Communications to the Editor

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NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 57.[1] A STEREOSELECTIVE SYNTHESIS OF A DERIVATIVE OF D-RISTOSAMINE

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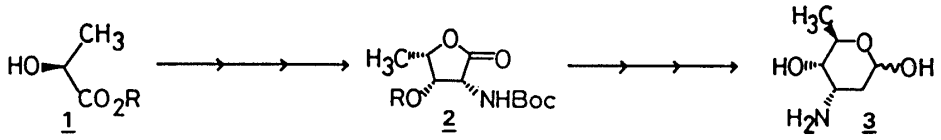
A derivative of D-ristosamine, the enantiomer of a carbohydrate component of the antibiotics ristomycin, has been prepared from ethyl L-lactate in a stereoselective manner using the Mitsunobu reaction as a key step.

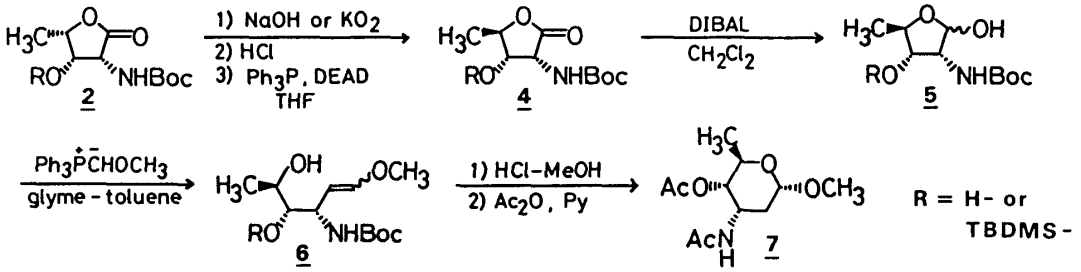
KEYWORDS —— D-ristosamine; C-acylation; diphenyl phosphorazidate; methyl isocyanoacetate; amino sugar synthesis; Mitsunobu reaction; D-ribonolactone

Recently we described a highly efficient stereoselective synthesis of two amino sugars, L-daunosamine[2] and a derivative of L-vancosamine,[3] by a route starting with L-lactic acid (**1**, R=H), involving the direct C-acylation of methyl isocyanoacetate with the lithium salt of O-methoxymethyl-L-lactic acid using diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$),[4] and choosing the L-lyxono-1,4-lactone **2** (R=H) as a common key intermediate.

We now report a convenient stereoselective synthesis of D-ristosamine **3**,[5] the enantiomer of the carbohydrate component of the antibiotics ristomycin, as its N,O-diacetyl methyl glycoside, involving a synthetic method analogous to the amino sugar synthesis.[2,3] The key feature of our synthesis is the inversion of the chiral center at the C-4 position of **2**.



Commercially available ethyl L-lactate (**1**, R=C_2H_5) was first efficiently converted to the L-lyxono-1,4-lactone **2** (R=H) in 6 steps in an overall yield of 52% according to the method developed by us.[2] Treatment of **2** (R=H) with t-butylchlorodimethylsilane (2 eq) in the presence of imidazole (2.6 eq) in dimethylformamide (room temp., 2 days) quantitatively afforded the silyl ether **2** (R=TBDMS[6]) as a colorless oil. Hydrolysis of the silyl ether **2** with 1N aqueous sodium hydroxide in methanol (-20°C, 16 h; room temp., 3 h), followed by neutralization with 1N hydrochloric acid, produced the ring-opened hydroxy acid. Inversion of the chiral center at the C-4 position was achieved by the Mitsunobu reaction[7] with a mixture of triphenylphosphine (1.5 eq) and diethyl azodicarboxylate (DEAD, 1.5 eq) in tetrahydrofuran (room temp., 18 h) to give the D-ribonolactone **4** (R=TBDMS) as a colorless oil, $[\alpha]_D^{23}$ -17.0° (c=0.28, MeOH), in 54% yield from **2** (R=TBDMS). Reduction of **4** (R=TBDMS) with diisobutylaluminum hydride (2.5 eq) in dichloromethane



(−65 ∿ −70°C, 3 h, under argon) gave the lactol 5 (R=TBDMS) as a colorless oil in 82% yield. The reaction of 5 with methoxymethylenetriphenylphosphorane[2] (4.2 eq) in glyme-toluene (−10°C, 40 min; room temp., 1.5 h; under argon) afforded the methyl ether 6 (R=TBDMS) in 51% yield with the recovery of the starting 5 in 17% yield. Final construction of D-ristosamine as its N,O-diacetyl methyl glycoside was achieved by treating 6 (R=TBDMS) with 5% methanolic hydrogen chloride (45°C, 17 h) and the subsequent acetylation with acetic anhydride in pyridine (room temp., 15 h), giving 7, mp 50–52°C, $[\alpha]_D^{23}$ +127.6° (c=0.30, $CHCl_3$), in 51% yield. Synthetic methyl N,O-diacetyl α-D-ristosaminide (7) was indistinguishable from its L-isomer[5c] by IR, Mass, ^1H- and ^{13}C-NMR spectral data and by chromatographic mobility on silica gel, except for the sign of its specific rotation.

This D-ristosamine derivative 7 was prepared more efficiently by an alternative route without protection of the C-3 hydroxyl function of the lyxono-1,4-lactone 2 (R=H). Hydrolysis of 2 (R=H) with potassium superoxide (3 eq) and 18-crown-6 (0.3 eq) in tetrahydrofuran-methanol-water (4:1:1) (0°C, 4 h), acidification with 20% hydrochloric acid to pH 4, followed by the Mitsunobu reaction as described above afforded an inseparable mixture of the D-ribonolactone 4 (R=H) and diethyl hydrazinedicarboxylate in a ratio of 1.3:1. Reduction of this mixture with diisobutylaluminum hydride (5 eq) in dichloromethane (−73°C, 10 h; under argon) gave the pure lactol 5 (R=H), mp 90–92°C, $[\alpha]_D^{25}$ −11.3° (equil., c=1, MeOH), in 71% yield from 2 (R=H). Sequential Wittig reaction, acid treatment, and acetylation as described above afforded the D-ristosamine derivative 7.

The above synthetic methodology using the lactone 2 as a key intermediate will be applicable to the synthesis of other amino sugars.

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