H, d, $J_{1'-2'}$ = 3.6Hz ; H-1') ; 7.26-7.38 (5H, m, Ph).

The reaction was also carried out on a larger scale : N-benzyloxycarbonyl-glycine (8.37 g, 40 mmol), dicyclohexylcarbodiimide (8.46 g, 41 mmol), diacetone-D-glucose (10.67 g, 41 mmol), 4-dimethylamino-pyridine (5 g, 41 mmol) in THF (60 mL). In this case the chromatographic separation (silica gel, Φ = 7 cm, eluent: CH_2Cl_2/AcOEt : 90/10) of the product **5** and the starting diacetone-D-glucose in excess was rather difficult. We isolated a **2/5** mixture in the ratio 28/72, determined by ^{1}H NMR of the H-1 signal of **2** (d, 5.94 ppm, J = 3.6 Hz) and the H-1' signal of **5** (d, 5.86 ppm, J = 3.6 Hz) and corresponding to 70% yield in compound **5**. Similar mixtures were used in the next step without further purification.

2) 1,2:5,6-Di-O-isopropylidene-D-glucofuranos-3-yl-glycinate, 6.

A 1 to 1 mixture of diacetone-D-glucose and **5** (4.98 g, 7 mmol of **5**) in AcOEt (100mL, dried on molecular sieves) was treated at rt for 2h with hydrogen (30 bars) in presence of 10% Pd/C (0.67 g). After filtration on celite and washing with EtOAc, the solvent was evaporated and the resulting yellow oil (4g, 1/1 mixture of diacetone-D-glucose/**6**) was used without further purification in the next step.

3) 1,2:5,6-Di-O-isopropylidene-D-glucofuranos-3-yl-(N-diphenylmethylene)-glycinate, 9.

The 1/1 mixture of **2/6** (4.0 g, 7.0 mmol of **6**) and diphenyl ketiminium chloride (1.60 g, 7.35 mmol) in CH_2Cl_2 (180 mL) were stirred at rt for 24h. After evaporating the solvent, the residue was purified by chromatography on silica gel (treated by a mixture ether/triethylamine : 95/5) (Φ = 6 cm, eluent: hexane/AcOEt : 80/20) to give glycinate **9** in 88% yield (2.97g, 6.17 mmol) as a colorless oil, Rf = 0.21. $[\alpha]_D$ -26 (c 1, $CHCl_3$). ^{1}H NMR

($CDCl_3$) : 1.26 ; 1.30 ; 1.40 and 1.52 (12H, 4s, 4 CH_3) ; 3.98-4.01 (2H, m, H-6') ; 4.20-4.23 (4H, m, H-4', H-5' and H-2) ; 4.5 (1H, d, $J_{1'-2'}$ = 3.7Hz, H-2') ; 5.32 (1H, d, $J_{3'-4'}$ = 2.2Hz, H-3') ; 5.85 (1H, d, $J_{1'-2'}$ = 3.7Hz, H-1') ; 7.16-7.49 (8H, m, H arom.) ; 7.63-7.68 (2H, m, H arom.). ^{13}C NMR ($CDCl_3$) : 25.0 ; 26.0 ; 26.6 and 26.7 (CH_3) ; 55.3 (CH_2-2) ; 66.9 (CH_2-6') ; 72.2 (CH-4' or 5') ; 76.3 (CH-3') ; 79.6 (CH-5' or 4') ; 83.1 (CH-2') ; 104.7 (CH-1') ; 109.1 and 112.1 (C acetonides) ; 127.5-130.5 (CH arom.) ; 135.6 and 136.9 (C arom.); 169.1 and 172.0 (C-1 and C=N). IR ($CHCl_3$) : 1755 (C=O), 1625 (C=N). Anal.: Calc.for $C_{27}H_{31}NO_7$: C, 67,35; H, 6,49; N, 2.91. Found: C, 67.09; H, 6.52; N, 2.93.

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