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Synthesis of Acosamine and Daunosamine from Sugar δ-Enelactones

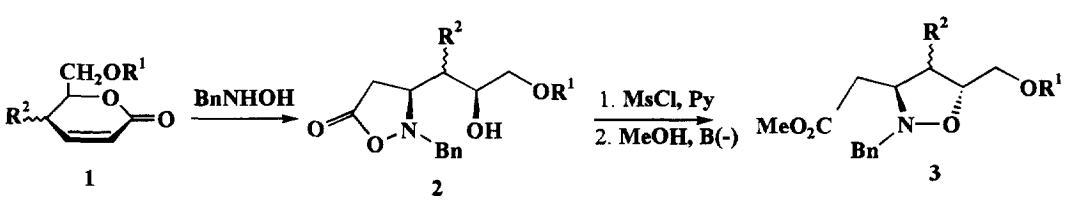
Dariusz Socha, Margarita Jurczak and Marek Chmielewski*

Institute of Organic Chemistry of the Polish Academy of Sciences, 01-224 Warsaw, Poland

Abstract: Conjugate addition-rearrangement of *N*-benzylhydroxylamine to lactones **11** and **12** provided respective isoxazolidin-5-ones **13** and **14** which were in turn mesylated at the hydroxy group and subjected to the next skeleton rearrangement to afford *N*,3,4,5-tetrasubstituted isoxazolidines **18** and **19** in such a way that inversion of configuration at C-5 of the sugar chains occurred. Standard transformation of isoxazolidines **18** and **19** provided methyl glycosides of *N,O*-diacetate of acosamine **33** and daunosamine **34**, respectively. Copyright © 1996 Elsevier Science Ltd

Conjugate addition - rearrangement of *N*-benzyhydroxylamine to α,β-unsaturated lactones **1** leads to 3-substituted isoxazolidin-5-ones **2**[1]. High yield and defined stereochemistry of this reaction with simultaneous liberation of the 5-OH group, while all other groups remain protected, offers a possibility to switch from sugars of the D-configurational series to those of the L-series, thus providing an attractive entry to important 3-amino-2,3-dideoxy L-sugars. Mesylation of hydroxy group and subsequent treatment of the molecule with a nucleophile causes isoxazolidin-5-one - isoxazolidine rearrangement with inversion of the configuration at the C-5 carbon atom of the sugar skeleton[2,3] (Scheme 1).

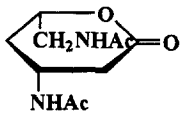
Scheme 1



1 **2** **3**

R_1 = Bn, Si*t*-BuPh_2
R_2 = H, OR^1

Recently we have reported the synthesis of *N,N*-diacetylnegamycin lactone **4**, which has illustrated the above presented idea[2]. The present paper describes the synthesis of sugar components of anthracycline antibiotics: acosamine **5**[4] and daunosamine **6**[5]. Both sugars have been synthesized frequently in the past[6].



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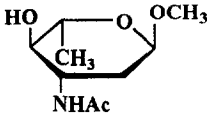

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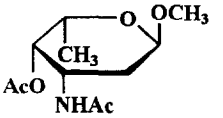
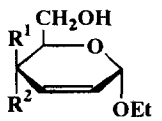
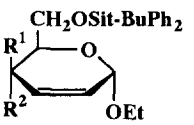


6

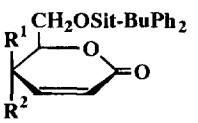
For the synthesis of sugars **5** and **6** we selected readily available unsaturated glycosides **7** and **8**. Compounds **7** and **8** were transformed into lactones **11** and **12,** respectively, by a standard reaction sequence which consisted of silylation - benzylation followed by anomeric oxidation[7].



7: R^1= OH, R^2= H
8: R^1= H, R^2= OH

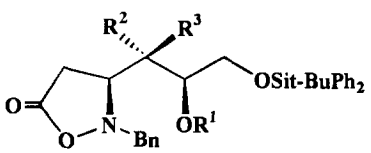


9: R^1= OBn, R^2= H
10: R^1= H, R^2= OBn

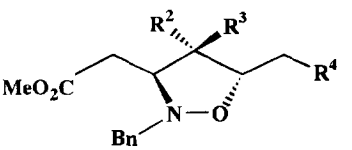


11: R^1 = OBn, R^2 = H
12: R^1 =H R^2 = OBn

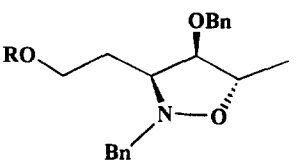
Addition of *N*-benzylhydroxylamine to lactones **11** and **12** according to the known procedure[1], afforded respective isoxazolidin-5-ones **13** and **14**. Compounds **13** and **14** were subsequently subjected to the isoxazolidin-5-one - isoxazolidine rearrangement[3] to give esters **18** and **19.**



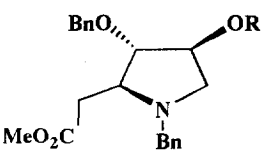
13: R^1 = R^2= H, R^3 = OBn
14: R^1 = R^3= H, R^2 = OBn
15: R^1 = Ac, R^2 = H, R^3 = OBn
16: R^1 = Ms, R^2 = H, R^3 = OBn
17: R^1 = Ms, R^2 = OBn, R^3 = H



18: R^2 = H, R^3 = OBn, R^4 = OSi*t*-$BuPh_2$
19: R^2 = OBn, R^3 = H, R^4 = OSi*t*-$BuPh_2$
20: R^2 = H, R^3 = OBn, R^4 = OH
21: R^2 = OBn, R^3 = H, R^4 = OH
22: R^2 = H, R^3 = OBn, R^4 = Br
23: R^2 = OBn, R^3 = H, R^4 = Br
24: R^2 = R^4 = H, R^3 = OBn
25: R^2 = OBn, R^3 = R^4 = H



26: R = H
27: R = Ac



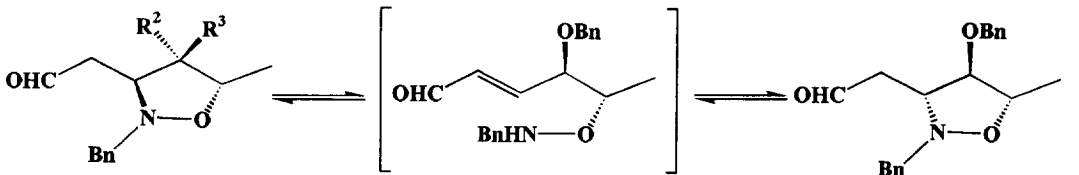
28: R = H
29: R = Ac

Standard reaction sequences involving desilylation with fluoride anion and Appel reaction (CBr_4, PPh_3) transformed compounds **18** and **19** into respective bromides **22** nd **23**. Reduction of bromide **22** with sodium

borohydride in the presence of the PTC catalyst provided compound **24** with terminal methyl substituent. Compound **24** was accompanied with traces of alcohol **26**. Due to the *cis* location of substituents at C-4 and C-5 of the isoxazolidine ring, bromide **23** under the same conditions remained unchanged. Debromination of **23** was achieved by sodium cyanoborohydride reduction in boiling DMF. The product **25** was accompanied with pyrrolidine derivative **28** which was the result of splitting of the nitrogen - oxygen bond followed by intramolecular alkylation of the nitrogen atom.

Reduction of the ester group in **24** and **25** with DIBAL-H gave respective aldehydes **30** and **31**. Aldehyde **30**, which could also be obtained by oxidation of **26** with PDC, was found to be unstable. Upon prolongated chromatographical purification of **30**, the product was found to be contaminated with the C-3 epimer **32**. The relative *cis* configuration of substituents at C-3 and C-4 carbon atoms in **30** is most likely a driving force of the epimerisation which proceeds *via retro* Michael reaction (Scheme 2).

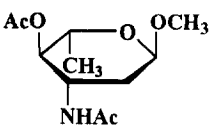
Scheme 2



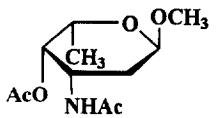
30: $R^2 = H$, $R^3 = OBn$
31: $R^2 = OBn$, $R^3 = H$

32

Hydrogenation of aldehydes **30** and **31** over palladium hydroxide on carbon followed by methanol/HCl treatment and acetylation of the hydroxy and amino functions afforded methyl glycosides **33** and **34**, respectively. The structures and configurations of **33** and **34** were proved by comparison of their spectral and analytical data with respective literature data[8,9].



33



34

We demonstrated a simple and general conception leading to 3-amino-2,3,6-trideoxy L-sugars, in which configuration at the C-5 carbon atom of the hexopyranoid substrate (**11**, **12**) determines configuration of the newly formed stereogenic center at the C-3. The desired configuration of amino sugar was achieved

subsequently by staightforward inversion of configuration at C-5, which involved the isoxazolidin-5-one - isoxazolidine rearrangement

EXPERIMENTAL

^{1}H NMR spectra were recorded with a Bruker AM 500 spectrometer. IR spectra were obtained on a FT-IR-1600 Perkin-Elmer spectrophotometer. Optical rotations were measured with a JASCO-DIP-360 digital polarimeter. Column chromatography was performed on Merck silica gel 230-400 mesh. Synthesis and spectral data of compounds **14**, **17** and **19** have been described earlier[3].

Ethyl 4-*O*-benzyl-6-*O*-*t*-butyldiphenylsilyl-2,3-dideoxy-α-D-threohex-2-enopyranoside (9). Compound **7** (12.0 g, 46.5 mmol) was dissolved in dichloromethane (60 ml), treated with imidazole (3.4 g, 2.2 molar equiv.) and *t*-butyldiphenylchlorosilane (6.5 ml, 1.1 molar equiv.). After disappearance of the substrate (about 0.5 h) the mixture was poured into water, and extracted with dichloromethane. The extract was washed with brine, dried and evaporated. The crude syrup was purified by chromatography to give 6-*O*-silyl derivative (8.7 g, 92%) which was in turn used for benzylation. To the 6-*O*-silyl derivative (4.5 g, 11 mmol) in toluene (60 ml) benzyl bromide (1.7 ml, 14.3 mmol), pulverized KOH (1.5 g), and tetrabutylammonium bromide (0.025 g) were added. The mixture was stirred at room temperature for 24 h. Subsequently, the mixture was filtered through Celite. The solution was washed, dried and evaporated. The crude product was purified using hexane - ethyl acetate 12:1 $^v/_v$ as an eluent to afford **9** (4.2 g, 77%); $[\alpha]_D$ -75.0° (*c* 1.1, CH_2Cl_2); IR (film): 1113 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.07 (s, 9H, *t*-Bu), 1.19 (t, 3H, Et), 3.50, 3.80 (2dq, 2H, Et), 3.77 (dd, 1H, *J* 2.4, 5.3 Hz, H-4), 3.88 (dd, 1H, *J* 6.5, 10.4 Hz, H-6), 4.00 (dd, 1H, *J* 6.6, 10.4 Hz, H-6'), 4.17 (dt, 1H, *J* 2.5, 6.5, 6.6 Hz, H-5), 4.58, 4.64 (2d, 2H, *J* 11.8 Hz, Bn), 5.05 (dd, 1H, *J* 1.0, 3.0 Hz, H-1), 5.98 (ddd, 1H, *J* 0.4, 3.0, 10.1 Hz, H-2), 6.12 (ddd, 1H, *J* 1.0, 5.3, 10.1 Hz, H-3); MS (EI/HR) m/z, $(M-C_4H_9)^+$, calcd for $C_{27}H_{29}O_4Si$: 445.1835. Found: 445.1828.

Ethyl-4-*O*-benzyl-6-*O*-*t*-butyldiphenylsilyl-2,3-dideoxy-α-D-erythrohex-2-enopyranoside (10). Compound **10** was obtained from **8** according to the procedure described above (70% overall yield); $[\alpha]_D$ +53.0° (*c* 1.0, CH_2Cl_2); IR (film): 1113 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.06 (s, 9H, *t*-Bu), 1.22 (t, 3H, *J* 7.1 Hz, Et), 3.55, 3.89 (2m,2H, Et), 3.88 (dd, 1H, *J* 5.4, 11.4 Hz, H-6), 3.91-3.98 (m, 2H, H-5, 6'), 4.08 (dq, 1H, *J* ~1.5, ~1.7, ~1.7, 9.3 Hz, H-4), 4.47, 4.60 (2d, 2H, *J* 11.7 Hz, Bn), 5.03 (m,1H, H-1), 5.79 (ddd, 1H, *J* 2.0,2.6, 10.2 Hz, H-2), 6.08 (bd, 1H, *J* 10.2 Hz, H-3); MS (LSIMS/HR) m/z, $(M+Na)^+$, calcd for $C_{31}H_{38}O_4SiNa$: 525.2437. Found: 525.2442.

4-*O*-Benzyl-6-*O*-*t*-butyldimethylsilyl-2,3-dideoxy-D-threohex-2-eno-1,5-aldonolactone (11). Compound **9** (4.0 g, 8 mmol) and molybdenum trioxide (0.5 g) were suspended in 60% hydrogen peroxide (75 ml) and t-butanol (5 ml). The mixture was stirred at room temperature for 2 days until disappearance of the substrate. Subsequently it was poured into water and extracted with dichloromethane. The extract was washed eight times with water, dried and carefully evaporated at room temperature. The crude hydroperoxide was dissolved in dichloromethane (50 ml) at 0° C and treated slowly with acetic anhydride - pyridine mixture 1:1 $^v/_v$ (10 ml). Subsequently the mixture was poured into ice - water and extracted with dichloromethane. The extract was washed with water, sodium hydrogen carbonate solution, sodium bisulfite solution, water, then dried and evaporated. The crude product was purified on a silica gel column using hexane - ethyl acetate 8:1 $^v/_v$ as an eluent to afford **11** (2.5 g, 65%); mp. 91-94 °C; $[\alpha]_D$ -124.0 ° (*c* 1.2, CH_2Cl_2); IR (film): 1733 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.07 (s, 9H, *t*-Bu), 3.95 (dd, 1H, *J* 5.4, 10.2 Hz, H-6), 4.14 (dd, 1H, *J* 8.3, 10.2 Hz, H-6'), 4.22 (dd, 1H, *J* 3.1, 5.4 Hz, H-4), 4.47 (ddd, 1H, *J* 3.1, 5.4, 8.3 Hz, H-5), 4.64 (s, 2H, Bn), 6.13 (d, 1H, *J* 9.8 Hz, H-2), 6.91 (dd, 1H, *J* 5.4, 9.8 Hz, H-3); MS (EI/HR) m/z, $(M-C_4H_9)^+$, calcd for $C_{25}H_{23}O_4Si$: 415.1366. Found 415.1365.

4-*O*-Benzyl-6-*O*-*t*-butyldiphenylsilyl-2,3-dideoxy-D-erythrohex-2-eno-1,5-aldonolactone (12). Compound **12** was obtained from **10** according to the procedure described above (67% overall yield); $[\alpha]_D$ +60.4° (*c* 1.0, CH_2Cl_2); IR (film): 1738 cm^{-1}; ^1H NMR ($CDCl_3$): 1.06 (s, 9H, *t*-Bu), 3.89 (dd, 1H, *J* 3.6, 11.5 Hz, H-6), 3.96 (dd, 1H, *J* 3.2, 11.5 Hz, H-6'), 4.44 (dt, 1H. *J* 3.2, 3.6, 7.6, Hz, H-5), 4.55, (ddd, 1H, *J* 2.8, 7.6 Hz, H-4), 4.61, 4.67 (2d, 2H, *J* 11.5 Hz, Bn), 6.00 (dd, 1H, *J* 1.7, 10.0 Hz, H-2), 6.83 (dd, 1H, *J* 2.8, 10.0 Hz, H-3); MS (LSIMS/HR) m/z, (M+Na)°, calcd for $C_{29}H_{32}O_4SiNa$: 495.1968. Found: 495.1970.

(3S, 1'R, 2'R)-2-Benzyl-3-(1'-benzyloxy-3'-*t*-butyldiphenylsiloxy-2'-hydroxy)propylisoxazolidin-5-one (13). Compound **11** (1.5 g, 3.2 mmol) was dissolved in ethanol (40 ml) and treated with *N*-benzylhydroxylamine (0.43 g, 3.5 mmol). After 1h at room temperature the solvent was evaporated and the product was purified on a silica gel column using hexane - ethyl acetate 8:1 $^v/_v$ as an eluent to afford **13** (1.82 g, 95 %), which was characterized as 2'-*O*-acetate **15**: $[\alpha]_D$ -38.6 ° (*c* 1.0, CH_2Cl_2); IR (film): 1786, 1744 cm^{-1}; ^1H NMR ($CDCl_3$): 1.05 (s, 9H, *t*-Bu), 1.99 (s, 3H, Ac), 2.45 (dd, 1H, *J* 6.7, 17.7 Hz, H-4a), 2.68, (dd, 1H, *J* 8.7, 17.7 Hz, H-4b), 3.53 (dt, 1H, *J* 6.7, 7.1, 8.7 Hz, H-3), 3.58 (dd,1H, *J* 5.7, 10.9 Hz, H-3'a), 3.75 (dd, 1H, *J* 5.3, 10.9 Hz, H-3'b), 3.81 (dd, 1H, *J* 3.8, 7.1 Hz, H-1'), 4.09, 4.23 (2d, 2H, *J* 13.9 Hz, NBn), 4.64, 4.68 (2d, 2H, *J* 11.4 Hz, OBn), 5.12 (dt, 1H, *J* 3.8, 5.3, 5.7 Hz, H-2'); MS (EI/HR) m/z, $(M-C_4H_9)^+$, calcd for $C_{34}H_{34}NO_6Si$: 580.2155. Found: 580.2157.

(3S, 1'R, 2'R)-2-Benzyl-3-(1'-benzyloxy-3'-*t*-butyldiphenylsiloxy-2'-mesyloxy) propyl-isoxazolidin-5-one (16). Compound **13** (15 g, 2.5 mmol) was mesylated with mesyl chloride (0.23 ml, 3 mmol) in dichloromethane (40 ml) and pyridine (0.48 ml, 6 mmol) under standard conditions to afford **16** (1.37 g, 81%); $[\alpha]_D$ -31.6° (*c* 1.1, CH_2Cl_2); IR (film): 1787 cm^{-1}; ^1H NMR ($CDCl_3$): 1.05 (s, 9H, *t*-Bu), 2.13 (dd, 1H, *J* 4.7, 17.7 Hz, H-4a), 2.70 (dd, 1H, *J* 8.8, 17.7 Hz, H-4b), 3.45 (dd, 1H, *J* 5.5, 12.1 Hz, H-3'a), 3.49 (dt, 1H, 4.7, 6.2, 8.8 Hz, H-3), 3.74 (t, 1H, *J* 4.7, 6.2 Hz, H-1'), 3.84 (dd, 1H, *J* 3.6, 12.1 Hz, H-3'b), 4.06, 4.08 (2d, 2H, *J* 13.8 Hz, NBn), 4.64, 4.68 (2d, 2H, *J* 11.4 Hz, OBn), 4.68 (dt, 1H, *J* 3.6, 5.5, 9.1 Hz, H-2'); MS (EI/HR) m/z, $M^{+\cdot}$, calcd for $C_{37}H_{43}NO_7SSi$: 673.2530. Found: 673.2528.

(3S, 4R, 5S)-2-Benzyl-4-benzyloxy-5-*t*-butyldiphenylsiloxymethyl-3-methoxy-carbonylmethyl-isoxazolidine (18). Compound **16** (0.8 g, 1.2 mmol) was dissolved in dry methanol (30 ml) and reacted at room temperature with anhydrous K_2CO_3 (1 molar equiv.) until disappearance of the substrate. Subsequently, the solution was filtered through Florisil, and evaporated to dryness. The crude product was purified on a silica gel column using hexane - ethyl acetate 9:1 $^v/_v$ as an eluent to give **18** (0.43 g, 60%); $[\alpha]_D$ +51.2 ° (*c* 1.2, CH_2Cl_2); IR (film): 1738 cm^{-1}; ^1H NMR ($CDCl_3$): 1.06 (s, 9H, t-Bu), 2.44 (bdd, 1H, *J* 4.8, 16.7 Hz, $CH_AH_BCO_2Me$), 2.93 (dd, 1H, *J* 9.2, 16.7 Hz, $CH_AH_BCO_2Me$), 3.35 (bs, 1H, H-3), 3.61 (s, 3H, OCH_3), 3.62 (dd, 1H, *J* 3.9, 11.2 Hz, CH_AH_BO), 3.69 (dd, 1H, *J* 4.5, 11.2 Hz, CH_AH_BO), 3.85, 4.00 (2d, 2H, *J* 13.8 Hz, NBn), 4.07 (bm, 1H, H-5), 4.41, 4.54 (2d, 2H, *J* 11.8 Hz, OBn), 4.48 (dd, 1H, *J* 3.7, 6.1 Hz, H-2'); MS (EI/HR) m/z, $M^{+\cdot}$, calcd for $C_{37}H_{43}NO_5Si$: 609.2911. Found: 609.2906.

(3S, 4R, 5S)-2-Benzyl-4-benzyloxy-5-hydroxymethyl-3-methoxycarbonylmethyl-isoxazolidine (20). Compound **18** (0.35 g, 0.57 mmol) in THF (15 ml) was treated with tetrabutylammonium fluoride trihydrate (0.182 g, 0.57 mmol). After disappearance of the substrate (0.5 h) the mixture was evaporated and purified on a silica gel column to give **20** (0.195 g, 92%) which was characterized as the acetate: $[\alpha]_D$ +60.6° (*c* 1.1, CH_2Cl_2); IR (film): 1739 cm^{-1}; ^1H NMR ($CDCl_3$): 2.05 (s, 3H, Ac), 2.41 (bdd, 1H, *J* 4.3, 16.9 Hz, $CH_AH_BCO_2Me$), 2.87 (dd, 1H, *J* 9.3, 16.9 Hz, $CH_AH_BCO_2Me$), 3.33 (bs, 1H, H-3), 3.61 (s, 3H, OCH_3), 3.90, 4.01 (2d, 2H, *J* 14.0 Hz, NBn), 4.03 (m, 1H, CH_AH_BOAc), 4.14 (m, 2H, H-5, CH_AH_BOAc), 4.21 (dd, 1H, *J* 4.0, 6.3 Hz, H-4), 4.45, 4.53 (2d, 1H, *J* 11.7 Hz, OBn); MS (EI/HR) m/z, $M^{+\cdot}$, calcd for $C_{23}H_{27}NO_6$: 413.1838. Found: 413.1837.

(3S, 4S, 5S,)-2-Benzyl-4-benzyloxy-5-hydroxymethyl-3-methoxycarbonylmethyl-isoxazolidine (21). Compound **21** was obtained from **19** according to the procedure described above, and was characterized as the acetate: $[\alpha]_D$ +59.0° (*c* 1.1, CH_2Cl_2); IR (film): 1738 cm^{-1}; ^1H NMR ($CDCl_3$): 2.03 (s, 3H, OAc), 2.38 (dd, 1H, *J* 8.3, 16.0 Hz, $CH_AH_BCO_2Me$), 2.45 (dd, 1H, *J* 5.6, 16.0 Hz, $CH_AH_BCO_2Me$), 3.61 (ddd, 1H, *J* 1.5, 5.6,

8.3 Hz, H-3), 3.63 (s, 3H, OCH_3), 4.13, 4.24 (2d, 2H, *J* 13.0 Hz, NBn), 4.24 (m, 2H, H-4, H-5), 4.32 (m, 1H, CH_AH_BOAc), 4.49 (m, 1H, CH_AH_BOAc), 4.53, 4.69, (2d, 2H, *J* 11.9 Hz, OBn); MS (EI/HR) m/z, $M^{+\bullet}$, calcd for $C_{23}H_{27}NO_6$: 413.1838. Found: 413.1837.

(3S, 4R, 5R)-2-Benzyl-4-benzyloxy-5-bromomethyl-3-methoxycarbonylmethyl-isoxazolidine (22). Compound **20** (0.16 g, 0.43 mmol) in dry toluene (10 ml) was treated with triphenylphosphine (0.225,g, 0.86 mmol) and carbon tetrabromide (0.285,g, 0.86 mmol). After 12 h at room temperature the precipitate was filtered off and the solvent was evaporated. Chromatographical purification using hexane - ethyl acetate 8:1 $^{v}/_{v}$ as an eluent gave **22** (0.155 g, 83%); $[\alpha]_D$ +112.7° (*c* 1.3, CH_2Cl_2); IR (film): 1736 cm^{-1}; ^1H NMR ($CDCl_3$): 2.42 (bdd, 1H, *J* 4.3, 16.9 Hz, $CH_AH_BCO_2Me$), 2.89 (dd, 1H, *J* 9.2, 16.9 Hz, $CH_AH_BCO_2Me$), 3.24 (d, 2H, CH_2Br), 3.36 (bs, 1H, H-3), 3.60 (s, 3H, OCH_3), 3.88, 4.02 (2d, 2H, *J* 14.0 Hz, NBn), 4.16 (bm, 1H, H-5), 4.29 (dd, 1H, *J* 3.3, 6.0 Hz, H-4), 4.50, 4.59 (2d, 2H, *J* 11.7 Hz, OBn); MS (EI/HR) m/z, $M^{+\bullet}$, calcd for $C_{21}H_{24}NO_4Br$: 433.0889. Found: 433.0881.

(3S, 4S, 5R)-2-Benzyl-4-benzyloxy-5-bromomethyl-3-methoxycarbonylmethyl-isoxazolidine (23). Compound **23** was obtained from **21** according to the procedure described above; 62%; $[\alpha]_D$ +113.4 ° (*c* 1.0, CH_2Cl_2); IR (film): 1737 cm^{-1}; ^1H NMR ($CDCl_3$) 2.41, (dd, 1H, *J* 8.2, 16.1 Hz, $CH_AH_BCO_2Me$), 2.49 (dd, 1H, *J* 5.9, 16.1 Hz, $CH_AH_BCO_2Me$), 3.50 (dd, 1H, *J* 5.1, 9.6 Hz, CH_AH_BBr), 3.64 (s, 3H, OCH_3), 3.68 (ddd, 1H, *J* 1.3, 5.9, 8.2 Hz, H-3), 3.72 (dd, 1H, *J* 9.0, 9.6 Hz, CH_AH_BBr), 4.11, 4.22 (2d, 2H, *J* 12.9 Hz, NBn), 4.27 (dd, 1H, *J* 1.3, 5.0 Hz, H-4), 4.34, (dt, 1H, *J* 5.0, 5.1, 9.0 Hz, H-5), 4.60, 4.72 (2d, 2H, *J* 11.4 Hz, OBn); MS (EI/HR) m/z, $M^{+\bullet}$, calcd for $C_{21}H_{24}NO_4Br$: 433.0889. Found: 433.0898.

(3S, 4R, 5S)-2-Benzyl-4-benzyloxy-3-methoxycarbonylmethyl-5-methyl-isoxazolidine (24) and **(3S, 4R, 5S)-2-benzyl-4-benzyloxy-3-(2'-hydroxyethyl)-5-methyl-isoxazolidine (26).** Compound **22** (0.14 g, 0.32 mmol) in toluene (6 ml) was treated with tetrakis(decyl)ammonium bromide (0.021 g, 1 molar equiv.), sodium borohydride (0.05 g, 1.3 mmol) and water (5 ml). The mixture was stirred and heated at 85 °C for 5 h. After disappearance of the substrate, the mixture was diluted with chloroform (20 ml) and the organic layer was separated. The water solution was extracted with chloroform and organic solutions were combined, washed, dried and evaporated. The crude syrup was separated on a silica gel column using hexane - ethyl acetate 7:1 $^{v}/_{v}$ as an eluent to afford **24** (0.083 g, 73%) and **26** (0.014 g, 13%).

24: $[\alpha]_D$ +105.0° (*c* 1.0, CH_2Cl_2); IR (film): 1736 cm^{-1}; ^1H NMR ($CDCl_3$) 1.22 (d, 3H, *J* 6.3 Hz, CH_3), 2.37 (bdd, 1H, *J* 4.5, 16.8 Hz, $CH_AH_BCO_2Me$), 2.87 (dd, 1H, *J* 9.4, 16.8 Hz, $CH_AH_BCO_2Me$), 3.34 (bs, 1H, H-3), 3.60 (s, 3H, OCH_3), 3.85, 3.99 (2d, 2H, *J* 14.0 Hz, NBn), 3.91 (dd, 1H, *J* 4.7, 6.7 Hz, H-4), 4.01 (bm, 1H, H-5), 4.44, 4.52 (2d, 2H, *J* 11.7 Hz, OBn); MS (EI/HR) m/z, $M^{+\bullet}$, calcd for $C_{21}H_{25}NO_4$: 355.1784. Found: 355.1787.

26 was characterized as its acetate **27**: $[\alpha]_D$ +81.8° (*c* 1.2, CH_2Cl_2), IR (film): 1738 cm^{-1}; ^1H NMR ($CDCl_3$) 1.25 (d, 1H, *J* 6.3 Hz, CH_3), 1.81 (bs, 1H, CH_AH_B), 2.00 (s, 3H, Ac), 2.16 (m, 1H, CH_AH_B), 2.91 (bs, 1H, H-3), 3.81, 4.08 (2d, 2H, *J* 14.0 Hz, NBn), 3.82 (dd, 1H, *J* 4.3, 6.3 Hz, H-4), 4.14 (t, 2H, CH_2OAc), ~ 4.09 (bm, 1H, H-5), 4.48, 4.60 (2d, 2H, *J* 11.7 Hz, OBn); MS (EI/HR) m/z, $M^{+\bullet}$, calcd for $C_{22}H_{27}NO_4$: 369.1940. Found: 369.1947.

(3S, 4S, 5S)-2-Benzyl-4-benzyloxy-3-methoxycarbonylmethyl-5-methyl-isoxazolidine (25) and **(3S, 4S, 2S)-*N*-Benzyl-3-benzyloxy-4-hydroxy-2-methoxycarbonylmethyl-pyrrolidine (28).** Compound **23** (0.175 g, 0.4 mmol) and sodium cyanoborohydride (0.075 g, 1.2 mmol) in DMF (5 ml) were kept under reflux for 3.5 h. Subsequently, the mixture was poured into water and extracted with ether. The extract was washed, dried and evaporated. The crude syrup was separated on a silica gel column using hexane - ethyl acetate 3:1 $^{v}/_{v}$ as an eluent to give **25** (0.085 g, 60%) and **28** (0.045 g, 32%)

25: $[\alpha]_D$ +91.5° (*c* 1.0, CH_2Cl_2); IR (film): 1738 cm^{-1}; ^1H NMR ($CDCl_3$): 1.34 (d, 3H, *J* 6.4 Hz, CH_3), 2.43 (dd,1H, *J* 7.6, 15,5 Hz, $CH_AH_BCO_2Me$), 2.46 (dd, 1H, *J* 6.0, 15.5 Hz, $CH_AH_BCO_2Me$), 3.46 (ddd, 1H, *J* 2.4, 6.0, 7.6 Hz, H-3), 3.63 (s, 3H, OCH_3), 4.01 (dd, 1H, *J* 2.4, 4.7 Hz, H-4), 4.06, 4.14 (2d, 2H, *J* 13.2 Hz, NBn), 4.10 (dq, 1H, *J* 4.7, 6.4 Hz, H-5), 4.54, 4.65 (2d, 2H, *J* 11.9 Hz, OBn); MS (EI/HR) m/z, $M^{+\bullet}$, calcd for $C_{21}H_{25}NO_4$: 355.1784. Found: 355.1787.

28 was characterized as its acetate **29**: $[\alpha]_D$ +37.6° (*c* 1.0, CH_2Cl_2); IR (film): 1737 cm^{-1}; ^1H NMR ($CDCl_3$): 2.03 (s, 3H, Ac), 2.57 (dd, 1H, *J* 7.3, 14.4 Hz, C**H**$_A$H$_B$CO$_2$Me), 2.68 (dd, 1H, *J* 4.8, 14.4 Hz, CH$_A$**H**$_B$CO$_2$Me), 2.71 (dd, 1H, *J* 6.0, 11.5 Hz, H-5), 2.84 (bd, 1H, *J* 11.5 Hz, H-5'), 2.96 (dt, 1H, *J* 4.8, 5.7, 7.3 Hz, H-2), 3.30, 4.00 (2d, 2H, *J* 13.1 Hz, NBn), 3.63 (s, 3H, OCH_3), 3.95 (bdd, 1H, *J* 2.0, 5.7 Hz, H-3), 4.55, 4.67 (2d, 2H, *J* 11.7 Hz, OBn), 5.05 (dt, 1H, *J* 1.4, 2.0, 6.0 Hz, H-4); MS (LSIMS/HR) m/z, $(M+H)^+$, calcd for $C_{23}H_{28}NO_5$: 398.1967. Found: 398.1963.

(3S, 4R, 5S)-2-Benzyl-4-benzyloxy-3-formylmethyl-5-methyl-isoxazolidine (30).

Procedure A. Compound **24** (0.072 g, 0.2 mmol) was dissolved in dry toluene (5 ml) under argon, cooled to -78°C and treated with 1.5 M toluene solution of DIBAL-H (215 µl, 0.32 mmol). After 20 min., maintaining temperature, methanol (100 µl) was added. Subsequently the mixture was diluted with chloroform and upon stirring 1N hydrochloric acid (5 ml) was added. The mixture was then poured into water, neutralized and organic layer was separated. The aqueous solution was extracted with chloroform and extracts were combined, washed with brine, dried and evaporated. The aldehyde **30** was obtained by chromatographical purification using hexane - ethyl acetate 4:1 $^v/_v$ as an eluent (0.05 g, 77%); $[\alpha]_D$ +87.8 (*c* 1.2, CH_2Cl_2); IR (film): 1721 cm^{-1}; ^1H NMR ($CDCl_3$): 1.24 (d, 3H, *J* 6.3 Hz, CH_3), 2.45 (bd, 1H, C**H**$_A$H$_B$), 2.91 (ddd, 1H, *J* 1.1, 8.7, 18.0 Hz, CH$_A$**H**$_B$), 3.32 (bs, 1H, H-3), 3.86, 3.97 (2d, 2H, *J* 13.9 Hz, NBn), 3.91 (dd, 1H, *J* 4.7, 6.8 Hz, H-4), 4.02 (bq, 1H, H-5), 4.41, 4.49 (2d, 2H, *J* 11.6 Hz, OBn), 9.77 (bt, 1H, CHO); MS (EI/HR) m/z, $M^{+\bullet}$, calcd for $C_{20}H_{23}NO_3$: 325.1678. Found: 325.1685.

Procedure B. Compound **26** (0,02 g, 0.06 mmol) in dichloromethane, upon stirring, was treated with a freshly prepared mixture of PDC (0.016 g, 0.042 mmol) and acetic anhydride (17 µl, 0.18 mmol) in dichloromethane (0.05 ml). The mixture was kept under reflux for 1 h. Subsequently, it was passed through a silica gel column using hexane - ethyl acetate 4:1 $^v/_v$ as an eluent to afford **30** (0.014 g, 69%).

Upon prolongation of time of chromatographical purification of **30,** the product becomes contaminated with the C-3 epimer, **(3R, 4R, 5S)-2-Benzyl-4-benzyloxy-3-formylmethyl-5-methyl-isoxazolidine (32)**; $[\alpha]_D$ -35.2° (*c* 1.0, CH_2Cl_2); IR (film): 1723 cm^{-1}; ^1H NMR ($CDCl_3$): 1.31 (d, 1H, *J* 6.4 Hz, CH_3), 2.44 (ddd, 1H, *J* 1.6, 6.3, 17.1 Hz, C**H**$_A$H$_B$), 2.72 (ddd,1H, *J* 1.7, 7.9, 17.1 Hz, CH$_A$**H**$_B$), 3.72 (ddd, 1H, *J* 1.4, 6.3, 7.9 Hz, H-3), 3.74 (dd, 1H, *J* 1.4, 4.0 Hz, H-4), 4.17, 4.31 (2d, 2H, *J* 12.6 Hz, NBn), 4.50 (dq, 1H, *J* 4.0, 6.4 Hz, H-5), 4.57, 4.64 (2d, 2H, *J* 11.8 Hz, OBn), 9.59 (t, 1H, *J* 1.6, 1.7 Hz, CHO); MS (EI/HR) m/z, $M^{+\bullet}$, calcd for $C_{20}H_{23}NO_3$: 325.1678. Found: 325.1675.

(3S, 4S, 5S)-2-Benzyl-4-benzyloxy-3-formylmethyl-5-methyl-isoxazolidine (31). Compound **31** was obtained from **25** according to the procedure **A** described for **30** (78%); $[\alpha]_D$ + 73.2° (*c* 1.2, CH_2Cl_2); IR (film): 1722 cm^{-1}; ^1H NMR ($CDCl_3$): 1.35 (d, 1H, *J* 6.4 Hz, CH_3), 2.48 (ddd, 1H, 1.9, 7.2, 17.1 Hz, C**H**$_A$H$_B$), 2.53 (ddd, 1H, *J* 1.6, 5.5, 17.1 Hz, CH$_A$**H**$_B$), 3.53 (ddd, 1H, 2.7, 5.5, 7.2 Hz, H-3), 3.94 (dd, 1H, *J* 2.7, 4.9 Hz, H-4), 4.05, 4.17 (2d, 2H, *J* 13.0 Hz, NBn), 4.12 (2q, 1H, *J* 4.9, 6.4 Hz, H-5), 4.58, 4.63 (2d, 2H, *J* 11.9 Hz, OBn), 9.63 (t, 1H, *J* 1.6, 1.9 Hz, CHO); MS (EI/HR) m/z, $M^{+\bullet}$, calcd for $C_{20}H_{23}NO_3$: 325.1678. Found: 325.1690.

Methyl 3-*N*-acetyl-4-*O*-acetyl-2,3,6-trideoxy-α-L-arabinohexopyranoside (methyl 3-*N*-acetyl-4-*O*-acetyl-α-L-acosaminide) (33). Compound **30** (0.03 g, 0.09 mmol) in methanol (4 ml) was hydrogenated over $Pd(OH)_2$/C under 70 psi of hydrogen for 7 h. Subsequently the mixture was filtered and treated with 10% HCl and methanol (4 ml) and left for 4 h. at room temperature. After evaporation of methanol the mixture was acetylated with acetic anhydride - pyridine mixture. The mixture was then diluted with ethyl acetate, filtered and evaporated. The crude product was purified by chromatography to give **33** (0.014 g, 65%) mp. 160-164°C, lit. Ref. 8, 158-163°C; $[\alpha]_D$ -91.7° (*c* 0.65, MeOH), lit. Ref. 8, $[\alpha]_D$ -84.0° (*c* 0.5, MeOH); IR (film): 3302, 1740, 1655 cm^{-1}; ^1H NMR ($CDCl_3$): 1.18 (d, 3H, *J* 6.3 Hz, CH_3), 1.58 (m, 1H, H-2); 1.9 (s, 3H, NAc), 2.08 (s, 3H, OAc), 2.23 (dd, 1H, *J* 1.2, 4.6, 13.2 Hz, H-2'), 3.34 (s, 3H, OCH_3), 3.91 (dq, 1H, *J* 6.3, 9.0 Hz, H-5), 4.42 (m, 1H, H-3), 4.47 (t, 1H, *J* 9.0, 10.5 Hz, H-4), 4.71 (bd, 1H, H-1), 5.49 (bd,1H, NH); MS (EI/HR) m/z, $(M-OCH_3)^+$, calcd for $C_{10}H_{16}NO_4$: 214.1079. Found: 214.1080.

Methyl 3-*N*-acetyl-4-*O*-acetyl-2,3,6-trideoxy-α-L-lyxohexopyranoside (methyl 3-*N*-acetyl-4-*O*-acetyl-α-L-daunosaminide) (34). Compound 34 was obtained from **31** according to the procedure described above (50%); mp. 174-178°C, lit. Ref. 5 and 9, 176-178 °C; $[\alpha]_D$ -132.0° (*c* 0.8, $CHCl_3$), lit. Ref. 5 and 9, $[\alpha]_D$ -130.0° ($CHCl_3$); IR (film): 3323, 1740,1651 cm^{-1}; ^1H NMR ($CDCl_3$): 1.11 (d, 3H, *J* 6.6 Hz, CH_3), 1.80 (m, 1H, H-2), 1.83 (m, 1H, H-2'), 1.93 (s, 3H, NAc), 2.18 (s, 3H, OAc), 3.34 (s, 3H, OCH_3), 4.05 (bq, 1H, H-5), 4.55 (m, 1H, H-3), 4.81 (m, 1H, H-4), 5.09 (m, 1H, H-1), 5.41 (bd, 1H, H-1, NH); MS (EI/HR), m/z, $M^{+\cdot}$, calcd for $C_{11}H_{19}NO_5$: 245.1263. Found: 245.1263.

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