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Note

Concise syntheses of D-desosamine, 2-thiopyrimidinyl desosamine donors, and methyl desosaminide analogues from D-glucose

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Abstract—A concise synthesis of D-desosamine has been accomplished in five steps and in 15% overall yield from methyl α-D-glucopyranoside. Desosamine was then transformed into two known 2-thiopyrimidinyl donors (Woodward and Tatsuta donors), each in two steps. Finally, analogues of methyl desosaminide at the C-3 position were prepared (3-pyrrolidino, 3-piperidino, 3-morpholino) from a common 2,3-anhydrosugar intermediate.
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Keywords: Synthesis; Desosamine; Donors; Analogues

The biological activity of many glycosylated natural products is compromised in the absence of the carbohydrate portion, or glycone.[1] The deoxy amino sugar D-desosamine (3,4,6-trideoxy-3-dimethylamino-D-*xylo*-hexopyranose, **1**), which is a structural component of many macrolide antibiotics such as erythromycin, azithromycin, and telithromycin, is essential for the efficacy of these drugs.[2] After structure determination by chemical degradation and spectroscopic analyses was established, several syntheses of desosamine were reported with the most recent being disclosed in 2004.[3] As part of a program in medicinal carbohydrate chemistry, we sought to develop a route to D-desosamine from cheap, commercial sources that would allow ready access to known 2-thiopyrimidinyl donors **2** and **3**, initially reported from the laboratories of Woodward[4] and Tatsuta,[5] respectively. These donors have been utilized in the total synthesis of erythromycin A by the groups of Woodward[4] and Tatsuta,[6] as well as by Martin et al. in the total synthesis of erythromycin B.[7] In addition, the route should enable facile preparation of C-3 amino analogues **4** in a modular fashion, a structural class inaccessible from D-desosamine isolated from natural sources. Furthermore, this route could be utilized in the synthesis of TDP-α-D-desosamine, the glycosyl donor used in the biosynthesis of desosamine-containing natural products, as well as analogues thereof[8] (Fig. 1).

The synthesis of D-desosamine (**1**) begins with commercially available methyl α-D-glucopyranoside (**5**). Deoxygenation of both C-4 and C-6 positions was accomplished in two steps by (1) treating **5** with sulfuryl chloride in pyridine/chloroform followed by aqueous sodium iodide in methanol[9] and (2) hydrogenation of dichloride **6** with Raney nickel in the presence of potassium hydroxide to afford diol **7** in 47% yield over two steps.[10] Subjection of diol **7** to Mitsunobu conditions furnished 2,3-anhydrosugar **8**, an intermediate which is critical for the regioselective synthesis of C-3 analogues of desosamine.[11] Aminolysis of **8** with aqueous dimethylamine afforded a 6:1 ratio of chromatographically separable regioisomers (C-3/C-2) wherein the C-3 isomer, methyl desosaminide (**9**), was isolated in 76% yield.[12] Hydrolysis of **9** with under standard acidic conditions followed by basic work-up (Amberlyst A-26 hydroxide form) delivered D-desosamine (**1**) in 74% yield (Scheme 1). The overall yield for the synthesis of **1** from **5** was 15% over five steps.

Previous syntheses of **1** have utilized a variety of strategies. Richardson prepared methyl 3-acetamido-4,6-

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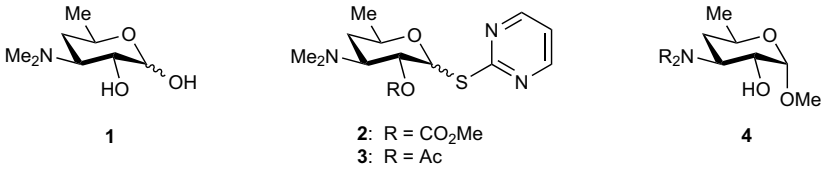
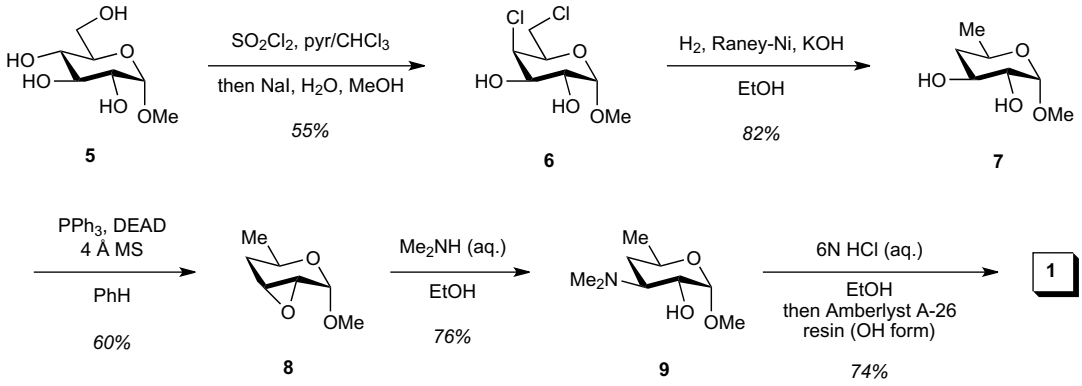


Figure 1. Structures of D-desosamine (**1**), 2-thiopyrimidinyl donors **2**–**3**, C-3 analogues **4**.



Scheme 1. Synthesis of D-desosamine (**1**) from methyl α-D-glucopyranoside (**5**).

di-*O*-benzylidene-α-D-glucopyranoside as a key intermediate,[3f] which was in turn prepared by the reaction of phenylhydrazine with periodate-oxidized methyl 4,6-di-*O*-benzylidene-α-D-glucopyranoside, originally reported by Guthrie and Johnson.[3j] Tietze and Hartfiel[3g] employed a Hetero Diels–Alder reaction to access racemic **1** whereas Baer synthesized *ent*-**1** by borohydride reduction of methyl 3,4,6-trideoxy-3-nitro-α-L-*erythro*-hex-3-enopyranoside, followed by catalytic hydrogenation of the nitro group.[3h] Finally, McDonald recently assembled **1** from a glycal precursor, which was prepared via a tungsten carbonyl-catalyzed cycloisomerization of a suitably protected amino alkynol.[3i]

With a concise route to **1** in hand, attention was directed at preparing known donors **2**[4] and **3**.[5] Activation of the anomeric hydroxyl of desosamine (**1**) under Mitsunobu conditions with tributylphosphine and DEAD in the presence of 2-mercaptopyrimidine led to a 7:1 mixture of β/α anomers in 64% yield after flash column chromatography.[13] Treatment of alcohol **10** with methyl chloroformate in a mixture of THF and aqueous sodium bicarbonate yielded Woodward's desosamine donor **2** in 82% yield.[4,14] Alternatively, acetylation of the C-2 hydroxyl under standard conditions afforded Tatsuta's desosamine donor **3** in 76% yield (Scheme 2).[5,13]

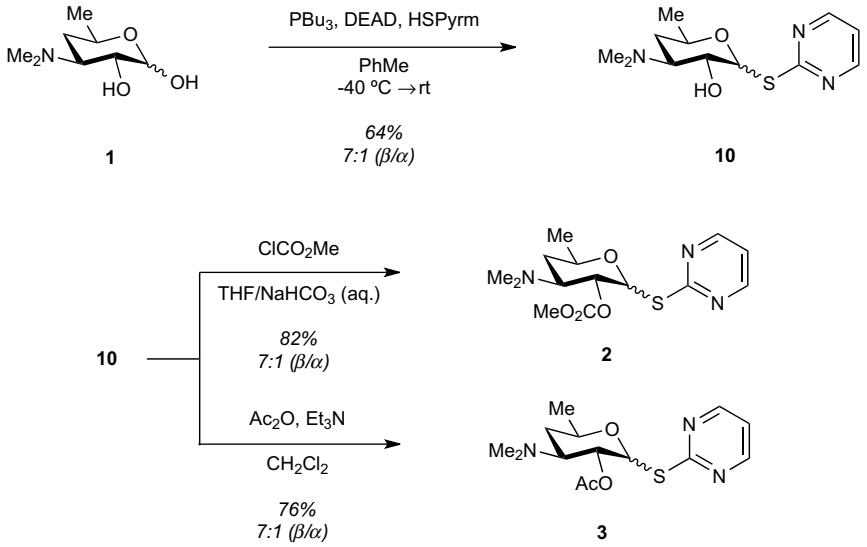
In addition to efficiency, a key design element in the synthetic plan was the preparation of an intermediate that would allow ready access to many C-3 amino analogues of desosamine, particularly those analogues inaccessible from desosamine derived from natural sources. Toward this end, we identified known 2,3-anhydrosugar **8**, which has been shown to undergo regioselective ring opening at the C-3 position with various secondary amines in alcoholic solvents either at ambient temperature or reflux (Table 1).[11b,12] In the event, reaction of **8** with pyrrolidine (**11**), piperidine (**12**), and morpholine (**13**) proceeded in a highly regioselective manner to afford exclusively C-3 analogues of methyl desosaminide **4a**–**c** in good yields after chromatography.

Accordingly, hydrolysis of these methyl glycosides and transformation into 2-thiopyrimidinyl donors via two steps would deliver novel C-3 desosamine analogue donors for study vis-à-vis **2** and **3**.

1. Experimental

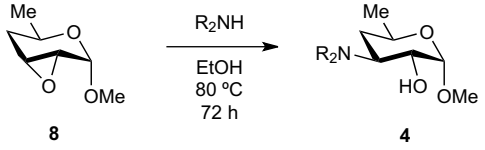
1.1. General methods

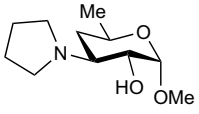
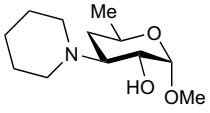
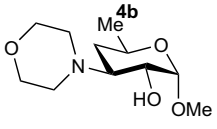
All reactions containing water or air sensitive reagents were performed in oven-dried glassware under nitrogen or argon. Molecular sieves (4 Å) were flame-dried under vacuum prior to use. Tetrahydrofuran and dichloromethane were passed through two columns of neutral alumina. Toluene was passed through one column of neutral alumina and one column of Q5 reactant. Benzene, Et_3N, pyrrolidine, piperidine, and morpholine were distilled from calcium hydride. MeOH and ethanol were distilled from magnesium. Chloroform was distilled from P_2O_5. All other reagents were purchased from commercial sources and used without further purification. All solvents for work-up procedures were used as received. Flash column chromatography was performed according to the procedure of Still[15] using ICN



Scheme 2. Synthesis of donors **2** and **3** from common 2-thiopyrimidinyl intermediate **10**.

Table 1. Regioselective ring-opening of **8** to yield analogues of methyl desosaminide **4a–c**



Entry	R_2NH	Product	Yield (%)
1	 **11**	 **4a**	86
2	 **12**	 **4b**	83
3	 **13**	 **4c**	78

Silitech 32–63 D 60 Å silica gel with the indicated solvents. Thin layer chromatography was performed on Analtech $60F_{254}$ silica gel plates. Detection was performed using either UV light or phosphomolybdic acid (PMA) stain and subsequent heating. Amberlyst A-26 (OH form) resin was washed with MeOH prior to use (10 mL/g). ^1H and ^{13}CNMR spectra were recorded at the indicated field strength in $CDCl_3$ at rt. Chemical shifts are indicated in parts per million (ppm) downfield from tetramethylsilane (TMS, $\delta = 0.00$) and referenced to the $CDCl_3$. Splitting patterns are abbreviated as follows: s (singlet), d (doublet), t (triplet) and m (multiplet).

1.2. Methyl 4,6-dideoxy-4,6-dichloro-α-D-galactopyranoside (6)

Methyl α-D-glucopyranoside (1.0 g, 5.14 mmol) was dissolved in pyridine (6 mL) and chloroform (6 mL). Sulfuryl chloride (3.35 g, 41.2 mmol) was added dropwise over 30 min at −78 °C. The reaction mixture was stirred for 2 h at this temperature, and the mixture was warmed

to rt. The reaction mixture was heated to 50 °C and stirred for 5 h. After cooling to rt, the solution was diluted with MeOH (3 mL) and water (3 mL) and subsequently neutralized by slow addition of solid Na_2CO_3. To this mixture was added a solution of NaI (0.38 g, 2.54 mmol) in H_2O/MeOH (2 mL, 1:1), and the reaction mixture was stirred an additional 5 min. The resulting solution was coevaporated with toluene (2 × 12 mL) and concentrated under reduced pressure. The solid was recrystallized from chloroform to afford 0.65 g (55%) of **6**. Spectral data of **6** matched those reported in Ref. 10b.

1.3. Methyl 4,6-dideoxy-α-D-xylo-hexopyranoside (7)

To a solution of KOH (0.90 g, 16.1 mmol) in EtOH (10 mL) was added **6** (1.0 g, 4.33 mmol). The reaction mixture was stirred at rt under a H_2 atmosphere in the presence of Ni-Raney (4.6 g, Aldrich) for 12 h. The reaction mixture was filtered through a bed of Celite (making sure to keep the filter cake moist) and quenched with an aqueous solution of 10% HCl (25 mL). The solution was then taken up in hot $CHCl_3$ (50 mL). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography eluting with CH_2Cl_2/acetone (70:30) to afford 0.57 g of **7** (82%) as a white solid. Spectral data of **7** matched those reported in Ref. 11b.

1.4. Methyl 2,3-anhydro-4,6-dideoxy-α-D-ribo-hexopyranoside (8)

PPh_3 (1.06 g, 4.06 mmol) and DEAD (0.70 g, 4.06 mmol) were added to a solution of **7** (0.6 g, 3.69 mmol) in benzene (36 mL) containing 4 Å molecular sieves (1.0 g). The reaction mixture was refluxed for 24 h and cooled to rt. The reaction mixture was concentrated under reduced pressure and purified by bulb-to-bulb distillation (bp = 140 °C, 18 mmHg) to afford 0.28 g of **8** (60%) as a clear liquid. Spectral data of **8** matched those reported in Ref. 11b.

1.5. Methyl desosaminide (9)

Dimethylamine (2 mL, 40% in H_2O) was added to a solution of **8** (70 mg, 0.56 mmol) in EtOH (2.3 mL) and stirred for 60 h at rt. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with MeOH/CH_2Cl_2/Et_3N (10:85:5) to afford 80 mg (76%) of **9** as a colorless oil. Spectral data of **9** matched those reported in Ref. 12.

1.6. D-Desosamine (1)

To a solution of **9** (110 mg, 0.58 mmol) in EtOH (5 mL) was added 6 N HCl (3 mL). The reaction mixture was refluxed for 4 h, cooled to rt and concentrated under reduced pressure. The residue was dissolved in MeOH (2 mL) and passed through a small column of Amberlyst A-26 resin (200 mg, OH form) to afford 75 mg (74%) of **1** as a yellow oil. Spectral data of **1** matched those reported in Ref. 3c.

1.7. 1-(2-Pyrimidinethio) 3,4,6-trideoxy-3-(dimethylamino)-D-xylo-hexopyranoside (10)

DEAD (59 mg, 0.34 mmol) was added to a solution of tri-*n*-butylphosphine (69 mg, 0.34 mmol) in toluene (1.5 mL) at −40 °C and stirred for 20 min at this temperature. A solution of **1** (50 mg, 0.28 mmol) in toluene (1.5 mL) was added rapidly. After 45 min, solid 2-mercaptopyrimidine (38.1 mg, 0.34 mmol) was added. The cooling bath was removed, and the reaction mixture was stirred for 15 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc/hexanes/Et_3N (75:20:5) to afford 48 mg (64%) of **10** as a yellow oil. Spectral data of **10** matched those reported in Ref. 13.

1.8. 1-(2-Pyrimidinethio) 3,4,6-trideoxy-2-*O*-methoxycarbonyl-3-(dimethylamino)-D-xylo-hexopyranoside (2)

Methyl chloroformate (21 mg, 0.22 mmol) was added to a solution of **10** (50 mg, 0.18 mmol) in THF (1 mL) and satd aq $NaHCO_3$ (1 mL) at rt. After 15 min the reaction mixture was diluted with EtOAc (10 mL) and washed with water (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc/hexanes/Et_3N (60:35:5) to afford 48 mg (82%) of **2** as a yellow oil. Spectral data of **2** matched those reported in Ref. 4.

1.9. 1-(2-Pyrimidinethio) 3,4,6-trideoxy-2-*O*-acetyl-3-(dimethylamino)-D-xylo-hexopyranoside (3)

Ac_2O (22 mg, 0.22 mmol) was added to a solution of **10** (50 mg, 0.18 mmol) and Et_3N (22 mg, 0.22 mmol) in CH_2Cl_2 (2 mL) at rt and stirred for 12 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 5% aq $NaHCO_3$ (5 mL) and brine (5 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc/hexanes/Et_3N (70:25:5) to afford 42 mg (76%) of **3** as a colorless oil. Spectral data of **3** matched those reported in Ref. 13.

1.10. General procedure for the aminolysis of 8 with secondary amines

A solution of **8** (1 equiv) in anhydrous EtOH (5 mL) was treated with the secondary amine (5.0 equiv) at rt. The reaction mixture was heated to 80 °C and stirred for 72 h at this temperature. After cooling to rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with $MeOH/CH_2Cl_2/Et_3N$ (20:75:5) to afford the corresponding 3-amino analogues **4a–c** as oils.

1.11. Methyl 3,4,6-trideoxy-3-pyrrolidino-α-D-xylo-hexopyranoside (4a)

Yield = 86%: $[\alpha]_D^{25}$ +126 (*c* 0.1, $CHCl_3$); IR (neat) 3457, 2969, 1272, 1049, 690 cm^{-1}; ^1H NMR (400 MHz): δ 4.81 (d, $J = 3.6$ Hz, 1H, H-1), 3.88 (m, 1H, H-5), 3.53 (dd, $J = 10.8$, 3.6 Hz, 1H, H-2), 3.36 (s, 3H, H–OMe), 3.05 (td, $J = 10.8$, 4.0 Hz, 1H, H-3), 2.61 (m, 4H, H-pyrr), 1.75 (m, 5H, H-pyrr, H-4), 1.31 (m, 1H, H-4), 1.18 (d, $J = 6.0$ Hz, 3H, H-6); ^{13}C NMR (100 MHz): δ 99.9 (C-1), 70.6 (C-2), 64.9 (C-5), 57.2 (C-3), 55.3 (C-pyrr × 2), 48.0 (C–OMe), 31.2 (C-4), 23.8 (C-pyrr × 2), 21.5 (C-6); FABMS calculated for $C_{11}H_{22}NO_3$ $[M+H]^+$: 216.1599, observed 216.1595.

1.12. Methyl 3,4,6-trideoxy-3-piperidino-α-D-xylo-hexopyranoside (4b)

Yield = 82%: $[\alpha]_D^{25}$ +132 (*c* 0.1, $CHCl_3$); IR (neat) 3422, 2967, 1457, 1272, 1090, 1048 cm^{-1}; ^1H NMR (400 MHz): δ 4.84 (d, $J = 3.6$ Hz, 1H, H-1), 3.86 (m, 1H, H-5), 3.55 (dd, $J = 10.8$, 3.6 Hz, 1 H, H-2), 3.41 (s, 3H, H–OMe), 2.89 (td, $J = 10.8$, 3.6 Hz, 1H, H-3), 2.63 (m, 2H, H-pip), 2.36 (m, 2H, H- pip), 1.74 (m, 1H, H-4), 1.55 (m, 4H, H-pip), 1.41 (m, 2H, H-pip), 1.21 (m, 1H, H-4), 1.15 (d, $J = 4.0$ Hz, 3H, H-6); ^{13}C NMR (100 MHz): δ 99.9 (C-1), 68.1 (C-2), 65.3 (C-5), 61.8 (C-3), 55.3 (C–OMe), 49.8 (C-pip × 2), 31.1 (C-4), 26.7 (C-pip × 2), 25.0 (C-pip), 21.5 (C-6); FABMS calculated for $C_{12}H_{24}NO_3$ $[M+H]^+$: 230.1756, observed 230.1747.

1.13. Methyl 3,4,6-trideoxy-3-morpholino-α-D-xylo-hexopyranoside (4c)

Yield = 78%: $[\alpha]_D^{25}$ +144 (*c* 0.1, $CHCl_3$); IR (neat) 3440, 2975, 1641, 1454, 1110, 1043, 674 cm^{-1}; ^1H NMR (400 MHz): δ 4.86 (d, $J = 3.4$ Hz, 1H, H-1), 3.88 (m, 1H, H-5), 3.68 (m, 4H, H-morph), 3.57 (dd, $J = 10.6$, 3.4 Hz, 1H, H-2), 3.42 (s, 3H, H–OMe), 2.90 (td, $J = 10.6$, 3.6 Hz, 1H, H-3), 2.67 (m, 2H, H-morph), 2.45 (m, 2H, H-morph), 1.76 (m, 1H, H-4), 1.29 (m, 1H, H-4), 1.19 (d, $J = 6.4$ Hz, 3H, H-6); ^{13}C NMR (100 MHz): δ 99.7 (C-1), 68.0 (C-2), 67.7 (C-morph × 2), 65.1 (C-5), 61.5 (C-3), 55.3 (C–OMe), 48.8 (C-morph × 2), 31.1 (C-4), 21.5 (C-6); FABMS calculated for $C_{11}H_{22}NO_4$ $[M+H]^+$ 232.1549, observed 232.1539.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.10.004.

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