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Readily available carbohydrate-derived imines and amides as chiral ligands for asymmetric catalysis

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Abstract—An easy and diastereoseletive strategy for the synthesis of a new tetrahydrofuranic chiral aldehyde and a new tetrahydrofuranic acid derived from D-ribose is reported. These compounds have been shown to be useful starting materials for obtaining a never described before class of iminic- and amidic-carbohydrate-based chiral ligands, endowed with stability to purification on silica flash column and to storage, and characterised by the presence of a stereogenic centre α to the iminic or amidic bond. The first results obtained from the application of these chiral ligands in a model reaction, conjugate addition of Et_2Zn to cyclohexenone, are discussed.

1. Introduction

Carbohydrates are widespread chiral natural products, generally cheap and easily obtainable in pure form.[1,2] Their great variety of functional groups and stereogenic centres allows the regio and stereoselective introduction of different functionalities. As a consequence, carbohydrates are used as chiral reagents in the synthesis of many chemically and biologically interesting products: a great variety of cyclic and linear structures are, in fact, easily obtainable from them.[3] In connection with a program directed to broaden the application of carbohydrates in organic chemistry, we focused our attention on the development of new imine- and amido-carbohydrate-based chiral ligands for asymmetric catalysis.

A great variety of chiral ligands are described in the literature, successfully used in several asymmetric reactions,[4a–f] such as conjugate additions of organometallic reagents on linear and cyclic α–β unsatured compounds, allylic alkylations, Strecker reactions and Diels Alder reactions.[1] They derive from very different substrates[5a–c] but many authors underline the importance of using economic and easily accessible chiral sources for ligands.

Despite ten years of successful studies concerning synthesis and reactivity of ligands in asymmetric induction, a clear understanding of the origin of a pronounced dependence of the enantioselectivity on their electronic properties is still lacking. An empirical approach to the synthesis of good substrates could be a valid instrument in order to develop new chiral ligands, especially for those reactions in which the mechanism of the asymmetric induction is still unknown or poorly understood.[6] This approach finds its driving force in the ability to make systematically structural changes in ligand scaffolding, to produce a broad variety of electronic and stereochemical properties.

Carbohydrates seem to be very suitable for this target. Even if widely used as starting compounds for the synthesis of chiral organic molecules, carbohydrates are still considered exotic as substrates for ligands. Only a few examples are reported in the literature,[7] derived from D-glucose,[8] D-mannose,[6] D-glucosamine[9] and D-xylose.[10]

A variety of iminic and amidic chiral ligands constituted by a chiral amino part and an achiral aldehydic or acidic part can be easily found in the literature.[4f,11] Our innovative work was the synthesis of ligands constituted by a chiral aldehyde or chiral acid from carbohydrates, and an aromatic achiral amine, containing a set of different metal binding sites, with the expectation that such a multidentate array would favour the formation of organometallic complexes with well-organised spatial arrangements.

We found D-ribose as a potential ideal source of substrates for the synthesis of carbohydrates-based chiral ligands. We selected this five-membered ring because of its high rigidity with respect to a six-membered one, such as D-glucose.

Previous studies in our laboratory led us to an original protocol for synthesising new tetrahydrofuran-based chiral aldehydes (Fig. 1), derived from D-hexopyranoses in six

Keywords: carbohydrate-based chiral ligands; imines; amides; asymmetric catalysis.

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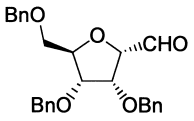
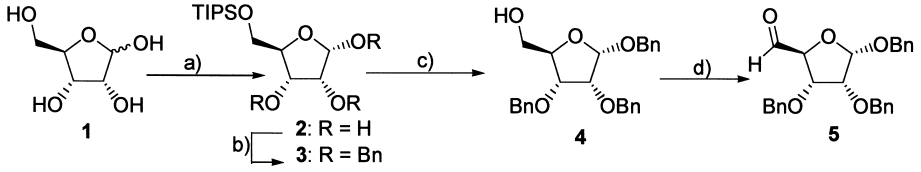


Figure 1.

Et_3N in DMSO. The aldehyde **5** obtained was stable during purification on silica gel and was isolated in good yield as a viscous and air-stable oil. We elected aldehyde **5** as a suitable substrate for the synthesis of new chiral ligands.

Concerning our synthesis, a significant outcome was the



Scheme 1. (a) TIPSCI, DMF, imidazole, 0°C, 80%; (b) NaH, BrBn, DMF, 0°C, 60%; (c) TBAF, THF, 0°C, 98%; (d) SO_3-py, DMSO, Et_3N, 70%.

steps with high yields.[12] However, this way seemed to be too long for our purpose: we needed an easy and rapid synthesis of chiral substrates for ligands in order to synthesise a library of molecules to be tested in several asymmetric reactions involving transition metals.

2. Results and discussion

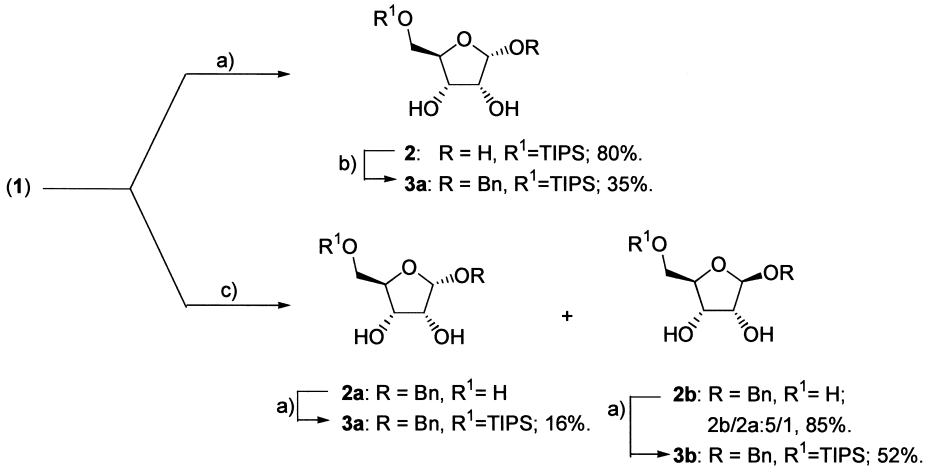
The chiral aldehyde **5** was prepared form D-ribose **1** according to the strategy outlined in Scheme 1.

At first, the regioselective protection of the primary OH group at the C-5 atom was carried out by treatment of D-ribose **1** with triisopropylsilyl chloride (TIPSCl) to give compound **2** in good yield. Interestingly, this protection gave a product in which the α-anomer predominated.

By incorporation of the bulky TIPS protecting group on C-5, an excellent stereoselectivity was obtained in the direct perbenzylation of compound **2**, providing the α-anomer **3** in good yield. The following step was removal of the silyl group by treatment with tetrabutylammoniumfluoride (TBAF) in THF at 0°C for 30 min, with formation of the pure deprotected alcohol **4** in almost quantitative yield. Finally, an efficient oxidation to aldehyde **5** was realised by reaction of the alcohol **4** with the complex SO_3-py and total diastereoselectivity observed in the perbenzylation of **2** to give **3**. In the ^{1}H NMR spectrum of compound **3**, a well resolved doublet at δ=5.06 with a coupling constant $J_{1,2}$=4.4 Hz corresponds to the proton on the anomeric position; moreover ^{13}C NMR spectra exhibit a signal at δ=99.7, corresponding to the anomeric carbon. These data indicate that a pure diastereoisomer **3** was obtained.

In order to assign the stereochemistry of the anomeric position, we compared the compound **3a**, obtained according to our NaH-based protocol for the monobenzylation of the TIPS-5-protected-D-ribose **2** (Scheme 2, route a) with the epimeric compounds **3a** and **3b**, obtained according to a different procedure as shown in Scheme 2, route c. These two diastereoisomers were prepared by a two step sequence from D-ribose: a first acid-catalysed mono-benzylation reaction and then a 5-*O*-protection reaction by TIPSCl. As is well known, in the acid catalysed mono-benzylation reaction of **1**, the β anomer **2b** usually predominates over the α one **2a**.[13a,b]

Then, after the 5-*O*-protection reaction by the TIPS group on the anomeric mixture and separation by flash chromatography of the two epimers **3a** and **3b**, we found a total coincidence of ^{1}H NMR and ^{13}C NMR spectra of the compound **3a** prepared according to the two different routes outlined in Scheme 2. The result clearly indicates that the



Scheme 2. TIPSCI, DMF, 0°C; (b) NaH, BrBn, DMF, 0°C; (c) BnOH, H^+.

formation of the C-1 α anomer on the 5-*O*-protected-D-ribose by the NaH benzylation protocol is a stereocontrolled reaction.

It can be supposed that the anion derived from **2** during the benzylation in basic conditions by the NaH-based protocol exhibits a 4 centre crown ether-like geometry, thus favouring the α-configuration on C-1.[14] (Fig. 2).

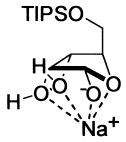
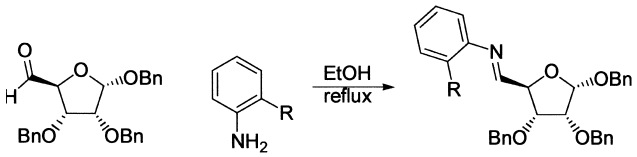


Figure 2.

In fact, whereas for the pyranoses the higher nucleophilicity of the β-oxide can be justified with a stereoelctronic effect resulting from a repulsion of the lone electron pair or from an unfavourable dipole dipole interaction, for furanose substrates steric and chelate effects primarily control the stereochemistry.[15]

The aldehyde **5** reacting with differently functionalised aromatic achiral amines gave a *new class of iminic chiral ligands* **6** (Scheme 3 and Table 1).



5

6a: R = NH_2; 70%.
6b: R = SH; 65%.
6c: R = OH; 30%.
6d: R = OCH_3; 35%.

Scheme 3.

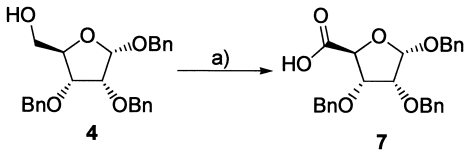
Table 1. Reaction of the aldehyde **5** with aromatic amines

Amine	Product	R	Yield (%)
1,2-Phenylenediamine	**6a**	NH_2	70
2-Aminobenzenethiol	**6b**	SH	65
2-Aminophenol	**6c**	OH	30
2-Methoxyphenylamine	**6d**	OCH_3	35

Interestingly, our synthetic strategy proceeded stereoselectively: we obtained only the *E* double-bound isomer of compounds **6**. Our iminic ligands present important peculiarities:

- They are *unexpectedly stable*: they have been purified by flash chromatography on silica gel column and stored—even for long periods—at low temperature under a nitrogen atmosphere.
- They present a *stereogenic centre α to the iminic double bond* which, together with the N atom, is expected to be responsible for the coordination of transition metal ions in catalytic asymmetric reactions.

Analogously, we used the same versatile synthetic strategy, described above, for the synthesis of the acid **7**, by oxidation of the alcohol **4** with [bis (acetoxy)iodo]benzene (BAIB) and TEMPO[16a,b] in a 1:1 CH_3CN/H_2O solution. (Scheme 4).



4 **7**

Scheme 4. TEMPO, BAIB, CH_3CN/H_2O=1:1, >99%.

The reaction between the acid **7** with differently functionalised aromatic achiral amines was employed for the synthesis of new amidic chiral ligands **8** in high yields, according to a previously described synthetic strategy applied on analogous substrates.[17]

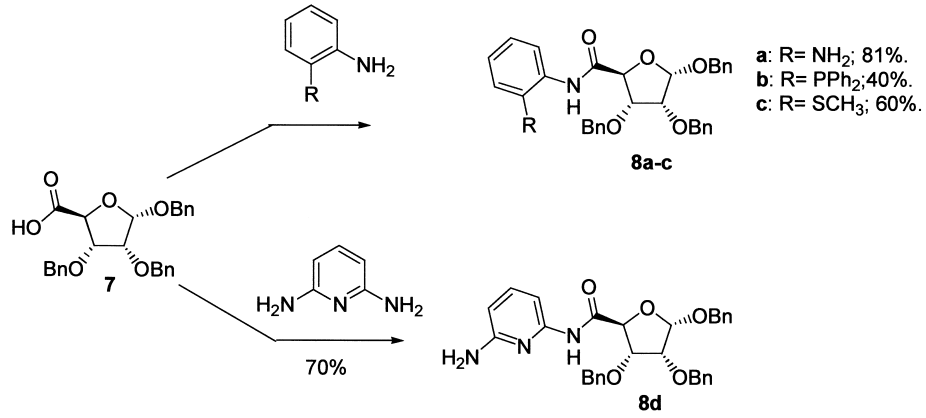
Moreover, we completed our library of amidic chiral ligands through a *one-pot* synthesis of the acid chloride derived from **7** and its subsequent reaction with various aromatic achiral amines (Scheme 5 and Table 2).

According to this protocol we obtained a *new class of amidic chiral ligands* endowed with the same qualities as our iminic ligands in terms of *stability to purification on silica flash coloumn*, *storage* and presence of *a stereogenic centre α to the amidic bond*; moreover they have the advantage of being extremely resistant to attack by strong nucleophilic agents.

In connection with our work devoted to the synthesis of natural substances, such as lignans, via tandem conjugate addition–alkylation to furan-2(*5H*)-one,[18] this new class of ligands has been exploited in the asymmetric Michael addition to a model α,β-unsatured ketone, cyclohexenone. Unfortunately, the attempts of Et_2Zn conjugate addition to cyclohexenone in the presence of such ligands with $Cu(OTf)_2$ as catalyst (5%) gave modest results. We observed the formation of 3-ethylcyclohexanone in high yields (>90%), but we found no significant enantiomeric excess (10–15%) (Scheme 6). However, an important result was the increased efficiency of the catalysis: in the presence of our chiral ligands, the reaction times are reduced even to a half of the time observed in the presence of the $Cu(OTf)_2$ only. In fact, diorganozincs smoothly react with enones in the presence of catalytic amounts of Cu^I salts and cosolvents, such as hexamethylphosphonyltriamide (HMPA) and tetramethylethylenediamine (TMEDA), which co-ordinate to the metal leading to a marked increase in the reactivity of these reagents.[19]

3. Conclusions

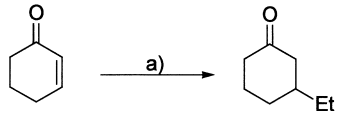
In conclusion, we performed a valid, easy and diastereoselective strategy for the synthesis of a new tetrahydrofuranic chiral aldehyde and a new tetrahydrofuranic acid derived from D-ribose, which have then been converted into a never described before class of chiral ligands, endowed with stability to purification on silica flash column



Scheme 5.

Table 2. Reaction of the acid **7** with aromatic amines

Amine	Reaction conditions	Product	Yield (%)
1,2-Phenylenediamine	(1) EDAC, HOBT, 0°C, DMF/CH_2Cl_2=1/2.5, (2) (*i*-Pr)$_2$NEt, CH_2Cl_2, amine	**8a**	81
2-Diphenylphosphanyl-phenylamine	(1) $(COCl)_2$, CH_2Cl_2, (2) amine, Et_3N, THF	**8b**	40
2-Methylsulfanyl-phenylamine	(1) $(COCl)_2$, CH_2Cl_2, (2) amine, Et_3N, THF	**8c**	60
2,6-Diaminopyridine	(1) $(COCl)_2$, CH_2Cl_2, (2) amine, Et_3N, THF	**8d**	70



Scheme 6. (a) Et_2Zn, $Cu(OTf)_2$, ligand.

and to storage, and characterised by the presence of a stereogenic centre α to the iminic or amidic bond. The results obtained from the application of the new chiral ligands in a model reaction (the Et_2Zn conjugate addition to cyclohexenone) are good in terms of increasing the reaction rate, but the obtained enantiomeric excess was modest. Studies are in progress to exploit our chiral ligand library in other asymmetric reactions, involving different transition metals. It is well known that ligands provided with O, N substituents are suitable to complex early transition metals such as Ti or Zr, while the coordination of late transition metals such as Ni, Cu and Pd is promoted by ligands provided with P or S binding sites.[20]

4. Experimental

4.1. General

Solvents were purified and dried by standard procedures before use. Analytical TLC was performed using silica gel 60 F_{254} plates (Merck). Flash chromatography was executed with Merck Kiesegel 60 (230–400) using a mixture of ethyl acetate and hexane as eluant. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer at room temperature with $CDCl_3$ as solvent and as internal standard. Coupling constants are quoted in Hz. D-Ribose, 1,2-phenylenediamine, 2-aminophenol, 2-aminobenzenethiol, 2-methoxyphenylamine, 2,6-diaminopyridine were utilised as purchased. 2-Diphenylphosphanyl-phenylamine[21] and 2-methylsulfanyl-phenylamine[22] were synthesised and purified according procedures described in the literature. The enantiomeric excess was determined by gas chromatography (HP 5890-GC) using a chiral capillary column with Daetbusililbeta CDX as stationary phase. Optical rotations were measured at 589 nm on a digital DIP-370 polarimeter (using 1 cm and 10 cm microcells).

4.1.1. 5-*O*-Triisopropylsilyl-α-D-ribofuranose 2. Compound **2** was prepared according to the following procedure.[23]

A solution of D-ribose (**1**) (300 mg, 2 mmol) in dry DMF (5 mL) under argon was treated with imidazole (306 mg, 4.5 mmol). The reaction was cooled to 0°C and TIPSCl (307 mg, 1.6 mmol) was added dropwise; after an hour, the same amount of TIPSCl was added again. The reaction mixture was stirred for 4–5 h until all the D-ribose was consumed. After dilution with ethyl acetate (20 mL) the organic layer was washed with water (3×5 mL), brine (2×10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel with hexane/ethylacetate (4:1) to give **2**α/β=7:1 (490 mg, 1.6 mmol, 80%) as a viscous colourless oil. ^{1}H NMR ($CDCl_3$): δ=5.35 (d, 1H, H1-α, J_{1-2}=4.4 Hz), 5.02 (s broad, 1H-β), 4.49 (t, 1H, H3, J_{3-2}=J_{2-3}=5.3 Hz), 4.18–3.52 (m, 7H, 3OH, H4, H2, 2H5), 3.01 (m, 21H, 3($CH(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ=96.97 (C1); 84.57, 71.98, 71.81 (C2, C3, C4), 63.97 (C5), 18.07, 11.95 [$CH(CH_3)_2$]. IR ($CHCl_3$): ν_{max}=3410 cm^{-1} (O–H); 2900 cm^{-1} [$CH(CH_3)_2$]. Anal. calcd for $C_{14}H_{30}O_5Si$: C, 54.87% H, 9.87%. Found: C, 54.85% H, 9.89%.

4.1.2. 5-*O*-Triisopropylsilyl-1,2,3-tri-*O*-benzyl-α-D-ribofuranose 3. In a 50 mL flamed three necked flask the compound **2** (1.00 g, 3.26 mmol) was dissolved in dry

DMF (12 mL) and cooled to 0°C under argon. NaH (314 mg, 13.04 mmol) was added portionwise throughout the solution. After stirring for 10 min, BrBn (1.55 mL, 13.04 mmol) was added and the reaction mixture was stirred for 3 h at 0°C. The reaction was quenched by addition of CH_3OH (5 mL) and diluted with hexane (50 mL). The organic layer was washed with water (3×10 mL), brine (2×10 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography using hexane/ethylacetate (25:1) as eluent to give **3** (12.270 g, 2.12 mmol, 65%) as colourless viscous oil. ^{1}H NMR ($CDCl_3$): δ=7.52–7.28 (m, 15H, Ph), 5.06 (d, 1H, H1, J_{1-2}=4.4 Hz), 4.97–4.47 (m, 6H, $3CH_2Ph$), 4.24 (dd, H3, J_{3-4}=3.3 Hz, J_{3-2}=6.6 Hz), 4.03 (dd, 1H, H4, J_{4-3}=3.3 Hz, J_w=6.4 Hz), 3.82 (dd, 1H, H2, J_{2-1}=4.4 Hz, J_{2-3}=6.6 Hz), 3.65 (d, 2H, H5, J_{5-4}=3.5 Hz), 1.01 (m, 21H, $3CH(CH_3)_2$) ^{13}C NMR: δ=138.74, 138.53, 138.18, (C_{quat}Ph), 128.44, 128.38, 128.32, 128.20, 128.15, 127.94, 127.79, 127.64, 127.47 (Ph), 99.7 (C1), 84.01, 78.26, 75.54 (C2, C3, C4), 72.48, 72.34, 68.88 ($3CH_2Ph$), 63.94 (C5); 18.07, 12.00 [$CH(CH_3)_2$]. ν_{max}=2945 cm^{-1} [$CHCH_3)_2$]; 1119 cm^{-1}, 1036 cm^{-1} (CO–C). $[\alpha]_D^{20}$=+73.3° (*c* 2.44, $CHCl_3$). Anal. calcd for $C_{35}H_{48}O_5Si$: C, 72.88% H, 8.39%. Found: C, 72.89% H, 8.36%.

4.1.3. 1-*O*-Benzyl-5-*O*-triisopropylsilyl-α-D-ribofuranose 3a and 1-*O*-benzyl-5-*O*-triisopropylsilyl-β-D-ribofuranose 3b. 3a (basic conditions): in a 50 mL flamed three necked flask, the compound **2** (1.00 g, 3.26 mmol) was dissolved in dry DMF (8 mL) and cooled to 0°C under argon. NaH (94 mg, 3.91 mmol) was added portionwise to the solution. After stirring for 10 min, BrBn (0.5 mL, 3.91 mmol) was added and the reaction mixture was stirred for 3 h at 0°C. The reaction was quenched by addition of CH_3OH (5 mL) and diluted with *n*-hexane. The organic layer was washed with water (3×10 mL), brine (2×10 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography: after eluting byproducts with hexane/ethylacetate=10:1, we obtained 453 mg (1.41 mmol, 35%) of **3a**, as colourless oil, using hexane/ethylacetate=7:1 as eluent.

^{1}H NMR ($CHCl_3$): δ=7.36–7.28 (m, 5H, Ph), 5.12 (d, 1H, H1, J_{1-2}=4.4 Hz), 4.75 (d, 1H, J_{AB}=11.2 Hz), 4.74 (d, 1H, J_{A-B}=11.2 Hz), 4.24–4.03 (m, 3H, H2, H3, H4), 3.9–3.8 (m, 2H, 2H5), 2.96 (s broad, 1H, OH), 2.93 (s broad, 1H, OH), 1.15–1.01 (m, 21H, $3CH(CH_3)_2$). ^{13}C NMR: δ=136.46 (C_{quat}Ph), 128.65, 128.63, 128.06 (Ph), 101.20 (C1), 86.23, 72.25, 71.40 (C2,C3,C4), 69.71 (CH_2Ph), 63.87 (C5), 18.02, 12.01 [$CH(CH_3)_2$]. Anal. calcd for $C_{21}H_{36}O_5Si$: C, 63.60% H, 9.16%. Found: C, 63.57% H, 9.19%.

3a and **3b** (acid conditions): to a stirred solution of D-ribose (2 g, 13.33 mmol) dissolved in neat benzylic alcohol (60 mL, 580.56 mmol, *d*=1.045 g/mL), a 37% solution of HCl (1.4 mL, 16.80 mmol) was added dropwise. The mixture was stirred at room temperature for 12 h. The excess of benzylic alcohol is removed by distillation under reduced pressure.[13] The crude product is finally purified via flash chromatography on silica gel (EtOAc first, then $CHCl_3$/EtOAc=3:1) to give 2.71 g (3.85 mmol) of **2b/2a**=5/1 mixture in 85% overall yield, as viscous oil. The ratio was assigned by ^{1}H NMR spectroscopy: δ_H (CD_3OD)=5.03 (d, 1H-β, J_{1-2}=0.7 Hz), 5.12 (d, 0.2 H-α, J_{1-2}=4.4 Hz). The mixture was used in the next reaction. In a 25 mL flamed three necked flash, the **2a/2b** mixture (2.71 g, 3.85 mmol) was dissolved in 10 mL of dry DMF, under nitrogen atmosphere.

When the substrate was completely dissolved under stirring, imidazole (590 mg, 8.66 mmol) was added portionwise. Then the stirred solution was cooled to 0°C under nitrogen atmosphere and TIPSCl (591 mg, 3.08 mmol) was dropped during 10 min. After 1 h an identical amount of TIPSCl was added to the stirred solution, always kept at 0°C under nitrogen atmosphere.

The reaction is completed within 4.5 h, as revealed by TLC chromatography.

The mixture was poured into a separating funnel, diluted with EtOAc (150 mL) and washed with H_2O until neutrality (3×10 mL), finally with brine (2×10 mL). The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash chromatography on 10 g of silica gel column to give 776 mg (1.96 mmol, 52%) of **3b**, as colourless oil, eluted with *n*-hexane/EtOAc=8:1, and 250 mg (0.62 mmol, 16%) of **3a**, as colourless oil, eluted with *n*-hexane/EtOAc=7:1.

3b: ^{1}H NMR ($CDCl_3$): δ=7.43–7.21 (m, 5H, Ph), 5.03 (d, 1H, H1, J_{1-2}=0.7 Hz), 4.63 (d, 1H, J_{AB}=11.7 Hz), 4.62 (d, 1H, J_{AB}=11.7 Hz), 4.43 (q broad, 1H), 4.14 (s broad, 1H), 4.07–3.72 (m, 3H, 2H5, H2), 3.12 (s broad, 1H, OH), 2.74 (s broad, 1H, OH), 1.15–1.01 (m, 21H, $3CH(CH_3)_2$). ^{13}C NMR: δ=136.78 (C_{quat}arom), 128.49, 128.06, 127.86 (Ph.), 106.33 (C1), 83.16, 75.48, 73.48 (C2, C3, C4), 69.43 (CH_2Ph), 65.45 (C5), 18.05, 11.98 [$CH(CH_3)_2$].

Anal. calcd for $C_{21}H_{36}O_5Si$: C, 63.60% H, 9.16%. Found: C, 63.57% H, 9.19%.

4.1.4. 1,2,3-Tri-*O*-benzyl-α-D-ribofuranose 4.[24] A solution of TBAF 1 M in THF (1.3 mL, 1.3 mmol) was added at 0°C to a solution of **3** (501 mg, 0.87 mmol) in dry THF (5 mL) under argon and the reaction mixture was stirred for about 1 h until the starting material was consumed. After dilution with ethyl acetate (20 mL), the organic layer was washed with water (3×10 mL), brine (2×10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel with hexane/ethylacetate (7:1) as eluent to give 256 mg of **4** (0.845 mmol, 98%), as viscous oil. ^{1}H NMR ($CDCl_3$): δ=7.50–7.28 (m, 15H, Ph), 5.1 (d, 1H, H1, J_{1-2}=4.4 Hz), 4.24 (dd, 1H, H3, J_{3-2}=7.3 Hz, J_{3-4}=3.7 Hz), 3.9 (dd, 1H, H2, J_{2-1}=4.4 Hz, J_{2-3}=7.3 Hz), 3.8–3.65 (m, 2H, H5), 3.48 (dd, 1H, H4, J_{4-3}=3.7 Hz, J_w=12.5 Hz). ^{13}C NMR ($CDCl_3$): δ=138.47, 138.02 (C_{quat}Ph), 128.49, 128.42, 128.26, 128.18, 127.96, 127.88, 127.83, 127.71 (Ph), 99.84 (C1), 83.07, 78.18, 75.24 (C2, C3, C4), 72.75, 72.59, 69.05 [$3CH_2Ph$], 62.72 (C5). Anal. calcd for $C_{26}H_{28}O_5$: C, 74.25% H, 6.72%. Found: C, 74.29% H, 6.66%.

4.1.5. 1,2,3-Tri-*O*-benzyl-α-D-ribo-pentodialdo-1,4-furanose 5. Alcohol **4** (150 mg, 0.36 mmol) was dissolved in dry DMSO (1.5 mL) and then Et_3N (1.5 mL) and the complex

SO_3-py (273 mg, 1.7 mmol) were added; the reaction mixture was stirred for 30 min. After dilution with ethyl acetate (20 mL), the organic layer was washed with water (3×10 mL), brine (2×10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel with *n*-hexane/ethylacetate (3:1) as eluent to give 106 mg of **5** (0.25 mmol, 70%), as colourless viscous oil. ^{1}H NMR ($CDCl_3$): δ=9.45 (d, 1H, CHO), 7.46–7.20 (m, 15H, Ph), 5.11 (d, 1H, H1, J_{1-2}=4.4 Hz), 4.90–4.47 (m, 7H, H3, $3CH_2Ph$), 3.95 (d, 1H, H4, J_{4-2}=6.6 Hz, J_{4-3}=2.9 Hz), 3.60 (dd, 1H, H2, J_{2-1}=4.4 Hz, J_{2-3}=6.6 Hz). ^{13}C NMR ($CDCl_3$): δ=199.6 (CHO), 128.47, 128.40, 128.15, 128.00, 127.91, 127.76 (Ph), 100.01 (C1), 87.18, 77.38, 74.98 (C2, C3, C4), 72.52, 72.48, 69.45 ($3CH_2Ph$). IR ($CHCl_3$): ν_{max}=2700–2820 cm^{-1} (CO–H), 1720 cm^{-1} (CO). $[\alpha]_D^{20}$=+53.2° (*c* 3.1, $CHCl_3$). Anal. calcd for $C_{26}H_{26}O_5$: C, 74.61% H, 6.27%. Found: C, 74.59% H, 6.28%.

4.2. General procedure for the synthesis of imines

Imines **6a**, **6b**, **6c** and **6d** were prepared according to the following procedure.

Amine (0.19 mmol) was added to a solution of **5** (100 mg, 0.24 mmol) in absolute ethanol (10 mL) and the reaction mixture was stirred at 100°C for 24 h. For the work-up, the solution was concentrated in vacuo and purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate).

4.2.1. 5-Deoxy-5-(2′-amino-phenyl-imino)-1,2,3-tri-*O*-benzyl-α-D-ribofuranose 6a. From 1,2-phenylenediamine (21 mg, 0.19 mmol): 73 mg, 0.14 mmol, (70%), colourless oil. ^{1}H NMR ($CDCl_3$): δ=7.58–7.23 (m, 19H, Ph), 5.44 (d, 1H, H5, J_{5-4}=3.7 Hz), 5.27 (d, 1H, H1, J_{1-2}=4.4 Hz), 5.01–4.51 (m, 9H, H4, $3CH_2Ph$, NH_2), 4.37 (dd, 1H, H3, J_{3-4}=4.51 Hz, J_{3-2}=6.6 Hz), 3.90 (dd, 1H, H2, J_{2-1}=4.4 Hz, J_{2-3}=6.6 Hz). ^{13}C NMR ($CDCl_3$): δ=152.34 (C5), 137.77, 137.60, 136.80 (C_{quat}Ph), 128.68, 128.44, 128.21, 127.94, 126.85, 122.96 (Ph), 100.32 (C1), 79.46, 78.96, 77.29 (C2, C3, C4), 74.47, 72.77, 69.64 ($3CH_2Ph$). IR ($CHCl_3$): ν_{max}=1653 cm^{-1}.

Anal. calcd for $C_{32}H_{32}O_4N_2$: C, 75.56% H, 6.35% N, 5.51%. Found: C, 75.59% H, 6.32% N, 5.50%.

4.2.2. 5-Deoxy-5-(2′-mercapto-phenyl-imino)-1,2,3-tri-*O*-benzyl-α-D-ribofuranose 6b. From 2-aminobenzenethiol (24 mg, 0.19 mmol): 68 mg, 0.13 mmol (65%), colourless oil. ^{1}H NMR ($CDCl_3$): δ=8.14–7.15 (m, 19H, Ph), 5.61 (d, 1H, H5, J_{5-4}=2.93 Hz), 5.30 (d, 1H, H1, J_{1-2}=4.4 Hz), 5.07–4.47 (m, 7H, H3, $3CH_2Ph$), 4.24 (dd, 1H, H4, J_{3-4}=6.6 Hz, J_{4-5}=2.9 Hz), 3.93 (dd, 1H, H2, J_{1-2}=4.4 Hz, J_{2-3}=6.6 Hz). ^{13}C NMR ($CDCl_3$): δ=153.88 (C5), 137.77, 137.68, 137.42 (C_{quat}Ph), 128.59–121.84 (9C, Ph), 100.31 (C1), 83.07, 79.41, 77.29 (C2, C3, C4), 72.49, 72.31, 69.47 ($3CH_2Ph$). IR ($CHCl_3$): ν_{max}=1655 cm^{-1}.

Anal. Calcd for $C_{32}H_{31}NO_4S$: C, 73.12% H, 5.95% N, 2.67%. Found: C, 73.09% H, 5.92% N, 2.64 %.

4.2.3. 5-Deoxy-5-(2′-hydroxy-phenyl-imino)-1,2,3-tri-*O*-benzyl-α-D-ribofuranose 6c. From 2-aminophenol (21 mg, 0.19 mmol): 31 mg, 0.06 mmol (30%), colourless oil. ^{1}H NMR ($CDCl_3$): δ=9.58 (s, 1H, OH), 7.58–6.67 (m, 19H, Ph), 5.35 (d, 1H, H5, J_{5-4}=2.93 Hz), 5.16 (d, 1H, H1, J_{1-2}=4.4 Hz), 5.2–4.3 (m, 7H, H3, $3CH_2Ph$), 4.00 (dd, 1H, H4, J_{4-5}=2.9 Hz), 3.64 (dd, 1H, H2, J_{1-2}=4.4 Hz). ^{13}C NMR ($CDCl_3$): δ=152.83 (C5), 138.68, 136.23 (C_{quat}Ph), 130.59–120.79 (Ph), 100.11 (C1), 82.72, 79.81, 77.29 (C2, C3, C4), 72.38, 72.21, 69.17 ($3CH_2Ph$). IR ($CHCl_3$): ν_{max}=1657 cm^{-1}. Anal. calcd for $C_{32}H_{31}NO_5$: C, 75.41% H, 6.14% N 2.75%. Found: C, 75.39% H, 6.17% N, 2.70%.

4.2.4. 5-Deoxy-5-(2′-methoxy-phenyl-imino)-1,2,3-tri-*O*-benzyl-α-D-ribofuranose 6d. From 2-methoxyphenylamine (24 mg, 0.19 mmol): 35 mg, 0.07 mmol (35%), colourless oil. ^{1}H NMR ($CDCl_3$): δ=7.70–6.67 (m, 19H, Ph), 5.52 (d, 1H, H5, J_{5-4}=4.4 Hz), 5.06 (d, 1H, H1, J_{1-2}=4.4 Hz), 4.75–3.68 (m, 9H, H2, H3, H4, $3CH_2Ph$), 3.98 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ=153.68 (C5), 139.60, 138.68, 136.23, (C_{quat}Ph), 131.57–120.12 (Ph), 100.23 (C1), 84.72, 79.61, 77.39 (C2, C3, C4), 72.58, 72.21, 69.74 ($3CH_2Ph$), 55.8 (OCH_3). IR ($CHCl_3$): ν_{max}=1652 cm^{-1}. Anal. calcd for $C_{33}H_{33}NO_5$: C, 75.68% H, 6.36% N, 2.68%. Found: C, 75.70% H, 6.34% N, 2.65%.

4.2.5. 1,2,3-Tri-*O*-benzyl-α-D-ribofuranuronic acid 7. Compound **4** (237 mg, 0.562 mmol), TEMPO (18 mg, 0.112 mmol) and BAIB (398 mg, 1.232 mmol) were dissolved in CH_3CN/H_2O=1:1 (2 mL) and the reaction mixture stirred at room temperature until the starting material was consumed. After stirring at room temperature for half an hour, the reaction mixture was worked up at 0°C by adding HCl 2N (2 mL); the solution was diluted with diethyl ether (20 mL), washed with water (3×10 mL), then brine (2×10 mL), dried over Na_2SO_4 and evaporated in vacuo, giving **7** as a pure colourless oil in quantitative yield ^{1}H NMR ($CDCl_3$): δ=10.08 (s, 1H, COOH), 7.76 (d, 3H, Ph), 7.51–7.12 (m, 12H, Ph), 5.24 (d, 1H, H1, J_{1-2}=4.6 Hz), 4.99–4.52 (m, 7H, H3, $3CH_2Ph$), 4.12 (dd, 1H, H4, J_{4-3}=6.2 Hz, J_w=2.6 Hz), 3.78 (dd, 1H, H2, J_{2-1}=4.6 Hz, J_{2-3}=5 Hz). ^{13}C NMR ($CDCl_3$): δ=174.66 (CO), 137.62, 137.59, 137.45, 137.41, 130.34, 128.61, 128.52, 128.44, 128.34, 128.24, 128.15, 128.01, 127.91, 127.80, 127.56 (Ph), 100.13 (C1), 81.08, 76.94, 72.45 (C2, C3, C4), 72.25, 69.53, 65.95 ($3CH_2Ph$). IR ($CHCl_3$): ν_{max}=3300–2500 cm^{-1} (O–H); 1710 cm^{-1} (CO). $[\alpha]_D^{20}$=+40.0° (*c* 3.4, $CHCl_3$). Anal. calcd for $C_{26}H_{26}O_6$: C, 71.86% H, 6.04%. Found: C, 71.90% H, 6.02%.

4.3. General procedures for the synthesis of amides

Compound **8a** was prepared according to the following procedure.[17]

Compound **7** (114 mg, 0.26 mmol) was dissolved in dry DMF/CH_2Cl_2 (1:2, 6 mL) and then EDAC (61 mg, 0.314 mmol) and HOBT (42 mg, 0.312 mmol) were added at 0°C under argon; after half an hour, diisopropylethylamine (0.14 mL, 2.4 equiv.) in CH_2Cl_2 (2 mL) and 1,2-phenylenediamine (22 mg, 0.208 mmol) were added and the reaction mixture stirred until **7** was consumed. The solution was worked up at 0°C by adding HCl 0.5N (1 mL); then was diluted with diethyl ether (20 mL), washed with water

(3×10 mL), brine (2×10 mL), dried over Na_2SO_4, concentrated in vacuo and purified by flash chromatography on column giving the corresponding amide as a colourless oil.

Compounds **8b**–**8d** were prepared according to the following procedure.[25a,b,c]

To a solution of **7** (140 mg, 0.321 mmol) in dry solvents (4 mL) was added oxalyl chloride (0.2 mL, 0.321 mmol) and the reaction mixture was stirred at room temperature for 12 h under argon. After this time, the solvent was evaporated in vacuo and the residue dissolved in dry THF (4 mL). Amine (0.321 mmol) and dry Et_3N (0.1 mL) were added at room temperature and the reaction mixture was stirred overnight. After dilution with CH_2Cl_2 (20 mL), the organic layer was washed with water (3×10 mL), brine (2×10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel to give the corresponding amides as colourless oils. Yields were calculated after purification.

4.3.1. *N*-(2′-Amino-phenyl)-1,2,3-tri-*O*-benzyl-α-D-ribofuranuronamide 8a. From 2-phenylenediamine: 81% yield, colourless oil. ^{1}H NMR ($CDCl_3$): δ=7.97 (s, 1H, NH), 7.5–6.67 (m, 17H, Ph, NH_2), 5.11 (d, 1H, H1, J_{1-2}=4.2 Hz), 4.9–4.67 (m, 5H, H3, J_{3-2}=6.8 Hz, J_{3-4}=2.5 Hz, CH_2Ph, 4.44 (dd, 2H, CH_2Ph, J_{A-B}=12.5 Hz), 4.12 (dd, 1H, H4, J_{3-4}=2.5 Hz, J_W=6.5 Hz), 3.65 (dd, 1H, H2, J_{2-1}=4.4 Hz, J_{2-3}=6.8 Hz). ^{13}C NMR ($CDCl_3$): δ=168.53 (CO), 137.65, 128.98, 128.48, 128.38, 128.14, 127.98, 127.91, 127.85, 127.39, 124.83 (Ph), 118.44, 100.22, 83.45, 77.75, 77.07 (C2, C3, C4), 72.24, 71.69, 69.58 ($3CH_2Ph$). IR ($CHC1_3$): ν_{max}=1678 cm^{-1} Anal. calcd for $C_{32}H_{32}O_5N_2$: C, 73.26% H, 6.15% N, 5.34%. Found: C, 73.29% H, 6.11% N, 5.32%.

4.3.2. *N*-(2′-Diphenylphosphanyl-phenyl)-1,2,3-tri-*O*-benzyl-α-D-ribofuranuronamide 8b. From 2-diphenylphosphanyl-phenylamine: 40% yield, colourless oil. ^{1}H NMR ($CDCl_3$): δ=9.41 (d, 1H, NH), 8.2 (m, 1H, Ph), 7.5–6.9 (m, 28H, Ph), 5.21 (d, 1H, H1, J_{1-2}=3.3 Hz), 4.91–4.66 (dd, 2H, CH_2Ph, J_{AB}=12.3 Hz), 4.54–4.42 (m, 5H, H3, J_{3-2}=3.8 Hz, J_{3-4}=4.6 Hz, CH_2Ph), 4.18 (dd, 1H, H4, J_{4-3}=4.6 Hz, J_w=4.6 Hz), 3.74 (dd, 1H, H2, J_{2-1}=3.3 Hz, J_{2-3}=3.8 Hz). ^{13}C NMR ($CDCl_3$): δ=169.18 (CO), 137.77, 137.29, 134.16, 133.89, 133.77, 133.52, 130.23, 129.27, 128.99, 128.88, 128.74, 128.62, 128.45, 128.18, 128.11, 127.85, 125.27, 122.17 (Ph), 106.32 (C1), 81.95, 81.05, 80.08 (C2, C3, C4), 72.65, 72.45, 71.27 ($3CH_2Ph$). IR ($CHCl_3$): ν_{max}=1675 cm^{-1} Anal. calcd for $C_{44}H_{40}NO_5P$: C, 76.16% H, 5.81% N, 2.02%. Found: C, 76.19% H, 5.82% N, 2.01%.

4.3.3. *N*-(2′-Methylsulfanyl-phenyl)-1,2,3-tri-*O*-benzyl-α-D-ribofuranuronamide 8c. From 2-methylsulfanyl-phenylamine: 60% yield, colourless oil. ^{1}H NMR ($CDCl_3$): δ=9.23 (s, 1H, NH), 8.26 (dd, 1H, Ph), 7.58–7.03 (m, 18H, Ph), 5.24 (d, 1H, H1, J_{1-2}=4.4 Hz), 4.99–4.76 (m, 5H, H3, J_{3-2}=6.6 Hz, J_{3-4}=2.8 Hz), 4.64–4.44 (dd, 2H, CH_2Ph, J_{AB}=12.4 Hz), 4.19 (dd, 1H, H4, J_{4-3}=2.8 Hz, J_w=6.6 Hz), 3.73 (dd, 1H, H2, J_{2-1}=4.4 Hz, J_{2-3}=6.6 Hz), 2.25 (s, 3H, SCH_3). ^{13}C NMR ($CDCl_3$): δ=168.27 (CO), 137.77, 137.45, 137.13, 132.42, 128.88, 128.68, 128.49, 128.39, 128.21, 127.95, 127.89, 127.83, 126.50, 125.06, 120.75 (Ph), 100.34 (C1), 83.66, 77.35, 76.91 (C2, C3, C4), 72.24, 71.74, 69.69 ($3CH_2Ph$). IR ($CHC1_3$): ν_{max}=1679 cm^{-1} Anal. calcd for $C_{33}H_{33}NO_5S$: C, 71.32% H, 5.99% N, 2.52%. Found: C, 72.59% H, 6.25% N, 2.50%.

4.3.4. *N*-(6′-Amino-pyridin-2′-yl)-1,2,3-tri-*O*-benzyl-α-D-ribofuranuronamide 8d. From 2,6-diaminopyridine: 70% yield, colourless oil. ^{1}H NMR ($CDCl_3$): δ=8.53 (s, 1H, NH), 7.51–7.25 (m, 19H, Ph); 6.34 (d, 1H, Ph), 5.27 (d, 1H, H1, J_{1-2}=3.2 Hz), 4.94–4.72 (dd, 2H, CH_2Ph, J_{AB}=11.6 Hz), 4.64–4.5 (m, 5H, H3, J_{2-3}=4.5 Hz, J_{3-4}=4.5 Hz, $2CH_2Ph$), 4.33 (dd, 1H, H4, J_{3-4}=4.5 Hz, J_w=4.5 Hz), 4.29 (s broad, 2H, NH_2), 3.86 (dd, 1H, H2, J_{1-2}=3.2 Hz, J_{2-3}=4.5 Hz). ^{13}C NMR ($CDCl_3$): δ=169.36 (CO), 157.19 (C1′), 148.98, 140.17 (C3′), 137.68, 137.62, 137.03, 128.52, 128.33, 128.19, 128.07, 127.94 (Ph), 106.84, 104.75 (C2′, C4′), 103.13 (C1), 82.21, 81.33, 80.42 (C2, C3, C4), 72.80, 72.59, 71.46 ($3CH_2Ph$). IR ($CHCl_3$): ν_{max}=1680 cm^{-1} Anal. calcd for $C_{31}H_{31}N_3O_5$: C, 70.80% H, 5.94% N, 8.00%. Found: C, 70.83% H, 5.92% N, 7.98%.

4.3.5. $ZnEt_2$ Michael addition to cyclohexenone. The conjugate addition to cyclohexenone was performed according to the following procedure.[4e] A solution of $Cu(OTf)_2$ (14 mg, 0.039 mmol) and a ligand **6a**–**d** or **8a**–**d** (0.039 mmol) in dry toluene (5 mL) was stirred for half an hour at room temperature under argon. The solution was cooled to −20°C and cyclohexenone (75 mg, 0.78 mmol) followed by Et_2Zn (213 mg, 1.72 mmol) were added dropwise. After stirring for 5 h at −20°C, the reaction mixture was worked up. After addition of ethyl acetate (20 mL), the organic layer was washed with water (3×10 mL), then with brine (2×10 mL), dried over Na_2SO_4 and concentrated. An aliquot of the organic layer was analysed by GC.

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