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STEREOSELECTIVE SYNTHESIS OF t-BUTYL 2-AMINO-2,5-DIDEOXY-L-LYXO-PENTANOATE: FORMAL SYNTHESIS OF L-DAUNOSAMINE

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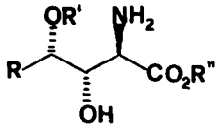
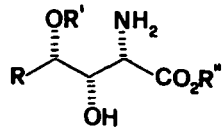
Abstract: Enantiomerically pure t-Butyl 2-amino-2,5-dideoxy-L-lyxo-pentanoate 4c is synthesized via the highly diastereoselective $MgBr_2$ mediated addition of dibenzylamino acetate silylketene acetal 2 to O-benzyl lactic aldehyde 3. The synthesis of γ-lactone 5c, a known intermediate in the synthesis of L-daunosamine and L-vancosamine, is also described.

Amino sugars represent a highly significant class of natural products, and are frequently employed as chiral synthons and templates for the stereospecific synthesis of compounds containing multiple asymmetric centers.[1] During the course of a project directed towards the stereoselective synthesis of unusual sugars[2] from non-carbohydrate precursors, we focused our attention on 2-amino-2-deoxy esters of general formula 1, whose utility as intermediates for the synthesis of 3-amino-2,3,6-trideoxy hexoses has been demonstrated in the lyxo series by Hamada et al.[3]

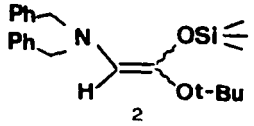


1-lyxo



1-xylo

A simple retrosynthetic analysis shows that the polyfunctional framework of molecules 1 can be assembled in only one step by the disconnection of the C-2,C-3 bond. An aldol type condensation between α-alkoxy aldehydes and α-amino esters enolate equivalents should then be a suitable way to achieve our goal. Furthermore, it is well known that under chelating Lewis acid catalysis α-alkoxy aldehydes and silylketene acetals react to give 3,4-syn aldols[4] (chelation controlled products). The use therefore of the 2-amino acetate derivative 2 was expected to provide an easy and highly stereoselective access to lyxo and/or xylo derivatives 1.



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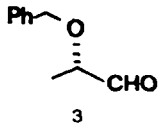


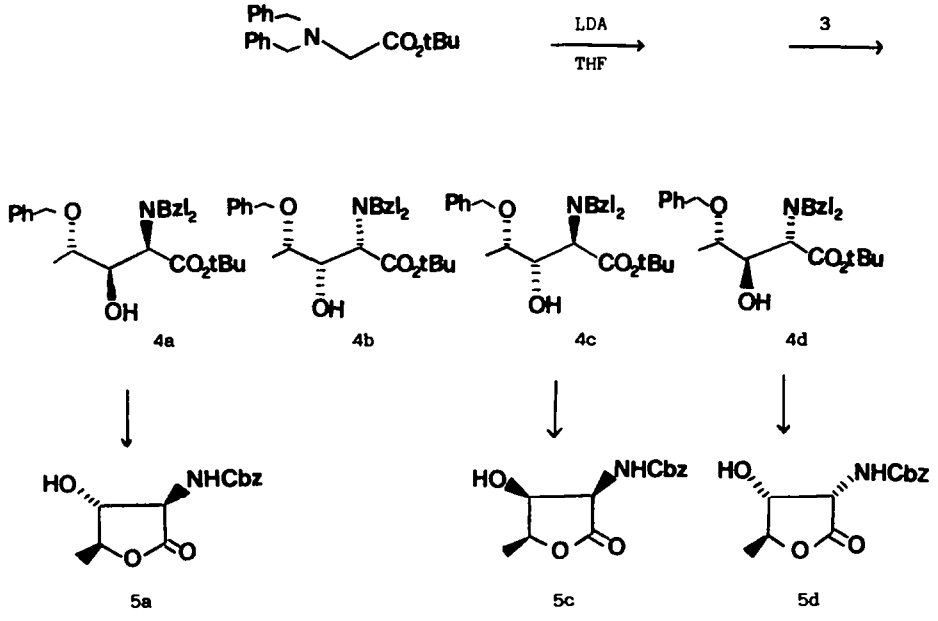
3

In a preliminary communication we reported on the rather disappointing results obtained when the reaction between 2 and 2-benzyloxy octyl aldehyde is promoted by the more commonly employed Lewis acids, like $SnCl_4$, $TiCl_4$ and BF_3Et_2O.[5]
However, since this first attempt, investigations on the reactions of 2- and 3-sulfur[6a,b] and oxygen[6a,c] substituted silylketene acetals with α- or α,β-alkoxy aldehydes have been undertaken by Heathcock's and our own group. These studies have shown that, whereas the more usual catalysts fail to promote the reactions or show an almost complete lack of stereoselectivity, $MgBr_2$ secures a diastereoface selection (C-3,C-4) up to 100:1.
In the light of this finding, we decided to reexamine Lewis acid promoted condensations of 2 using the more easily accessible and synthetically useful (S)-O-benzyllactic aldehyde 3.

RESULTS AND DISCUSSION.

Characterization of diastereomeric products.

SCHEME 1.



In order to define the products' stereochemistry, it was necessary to prepare and identify the diastereomeric aldols. This was accomplished as shown in Scheme 1. Reaction of the Li-enolate of t-butyl amino acetate with 3 gave a mixture of all four diastereoisomers (Table I, Entry 3).
The products were separated by flash chromatography and transformed into the corresponding γ-lactones. Lactones 5a, 5c and 5d were obtained in 60-65% overall isolated yields by sequential hydrogenolysis (Pd/C, $MeOH/H_2O$), N-protection ($PhCH_2OCOCl$, $NaHCO_3$, THF/H_2O) and treatment with CF_3COOH at room temperature. Hydrogenolysis of the minor isomer 4b resulted in extensive decomposition. It is well known that, in ^{1}H-NMR analysis, the coupling constants of γ-lactone protons show a very characteristic trend dependent on the lactones' stereostructure.[7] As appears from Table II, the most diagnostic feature is the C-3 proton signal from which trans-trans, cis-cis and 2,3-cis-3,4-trans configurations can be inferred for 5a, 5c and 5d respectively.

TABLE I.

Entry	Reagent	Yield%[a]	Product distribution[b]			
			4a	4b	4c	4d
1	2/$MgBr_2$	40	-	<1.6	>96.8	<1.6
2	2/$SnCl_4$	50	-	16.2	82.4	1.4
3	Li-enolate	56	27	9.2	22.9	40.9

a. Isolated yields based on 3.
b. The ratio was determined by HPLC. The order of elution (hexane/AcOEt 85/15) is a, b, c, d.

TABLE II. ^{1}H-NMR Parameters for lactones 5a,c,d[a]

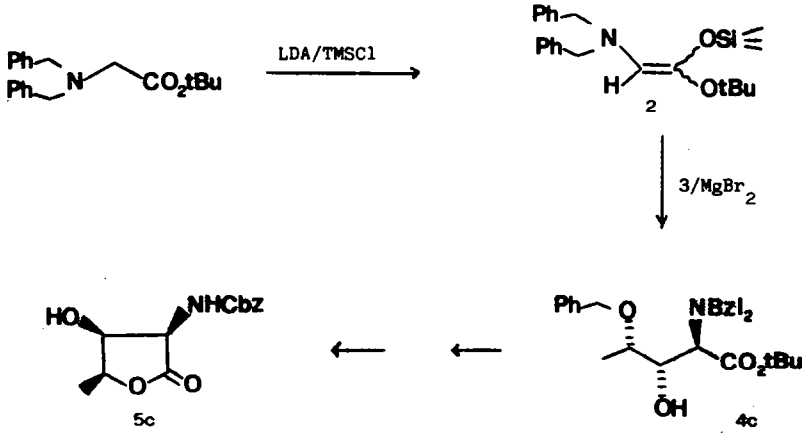
	5a[b]	5c[c]	5d[c]
$J_{2,3}$	8.8	4.9	5.6
$J_{3,4}$	8.8	2.8	1.1
$J_{4,Me}$	6.5	6.6	6.9
H-2	4.26 (d)	4.71 (d)	4.59 (d)
H-3	4.03 (t)	4.13 (dd)	4.03 (dd)
H-4	4.29-4.43 (dq)	4.47-4.72 (dq)	4.30-4.57 (dq)
CH_3	1.52 (d)	1.23 (d)	1.32 (d)

a. Chemical shift are in ppm from Me_4Si as internal standard; coupling constants (J) are in Hz.
b. Solvent $CDCl_3/D_2O$. c. Solvent DMSO-d_6-D_2O.

The ^{13}C-NMR spectra are also useful in confirming the assigned stereostructure: the relevant diagnostic resonance is that due to C-5, which, in lactone 5c is shielded by ~4ppm by the cis hydroxy group at C-3.[9]

Lewis acid promoted condensations: synthesis of t-Butyl 2-amino-2,5-dideoxy-L-lyxo-pentanoate.

Silylketene acetal 2 was obtained by the previously reported procedure (LDA, -78°C, then Me_3SiCl)[6] or better via in situ silylation[10] treating a THF solution of LDA and TMSCl with t-Butyl dibenzyl



amino acetate at -78°C for 15min and for 3h at room temperature. Reactions were worked up by evaporation under reduced pressure avoiding water quenching, and the product was stored at -20°C as a 1M CH_2Cl_2 solution. In both cases only one isomer was detected by ^{1}H-NMR.

Condensations were carried out by addition of the indicated Lewis acid to a solution of O-benzyl lactic aldehyde in CH_2Cl_2 at -78°C, followed by addition of silylketene acetal 2. After 30min at -78°C, the mixture was stirred for 2h at -40°C. A crude sample of the condensation product was checked by HPLC analysis and the diastereoisomeric ratios are reported in Table I. As shown in Table I (Entry 1), $MgBr_2$ turned out to be very effective resulting in an almost complete control of both facial (C-3, C-4) and simple (C-2, C-3) diastereoselection. In fact condensation of 2 with 3/$MgBr_2$ complex afforded, in acceptable chemical yield, aldol 4c as the only detectable product. With $SnCl_4$ a 98.6:1.4 chelation/non-chelation diastereoface selection and 83.8:16.2 2,3-anti/2,3-syn simple diastereoselection (Table 1, Entry 2) were obtained. These are unusally high values for hetero substituted silylketene acetals.[6] Furthermore this result, when compared with the previously reported 25:59:0:16 mixture for 2/2-benzyloxy octyl aldehyde/$SnCl_4$,[5] shows that the stereochemical outcome of these reactions depends, to some extent, also on the aldehyde alkyl group. It should also be pointed out that with both $SnCl_4$ and $MgBr_2$ the major aldol shows C-2, C-3 anti configuration. This is a very different trend from that observed by Heathcock and coworkers[6c] for the reaction between aldehyde 3 and O-benzyllactic acid (bistrimethylsilyl) ketene acetal. In fact in that case an inversion of simple diastereoselection on passing from $SnCl_4$ (C-2, C-3 anti) to $MgBr_2$ (C-2, C-3 syn) was obtained.

Although a mechanistic explanation of the stereochemical outcome of hetero substituted silylketene acetal condensations is still to be reached, $MgBr_2$ promoted addition here described is an effective way to synthesize the lyxo-pentanoate 4c and the corresponding γ-lactone 5c, which is a known intermediate for the synthesis of the rare hexoses L-daunosamine and L-vancosamine.[3]

EXPERIMENTAL SECTION.

^{1}H-NMR were recorded with a XL-200 or a Bruker WP-80, while ^{13}C-NMR spectra were recorded with a Varian XL-200 instrument in the FT mode with tetramethylsilane as internal standard. Optical rotations were measured in a 1-dm cells of 1-ml capacity by using a Perkin-Elmer 241 polarimeter. Silica gel 60 F_{254} plates (Merck) were used for analytical TLC; 270-400 mesh silica gel (Merck) for flash chromatography. HPLC analyses were performed on a Varian 500 equipped with a LiChrosorb Column and a U.V. (254) detector using a Hewlett-Packard 3390A integrator. "Dry" solvents were distilled under N_2 just before use: tetrahydrofuran (THF) was distilled from sodium metal in the presence of benzophenone, CH_2Cl_2 and diisopropylamine from CaH_2. All reactions employing "dry" solvents were run under a nitrogen (from liquid N_2) atmosphere.

t-Butyl 2-dibenzylamino acetate.

20 Ml (20.6 g; 136 mmol) of t-butyl bromoacetate were dissolved in 40 ml of dioxane and 50 ml of absolute ethanol and treated with 53 ml (54.4 g; 276 mmol) of dibenzylamine. The mixture was refluxed for 5h, then the solvent was evaporated under reduced pressure. The crude product was taken up with Et_2O and 1N KOH, and extracted three times with Et_2O. The organic layers were dried over Na_2SO_4, filtered and the solvent evaporated. The crude was purified by flash chromatography (hexane/AcOEt 85:15) affording 37.7 g of pure product (yield 89%). ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s); 3.17 (2H, s); 3.79 (4H, s); 7.31-7.34 (10H, m).

Aldols 4a-4d.

To a solution of 1.04 ml (746.8 mg; 7.38 mmol) of diisopropylamine in 12 ml of THF at 0°C, 4.47 ml (6.71 mmol) of 1.5M solution of n-butyllithium in hexane were added. After 10min the mixture was cooled at -60°C and a solution of 1.9 g (6.10 mmol) of t-butyl dibenzylamino acetate in 9 ml of THF were added. After 10min, 1 g (6.10 mmol) of (S)-O-benzyllactic aldehyde in 9 ml of THF was added and, after 30min, the mixture was quenched with pH=7 phosphate buffer, extracted with AcOEt, dried over Na_2SO_4 and evaporated. The crude was purified by flash chromatography (hexane/AcOEt 9/1) affording pure 4a-4d in 56% total yield.

4a: ^{1}H-NMR ($CDCl_3/D_2O$) δ: 1.01 (3H, d, J=6.1Hz); 1.51 (9H, s); 3.17 (1H, d, $J_{1,2}$=9.8Hz); 3.04-

3.40 (1H, m); 3.33-3.41 (4H, AB_{syst} ν_A=4.01 ν_B=3.44, J_{AB}=13.6Hz); 4.03 (1H, dd, $J_{2,3}$=4.5Hz, $J_{2,1}$=9.8Hz); 4.24-4.59 (2H, AB_{syst} ν_A=4.47 ν_B=4.35, J_{AB}=11.7Hz); 7.13 (5H, s); 7.38 (10H, s). ^{13}C-NMR ($CDCl_3$) selected data δ : 15.44; 28.42; 54.70; 62.71; 68.84; 70.39; 76.54; 81.69; 168.80. $[\alpha]_D^{25}$=+96.7° (C=1.22 $CHCl_3$); m.p. 88-92°C.

4b: ^{1}H-NMR ($CDCl_3/D_2O$) δ : 1.19 (3H, d, J=6.4Hz); 1.50 (9H, s); 3.41-3.66 (1H, m); 3.57 (1H, d, $J_{1,2}$=9.5Hz); 3.42-4.14 (4H, AB_{syst} ν_A=3.97 ν_B=3.56, J_{AB}=13.8Hz); 3.93 (1H, dd, $J_{2,3}$=2.6Hz, $J_{2,1}$=9.5Hz); 4.14-4.57 (2H, AB_{syst} ν_A=4.46 ν_B=4.23, J_{AB}=11.8Hz); 7.11-7.35 (15H, m). ^{13}C-NMR ($CDCl_3$) selected data δ: 15.46; 28.39; 54.89; 61.56; 70.07; 70.73; 74.04; 81.69; 169.53. $[\alpha]_D^{25}$=-75.9° (C=3.47 $CHCl_3$).

4c: ^{1}H-NMR ($CDCl_3/D_2O$) δ: 1.14 (3H, d, J=6.4Hz); 1.56 (9H, s); 3.44 (1H, d, $J_{1,2}$=8.5Hz); 3.48-4.05 (4H, AB_{syst} ν_A=3.97 ν_B=3.58, J_{AB}=13.9Hz); 3.57-3.95 (2H, m); 3.84-4.37 (2H, AB_{syst} ν_A=4.30 ν_B=3.92, J_{AB}=10.6Hz); 7.10-7.35 (15H, m). ^{13}C-NMR ($CDCl_3$) selected date δ : 16.44; 28.53; 55.57; 63.90; 70.85; 73.08; 73.87; 81.47. $[\alpha]_D^{25}$=+69.4° (C=0.97 $CHCl_3$).

4d: ^{1}H-NMR ($CDCl_3$) δ : 0.69 (3H, d, J=6.3); 1.60 (9H, s); 3.24 (1H, d, $J_{1,2}$=9.1Hz); 3.67-3.95 (1H, dq, $J_{3,2}$=2.7Hz, J=6.3Hz); 3.37-3.98 (4H, AB_{syst} ν_A=3.89 ν_B=3.47, J_{AB}=13.5Hz); 4.22 (1H, dd, $J_{2,1}$=9.1Hz, $J_{2,3}$=2.7Hz); 4.30-4.62 (2H, AB_{syst} ν_A=4.52 ν_B=4.40, J_{AB}=11.1Hz); 7.28 (15H, s). ^{13}C-NMR ($CDCl_3$) selected data δ : 12.05; 28.63; 55.44; 62.42; 70.42; 71.22; 74.46; 81.91; 170.67. $[\alpha]_D^{25}$=-58.5° (C=0.99 $CHCl_3$).

Lactones 5a-d. General Procedure.

90 mg (0.189 mmol) of aldol 4 in 3 ml of MeOH/H_2O (4:1) was hydrogenated in the presence of 10% Pd/C (10 mg) for 24h at room temperature. The reaction mixture was filtered and the solvent evaporated. To a solution of the crude and 50.8 mg (0.604 mmol) of $NaHCO_3$ in 3 ml of H_2O/THF (3/1) at 0°C, 43.2 µl (51.6 mg, 0.302 mmol) of $PhCH_2OCOCl$ were added . The mixture was stirred for 2h at room temperature, and pH=7-8 was mantained by adding a saturated aqueous solution of $NaHCO_3$. The mixture was extracted with Et_2O, dried over Na_2SO_4 and evaporated. The crude product was treated with 3 ml of CF_3COOH at room temperature for 1h, then the solvent was evaporated under reduced pressure and the crude purified by flash chromatography (AcOEt/hexane 55:45) affording pure 5a, 5c and 5d (overall yield 60-65%).

5a: ^{1}H-NMR ($CDCl_3/D_2O$) δ : 1.52 (3H, d, J=6.5Hz); 4.02 (1H, t, $J_{2,3}$=$J_{3,4}$=8.8Hz); 4.26 (1H, d, $J_{2,3}$=8.8Hz); 4.29-4.43 (1H, dq, J=6.5Hz, $J_{3,2}$=8.8Hz); 5.14 (2H, s); 7.33 (5H, s). ^{13}C-NMR ($CDCl_3$) selected data δ : 17.91; 59.62; 67.91; 78.89; 80.15; 157.71; 171.04. $[\alpha]_D^{25}$=-57.0° C=0.59 $CHCl_3$); m.p. 143-144°C.

5c: ^{1}H-NMR (DMSO-d_6/D_2O) δ : 1.23 (3H, d, J=6.6Hz); 4.13 (1H, dd, $J_{2,3}$=4.9Hz, $J_{3,4}$=2.8Hz); 4.47-4.72 (1H, dq, J=6.6Hz, $J_{3,4}$=2.8Hz) 4.71 (1H, d, $J_{2,3}$=4.9Hz); 5.09 (2H, s); 7.35 (5H, s). ^{13}C-NMR ($CDCl_3$) selected data δ : 13.75; 56.74; 67.75; 70.56; 78.14; 156.36; 173.26. $[\alpha]_D^{25}$=-34.2° (C=0.49 $CHCl_3$); m.p. 129-131°C.

5d: ^{1}H-NMR (DMSO-d_6/D_2O) δ :1.32 (3H, d, J=6.9Hz); 4.03 (1H, dd, $J_{2,3}$=5.6Hz, $J_{3,4}$=1.1Hz); 4.30-4.57 (1H, dq, J=6.9Hz, $J_{3,4}$=1.1Hz); 4.59 (1H, d, $J_{2,3}$=5.6Hz); 5.09 (2H, s); 7.40 (5H, s). ^{13}C-NMR ($CDCl_3$) selected data δ : 18.07; 53.78; 67.79; 72.26; 82.48; 156.51; 173.26. $[\alpha]_D^{25}$=+7.2° (C=0.69 $CHCl_3$); m.p. 130-133°C.

Silylketene acetal 2.

To a solution of 0.275 ml (1.9 mmol) of diisopropylamine in 6 ml of THF at 0°C, 1.18 ml (1.76 mmol) of 1.5M solution of n-butyllithium in hexane were added. After 10min the solution was cooled at -78°C and, sequentially, 0.406 ml (3.2 mmol) of TMSCl and a solution of 0.5 g (1.6 mmol) of t-Butyl dibenzylamino acetate in 2 ml of THF were added. The mixture was stirred at room temperature for 3h, then the solvent was quickly evaporated under reduced pressure and 1.6 ml of dry CH_2Cl_2 were added. The 1M solution of silylketene acetal 2 can be stored for a week at -20°C. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (9H, s); 1.32 (9H, s); 3.80 (4H, s); 4.55 (1H, s); 7.18-7.42 (10H, m).

Lewis acids mediated aldol-condensations. General Procedure.

To a solution of 164 mg (1 mmol) of (S)-O-benzyllactic aldehyde and 1.1 mmol of Lewis acid in 5 ml

of CH_2Cl_2 at -78°C, 1.6 ml (1.6 mmol) of a 1M solution of silylketene acetal 2 were added dropwise. After stirring for 30min at -78°C and 2h at -40°C, the mixture was quenched with pH=7 phosphate buffer (in the case of $MgBr_2$) or with 10% NaOH solution (in the case of $SnCl_4$), extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated. The crude was purified by flash chromatography (hexane/AcOEt 85:15). The diastereoisomeric ratios and the yields are reported in Table I; for the product characterizations see above.

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