An Improved Synthesis of *N*-Trifluoroacetyl-L-daunosamine

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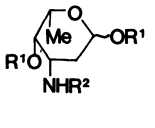
Synopsis. A process which can afford a large quantity of the title compound was explored by modifying the Horton's original route. The developed process features highly stereoselective reduction of the oxime with sodium dihydrobis(2-methoxyethanolato)aluminate(1-) and efficient dehydrobromination with 1,8-diazabicyclo[5.4.0]undec-7-ene.

L-Daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexopyranose) (**1**) attracts much attention in recent years as an aminosugar component of natural and unnatural anthracycline antibiotics which show prominent anticancer properties.[1,2]

In connection with synthetic studies on optically active anthracyclines,[3] we required a large quantity of *N*-trifluoroacetyl-L-daunosamine (**2**) from which the substrate for glycosidation reaction, 1,4-bis(*O*-*p*-nitrobenzoyl)-3-*N*-trifluoroacetyl-L-daunosamine (**3**), can be readily prepared. It is well known that a trifluoroacetyl group is well suited for protecting the amino group of **1** during glycosidation reaction since it can be readily removed under mild alkaline conditions without cleavage of the formed glycoside linkage.[1-3] However, while **2** can be usually prepared from *N*-



1: $R^1 = R^2 = H$
2: $R^1 = H$, $R^2 = CF_3CO$
3: $R^1 = p\text{-}NO_2C_6H_4CO$, $R^2 = CF_3CO$

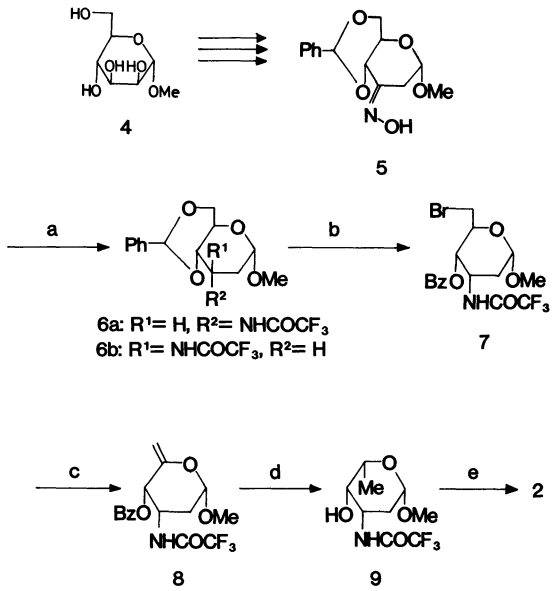
acetyl- or *N*-benzoyl-L-daunosamine through **1**-hydrochloride by protective group exchange,[1,2,5] direct preparation method of **2** has never been explored.

In this note, we wish to describe a new synthesis of **2** which is developed by modifying the Horton's original synthetic scheme for *N-acetyl*-L-daunosamine.[4] The developed method includes the following advantages over the Horton's procedure. (1) Trifluoroacetyl group is introduced at the early stage of the synthetic process. This can exclude the above-mentioned tedious protective group exchange. (2) Highly stereoselective reduction of the oxime **5** can be accomplished with sodium dihydrobis(2-methoxyethanolato)aluminate(1-) (Vitride or Red-Al) in toluene in place of lithium aluminum hydride (LAH) in ether. The latter reported reduction which should be carried out using a Soxhlet extraction apparatus is clealy not applicable to a large scale synthesis. (3) Cheap 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) can effect clean dehydrobromination in a similar manner to expensive silver fluoride. By employing these improved synthetic methods, we have succeeded in readily obtaining a large quantity of **2** from methyl α-D-mannopyranoside (**4**).

Thus, according to the reported method,[4] **5** was prepared in 52% overall yield starting from **4**. The reduction of **5** with Vitride in toluene was found to proceed more stereoselectively than with LAH, giving the trifluoroacetamide **6a** in 59% overall yield as a sole product after trifluoroacetylation. NMR analysis of **6a** definitely disclosed that the formation ratio of the desired *ribo*-isomer **6a** to the undesired *arabino*-isomer **6b** is more than 99:1. This result is clearly superior to the reported reduction of **3** with LAH in ether,[4] in which a mixture of the *ribo*- and *arabino*-isomers could be produced in a ratio of 88:12 by our hands. The highly stereoselective reduction observed for Vitride may be due to steric bulkiness of the reducing agent which carries two 2-methoxyethoxy groups.

Similarly to the original route,[4] treatment of **6a** with *N*-bromosuccinimide (NBS) gave the bromide **7** in 85% yield. Dehydrobromination of **7** with inexpensive DBU in benzene afforded **8** in 75% yield in a similar manner to that reported with silver fluoride. The unsaturated sugar **8** was elaborated to methyl *N*-trifluoroacetyl-L-daunosamine (**9**) in 53% yield, mp 155.5—156.5 °C, $[\alpha]_D^{20}$ −46.7° (methanol), by sequential transesterification with methanol and catalytic hydrogenation over palladium on carbon. Further hydrolysis of the methyl glycoside **9** with 20% acetic acid quantitatively produced **2**, mp 146—147 °C, $[\alpha]_D^{20}$ −127.2° (methanol).

Taking into account several novel aspects including high stereoselectivity, operational simplicity, and use of less expensive reagents, the explored synthetic scheme is expected to hold promise in a large scale preparation of **2**.



a: i) $NaAlH_2(OCH_2CH_2OMe)_2$–C_6H_5Me ii) $(CF_3CO)_2O$–Py, b: NBS, c: DBU, d: i) NaOMe–MeOH ii) 5% Pd–C, H_2, e: 20% AcOH

Scheme 1.

Experimental

Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-3-trifluoroacetamido-α-D-ribo-hexopyranoside (6a). A 70% toluene solution of Vitride (95 mL, 333 mmol) was added to a solution of **5**[4] (mp 202 °C, $[\alpha]_D^{23}$ +203° (*c* 1.21, $CHCl_3$)) (lit,[4] mp 203 °C, $[\alpha]_D^{23}$ +202° (*c* 1.2, $CHCl_3$)) (20.0 g, 71.6 mmol) in toluene (350 mL) with stirring at −40 °C. After stirring at −40 °C for 0.5 h and at 25 °C for 4 h, the reduction was quenched by successively adding H_2O (7 mL), 15% NaOH (7 mL), and H_2O (21 mL) to the reaction mixture. The upper toluene layer was separated, dried over anhyd K_2CO_3, filtrated through a pad of Celite, then concentrated in vacuo, to afford crude methyl 3-amino-4,6-*O*-benzylidene-2,3-dideoxy-α-D-hexopyranoside as a pale yellow viscous oil.

Pyridine (24.1 g, 305 mmol) and trifluoroacetic anhydride (44.0 g, 210 mmol) were successively added to an ethereal solution (200 mL) of the oily amine with stirring at −40 °C. After stirring at 0 °C for 3 h, the ethereal mixture was filtered to remove insoluble materials and the solid collected was washed with ether. The ethereal filtrates and washings were combined, washed successively with satd $NaHCO_3$ and satd NaCl, then dried over anhyd $MgSO_4$. Filtration and concentration in vacuo, gave an oily residue, which was purified by column chromatography (benzene/EtOAc=10/1) to give pure **6a** as a colorless oil (15.1 g, 59%), $[\alpha]_D^{21}$ +8.6° (*c* 1.47, $CHCl_3$). IR (neat): 3410, 1735, 1540 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.93—2.10 (m, 2H, 2-H_2), 3.41 (s, 3H, OCH_3), 3.60—4.80 (m, 6H, 1-, 3-, 4-, 5-H_4+6-H_2), 5.57 (s, 1H, PhC<u>H</u>), 7.15—7.43 (m, 5H, Ph), 7.67 (d, *J*=9 Hz, 1H, NH). MS *m/z*: 361 (M^+).

Methyl 4-*O*-Benzoyl-6-bromo-2,3,6-trideoxy-3-trifluoroacetamido-α-D-ribo-hexopyranoside (7). Following to the reported method,[4] a suspension of **6a** ($[\alpha]_D^{21}$ +8.6° (*c* 1.47, $CHCl_3$)) (15.1 g, 41.9 mmol), NBS (9.03 g, 50.7 mmol), and $BaCO_3$ (12.0 g, 60.8 mmol) in anhyd CCl_4 (350 mL) was heated at reflux with stirring under irradiation with a 60W tungsten lamp. After 1.5 h reaction, the whole mixture was cooled and filtered to remove insoluble materials. The solid collected was washed with CH_2Cl_2 (10 mL×3). The organic phases were combined, washed successively with 5% $NaHSO_3$ and satd $NaHCO_3$, then dried over anhyd $MgSO_4$. Filtration and concentration in vacuo gave a residue, which was purified by column chromatography (benzene/EtOAc=20/1) to afford **7** as a pale yellow solid (16.3 g, 88%), mp 100—102 °C. This was recrystallized from a mixture of benzene and hexane to give an analytical sample of **7**, mp 111.5—112 °C, $[\alpha]_D^{20}$ +39.3° (*c* 1.07, $CHCl_3$). IR (KBr): 3400, 1730, 1545 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.83—2.40 (m, 2H, 2-H_2), 3.33—3.77 (m, 2H, 6-H_2), 3.35 (s, 3H, OCH_3), 4.02—4.30 (m, 1H, 5-H), 4.67—5.00 (m, 2H, 1-H+3-H). 5.10 (dd, *J*=10 and 5 Hz, 1H, 4-H). 7.23—8.07 (m, 6H, NH+Ph). MS *m/z*: 439 (M^+), 441 ($[M+2]^+$). Found: C, 43.83; H, 3.69; N, 3.14%. Calcd for $C_{16}H_{17}BrF_3NO_5$: C, 43.66; H, 3.89; N, 3.18%.

Methyl 4-*O*-Benzoyl-2,3,6-trideoxy-3-trifluoroacetamido-α-D-erythro-hex-5-enopyranoside (8). A mixture of **7** (mp 100—102 °C) (8.26 g, 18.8 mmol) and DBU (3.76 g, 24.7 mmol) in benzene (10.5 mL) was heated at reflux for 2.5 h with stirring. After cooling, the mixture was filtered and the solid collected was washed with benzene. The combined filtrates were concentrated in vacuo to give a dark brown oil, which was purified by column chromatography (benzene/EtOAc=20/1) to give pure **8** as a pale yellow oil (5.07 g, 75%), $[\alpha]_D^{20}$ +17.6° (*c* 0.67, $CHCl_3$). IR (neat): 3400, 1735, 1670, 1540, 1000 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.90—2.46 (m, 2H, 2-H_2), 3.47 (s, 3H, OCH_3), 4.61—4.98 (m, 4H, 1,3-H_2+6-H_2), 5.57—5.73 (m, 1H, 4-H), 7.20—8.10 (m, 6H, NH+Ph). MS *m/z*: 359 (M^+).

Methyl *N*-Trifluoroacetyl-L-daunosamine (9). A 1.0 M† solution of sodium methoxide in MeOH (0.7 mL, 0.7 mmol) was added to a solution of **8** ($[\alpha]_D^{20}$ +17.6° (*c* 0.67, $CHCl_3$)) (5.07 g, 14.1 mmol) in MeOH (15 mL), and the mixture was stirred at room temperature for 15 h. After acetic acid (0.05 mL) was added to the mixture, the methanolic solution was concentrated in vacuo. The residue was purified by filtration through a short silica-gel column (ether) to give crude methyl 3-trifluoroacetamido-2,3,6-trideoxy-α-D-*erythro*-hex-5-enopyranoside as a yellow oil (4.9 g, quantitative yield).

A mixture of the oily unsaturated sugar derivatives (4.9 g) and 5% Pd-C (505 mg) in MeOH (100 mL) was stirred under a hydrogen atmosphere at atmospheric pressure for 4 h. Filtration and concentration in vacuo gave a pale yellow solid, which was purified by column chromatography (benzene/EtOAc=4/1) to afford pure **9** as a colorless crystals (1.94 g, 53%), mp 143—145 °C. A part of this sample was recrystallized from a mixture of EtOAc and hexane to give an analytical sample of **9**, mp 155.5—156.5 °C, $[\alpha]_D^{20}$ −46.7° (*c* 0.10, CH_3OH). IR (KBr): 3475, 3300, 1750, 1588 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.30 (d, *J*=6.5 Hz, 3H, CH_3), 1.58 (dd, *J*=12 and 9 Hz, 1H, 2-*ax*-H), 2.05 (ddd, *J*=12, 4.5, and 2 Hz, 1H, 2-*eq*-H), 2.15 (d, *J*=10 Hz, 1H, OH), 3.48 (s, 3H, OCH_3), 3.38—3.70 (m, 2H, 4-, 5-H_2), 3.80—4.25 (m, 1H, 3-H), 4.35 (dd, *J*=9 and 2 Hz, 1H, 1-H), 6.75 (brs, 1H, NH). Found: C, 41.98; H, 5.64; N, 5.42%. Calcd for $C_9H_{14}F_3NO_4$: C, 42.03; H, 5.49; N, 5.45%.

***N*-Trifluoroacetyl-L-daunosamine (2).** A 20% acetic acid (10 ml) was added to **9** (mp 143—145 °C) (200 mg, 0.78 mmol) and the mixture was stirred at 100 °C for 2 h. After cooling, the mixture was concentrated in vacuo below 30 °C, and the residue was purified by filtration through a short silica-gel column (EtOAc) to give pure **2** as a pale yellow solid (187 mg, 100%), mp 140—141.5 °C. A part of this sample was recrystallized from EtOAc to give an analytical sample of **2**, mp 146—147 °C, $[\alpha]_D^{20}$ −127° (*c* 0.10, MeOH, *equil.*) (lit,[5] mp 146—147 °C). IR (KBr): 3460, 3350, 1710, 1550, 1170 cm^{-1}. ^1H NMR ($(CD_3)_2SO$) δ=1.08 (d, *J*=6 Hz, 3H, CH_3), 1.40—2.30 (m, 2H, 2-H_2), 3.30—4.50 (m, 3H, 3-, 4-, 5-H_3), 4.83 (d, *J*=5 Hz, 1H, OH), 5.00—5.27 (m, 1H, 1-H). 6.08 (d, *J*=3 Hz, 1H, OH), 9.00 (brd, *J*=9 Hz, 1H, NH). Found: C, 39.51; H, 5.50; N, 5.70%. Calcd for $C_8H_{12}F_3NO_4$: C, 39.51; H, 4.98; N, 5.76%.

References

1) F. Arcamone, *Lloydia*, **40**, 45 (1977); F. Arcamone, "Doxorubicin Anticancer Antibiotics," Academic Press, New York (1981).

2) S. Terashima, *Yuki Gosei Kagaku Kyokai Shi*, **40**, 20 (1982).

3) Y. Kimura, M. Suzuki, T. Matsumoto, R. Abe, and S. Terashima, *Chem. Lett.*, **1984**, 501; Y. Kimura, M. Suzuki, and S. Terashima, ibid., **1984**, 2113.

4) D. Horton and W. Weckerle, *Carbohydr. Res.*, **44**, 227 (1975).

5) T. H. Smith, A. N. Fujiwara, W. W. Lee, H. Y. Wu, and D. W. Henry, *J. Org. Chem.*, **42**, 3653 (1977).

† 1 M=1 mol dm^{-3}.