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# Stereoselective U-4CRs with 1-amino-5-desoxy-5-thio-2,3,4-*O*-isobutanoyl-β-D-xylopyranose—an effective and selectively removable chiral auxiliary

Günther F. Ross, Eberhardt Herdtweck and Ivar Ugi*

*Organische Chemie 1, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany*

Dedicated to M. Bodanszky

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**Abstract**—The Ugi four component reaction (U-4CR) offers a short and direct route for the synthesis of α-amino acid and peptide derivatives. With 1-amino-5-desoxy-5-thio-2,3,4-*O*-isobutanoyl-β-D-xylopyranose as a chiral amine component excellent chemical yields and stereoselectivities are obtained. After the U-4CR the chiral auxiliary can be cleaved off selectively under mild conditions. The configuration of one of the products was confirmed by X-ray analysis. © 2002 Published by Elsevier Science Ltd.

## 1. Introduction

The four component reaction of isocyanides (U-4CR) was introduced in 1959, and it was shortly later recognized that it is also possible to prepare derivatives of α-amino carboxylic acids by stereoselective U-4CRs.[1–3] In the early 1960s it was realized that such stereoselective U-4CRs can best be accomplished by using suitable chiral primary amine components.[4–6]

The reaction mechanism of a stereoselective U-4CR was determined in 1967, and it was found that four pairs of reaction mechanisms compete, so that one product or the other one can preferentially be formed. Even in the same solvent and at the same temperature one or the other diastereomeric product can be formed, just by using different concentrations of the educts. These results were obtained from experimental and mathematically oriented combinatorial investigations.[3,7]

To carry out a U-4CR, it is generally advantageous to precondense the carbonyl compound **1** and the chiral primary amine **2** into the imine **3** (Fig. 1). This is mixed with the isocyanide **4** and the carboxylic acid **5**. Thereby the α-adduct **6** is formed. This rearranges irreversibly into the α-amino carboxylic acid derivative **7**.

In the course of the reaction two peptide bonds and one carbon–carbon bond are formed and a new chiral center is created.

In 1966 Bodanszky and Ondetti mentioned the potential preparative advantages of U-4CRs for the preparation of α-amino acid and peptide derivatives.[8] Especially if products contain α-amino acids, which cannot be obtained

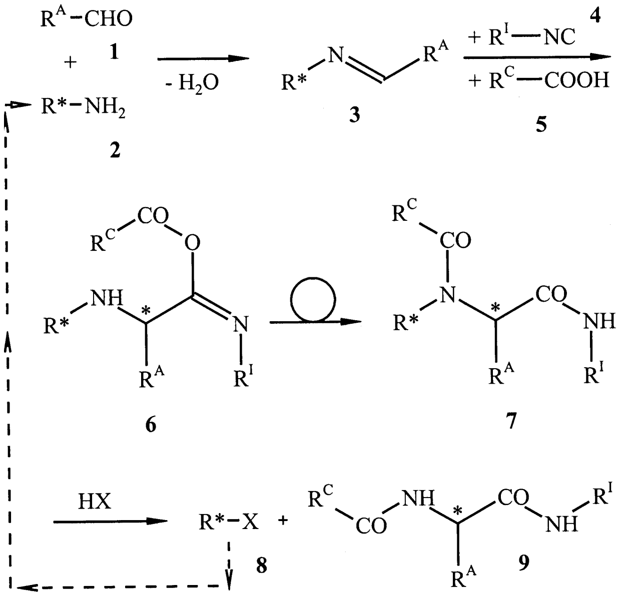

**Figure 1.** Synthesis of α-amino carboxylic acid derivatives by a stereoselective Ugi four component reaction with a chiral amine component **2**. The chiral auxiliary **R*** should be cleaved off and regenerated after the synthesis.

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*Keywords*: stereoselective Ugi four component reaction; chiral auxiliary; chiral amine component; amino thiocarbohydrate; α-amino acid derivatives.

* Corresponding author. Tel.: +49-89-289-13229; fax: +49-89-289-13249; e-mail: ivar.ugi@ch.tum.de

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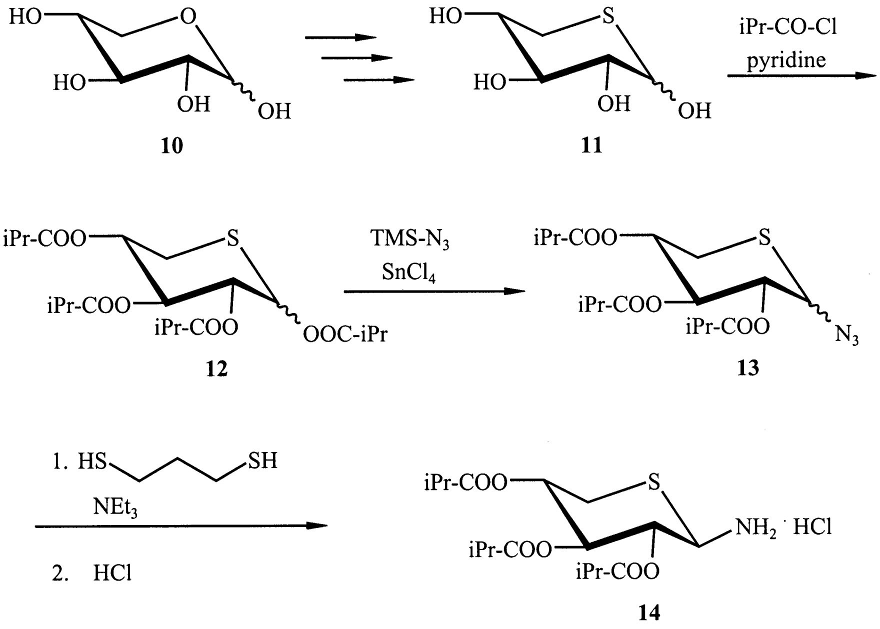

**Figure 2.** Synthesis of 1-amino-5-desoxy-5-thio-2,3,4-*O*-isobutanoyl-β-D-xylopyranose hydrochloride **14**.

from easily available natural sources or biochemical procedures, the application of U-4CRs would be advantageous.

For the synthesis of chiral α-amino acid derivatives by stereoselective U-4CRs it is most reasonable to use a chiral amine component. Then the chiral template is covalently bound in close vicinity to the newly synthesized chirality center. The amine residue **R**$^*$ of the product **7** must be removable under mild conditions such that the desired final product **9** is not destroyed.

A chiral amine component of the U-4CR has ideal properties if all of the following conditions are fulfilled: the amine component must form the desired diastereomeric products exclusively or at least with very high stereoselectivity and excellent yields of very pure products. The chiral auxiliary must be selectively cleavable from the product under mild conditions. The ideal compound should be readily available and a resynthesis of the chiral amine component from its cleavage product (**8**→**2**) would be desired.

For best results the most suitable solvent, optimal concentrations of educts and a Lewis-acid catalyst must be used at the optimal temperature.

More than 40 years ago, the search for a suitable amine component began. Since 1969 efficient way of preparing chiral α-ferrocenylalkylamines were developed and it was found that some of them have in principle all desired properties, but overall these amines were not sufficiently stereoselective (up to 76% de) and had too low final yields (30–40%).[5,6,9] Therefore, the development of the α-ferrocenylalkylamines was given up.[10]

In 1988 Kunz et al.[11] introduced per-*O*-pivaloyl pyranosylamines as chiral amine components for the U-4CR. In the presence of zinc chloride etherate the condensations proceeded with high stereoselectivity in excellent yields. If formic acid was used as the acid component ($R^C$=H), deformylation and cleavage of the chiral auxiliary could be achieved under mild acidic conditions. In a subsequent *N*-acylation step products identical to the U-4CR products **9** ($R^c$ presumably not H) were obtained. This methodology avoids the harsh conditions necessary to cleave *N*-acylated and thereby deactivated *N*-glycosides by switching to a two step process via the readily cleavable formamide. Recently this research group has also reported the use of *O*-acylpyranosylamine derivatives in U-4CRs[12] on solid support.

In 1994 Goebel et al.[13] accomplished high stereoselectivities (up to 98% de) and high yields by using per-*O*-alkylated pyranosylamines. But these chiral templates could still not be removed under sufficiently mild conditions to obtain the desired end products directly.

Lehnhoff et al.[14] produced a great collection of U-4CR products of the 1-amino-2-deoxy-2-*N*-acetyl-3,4,6-tri-*O*-acetyl-β-D-glucopyranose. However, also in these cases no satisfactory cleavage of the chiral auxiliary could be achieved.

Zychlinski et al.[15] performed U-4CRs with an amine component derived from xylopiperidinose, in which the endocylic O-atom was replaced by an acetylated N-atom. This auxiliary group could already be removed in neutral solutions. Since the synthesis of these amine components required a minimum of 11 steps, and since its products were not sufficiently stable, this chemistry was not optimal.

The previous development of various chiral amine components led to the assumption, that pyranosylamines in U-4CRs generally give excellent yields and stereoselectivities, especially in the presence of Lewis-acid catalysts.

If suitable ring-heteroanalogous pyranosylamines are used, the chiral auxiliary should be selectively cleavable under mild conditions. The homologous sulfur is an especially interesting candidate for the replacement of the endocyclic

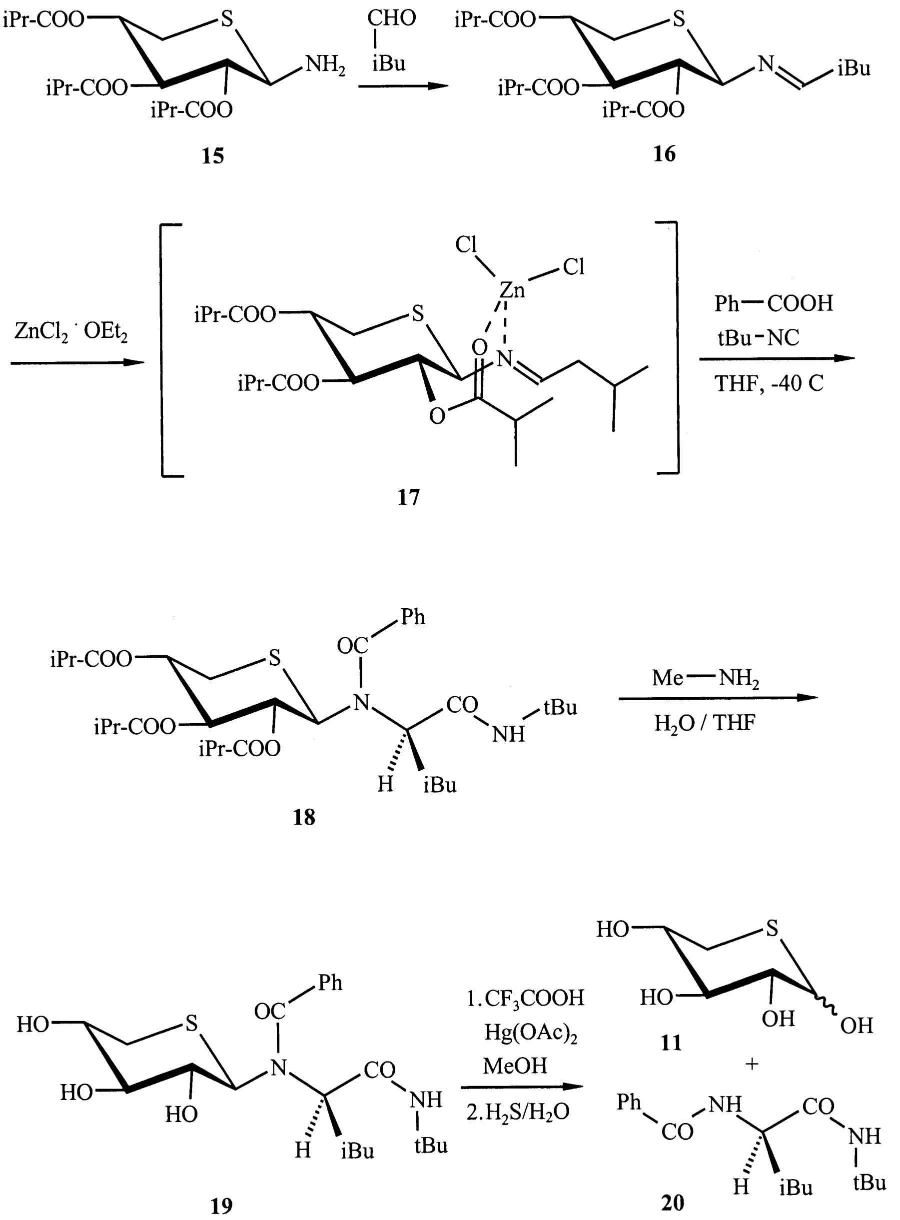

**Figure 3.** Stereoselective U-4CR with 1-amino-5-desoxy-5-thio-2,3,4-*O*-isobutanoyl-β-D-xylopyranose **15** and cleavage of the chiral auxiliary.

oxygen. The resulting condensation products can be seen as S/N analogous ketals, which can be attacked by soft electrophiles for cleavage. The activation of thioanalogous ketals by mercury salts and other soft Lewis acids is well known, for a review and mechanistic studies see, e.g. Satchell et al.[21] Johnston and Pinto[22] have used mercury(II)chloride as a catalyst when preparing S/N heteroanalogous 1,2-and 1,3-connected mannopyranose-disaccharides.

Thus the title compound 1-amino-5-desoxy-5-thio-2,3,4-*O*-isobutanoyl-β-D-xylopyranose **15** has a particularly suitable combination of desirable properties.

## 2. Synthesis of 1-amino-5-desoxy-5-thio-2,3,4-*O*-isobutanoyl-β-D-xylopyranose

Ingles and Whistler[16] found, that 5-desoxy-5-thio-D-xylose **11** can be prepared in six steps from D-xylose **10**. This product can be peracylated into **12** by an excess of isobutanoylchloride in pyridine[17] (Fig. 2). Because of the anomeric effect mainly the α-anomer is generated. **12** can be converted into **13** by replacing the anomeric acyloxy group of **12** with an azido function by trimethylsilylazide in the presence of tintetrachloride.[18]

The result is an anomeric mixture, in which the β-anomer slightly prevails. This means a distinct difference to the oxo-analogous compounds, where only the β-anomer is formed. In these, during the course of the reaction an intermediate anomeric carbenium ion is formed by abstraction of the anomeric acyloxy group. It is stabilized by the neighboring acyloxy group as a cyclic acylium ion which only allows the β-attack of the azide.[18] Obviously this effect is not as dominant in the thioanalogous system, probably due to the reduced electronegativity and enhanced donor properties of

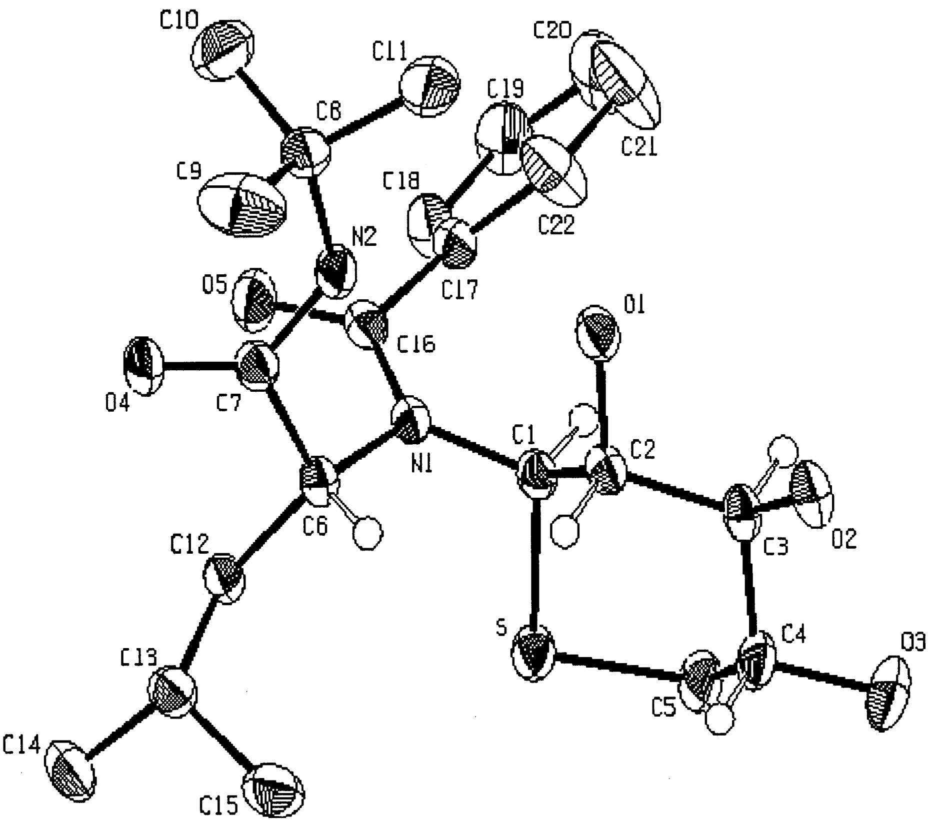

**Figure 4.** ORTEP drawing of the main part of the molecular structure of *N*-benzoyl-*N*-(5-desoxy-5-thio-β-D-xylopyranosyl)-*R*-leucine-*tert*-butylamide **19** in the solid state. Thermal ellipsoids are drawn at the 50% probability level. Only the hydrogen atoms bound to the chiral centers are shown, all other hydrogen atoms together with the atoms of the minor part of the disordered phenyl group are omitted for clarity.

the sulfur atom. This makes a neighboring group stabilization of the intermediate cation less necessary; the azide can attack from both sides.

The anomerically pure β-amine hydrochloride **14** is obtained from the α/β-azide mixture **13** by reduction with 1,3-propanedithiol (Fig. 2).[19] The β-azide is reduced much quicker than the α-azide. So during the workup the β-amine **15** can be precipitated from an etheric solution as the hydrochloride salt **14**, while the α-azide stays in solution. We assume, that the relative stabilization of the α-azide by the anomeric effect is the reason for this kinetic discrimination.

## 3. Sereoselective U-4CRs with 1-amino-5-desoxy-5-thio-2,3,4-*O*-isobutanoyl-β-D-xylopyranose and cleavage of the chiral auxiliary

The thiopyranosylamine **15** is relased from **14** with triethylamine. The **15** and isovaleraldehyde are subsequently converted into the imine **16** (Fig. 3). At −40°C in THF the latter is mixed with zinc chloride diethyl etherate, *tert*-butylisocyanide and benzoic acid.

After 72 h the product **18** is formed by the U-4CR with a stereoselectivity of 92% de (diastereomeric ratio 24:1 determined by HPLC-MS) and a yield of 91.8%.[20]

The readily crystallizing product **19** is obtained from **18** by removing its *O*-acyl groups by aminolysis with methylamine. The absolute configuration of the *R*-leucine derivative **19** was determined by X-ray analysis (Fig. 4). The right enantiomer is proved by Flack's parameter ($x=-0.03(5)$).[23] The phenyl group appears disordered over two positions with a ratio of 82:18.

The formation of the product with the *R*-configuration is strongly preferred. This is in agreement with the assumed steric course of this reaction via the seven membered imine chelate **17**.

The complexation with zinc chloride increases the rigidity of this intermediate compound, so that in the chirogenic α-addition step the prochiral imine function is fixed relatively to the chiral auxiliary. Thereby a distinct steric shielding of the Re-side of the imino function takes place and thus a distinct evident stereoselection is achieved. Besides, the zinc chloride activates the imine for the α-addition of the isocyanide. A related reaction mechanism was already discussed by Kunz et al.[11]

The *O*-deacylated chiral auxiliary group can be cleaved off under mild acidic conditions by a dilute methanolic solution of trifluoroacetic acid in the presence mercury(II)acetae. During the aqueous workup of the product the mercury compounds are precipitated by inducing hydrogen sulfide or by adding sodium hydorgensulfide. The *N*-benzoyl-*R*-leucine-*tert*-butylamide **20** and 5-desoxy-5-thio-D-xylose

**11** are thereby obtained. After 3 h at 20°C the cleavage of **19** into **11** and **20** is complete, and no byproducts are then found. From **11** the chiral amine **15** can be resynthesized.

The *O*-deacylation facilitates the subsequent acidolytic cleavage of the *N*-glycosidic bond in two ways: firstly, the steric shielding of the reaction center is thereby reduced. Secondly, the electron density of the anomeric carbon is enhanced by the removal of the electron withdrawing acyl groups (see also the armed/disarmed concept by Fraser-Reid et al.[25]).

The divalent mercury forms a complex with the endocyclic sulfur of the thiosugar moiety. Thereby the sulfur is activated as a leaving group and an open-chain form of the sugar is stabilized. This promotes the acid catalyzed solvolysis of the *N*-glycosidic bond.

If the use of mercury compounds should be avoided for safety reasons, other reagents in general use for the cleavage of thioketals could be tried. In literature, the use of different substances such as copper or silver compounds, Chloramine T, *tert*-butylhypochlorite and others has been reported.[24]

The application of alternative cleavage reagents and the removal of the chiral auxiliary in one step with or without previous *O*-deacylation remains an interesting task for future investigations.

In the experiments described here, the isobutanoyl substituents turned out to be the optimal compromise in regard of synthesis, reactivity and stereoselectivity of the thiosugar template. When pivaloyl substituents were used, the tetra-*O*-pivaloyl thioxylose (analogous to **12**) was not obtained in satisfying yields. With benzoyl substituents, the amine (analogous to **14** and **15**) could be synthesized without problems, but with the components tested no U-4CR was observed.[20a] In both cases sterical hindrance seems to be the reason for problems during synthesis or application of these compounds.

The *O*-acyl substituents of the chiral template can easily be varied in order to form different types of products using components with different steric demands.

The tri-*O*-isobutanoyl thioxylopyranosylamine **15** was also used in the syntheses of a phenylglycine derivative and a dipeptide derivative.[20a,b]

If desired, also the enantiomeric products can be prepared by this method, since also L-xylose is commercially available, although the higher price of this compound has to be considered.

## 4. Conclusions

A great variety of products can now be formed stereoselectively by the U-4CR of 1-amino-5-desoxy-5-thio-2,3,4-*O*-isobutanoyl-β-D-xylopyranose **15**. The chiral template is a ring-thioanalogous carbohydrate. It combines excellent stereoselectivities and chemical yields in the U-4CR with a mild and specific cleavage mechanism. The *O*-acyl substituents of the sugar ring can easily be varied in order to match reactants with different steric demands, thus increasing the versatility of this chiral auxiliary. The use of the readily available D-form of the sugar template induces the formation of *R*-amino acid derivatives. This is particularly useful since these 'unnatural' amino acids are rather rare in nature. If desired, also the L-xylose derivative is accessible, although at a higher price. This means a major advance in the development of the stereoselective U-4CR.

## 5. Experimental

### 5.1. General

$^1$H NMR spectra were recorded on a Bruker AC 200 (200 MHz), $^{13}$C NMR spectra were recorded on a Bruker AC 250 (63 MHz). The chemical shifts $\delta$ are given in ppm relative to tetramethylsilane as an internal standard.

**5.1.1. Compound 12.** Isobutanoylchloride (20.2 g, 190 mmol) is gradually dropped into an ice-cooled solution of 5-desoxy-5-thio-D-xylopyranose **11** (6.3 g, 38 mmol) in 20 mL of dry pyridine. The resulting suspension is diluted with dichloromethane till the mixture can be stirred well. Stirring is continued for 20 h at room temperature. Then 50 mL water are added and stirred for further 60 min. Subsequently 100 mL dichloromethane are added. The organic phase is separated and twice washed with 100 mL 1N hydrochloric acid and subsequently with 100 mL of saturated sodium hydrogencarbonate solution. After drying with magnesium sulfate the solvent is evaporated. The bright brown product is obtained in a yield of 16.1 g (95%) as an anomeric mixture (α/β=3.3:1).

$^1$H NMR (α-anomer, CDCl$_3$): $\delta$=6.11 (d, 1H, $^3J$=2.8 Hz); 5.52 (t, 1H, $^3J$=10.1 Hz); 5.24 (dd, 1H); 5.14 (m, 1H); 2.99 (dd, 1H, $^3J$=11.0 Hz, $^2J$=12.2 Hz); 2.78 (dd, $^3J$=3.7 Hz); 2.6 (m, 4H); 1.15 (m, 24H). $^{13}$C NMR (α-anomer, CDCl$_3$): $\delta$=175.14; 174.96; 174.8; 172.76; 73.7; 72.44; 70.84; 69.83; 34.02; 33.87; 33.86; 33.84; 26.5; 19.33; 19.15; 19.13; 19.10; 19.06; 19.04; 18.99; 18.94.

**5.1.2. Compound 13.** 1,2,3,4-Tetra-*O*-isobutanoyl-5-desoxy-5-thio-D-xylose **12** (4.3 g, 9.6 mmol) is dissolved in 50 mL of dry dichloromethane and at 0°C trimethylsilylazide (1.3 g, 11.04 mmol) is added. Subsequently tintetrachloride (2.1 g, 8.16 mmol) is added. The mixture is stirred at 20°C for 2 h. After adding 50 mL of icy water, the organic phase is filtered via Celite. It is twice washed with a saturated sodium hydrogencarbonate solution, dried by magnesium sulfate and evaporated. The yield of the bright brown product is 3.46 g (90%). Its ratio of anomers is α/β=1:2.3.

$^1$H NMR (β-anomer, CDCl$_3$): $\delta$=5.39 (t, 1H, $^3J$=9.8 Hz); 5.05 (m, 2H); 4.46 (d, 1H, $^3J$=9.2 Hz); 2.97 (dd, 1H, $^2J$=13.1 Hz); 2.7 (dd, 1H, $^3J$=3.7 Hz); 2.45 (m, 3H); 1.1 (m, 18H). $^{13}$C NMR (β-anomer, CDCl$_3$): $\delta$=175.49; 175.28; 175.13; 73.64; 73.33; 72.08; 63.24; 33.75; 33.73; 28.46; 18.74; 18.71; 18.64; 18.6; 18.56. IR (KBr): 2100 cm$^{-1}$ (s, azide).

**5.1.3. Compound 14.** 2,3,4-Tri-*O*-isobutanoyl-5-desoxy-5-thio-D-xylopyranosylazide **13** (5.82 g, 14.5 mmol) is dissolved in 50 mL dichloromethane. Subsequently 50 mL methanol, 1,3-propanedithiol (3.3 g, 29 mmol) and triethylamine (3.0 g, 29 mmol) are added. This is stirred at 20°C till the formation of nitrogen has ended (2–3 h). Then the volatile compounds are removed in vacuo. The residue is dissolved in 50 mL of diethyl ether and the insoluble 1,2-dithiolane is removed. The filtrate is cooled and 2 mL concentrated hydrochloric acid are added dropwise. The $\beta$-amine hydrochloride **14** precipitates, while the $\alpha$-anomeric azide remains in solution. The product is filtered off and dried in a high vacuum. 2.09 g (35%) of a white crystalline solid are obtained.

$^1$H NMR (DMSO-$d_6$+D$_2$O): $\delta$=5.26 (t, 1H, $^3J$=9.2 Hz); 5.17 (dd, 1H, $^3J$=9.5 Hz); 4.96 (ddd, 1H, $^3J$=10.7, 4.8 Hz); 4.75 (d, 1H, $^3J$=9.5 Hz); 3.09 (dd, 1H, $^2J$=13.4 Hz); 2.95 (dd, 1H); 2.7–2.4 (m, 3H); 1.05 (m, 18H). $^{13}$C NMR (DMSO-$d_6$+D$_2$O): $\delta$=175.36; 175.28; 174.98; 72.41; 71.95; 71.46; 50.54; 33.17; 33.02; 27.24; 18.67; 18.51; 18.34; 18.31; 18.12; 17.73.

**5.1.4. Compound 15.** The hydrochloride **14** is suspended in ether and an excess of triethylamine is added. This is stirred for 15 min, filtered and the solvent is removed in vacuo. 1-Amino-5-desoxy-5-thio-2,3,4-*O*-isobutanoyl-$\beta$-D-xylopyranose **15** is obtained as a white solid in a yield of 98%.

$^1$H NMR (CDCl$_3$): $\delta$=5.15–5.03 (m, 3H); 4.04 (d, 1H, $^3J$=9.3 Hz); 2.77 (dd, 1H, $^3J$=4.9 Hz, $^2J$=13.7 Hz); 2.68 (dd, 1H, $^3J$=10.2 Hz); 2.58–2.43 (m, 3H); 1.17–1.09 (m, 18H). $^{13}$C NMR (CDCl$_3$): $\delta$=176.54; 175.84; 175.57; 75.33; 72.67; 72.63; 57.76; 34.02; 33.95; 33.93; 29.29; 19.01; 18.87; 18.83; 18.8.

**5.1.5. Compound 16.** The amine hydrochloride **14** (2.06 g, 5 mmol) is suspended in 50 mL diethyl ether and isovaleraldehyde (0.52 g, 6 mmol) as well as triethylamine (0.61 g, 6 mmol) are added. 5 g Magnesium sulfate are added. This is stirred for 20 h, filtered and dried in vacuo. The imine **16** is obtained in a yield of 1.97 g (89%) as a white solid.

$^1$H NMR (CDCl$_3$): $\delta$=7.83 (t, 1H, $^3J$=4.9 Hz); 5.43 (t, 1H, $^3J$=9.5 Hz); 5.14 (m, 2H); 4.33 (d, 1H, $^3J$=9.2 Hz); 2.86 (dd, 1H, $^3J$=4.3 Hz, $^2J$=13.4 Hz); 2.73 (dd, 1H, $^3J$=10.1 Hz); 2.24 (m, 3H); 2.14 (t, 1H, $^3J$=5.8 Hz); 1.9 (m, 1H); 1.08 (m, 18H); 0.92 (2×d, 6H, $^3J$=6.4 Hz). $^{13}$C NMR (CDCl$_3$): $\delta$=175.38; 175.27; 174.96; 170.77; 74.96; 73.05; 72.89; 72.46; 58.15; 34.26; 34.24; 29.19; 26.32; 22.98; 22.67; 19.35–19.14.

**5.1.6. Compound 18.** The imine **16** (0.89 g, 2 mmol) is dissolved in 10 mL of dry THF. Then zinc chloride diethyl etherate (2.2 mmol, 1 mL of a 2.2 M solution in dichloromethane) is added. The mixture is cooled to −40°C and *tert*-butylisocyanide (0.18 g, 2.2 mmol) is added. After 15 min benzoic acid (0.27 g, 2.2 mmol) is added. When TLC-control (ethyl acetate/hexane 1:2) indicates the complete reaction of the imine (72 h) the THF is removed and the residue is dissolved in 50 mL diethyl ether. The organic layer is washed with 50 mL of 0.5N hydrochloric acid and two times with saturated sodium hydrogencarbonate solution. It is dried over magnesium sulfate. The solvent is removed in vacuo and a yield of 1.19 g (91.8%) of the white solid product **18** is obtained. According to the HPLC-MS two diastereomers are present, the diastereomeric ratio is 24:1 (92% de). The NMR shows two rotamers in a ratio of 2.7:1. The data presented here refer to the major rotamer.

$^1$H NMR (CDCl$_3$): $\delta$=7.95 (s, 1H); 7.6–7.45 (m, 5H); 5.31 (d, 1H, $^3J$=10.2 Hz); 5.18 (t, 1H, $^3J$=9.3 Hz); 5.08 (t, 1H); 4.97 (dt, 1H, $^3J$=4.2, 10.3 Hz); 4.01 (dd, 1H, $^3J$=4.9, 9.7 Hz); 2.83 (dd, 1H, $^2J$=13.3 Hz); 2.53–2.32 (m, 6H); 1.72 (m, 1H); 1.34 (s, 9H); 1.19–0.99 (m, 24H). $^{13}$C NMR (CDCl$_3$): $\delta$=175.71; 175.61; 175.6; 173.93; 169.49; 135.28; 131.12; 128.73; 126.65; 74.01; 72.94; 72.02; 64.00; 63.10; 50.87; 40.51; 33.96; 33.9; 33.79; 28.68; 28.31; 25.67; 23.55; 22.22; 18.93–18.53. MS (EI): 649 M+H; 671 M+Na; 687 M+K.

**5.1.7. Compound 19.** The condensation product **18** (3.0 g, 4.6 mmol) is dissolved in 100 mL THF and 60 mL of a 40% aqueous solution of methylamine are added. This is stirred at 20°C till the educt has reacted completely according to the TLC-control (ethyl acetate/hexane 1:2) (20 h). Then the solvent is removed and the residue is washed with ether several times. 1.94 g (96%) of **19** are received as a white powder that can be recrystallized from methanol.

$^1$H NMR (MeOH-$d_4$): $\delta$=7.52–7.40 (m, 5H); 4.66 (d, 1H, $^3J$=9.7 Hz); 3.87–3.79 (m, 2H); 3.72 (t, 1H, $^3J$=6.2 Hz); 3.51 (dt, 1H, $^3J$=4.4, 11.1 Hz); 2.69 (m, 2H); 2.62 (dd, 1H, $^2J$=13.3 Hz); 2.31 (dd, 1H); 1.9 (m, 1H); 1.33 (s, 9H); 1.01–0.98 (2×d, 6H, $^3J$=6.6 Hz). $^{13}$C NMR (MeOH-$d_4$): $\delta$=174.39, 172.00; 137.1; 131.07; 129.52; 127.16; 79.37; 74.66; 73.75; 66.00; 57.68; 52.36; 40.79; 32.48; 28.67; 27.70; 23.68; 22.40. MS (EI): 439 M+H; 461 M+Na; 477 M+K.

### 5.2. X-Ray analysis of 19

Single crystals of **19** suitable for a X-ray diffraction study were grown by slow evaporation of a methanolic solution of the compound. Preliminary examination and data collection were carried out on a kappa-CCD device (NONIUS Mach3) at the window of a rotating anode (NONIUS FR591: 50 kV, 80 mA, 4.0 kW) and graphite monochromated Mo K$_\alpha$ radiation ($\lambda$=71.073 pm). Data collection was performed at −100(±1)°C (173(±1) K).

*Crystal data.* C$_{22}$H$_{34}$N$_2$O$_5$S, $M$=438.58, colorless crystal of 0.43×0.38×0.28 mm, orthorhombic, space group $P2_12_12_1$ (No. 19), $a$=1039.63(1), $b$=1106.24(1), $c$=2007.99(2) pm, $V$=2309.35(4)×10$^6$ pm$^3$ (from 2441 reflections with 2.03<$\Theta$<25.35°), $Z$=4, $D_c$=1.261 g cm$^{-3}$, $F(000)$=944, $\mu$=0.175 mm$^{-1}$.

*Measurement and solution.* A total number of 41,816 reflections were integrated. Data were corrected for Lorentz and polarization effects. Corrections for absorption and decay effects were not applied. After merging a sum of 4237 independent reflections remained and were used for all calculations. The structure was solved by a combination of direct methods and difference Fourier syntheses. All non-hydrogen atoms of the asymmetric unit were refined with anisotropic thermal displacement parameters. A disorder (82:18) of the phenyl group could be resolved and refined. All hydrogen atoms were found in the difference Fourier map and refined freely with individual isotropic thermal displacement parameters, except those of the minor part of the disordered phenyl group, which were placed in calculated positions (riding model).

*Refinement*. Full-matrix least squares refinements were carried out by minimizing $\sum w(F_o^2 - F_c^2)^2$, converging at $R1$ ($F$, obs. data: 3692 $I>2.0\sigma(I)$)=0.0267, $wR2$ ($F^2$, all data)=0.0640, goodness of fit 1.024, 444 parameters, maximum shift/err<0.001, residual electron density $\Delta\rho_{max}=0.14$, $\Delta\rho_{min}=-0.14$ e Å$^{-3}$. SIR-92, SHELXL-97, and software for Nonius KappaCCD were used. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-179-984. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

**5.2.1. Compound 20.** The *O*-deacylated product **19** (0.5 g, 1.14 mmol) is dissolved in a mixture of 20 mL methanol and 10 mL trifluoroacetic acid. Subsequently mercury(II)acetate (0.36 g, 1.14 mmol) is added and stirred until the educt has completely reacted according to the TLC-control (ethyl acetate) (about 3 h). Then 150 mL of a saturated sodium hydrogencarbonate solution and 50 mL of diethylether are prepared and the reaction mixture is gradually added. After neutralizing this with sodium hydrogencarbonate 2 g of sodium hydrogensulfide monohydrate are added. As an alternative hydrogen sulfide can also be induced. The organic phase is separated, the aqueous phase is extracted by 50 mL of diethylether. The combined organic phases are filtered by Celite, washed by saturated sodium hydrogencarbonate solution and dried by magnesiumsulfate. A colorless solid mixture of **20** and **11** is received. This mixture is treated with chloroform, the organic phase is filtered over Celite and evaporated in vacuo. 0.2 g (60%) of **20** as a transparent solid are obtained.

$^1$H NMR (CDCl$_3$): $\delta$=7.79 (d, 2H, $^3J$=7.3 Hz); 7.51 (t, 1H, $^3J$=7.2 Hz); 7.43 (t, 2H); 6.77 (bd, 1H, $^3J$=8.2 Hz); 6.00 (bs, 1H); 4.54 (dt, 1H, $^3J$=8.2, 5.8 Hz); 1.76–1.60 (m, 3H); 1.35 (s, 9H); 0.97 (d, 6H). $^{13}$C NMR (CDCl$_3$): $\delta$= 171.75; 167.06; 133.86; 131.21; 128.15; 127.12; 52.67; 51.02; 41.22; 28.48; 24.76; 22.84; 22.10. MS (EI): 291 M+H; 313 M+Na; 329 M+K.

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