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CARBOHYDRATES AS CHIRAL TEMPLATES: DIASTEREOSELECTIVE UGI SYNTHESIS OF (S)-AMINO ACIDS USING O-ACYLATED D-ARABINOPYRANOSYLAMINE AS THE AUXILIARY

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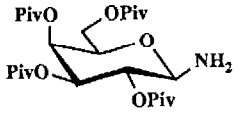
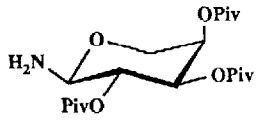
Summary: Enantiomerically pure (S)-amino acids are synthesized via a highly diastereoselective Ugi reaction using 2,3,4-tri-O-pivaloyl-α-D-arabinopyranosylamine as the chiral template.

The pivaloyl-D-galactosylamine **1** proved to be an effective chiral auxiliary in Strecker syntheses of amino nitriles.[1,2] If the reactions are carried out in isopropanol in the presence of zinc chloride, the (R)-diastereomeric amino nitriles are obtained in excess.[1] The direction of asymmetric induction in this process can be reversed by changing the solvent: In chloroform, the (S)-diastereomers are formed preferably.[2] The chirality and the complexing abilities of **1** are exploited even more effectively in Ugi reactions[3] to accomplish a highly diastereoselective synthesis of (R)-amino acid amides.[4] Furthermore, pure (R)-diastereomers are obtained in high yield after recrystallization or flash chromatography. However, in contrast to the situation in the Strecker synthesis[1,2] the sense of the asymmetric induction cannot be reversed in this process by changing the solvent.
With respect to their biological relevance, the (S)-configured amino acid derivatives have to be considered even more interesting. Therefore, we searched for a carbohydrate template useful for the selective Ugi synthesis of (S)-amino acid amides. L-Galactose cannot be considered as a realistic choice. In this situation, we recognized the 2,3,4-tri-O-pivaloyl-α-D-arabinopyranosylamine **2**, although belonging to the D-series, to be almost a mirror image of the D-galactosylamine **1**.

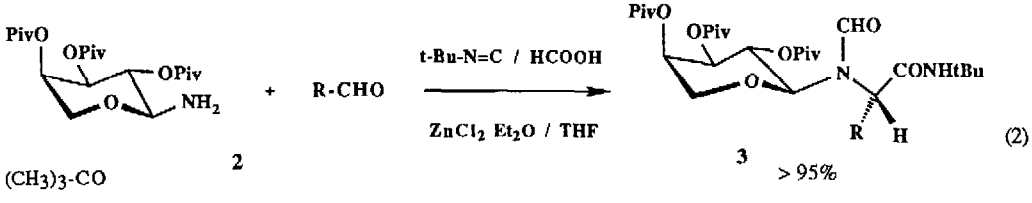


1



2 (1)

Compared with **1**, in **2** only the functionalized carbon-6 is missing. But, all functional groups necessary for the stereodifferentiation[1] are present in **2** and enantiomerically arranged. Consequently, the O-pivaloyl-arabinopyranosylamine **2** was used in Ugi reactions with aldehydes, tert-butyl isocyanide and formic acid in the presence of zinc chloride in tetrahydrofuran. At -25°C the one-pot reactions (scheme 2) are usually complete after 24h. The pivalaldehyde requires an extended reaction time. After the reactions are finished, hydrolytic work-up delivers the N-arabinopyranosyl-α-amino acid amide derivatives **3** in almost quantitative yields.

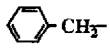
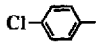


2 **3** > 95% (2)

Piv = $(CH_3)_3$-CO

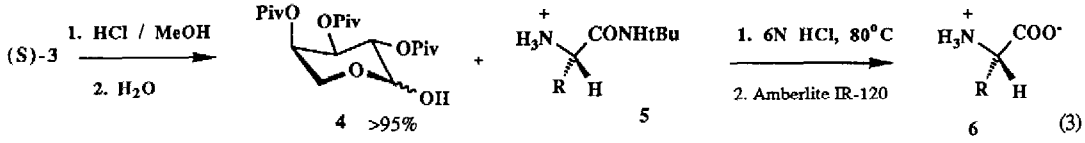
The (α-D,2S)-**3** diastereomers are formed with high selectivity. The ratios of diastereomers (Table 1) determined by analytical HPLC of the crude product range from 22 to 30:1. Simple recrystallization or flash-chromatography deliver pure (α-D,2S)-diastereomers in yields of 85% to more than 90%.
The pure N-formyl-N-α-D-arabinosyl-amino acid tert-butylamides **3** are easily converted to the free (S)-amino acids **6** by application of a two step hydrolysis. Treatment of (S)-**3** with hydrogen chloride in methanol and subsequent addition of water furnishes the removal of the formyl group and the

Table 1: Diastereoselective Ugi Synthesis of N-Arabinopyranosyl Amino Acid Amides 3 (eq. 2; the yields of diastereomeric mixtures 2S/2R are >95%).

Product	R	Reaction Temp.(°C)/Time(h)	Kinetic Ratio[a] 2S : 2R	Yield (%) of Pure (2S)-3[b]
3 a	$(CH_3)_3C$-	-25 / 72	97 : 3	85
3 b		-78 / 24	97 : 3	87[c]
3 c		-25 / 24	98 : 2	91
3 d		-25 / 24	96 : 4	85
3 e		-25 / 24	4 : 96	85 (2R)

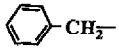
a) HPLC (diode array detection) directly from the product mixture after hydrolysis. b) Obtained by recrystallization from dichloromethane/heptane. c) Obtained by flash-chromatography.

cleavage of the N-glycoside. During work-up the pivaloyl-arabinopyranose **4** is recovered almost quantitatively by extraction. **4** can simply be reconverted to the starting auxiliary **2**. Acidic hydrolysis of the enantiomerically pure (S)-α-amino acid amides **5** yields the pure (S)-α-amino acids (Table 2).



(3)

Table 2: (S)-Amino Acids **6** via Hydrolysis of N-Arabinopyranosyl- (S)-Amino Acid Amides 3 (eq. 3).

Product	R	Overall Yield (%)	$[\alpha]_D^{22}$
6 a	$(CH_3)_3C$-	70	+ 8.5 (c 2, 1.5N HCl); lit.[5]: $[\alpha]_D^{20}$= +9.0 (c 3, 5N HCl)
6 b		82	-33.5 (c 0.5, H_2O); lit.[6]: $[\alpha]_D^{25}$= -34.8 (c 1, H_2O)
6 c		85	+139.5 (c 1, 1N HCl); lit.[7] for the(R)-enantiomer: $[\alpha]_D^{20}$=-138.7 (c 1, 1N HCl)

In conclusion, the application of the O-pivaloyl-α-D-arabinosylamine **2** as the chiral template in Ugi reactions provides a highly diastereoselective access to (S)-α-amino acids with alkyl-, branched-, aryl- and heteroaryl-side chains. It constitutes a useful method complementary to the stereoselective Ugi synthesis of (R)-amino acids achieved with the galactosylamine **1**.[4] The reactions carried out as one-pot procedures give high yields and diastereoselectivities. Flash-chromatography delivers pure (S)-diastereomers. Organometallic reagents and exclusion of oxygen are not required.

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