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THE FOUR-CARBON ELONGATION OF THREE-CARBON CHIRAL SYNTHONS USING 2-(TRIMETHYLSILOXY)FURAN: HIGHLY STEREOCONTROLLED ENTRY TO ENANTIOMERICALLY PURE SEVEN-CARBON α,β-UNSATURATED 2,3-DIDEOXY-ALDONOLACTONES[1]

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Abstract: The BF_3-promoted addition of 2-(trimethylsiloxy)furan to three carbon synthons derived from D- and L-glyceraldehyde, D- and L-serinal, and imines thereof furnishes C_7 α,β-unsaturated 2,3-dideoxy-aldonolactone derivatives in high yield, with very high level of diastereoselection. In all the cases, compounds having 4,5-*threo*:5,6-*erythro* relative stereodisposition preferentially emerge from the reactions, accompanied by only marginal amounts of 4,5-*erythro*:5,6-*erythro* epimers. An empirical rule for the rapid assigment of the configuration at C-4 (γ-carbon) of γ-substituted unsaturated and saturated γ-butyrolactones is given, based upon the sign of the optical rotation values.

Introduction

Chiral non-racemic γ-substituted γ-butyrolactones represent either the key entity itself or a substructure of a more complex assembly in numerous biologically

important natural and synthetic products.[3] Their α,β-unsaturated counterparts [2(5H)butenolides] have emerged as precious chiral synthons in recent years,[4] principally due to their chemical flexibility and functional diversity; and this created a need for efficent and stereoselective synthetic strategies.[5]

The objective of the present study was to find a practical route to homochiral subunits containing a broad spectrum of functional sites to be manipulated into higher monosaccharides and related important structures. We elected to aim our search toward the synthesis of enantiomerically pure α,β-unsaturated butyrolactones bearing γ-residues containing a carbohydrate-like pattern of substitution and stereochemistry. As these units contain multiple, contiguous, and diverse reaction sites and stereogenicity, one could imagine, in principle, a number of transformations to build a large variety of carbohydrate objectives at will. To assemble these molecules in a short manner, we exploited the use of commercially available 2-(trimethylsiloxy)furan (**1**; TMSOF) as the four-carbon donor to some simple aldehydo or imino templates ex sugars or aminoacids.[6]

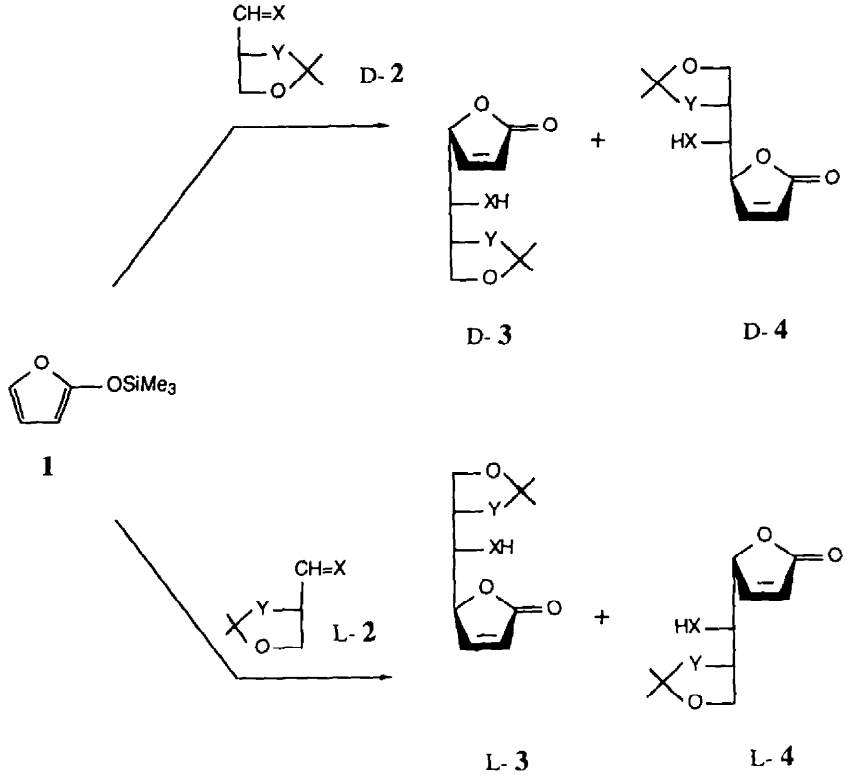
Results and Discussion

Three-carbon Templates: Synthesis of C_7 Units. 2,3-*O*-Isopropylidene-D-glyceraldehyde D-**2a** was first chosen as a C_3 representative for optimization of the reaction conditions and protocol. After several experiments, including a broad Lewis acid-solvent check under varied reaction conditions and quenching operations, a quite satisfactory procedure was realized as follows. Treatment of **2a** with a slight excess (1.2 equiv.) of TMSOF (**1**) in dichloromethane at -80°C in the presence of 1.0 equiv. of BF_3 etherate, reaction quenching at -80°C with an aqueous saturated $NaHCO_3$ solution, and subsequent treatment of the crude isolated products with citric acid in methanol at ambient temperature, provided 6,7-*O*-isopropylidene-2,3-dideoxy-D-*arabino*-hept-2-enono-1,4-lactone (D-**3a**) in 86% isolated yield, accompanied by only 4% of the D-*ribo* epimer D-**4a**.

The process was completely regioselective since of the two nucleophilic carbons in **1** (α and γ), the γ-carbon only was alkylated and, as a consequence of the non-

chelating Lewis acid conditions, the reaction was 5,6-*erythro* (*anti*) selective,[7] with no detectable amount of the opposite 5,6-*threo* (*syn*) stereoisomer evident in the HPLC analysis of the crude reaction mixture.[8]

Scheme I



2, 3, 4 a : X = Y = O
b : X = O; Y = N^{t}BOC
c : X = N*p*-Anisyl; Y = O
d : X = N*p*-Anisyl; Y = N^{t}BOC

We next sought to define the generality of this process by subjecting a series of oxygen and nitrogen containing three-carbon chiral synthons D-**2** and L-**2** to the optimized $BF_3{\cdot}OEt_2$ promoting reaction conditions (Table I).[9]

Table I. Sytnthesis of Seven-carbon Butenolides 3 and 4. According to Scheme I

Entry	C_3 synthon	Products	Yield,%[a]	$[a]_D^{20}$[b] (deg)	Diastereoisomeric ratio[a] 3:4
1	D-**2a**	D-**3a** D-**4a**	90	+69.6(*c* 1.0) -79.4(*c* 0.6)	96:4
2	L-**2a**	L-**3a** L-**4a**	94	-70.1(*c* 1.5) -78.9(*c* 0.5)	95:5
3	D-**2b**	D-**3b** D-**4b**	86	+79.1(*c* 1.2) -65.6(*c* 1.5)	95:5
4	L-**2b**	L-**3b** L-**4b**	83	-83.1(*c* 1.3) +66.7(*c* 0.5)	94:6
5	D-**2c**	D-**3c** D-**4c**	88	+20.4(*c* 2.6) +285.5(*c* 0.9)	94:6
6	L-**2c**	L-**3c** L-**4c**	88	-21.2(*c* 1.5) -281.6(*c* 0.5)	95:5
7	D-**2d**	D-**3d** D-**4d**	91	+180.1(*c* 2.5) -153.9(*c* 0.5)	86:14
8	L-**2d**	L-**3d** L-**4d**	90	-181.6(*c* 3.1) +156.0(*c* 0.4)	88:12

[a] Combined yield of pure isolated compounds.
[b] In chloroform; concentration in parentheses, 1 cm cell.
[c] Determined by HPLC.

The process proved general for both the D- (odd entries) and L-enantiomeric forms (even entries), and furnished D- and L-*arabino*-hept-2-enonolactones D-**3** and L-**3** respectively with a level of diastereoselection as high as 86%, accompanied by minor amounts of the corresponding D- and L-*ribo* epimers D-**4** and L-**4**. The isolation

of the major components from these reactions was always possible by flash chromatography, allowing preparation of enantiomerically pure substances in extremely gratifying yields.

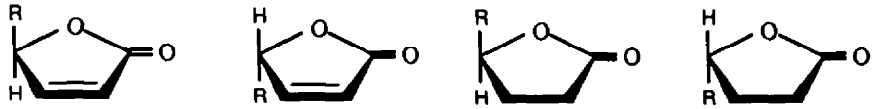
Structural Assignment. Compounds **3** are C-4 epimers of **4**, and this was substantiated by Et_3N-promoted epimerization of these compounds. Treatment of D **3a** in CH_2Cl_2 with 1.0 equiv. of Et_3N at ambient temperature resulted, after 4 h, in the formation of an equilibrium mixture of D-**3a** and D-**4a** in 55:45 epimeric ratio, and similar epimerization occurred by starting with D-**3b** (60:40 ratio), D-**3c** (50:50 ratio), and D-**3d** (60:40 ratio). Compounds D-**3** and L-**3**, and D-**4** and L-**4**, which came from the enantiomeric synthons D-**2** and L-**2**, represent enantiomeric pairs, being the ^1H NMR spectra for each couple superimposable, the optical rotation values opposite, and C.D. curves mirror images.

The *arabino* and *ribo* epimers **3a,b** and **4a,b** were distinguished by ^1H NMR spectroscopy. The spectra of the 4,5-*threo* compounds had $J_{4,5}$ of ca. 3 Hz, while a $J_{4,5}$ of ca. 5 Hz was observed for the 4,5-*erythro* derivatives. In addition, in the ^1H NMR spectra, the H-3 resonance in compounds **3a,b** appears ca. 0.1 ppm further upfield compared to the corresponding signal in the epimers **4a,b**. However, in the amino derivatives **3c,d**, the H-3 signal resonates downfield compared to the related signal in **4c,d**.

Dextrorotatory isopropylidene-blocked unsaturated lactone D-**3a** was considered to have the D-*arabino* structure shown, based upon chemical correlation to known 2,3-dideoxy-D-*arabino*-heptono-1,4-lactone (**6**) ($[\alpha]_D^{20}$ - 43, *c* 1, MeOH; lit.[10] $[\alpha]_D^{20}$ -43.5, *c* 1.36, MeOH), by a sequence involving double bond hydrogenation (C/Pd, MeOH) leading to 2,3-*O*-isopropylidene-2,3-dideoxy-D-*arabino*-heptono-1,4-lactone (**5**) and subsequent acetonide deblocking (80% AcOH/THF 1:1).

A relation between the structure and the sign of the optical rotatory power of 4-substituted 2,3-unsaturated γ-butyrolactones in this study was observed. Lactones having 4R absolute configuration are dextrorotatory, while those having 4S absolute configuration are levorotatory, and this relation applies also to a variety of closely related known substances.

Table II. Relation between Structure and Optical Rotatory Power for Lactones A-D[a].



A B C D

Lactone		R	$[a]_D^{20}$ (condition)	Configuration	References
A a			-140°(*c* 3.0, H_2O)	4S	12
B a			+140°(*c* 3.0, H_2O)	4R	12[b]
C a			+32,3°(*c* 3.56, EtOH)	4S	13
D a			-33.5°(*c* 3.12, EtOH)	4R	14
A b			-186°(*c* 1.01, H_2O)	4S, 5R (D-*erythro*)	12
B b			+119°(*c* 1.01, H_2O)	4R, 5R (D-*threo*)	12[b]
C b			+61.8°(*c* 2, MeOH)	4S, 5S (L-*threo*)	15
D b			-61.8°(*c* 2, MeOH)	4R, 5R (D-*threo*)	15[b]
A c	≡ **10**		-137° (*c* 1, MeOH)	4S, 5S, 6R (D-*ribo*)	c
B c	≡ **7**		+124° (*c* 1, EtOH)	4R, 5S, 6R (D-*arabino*)	c
C c	≡ **9**		+7° (*c* 1, MeOH)	4S, 5S, 6R (D-*ribo*)	c
D c	≡ **6**		-43.5° (*c* 1.36, MeOH)	4R, 5S, 6R (D-*arabino*)	10,c
A d	≡ **D-4a**		-79.4° (*c* 1, $CHCl_3$)	4S, 5S, 6R (D-*ribo*)	c
B d	≡ **D-3a**		+69.6° (*c* 1,$CHCl_3$)	4R, 5S, 6R (D-*arabino*)	c
C d	≡ **8**		+11.8° (*c* 1.53, MeOH)	4S, 5S, 6R (D-*ribo*)	c
D d	≡ **5**		-33.3°(*c* 1.26, MeOH)	4R, 5S, 6R (D-*arabino*)	c

[a]Lactones **5**, **6**, **7**, and **8**, **9**, **10** were obtained from **D-3** and **D-4** respectively via hydrogenation and/or deprotection (see text). [b]Optical rotation values judged as such based on the values of the corresponding enantiomers. [c]This work.

For easy reference, the optical rotation values of selected lactones of this work as well as some deprotected derivatives are listed in Table II, compared with the values of some previously reported compounds of this series. In addition, data for the corresponding saturated counterparts are included. With no exception, irrespective of the nature of the "tail" substituents at C-4, 2,3-unsaturated γ-lactones having the 'tail" group "up" in the conventional Haworth's depiction (formulae A, 4S-

configuration) display large levorotation, whilst those bearing this group "down" (formulae **B**, 4R-configuration) show large dextrorotation. Obeying the Hudson's lactone rule,[11] the saturated counterparts, namely compounds **C** and **D**, display inverted signs of rotation, being butanolides **C** dextrorotatory and butanolides **D** levorotatory.

Enantiomeric Purity. Butenolides **3** and **4** reported in this work were diastereoisomerically pure compounds as ascertained by ^{1}H NMR and HPLC analysis. However, in order to determine the enantiomeric purities accurately a ^{1}H NMR analysis in a chiral environment was carried out, on D-**3a** and L-**3a** and D-**3b** and L-**3b** as the chosen enantiomeric pairs. Enantiomeric purities of above 98% were ascertained for all four compounds, by comparing the ^{1}H NMR spectra of the synthetic compounds with those of their racemates in the presence of the chiral shift reagent Eu(hfc)$_3$. In no case, could signals from the opposite enantiomer be detected. Compounds D-**3c** and L-**3c**, D-**3d** and L-**3d**, and the minor epimers D-**4** and L-**4**, on which this analysis was not performed, should have similar enantiomeric purity, since the reaction conditions and the enantiomeric purity of the starting chiral synthons were the same.

Crystallography. To make sure of the structural assignments shown, we considered more rigorous elucidation of at least one structure via RX analysis was necessary and, since efforts to make crystals from any of the isopropylidene-blocked derivatives in this work were fruitless, we turned to deprotected 2,3-dideoxy-hept-2-enono-1,4-lactone **7** obtained from D-**3a** via quantitative and stereoconservative deblocking with a 90% AcOH/THF 1:1 mixture at room temperature. Colorless prysmatic crystals of **7** (mp 108°C; $[\alpha]_D^{20}$+ 124°, *c* 1 EtOH) were obtained from dichloromethane solutions. An X-ray diffraction study culminated in the perspective drawing in Figure I, which clearly demostrates that **7** (and hence D-**3a**) possesses the D-*arabino* configuration (4R,5S,6R), from D-**2** as the starting synthon.

The Figure I shows an ORTEP drawing of butenolide **7** with the atomic numbering scheme.

The 2,3-unsaturated butyrolactone ring is perfectly planar because of the presence of the double bond C(2)=C(3) [1.352(8) Å] while the saturated γ-lactone derivatives generally have an envelope conformation where the C(3) atom only deviates considerably from the mean plane through the other atoms of the ring. [16,17] The bond distance O(2)-C(1) (sp^2) is shorter than O(2)-C(4) (sp^3) [1.353(7) and 1.468(8) Å respectively] in accordance with the values reported for the other butyrolactones.[16]

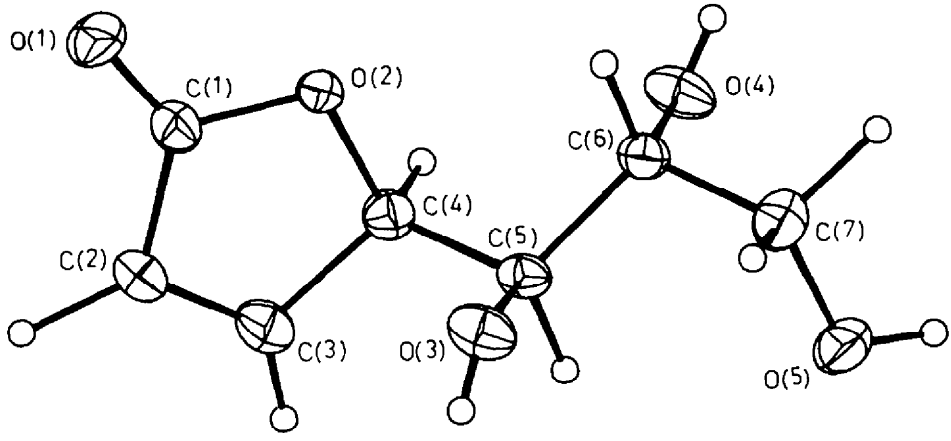


Figure I. ORTEP view of butenolide 7 with thermal ellipsoids at 50% probability. The hydrogen atoms are draw with an arbitrary diameter. The molecule is shown in its correct absolute configuration.

The arrangement of the glycerol chain with respect to the γ-lactone ring is defined by the torsional angles C(1)O(2)C(4)C(5)=-121.3(6)° and C(2)C(3)C(4)C(5)=117.8(7)°. The two alcholic groups O(3)-H and O(4)-H are *trans* to each other [torsion angle O(3)C(5)C(6)O(4)=-176.4(1.O)°]. Three short molecular hydrogen bonds O(3)-H···O(1) (-x-1, 1/2+y, -z) 2.84(1), O(4)-H···O(5) (-x,y-1/2,1-z) 2.76(1), O(5)-H···O(1) (x+1,y,z+1) 2.81(1) Å connect the molecules in a three dimensional network.

Conclusions We have presented a highly diastereoselective synthesis of enantiomerically pure seven-carbon α,β-unsaturated γ-butyrolactones bearing γ-substituents endowed with hydroxy and mixed hydroxy-amino functionalities. Both

D-*arabino* and L-*arabino* enantiomers are available by starting with readily accessible precursors, and the preparation of the corresponding C-4 epimers can be ensured by Et_3N treatment. During the carbon-carbon bond formation between the two reaction partners, the two newly formed stereogenic centres preferentially emerge in 4,5-*threo* : 5,6-*erythro* orientation (4,5-*syn*:5,6-*anti*) as a consequence of the non-chelating conditions of the BF_3-OEt_2 promoter favoring Felkin type approach of the incoming nucleophilic group[7] and the markedly 4,5-*syn* selective behavior of TMSOF addition to the aldehyde or imine centres.[18]

Synthetically, the approach is efficient and substantial quantities of pure materials may be prepared. The conversion of the lactones now available into seven-carbon sugars and related derivatives constitutes an objective for future efforts.

Experimental Section

General Methods. All reactions were carried out under a positive pressure of argon. All glassware and syringes were dried in an electric oven at 110°C prior to use. Dichloromethane was freshly distilled from calcium hydride. Flash chromatography was performed on silica gel 60 (Merck, 0.040-0.063 nm), and TLC on silica gel 60 F_{254} (Merck) with detection by ethanolic 7% phosphomolybdic acid. Melting points were determined with a Mel-Temp apparatus and are uncorrected. Optical rotation values were determined on a Perkin-Elmer 241 polarimeter. ^1H NMR spectra were obtained with either a Varian XL 200 or a Varian XL 300 spectrometer. Chemical shifts are reported in ppm on the δ scale relative to internal tetramethylsilane with coupling constants in Hertz. HPLC analyses were performed with a Perkin-Elmer LC-85B instrument using a μ-Bondapack C-18 column (4,6x250 mm, 5 mm) eluting with appropriate MeOH/H_2O solvent mixtures and with a UV-Vis detector set at 230 nm. Elemental analyses were measured by Mr. Antonello Canu, Microanalytical Laboratory, Sassari University. The X-ray analysis was done on a Siemens AED three-circle diffractometer under the control of a General Automation Jumbo 220 computer. Calculations were carried out on a GOULD 6040 Powernode computer of the Centro di Studio per la Strutturistica Diffrattometrica, CNR Parma. Volatile solvents were

removed under reduced pressure using a Buchi rotary evaporator and is referred to removing solvents in vacuo.

Materials. 2-(Trimethylsiloxy)furan (**1**) was purchased from either Aldrich or Fluka and used as received; however, for large scale preparation the procedure of Brimble[19] was followed. Aldehydes D-**2a** [20], L-**2a** [21], D-**2b** [22], and L-**2b** [22] were prepared by literature methods. Imines D-**2c** and L-**2c**, and D-**2d** and L-**2d** were prepared from the corresponding aldehydes by treatment with 4-methoxyaniline (*p*-anisidine) (1 mol. equiv) in diethyl ether in the presence of anhydrous magnesium sulphate[23],and used immediately.

General Procedure for Reaction of TMSOF (1) with Aldehydes or Imines 2. Synthesis of Unsaturated Lactones 3 and 4.

To a solution of the appropriate aldehyde or imine **2** (10 mmol) and TMSOF (**1**) (2.15 ml, 1.3 mmol) in anhydrous CH_2Cl_2 (30 ml) cooled to -80°C, BF_3 etherate (1.23 ml, 10 mmol) was added via a cannula under argon with stirring. The solution was allowed to stir for 6 h at -80°C, then quenched at this temperature by adding an excess of a saturated aqueous $NaHCO_3$ solution. The cooling bath was switched-off and, after ambient temperature was reached, the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated in vacuo to give a residue which was dissolved in methanol (10 ml). Solid citric acid (0.25 mg) was added with stirring and, after 3 h at ambient temperature, water (5 ml) was added and the mixture extracted with CH_2Cl_2. The organic layer was dried and concentrated in vacuo, and the residue was flash chromatographed, eluting the column with appropriate hexanes/ethyl acetate mixtures. The following lactones listed in Table I were prepared.

D-***arabino*-3a.** Mp 125°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (1H, dd, $J_{2,3}$=5.8, $J_{3,4}$=1.7, H-3), 6.17 (1H, dd, $J_{2,4}$=1.9, H-2), 5.26 (1H, ddd, $J_{4,5}$=3.7, H-4), 4.0-4.3 (3H, m,

H-6 and H_2-7), 3.66 (1H, dd, $J_{5,6}$=8.1 ,H-5), 2.80 (1H, bs, OH), 1.42 (3H, s, Me), 1.37 (3H, s, Me).

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found : C, 56.30; H, 6.45 .

D-***ribo*-4a**. An oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (1H, dd, $J_{2,3}$=5.6, $J_{3,4}$=1.5, H-3), 6.22 (1H, dd, $J_{2,4}$=2.0, H-2), 5.20 (1H, ddd, $J_{4,5}$=4,7, H-4), 4.0-4.2 (3H, m, H-6 and H_2-7), 3.97 (1H, dd, $J_{5,6}$=7.1, H-5), 2.60 (1H, bs, OH), 1.45 (3H, s, Me), 1.37 (3H, s, Me).

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.39; H, 6.40.

L-***arabino*-3a**. Mp 123-125°C. ^{1}H NMR characteristics as for D-**3a**.

Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.25; H, 6.52.

L-***ribo*-4a**. An oil. ^{1}H NMR characteristics as for D-**4a**.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.96; H, 6.67.

D-***arabino*-3b**. Mp 128°C. ^{1}H NMR (300 MHz, DMSO-d_6, 60°C) δ 7.71 (dd, 1H, $J_{2,3}$=5.7, $J_{3,4}$=1.5, H-3), 6.19 (dd, 1H, $J_{2,4}$=2.1, H-2), 5.19 (d, 1H, $J_{5,OH}$=6.9, OH), 5.05 (ddd, 1H, $J_{4,5}$=3.0, H-4), 3.8-4.1 (m, 4H, H-5, H-6, and H_2-7), 1.49 (s, 3H; Me), 1.45 (s, 3H, Me), 1.43 (s, 9H, *t*-Bu).

Anal. Calcd. for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.80; H, 7.55; N, 4.70.

D-***ribo*-4b**. Mp 163-164°C. ^{1}H NMR (300 MHz, DMSO-d_6, 60°C) δ 7.78 (dd, 1H, $J_{2,3}$=5.4, $J_{3,4}$=1.2, H-3), 6.23 (dd, 1H, $J_{2,4}$=1.8, H-2), 5.52 (d, 1H, $J_{5,OH}$=6.6, OH), 4.97 (ddd, 1H, $J_{4,5}$=4.1, H-4), 3.7-4.2 (m, 4H, H-5, H-6, and H_2-7), 1.50 (s, 3H, Me), 1.46 (s, 3H, Me), 1.43 (s, 9H, *t*-Bu).

Anal. Calcd. for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.75; H, 7.55; N, 4.62.

L-***arabino*-3b**. Mp 127-128°C. ^{1}H NMR characteristics as for D-**3b**.

Anal. Calcd. for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.72; H, 7.66; N, 4.67.

L-***ribo*-4b**. Mp 162°C. 1H NMR characteristics as for D-**4b**.

Anal. Calcd. for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.67; H, 7.65; N, 4.70.

D-***arabino*-3c**. Mp 93-95°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, 1H, $J_{2,3}$=5.7, $J_{3,4}$=1.5, H-3), 6.7 (AA'BB', 4H, arom.), 6.14 (dd, 1H, $J_{2,4}$=2.1, H-2), 5.31 (ddd, 1H, $J_{4,5}$=3.8, H-4), 3.95-4.15 (m, 3H, H-6 and H_2-7), 3.73 (s, 3H, OMe), 3.72 (dd, 1H, $J_{5,6}$=7.8, H-5), 3.45 (bs, 1H, NH), 1.45 (s, 3H, Me), 1.32 (s, 3H, Me).

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C,63.70; H, 6.40; N, 4.60.

D-***ribo*-4c**. An oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (dd, 1H, $J_{2,3}$=5.7, $J_{3,4}$=1.5, H-3), 6.6 (AA'BB', 4H, arom), 5.96 (dd, 1H, $J_{2,4}$=2.1, H-2), 5.52 (ddd, 1H, $J_{4,5}$=1.8, H-4) 4.21 (ddd, 1H, $J_{6,7a}$=6.0, $J_{6,7b}$=4.8, $J_{5,6}$=9.0, H-6), 4.14 (dd, 1H, $J_{7a,7b}$=8.7, H-7a), 3.90 (dd, 1H, H-7b), 3.73 (s, 3H, OMe), 3.62 (dd, 1H, H-5), 3.30 (bs, 1H, NH), 1.49 (s, 3H, Me), 1.38 (s, 3H, Me).

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.68; H, 6.70; N, 4.50.

L-***arabino*-3c**. Mp 92-93°C. ^{1}H NMR characteristics as for D-**3c**.

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found : C, 64.05; H, 6.52; N, 4.51.

L-***ribo*-4c**. An oil. ^{1}H NMR charateristics as for D-4c.

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.81; H, 6.50; N, 4.27.

D-***arabino*-3d**. A glassy solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, 1H, $J_{2,3}$=5.7, $J_{3,4}$=1,6, H-3), 6.6 (AA'BB', 4H, arom.), 6.19 (dd, 1H, $J_{2,4}$=2.0, H-2), 4.98 (m, 1H, H-4), 3.9-4.3 (m, 4H, H-5, H-6, and H_2-7), 3.73 (s, 3H, OMe), 3.49 (bs, 1H, NH), 1.51 (s, 9H, *t*-Bu), 1.49 (s, 3H, Me), 1.47 (s, 3H, Me).

Anal. Calcd. for $C_{22}H_{30}N_2O_6$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.46; H, 7.55; N, 6.85.

D-***ribo*-4d**. A glassy solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, 1H, $J_{2,3}$=5.7, $J_{3,4}$=1.5), 6.6 (AA'BB', 4H, arom), 6.14 (dd, 1H, $J_{2,4}$=1.9, H-2), 5.11 (m, 1H, H-4), 3.9-4.4 (m, 4H, H-5, H-6, and H_2-7), 3.72 (s, 3H, OMe), 3.44 (bs, 1H, NH), 1.49 (s, 9H, *t*-Bu), 1.46 (s, 3H, Me), 1.45 (s, 3H, Me).

Anal. Calcd. for $C_{22}H_{30}N_2O_6$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.29; H, 7.61; N, 6.54.

L-***arabino*-3d**. A glass ^1H NMR characteristics as for D-**3d**.

Anal. Calcd. for. $C_{22}H_{30}N_2O_6$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.55; H, 7.59; N, 6.36.

L-***ribo* -4d**. A glass ^1H NMR characteristics as for D-**4d**.

Anal. Calcd. for $C_{22}H_{30}N_2O_6$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.52; H, 7.49; N, 6.90.

Representative Epimerization Procedure. To a solution of D-**3a** (200 mg, 0.95 mmol), in anhydrous CH_2Cl_2 (5 ml), Et_3N (0.5 ml) and N,N-dimethylaminopyridine (20 mg) were added, and the mixture was allowed to react for 4 h at room temperature. At this point, a HPLC (see general methods) analysis was carried out and the ratio between D-**3a** and D-**4a** epimers determined as 55% to 45%.

By using the same procedure, epimerization of D-**3b**, D-**3c** and D-**3d** afforded the D-**3d**/D-**4b**, D-**3c**/D-**4c**, and D-**3d**/D-**4d** epimeric mixtures with 60:40, 50:50, and 60:40 ratios respectively.

Representative Double-Bond Hydrogenation Procedure. 6,7-*O*-Isopropylidene-2,3-dideoxy-D-*arabino*-heptono-1,4-lactone (5). The lactone D-**3a** (112 mg, 0.52 mmol) was dissolved in THF (6.0 ml) in the presence of CH_3CO_2Na (5 mg), and reduced by hydrogen with 10% Pd-C catalyst (10 mg) at room temperature (18 h). The catalyst was filtered off, and the filtrate evaporated to dryness to give the saturated lactone **5** (106 mg, 94%); as an oil, $[\alpha]_D^{20}$ - 33.3° (*c* 1.26, MeOH). ^1H NMR (200 MHz, CD_3OD) δ 4.79 (td, 1H, $J_{3a,4}=J_{3b,4}=6.9$, $J_{4,5}=1.5$, H-4), 4.11 (m, 2H, H2-7), 3.93 (m, 1H, H-6), 3.46 (dd, 1H, $J_{5,6}=7.4$, H-5), 2.54 (m, 2H, H_2-2), 2.27 (m, 2H, H_2-3), 1.38 (s, 3H, Me), 1.33 (s, 3H, Me).

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.35; H, 7.61.

6,7-*O*-Isopropylidene-2,3-dideoxy-D-*ribo*-heptono-1,4-lactone (8). According to the above hydrogenation procedure by starting with D-**4a**, the saturated

lactone **8** was prepared in 95% yield; an oil, $[\alpha]_D^{20}$ + 11.8° (*c* 1.53, MeOH). ^1H NMR (200 MHz, $CDCl_3$) δ 4.76 (td, 1H, $J_{3a,4}=J_{3b,4}=7.0$, $J_{4,5}=1.6$, H-4), 4.02 (m, 4H, H-5, H-6, and H_2-7), 3.28 (bs, 1H,OH), 2.63 (m, 2H, H_2-2), 2.35 (m, 2H, H_2-3), 1.42 (1, 3H, Me), 1.36 (s, 3H, Me).

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 56.02; H, 7.29.

Representative Acetonide-Deblocking Procedure. 2,3-Dideoxy-D-*arabino*-hept-2-enono-1,4-lactone (7). The lactone D-**3a** (100 mg, 0.46 mmol) was dissolved in a 80% AcOH:THF 1:1 mixture (5 ml) and allowed to react for 12 h of room temperature. The solution was evaporated to dryness to give pure lactone **7** (75 mg, 93%); m.p. 106-108°C, $[\alpha]_D^{20}$ + 124° (*c* 1, EtOH). ^1H NMR (200 MHz, DMSO d_6) δ 7.71 (dd, 1H, $J_{2,3}=5.7$, $J_{3,4}=1.5$, H-3), 6.19 (dd, 1H, $J_{2,4}=2.0$, H-2), 5.36 (m, 1H, H-4), 4.96 (d, 1H, J=4.4, OH), 4.93 (d, 1H, J=6.1,OH), 4.46 (t, 1H, J=5.56, OH), 3.6 (m, 2H, H_2-7), 3.45 (m, 2H, H-5 and H-6).

Anal. Calcd. for $C_7H_{10}O_5$: C, 48.28; H, 5.79. Found: C, 48.50; H, 5.90.

2,3-Dideoxy-D-*ribo*-hept-2-enono-1,4-lactone (10). According to the above deblocking procedure by starting with D-**4a**, the lactone **10** was prepared in 97% yield; as an oil, $[\alpha]_D^{20}$ -137° (*c* 1, MeOH). ^1H NMR (200 MHz, acetone d_6) δ 7.76 (dd, 1H, $J_{2,3}=5.8$, $J_{3,4}=1.46$, H-3), 6.14 (dd, 1H, $J_{2,4}=2.0$, H-2), 5.41 (ddd, 1H, $J_{4,5}=3.3$, H-4), 4.48 (d, 1H, J=5.6, OH), 4.19 (bs, 1H, OH), 4.01 (bs, 1H, OH), 3.5-3.9 (m, 4H, H-5, H-6, and H_2-7).

Anal. Calcd. for $C_7H_{10}O_5$: C, 48.28; H, 5.79. Found: C, 47.93; H, 5.89.

2,3-Dideoxy-D-*arabino*-heptono-lactone (6). The lactone **5** (80 mg., 0.37 mmol.) was deblocked according to the above deprotection procedure to afford **6** (60 mg, 92%); m.p. 109-111°C, $[\alpha]_D^{20}$ -43° (*c* 1, MeOH) [lit.[10] m.p. 111-112°C, $[\alpha]_D^{20}$ -43.5° (*c* 1.36, MeOH)]. ^1H NMR (200 MHz, CD_3OD) δ 4.95 (m, 1H, H-4), 3.66 (m, 4H, H-5, H-6, and H_2-7), 2.57 (m, 2H, H_2-3), 2.28 (m, 2H, H_2-2).

Anal. Calcd. for $C_7H_{12}O_5$: C, 47.73; H, 6.87. Found: C, 47.55; H, 6.50.

2,3-Dideoxy-D-*ribo*-heptono-lactone (9). The lactone **8** (75 mg, 0.34 mmol) was deblocked according to the above deprotection procedure to afford **9** (55 mg, 91%); an oil, $[\alpha]_D^{20}$ +7° (*c* 1, MeOH). ^{1}H NMR (200 MHz, CD_3OD) δ 4.98 (m, 1H, H-4), 3.60 (m, 4H, H-5, H-6, and H_2-7), 2.59 (m, 2H, H_2-3), 2.25 (m, 2H, H_2-2).
Anal. Calcd. for $C_7H_{12}O_5$: C, 47.73; H, 6.87. Found: C, 47.96; H, 6.98.

X-ray Determination for Compound 7.[24]
$C_7H_{10}O_5$, M=174.2, monoclinic, space group $P2_1$,a=9.243(2), b=9.568(2), c=4.588(1) Å, β=102.0(2), V=396.9 Å^3, Z=2, Dc=1.46 g cm.$^{-3}$, F(000)=184, Cu-Kα radiation, λ=1.54056 Å, μ=10.4 cm^{-1}, crystal size 0.05x0.05x0.26 mm. Intensities data for 901 reflections (2θ<140°) were measured with a computer controlled Siemens AED by the ϖ-2θ scan technique. The structure was solved by direct methods using the SHELX 86 program[25] and refined by full-matrix least-sqares cycles using the SHELX-76 [26] system of computer programs to a final R value of 5.5% for 789 reflections with $I<2\sigma(I)$ (unrefined isotropic hydrogen atoms, $\Delta\rho_{max}$=0.15, $\Delta\rho_{min}$=-0.21)

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