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Diastereoselective synthesis of glycosyl-α-aminoacids

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Abstract: Asymmetric synthesis of various glycosyl-α-aminoacids is described. The approach involves the diastereoselective condensation of glycine enolates on the carbonyl in position 3 of the suitably protected α-D-ribohexofuranos-3-ulose. © 1997 Elsevier Science Ltd. All rights reserved.

Glycopeptides constitute an important class of compounds which are widely distributed among living organisms. The sugar component can modulate the biological properties of the protein by playing an essential role in molecular recognition. The sugar group also improves protein solubility as well as the bio-availability of the protein by accelerating its transport across membranes.[1]

Sugar moieties are usually associated with proteins by a C–N or C–O bond. Our aim was to develop the synthesis of glycosyl-α-aminoacids and glycopeptide derivatives in which the sugar and the aminoacid are joined by a C–C bond resistant to enzyme cleavage. We describe here the diastereoselective synthesis of such glycosyl-α-aminoacids.

Various glycine enolates (prepared from aminoesters **2**, **3**, and **4**) by treatment with LDA in THF at −80°C) were reacted with the carbonyl group of 1,2:5,6-di-O-isopropylidene-α-D-ribohexofuranos-3-ulose **1**[2] (Scheme 1). Starting from compound **2**, the reaction takes place in excellent yield and with total diastereoselectivity implying a two-fold control of chirality. The afforded compound **5** contains the aminoester residue in the exo position. The structure and the stereochemistry of **5** were assigned from the spectral data and from the X-ray diffraction pattern[3–6] (Figure 1).

In the case of compound **3**, the reaction occurred in lower yield and with reduced diastereoselectivity. The major isolated diastereoisomer **6** had a stereochemistry identical to that of compound **5**. This stereochemistry was deduced from the X-ray diffraction pattern for its spirolactone derivative **12** (Scheme 3), described below.

Finally, following cyclisation of the intermediate **A** (Scheme 1) between the hydroxyl in position 3 and the carbon of the imine group, the enolate of the Schiff's base **4** affords a spirooxazolidine **7** rather than the expected condensation product **A** (Scheme 1). The structure of compound **7** was established by nmr, ir and mass spectra and its stereochemistry was confirmed by X-ray analysis (Figure 2).

Hydrogenolysis of compounds **5** and **6** takes place quantitatively in the presence of palladium hydroxide in a mixture of THF/ethanol affording the glycosylated aminoesters **8** and **9** (Scheme 2) with a free amine group. We were unable to cleave the tert-butyl ester of compound **5** in the presence of TFA without altering the molecule. However, we have obtained the corresponding glycosylaminoacid **10** by saponification of the methyl ester **6** under non-epimerizing conditions (dioxane/NaOH). The glucofuranos-3-yl-aminoester **11** with a free amino group was obtained by hydrolysis of compound **10** in the presence of 15% citric acid.

Four glycosyl-α-aminoesters (or acids) of controlled chirality were thus obtained and by coupling with properly protected aminoacids derivatives can afford glycopeptides. However, it should be noted that under the coupling conditions the glycosylaminoacid **10** tends to lactonise very readily. In the

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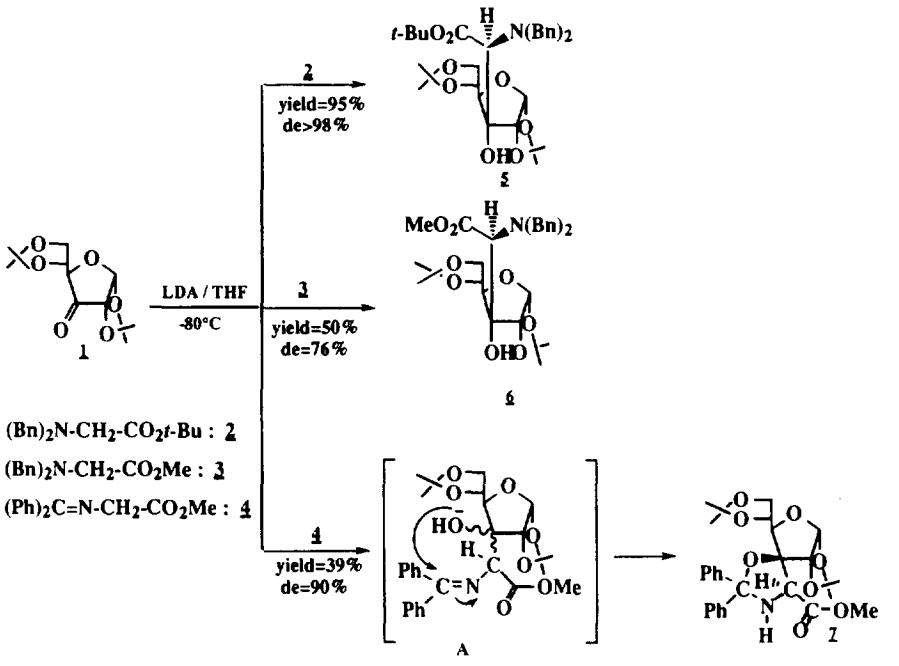


Scheme 1.

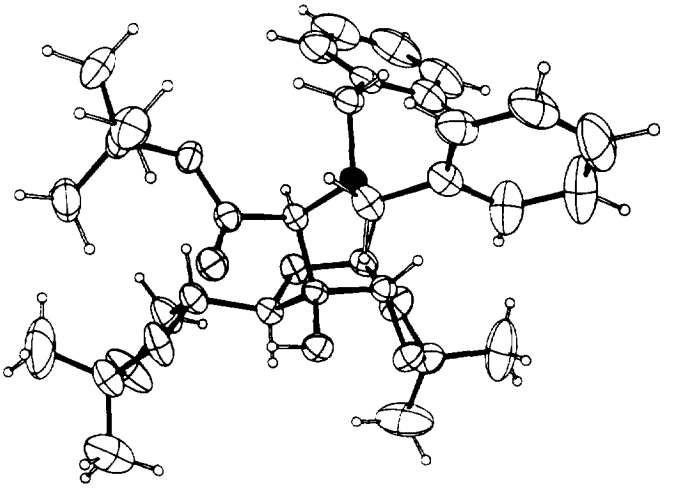


Figure 1. X-Ray structure of compound **5**.

presence of BOP/DIEA in dichloromethane the spirolactone **12** was obtained in high yield (Scheme 3). Its structure was ascertained from the spectral data and its stereochemistry from the X-ray diffraction pattern (Figure 3). This stereochemistry confirmed that of the precursors **6** and **10**.

We have also verified that compound **12** could be used as a synthon in peptide synthesis by opening the β-lactone ring with ammonia in acetonitrile. This is a purely O-acyl ring opening yielding the expected amide **13** in excellent yield (Scheme 3).

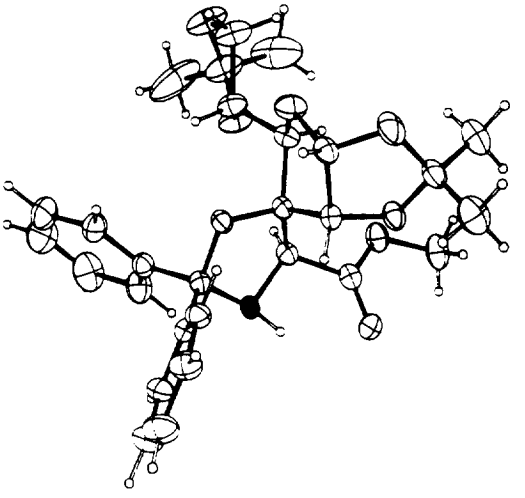
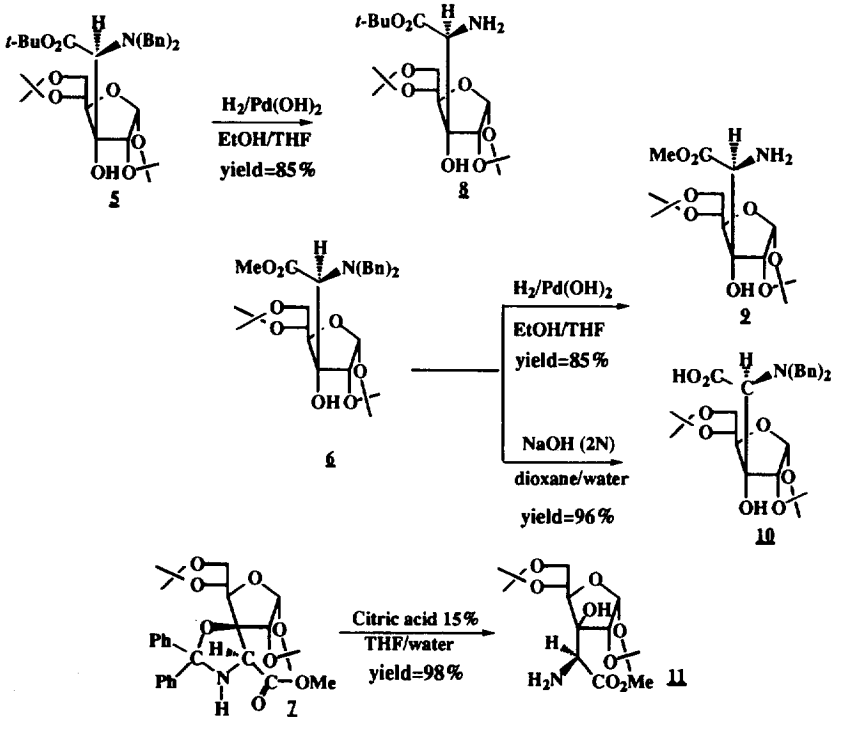


Figure 2. X-Ray structure of compound 7.

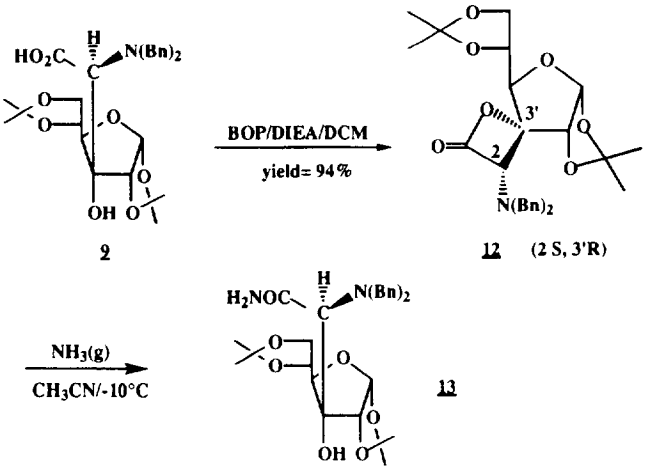


Scheme 2.

Experimental

General

Reagents and solvents were purified in the usual way. All reactions involving lithium derivatives were carried out under anhydrous conditions in nitrogen atmosphere. LDA was prepared from BuLi in ether. Thin layer chromatography was performed on Merck precoated silicagel 60F $_{254}$ plates and spots were visualized by ultraviolet light or by iodine vapour. Column chromatography was performed on



2 12 (2 S, 3'R) 13

Scheme 3.

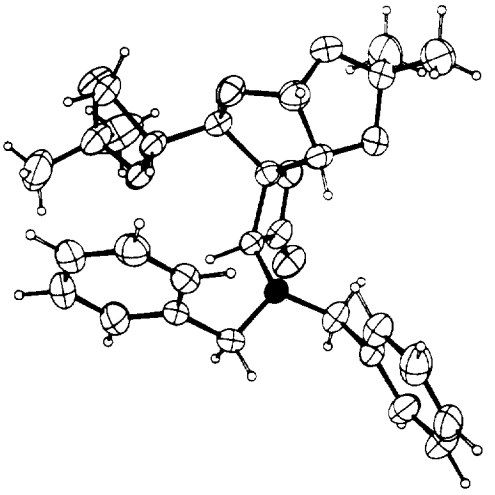


Figure 3. X-Ray structure of compound **12**.

silicagel Merck 60. Spectra were recorded with the following instruments: IR spectra: Perkin–Elmer FT-IR Parangon 1000, ^{1}H NMR spectra: Brücker AC-250, mass spectra: Jeol JMS DX 300. Optical rotations were determined with a Perkin–Elmer model 141 polarimeter. Melting points uncorrected were obtained on a Büchi 510 apparatus. Diastereomeric purity was checked by reverse phase HPLC on C-18 Nucleosyl. Routine analysis agreed with calculated values within +(−) 0.3%.

General procedure for condensation of enolates with sugar 1

A solution of n-butyllithium in ether[7] (5.75 mmoles, 35 ml) was prepared under nitrogen and mixed to the solution of diisopropylamine (6.25 mmole, 0.631 g) in anhydrous THF (5 ml) at 0°C. After 15 min the mixture was cooled to −80°C, then the aminoester derivative (**2**,[8] **3**[9] or **4**[10]), 5 mmoles, dissolved in THF (10 ml) was added. The mixture was stirred at −80°C, 20 min. After addition of the sugar **1** (5 mmoles, 1.290 g) dissolved in THF (10 ml), the mixture was stirred at −80°C for 5 h, then allowed to reach slowly −20°C (15 h). Washing with a saturated solution of NH_4Cl and extraction of the aqueous phase with ethylacetate (3×30 ml) followed. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure.

N,N-Dibenzyl-(2S)-2-(1,2:5,6-di-O-isopropylidene-α-D-allofuranos-3-yl)-Gly-OtBu **5**

This compound was recrystallized from ether. Yield: 2.620 g (92%). M.p.: 168–169°C (ether). Rf=0.60 (ether/hexane: 1/1). $[\alpha]_D=-88$ (c=1.6, CH_2Cl_2). ^{1}H-NMR (CDCl3): δppm: 1.28 (3H, s), 1.31 (3H, s), 1.40 (3H, s), 1.55 (3H, s), 1.67 (9H, s), 3.15 (1H, OH), 3.40 (1H, s), 3.45 (1H, s), 3.75–4.02 (4H, m), 4.17 (1H, d, J=3.6 Hz), 4.30 (2H, br.s), 4.63 (1H, s), 5.10 (1H, d, J=3.6 Hz), 7.25–7.35 (10H, m). $[M+H^+]$=570 (FAB^+/NBA).

N,N-Dibenzyl-(2S)-2-(1,2:5,6-di-O-isopropylidene-α-D-allofuranos-3-yl)-Gly-OMe **6**

This compound was purified by chromatography on silicagel (ether/hexane: 4/1). Yield: 1.025 g (39%). M.p.: 110–112°C (pentane). Rf=0.48 (ether/hexane: 1/1). $[\alpha]_D=-81$ (c=1.8, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δppm: 1.28 (3H, s), 1.34 (3H, s), 1.38 (3H, s), 1.55 (3H, s), 3.27 (1H, OH), 3.34 (1H, s), 3.36 (1H, s), 3.72–3.85 (4H, m), 3.90 (3H, s), 4.01 (1H, dd, J=8.0 Hz, J=5.3 Hz), 4.10 (1H, s), 4.32 (2H, br.s), 4.47 (1H, d, J=3.5 Hz), 5.10 (1H, d, J=3.5 Hz), 7.25–7.37 (10H, m). $[M+H^+]$=528 (FAB^+/NBA).

(3S),(4'S)-4'-Carbomethoxy-2',2'-diphenyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranos-3-spirooxazolidine **7**

This compound was purified by chromatography on silicagel (ether/hexane: 4/1). Yield: 0.945 g (36%). M.p.: 130–132°C (pentane). Rf=0.43 (ether/hexane: 2/3). $[\alpha]_D=-26$ (c=1, $CHCl_3$). ^{1}H-NMR (CDCl3): δppm: 1.20 (6H, s), 1.40 (3H, s), 1.54 (3H, s), 3.45 (1H, d, J=13.3 Hz), 3.67 (3H, s), 3.86 (1H, dd, J=8.6 Hz, J=2.9 Hz), 3.90–4.01 (2H, m), 4.15 (1H, d, J=8.2 Hz), 4.32 (1H, d, J=3.2 Hz), 4.50 (1H, OH), 5.93 (1H, d, J=3.2 Hz), 7.08–7.60 (10H, m). $[M+H^+]$=512 (FAB^+/NBA).

General procedure for hydrogenolysis of **5** *and* **6**

20% Palladium hydroxide (0.5 g) was added to a solution of the N-protected glycosylaminoester (5 mmoles) **5** or **6** in 15 ml THF/ethanol (1/1). The mixture was stirred at room temperature under H_2. When the requisite quantity of H_2 was absorbed, the mixture was filtered on celite and the solvents were concentrated under vacuo to yield componds **8** or **9**.

(2S)-2-(1,2:5,6-Di-O-isopropylidene-α-D-allofuranos-3-yl)-Gly-OtBu **8**

This compound was recrystallized from pentane. Yield: 1.653 g (85%). M.p.: 138–140°C (pentane). Rf=0.66 (ethyl acetate). $[\alpha]_D=+33$ (c=1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δppm: 1.32 (6H, s), 1.40 (3H, s), 1.43 (9H, s), 1.52 (3H, s), 2.50 (2H, NH_2), 3.42 (1H, m), 3.77 (1H, OH), 3.82 (1H, d, J=8.6 Hz), 3.89 (1H, dd, J=6.3 Hz, J=5.7 Hz), 4.05 (1H, dd, J=6.3 Hz, J=5.7 Hz), 4.34 (1H, m), 4.72 (1H, d, J=3.8 Hz), 5.68 (1H, d, J=3.8 Hz). $[M+H^+]$=390 (FAB^+/NBA).

(2S)-2-(1,2:5,6-Di-O-isopropylidene-α-D-allofuranos-3-yl)-Gly-OMe **9**

This compound was recrystallised from pentane. Yield: 1.601 g (92%). M.p.: 124–126°C (pentane). Rf=0.23 (ethylacetate). $[\alpha]_D=+13$ (c=1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δppm: 1.37 (3H, s), 1.39 (3H, s), 1.45 (3H, s), 1.59 (3H, s), 3.77 (3H, s), 3.85 (1H, m), 3.87 (1H, d, J=8.7 Hz), 3.95 (1H, dd, J=8.5 Hz, J=4.3 Hz), 4.02 (1H, OH), 4.13 (1H, dd, J=8.5 Hz, J=6.2 Hz), 4.37 (1H, m), 4.86 (1H, d, J=3.9 Hz), 5.73 (1H, d, J=3.9 Hz). $[M+H^+]$=348 (FAB^+/NBA).

Hydrolysis of compound **6**

Compound **6** (5 mmoles, 2.640 g) was dissolved in a mixture of dioxane (32 ml) and water (4 ml). NaOH 2 N (1.1 equiv.) was added at 0°C. The mixture was stirred at rt for 1 h then 4 h at 60°C. The dioxane was removed in vacuo, the aqueous layer extracted with ethyl acetate, then acidified with HCl 1 N to pH 2–3. The aqueous layer was extracted several times with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure.

N,N-Dibenzyl-(2S)-2-(1,2:5,6-di-O-isopropylidene-α-D-allofuranos-3-yl)-glycine **10**

This compound was recrystallized from pentane. Yield: 2.467 g (96%). M.p.: 67–69°C (pentane). Rf=0.48 (ethylacetate). $[\alpha]_D=-31$ (c=7, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δppm: 1.28 (3H, s), 1.31 (3H,

s), 1.35 (3H, s), 1.50 (3H, s), 3.30 (1H, s), 3.42 (1H, s), 3.48 (1H, s), 3.63 (1H, d, J=8.9 Hz), 3.65 (1H, dd, J=8.2 Hz, J=5.4 Hz), 3.86 (1H, m), 3.96 (1H, dd, J=8.2 Hz, J=5.9 Hz), 4.10 (2H, m), 4.44 (1H, d, J=3.8 Hz), 5.09 (1H, d, J=3.8 Hz), 7.20 (1H, OH), 7.30 (10H, m). $[M+H^+]$=514 (FAB^+/NBA).

Hydrolysis of compound 7

15% Aqueous citric acid (20 ml) was added to a solution of **7** (5 mmoles, 2.555 g) in THF (25 ml). The mixture was stirred at rt for 24 h; then the solvent removed in vacuo. The aqueous layer was extracted with ether. The organic layer was discarded and the aqueous layer brought to pH=8 with sodium carbonate. After several extractions with ether, the organic phase was dried ($MgSO_4$) and evaporated.

(2S)-2-(1,2:5,6-Di-O-isopropylidene-α-D-glucofuranos-3-yl)-Gly-OMe ***11***

This compound was recrystallised from pentane. Yield: 1.648 g (95%). M.p.: 124–126°C (pentane). Rf=0.50 (ethylacetate). $[\alpha]_D$=+64 (c=3, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δppm: 1.10 (3H, s), 1.20 (3H, s), 1.29 (6H, s), 3.70 (3H, s), 3.85 (1H, m), 4.00–4.10 (3H, m), 4.22 (1H, d, J=3.4 Hz), 4.38 (1H, m), 4.42 (1H, OH), 5.77 (1H, d, J=3.4 Hz). $[M+H^+]$=348 (FAB^+/NBA).

Synthesis of compound ***12***

To a solution of compound **9** (6 mmoles, 2.082 g), BOP (6 mmoles, 2.655 g) in DCM (7 ml) at 0°C, was added dropwise 15 mmoles of DIEA. The mixture was stirred at 0°C for 1 h, then at rt for 24 h. The solvent was removed in vacuo and ethyl acetate was added to the residue. The organic layer was washed with 0.1 N aqueous $KHSO_4$, saturated aqueous NaCl and saturated aqueous Na_2CO_3. The organic phase was dried ($MgSO_4$), evaporated and the residue was purified by chromatography.

(2S),(3'R)-3'-N-Dibenzyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranos-3-spiropropiolactone ***12***

Yield: 2.792 g (94%). M.p.: 140–142°C (ether). Rf=0.68 (ether/pentane: 1/1). $[\alpha]_D$=+5 (c=1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δppm: 1.11 (3H, s), 1.28 (3H, s), 1.30 (3H, s), 1.51 (3H, s), 3.74–3.84 (2H, m), 3.93–3.99 (2H, m), 4.03 (1H, d, J=9.3 Hz)), 4.90 (1H, d, J=4.8 Hz), 4.92 (1H, s), 5.78 (1H, d, J=4.8 Hz), 7.35 (10H, m). $[M+H^+]$=496 (FAB^+/NBA). IR ($CHCl_3$): ν_{CO}=1824 cm^{-1}.

Synthesis of compound ***13***

NH_3(g) was bubbled at −10°C in a solution of **12** (0.495 g, 1 mmole) in DCM (10 ml) for 0.5 h. The reaction mixture was stirred at rt for 4 h. The solution was concentrated and the residue was purified by chromatography on silica gel.

N,N-Dibenzyl-(2S)-2-(1,2:5,6-di-O-isopropylidene-α-D-allofuranos-3-yl)-glycinamide ***13***

This compound was recrystallized from pentane. Yield: 0.486 g (95%). M.p.: 72–74°C (pentane). Rf=0.16 (ether/pentane: 2/1). $[\alpha]_D$=−8 (c=1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δppm: 1.30 (3H, s), 1.32 (3H, s), 1.35 (3H, s), 1.50 (3H, s), 3.06 (1H, s), 3.35 (1H, OH), 3.50–3.52 (2H, m), 3.54–3.58 (2H, m), 3.62 (1H, dd, J=8.5 Hz, J=6.5 Hz), 3.94 (1H, dd, J=8.5 Hz, J=6.0 Hz), 3.86 (1H, m), 4.08 (2H, m), 4.25 (1H, d, J=3.9 Hz), 5.04(1H, d, J=3.9 Hz), 5.92 (2H, NH_2), 7.26 (10H, m). $[M+H^+]$=513 (FAB^+/NBA). IR ($CHCl_3$): ν_{NH}=3450 cm^{-1}, ν_{CO}=1675 cm^{-1}.

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