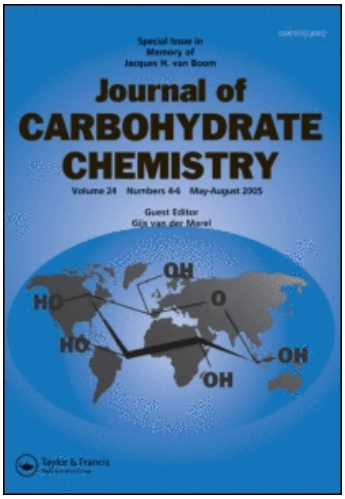

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Synthesis of the Four Configurational Isomers of a Protected Form of *N*-Trifluoroacetyl-4-*C*-Methyl-2,4,6-Trideoxy-4-Amino-*l*-Hexose from *l*-Threonin

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SYNTHESIS OF THE FOUR CONFIGURATIONAL ISOMERS OF A PROTECTED FORM OF N-TRIFLUOROACETYL-4-C-METHYL-2,4,6-TRIDEOXY-4-AMINO-L-HEXOSE FROM L-THREONIN

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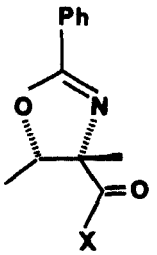
Abstract.

The synthesis of the four configurational isomers of the methyl glycosides of the N-trifluoroacetyl-2,4,6-trideoxy-4-C-methyl-4-amino-L-hexose (**25-28**) proceeds from **L**-threonin via the enantiomeric aldehydes (**3**) and (**4**) and addition onto the latter of allylmagnesium bromide. The anti/syn ratio in the adducts varies from 98:2 at -90 °C to 55:45 at 20 °C. The adducts **5** and **7** are converted into the **L**-arabino and **L**-ribo isomers (**21**) and (**22**) whereas the enantiomers **9** and **11**, via inversion at position 2, yield **L**-xylo and **L**-lyxo isomers (**23**) and (**24**).

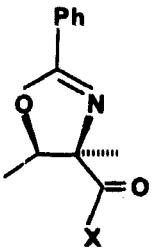
INTRODUCTION

It has been recently reported[1] that the substitution in the anti-tumor agent adriamycin of the **L**-daunosaminyl moiety by the isomeric 2,4,6-trideoxy-4-amino-**L**-lyxo hexose causes a significant rise in cellular take-up, while maintaining the drug potency. The new "iso" derivative appears less basic than adriamycin and this observation prompted us to study the activity profile of conceivably even less basic aminoglycosides such as those accessible by convergent synthesis from adriamycinone and suitable derivatives of the four isomers of

2,4,6-trideoxy-4-C-methyl-4-amino-L-hexose. An attempt[2] towards the synthesis of this set of materials starting from yeast-generated (2S,3RS)-3-methyl-5-phenylpent-4-en-2,3-diol along a route previously explored in the desmethyl series[3] appears to be rather inefficient and leads only to the methyl glycoside of the N-trifluoroacetyl-2,4,6-trideoxy-4-C-methyl-4-amino-L-lyxo hexose (**28**). We now report on the preparation of the four configurational isomers of N,O-protected 2,4,6-trideoxy-4-C-methyl-4-amino-L-hexose (**21-24**) using as starting materials the enantiomeric oxazolines (**1**) and (**2**), recently prepared through enantiodivergent routes from L-threonin by Seebach et al.,[4] and proceeding through the key intermediate aldehydes (**3**) and (**4**).



1 X = OMe
3 X = H



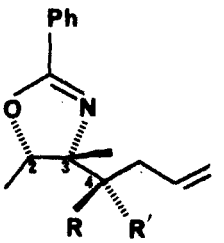
2 X = OMe
4 X = H

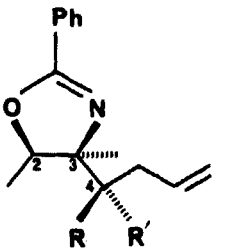
The choice of the enantiomeric α-C-methyl C_4-N aldehydes (**3**) and (**4**) for the elaboration of the C_6-N framework of the four 4-C-methyl-L-hexose derivatives (**21-24**) is based on the following considerations. Stereoselective elaboration of the chiral aldehydes **3** and **4** by addition of a suitable allyl metal onto the carbonyl carbon would lead to the 3-C-methyl C_7-N adducts **5** and **9**, and the diastereoisomer pair **7** and **11** respectively. Simple manipulation of the protecting groups and ozonolysis of the terminal vinyl group, would provide the L-arabino and L-ribo isomers (**21**) and (**22**) from the adducts **5** and **7** respectively. Conversely, diastereoisomers **9** and **11**, the precursors of the D-enantiomers of **21** and **22**, by manipulation of the protecting groups and regioselective inversion of configuration at position 2 would provide **19** and **20**, from which, as above, the L-xylo and L-lyxo isomers (**23**) and (**24**) become available. Thus would be completed in enantioconvergent fashion from the oxazolines **1** and **2**, the total synthesis of the set **21-24** from L-threonin.

RESULTS AND DISCUSSION

Conversion of the ester **1** into the aldehyde **3** was carried out in two steps, $LiAlH_4$ reduction to the carbinol followed by Swern[5] oxidation. Attempts to directly convert **1** into **3** by DIBAH reduction were unsatisfactory. The aldehyde **3**, on reaction with allylmagnesium bromide in ethyl ether at -90 °C, affords the 3,4-anti adduct **7** in 98:2 ratio with the 3,4-syn diastereoisomer (**5**). The facial selectivity of the addition of the above organometallic is strongly dependent upon the reaction temperature. At -50 °C and at 20 °C the adducts **7** and **5** were obtained from **3** in 70:30 and 55:45 ratios, respectively, as determined by GLC analysis of the O-benzyl derivatives **6** and **8**.[6] Diallylzinc behaves towards **3** as allylmagnesium bromide. Accordingly, we decided to complete our synthetic design with the adducts obtained in this way and to postpone to a future work the study of the factors governing the facial selectivity in the addition of organometallic reagents onto **3**.[7] The next step in the synthesis is the hydrolysis of the oxazoline ring of **5** and **7**. This proved to be a difficult operation. Direct acid hydrolysis of **5** and **7** caused extensive degradation. Even mild acid conditions (i.e. silica gel during chromatography) led to (2S,3S,4S) **29a** and (2S,3S,4R) **29b**, respectively, as supported by ^1H NMR evidence. The spectrum of **29** in DMSO-d_6 displays a well resolved doublet for the hydroxyl group, which was shown to be coupled with the methine bearing the methyl group (J(OH,CH) 5.3 Hz). However, when **5** and **7** were converted into the 4-O-benzyl derivatives **6** and **8** the two diastereoisomers were easily separated by silica gel column chromatography and subsequent acid hydrolysis to the aminobenzoate derivatives (**13**) and (**14**) proceeded with acceptable yields. Compounds **13** and **14**, upon N-trifluoroacetylation, basic hydrolysis, N-trifluoroacetylation, ozonolysis at -70 °C and Me_2S treatment, afforded in separate runs, the required L-arabino and L-ribo derivatives **21** and **22**. These latter compounds were converted via methyl glycosidation and catalytic debenzylation into the final compounds **25** and **26**. The preparation of the L-xylo and L-lyxo isomers **27** and **28**, starts from the 3,4-anti and the 3,4-syn adducts **11** and **9** respectively, prepared, as above, from **4**. To this end, the 4-O-benzyl derivatives **10** and **12**, on controlled acid hydrolysis, followed by basic treatment, afforded the N-benzoyl deri-

vatives **15** and **16**, from which, upon treatment with $SOCl_2$, the oxazolines (**17**) and (**18**) were obtained. Indeed, the latter product, through the above hydrolytic sequence, afforded the intermediates **19** and **20**, from which the L-xylo and the L-lyxo isomers **23** and **24** were obtained. Methyl glycosidation and catalytic debenzylation as above gave **27** and **28**.





5 R = H ; R′ = OH

6 R = H ; R′ = OCH_2Ph

7 R = OH ; R′ = H

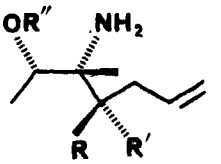
8 R = OCH_2Ph ; R′ = H

9 R = OH ; R′ = H

10 R = OCH_2Ph ; R′ = H

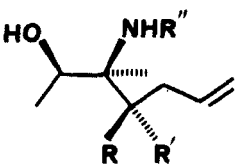
11 R = H ; R′ = OH

12 R = H ; R′ = OCH_2Ph



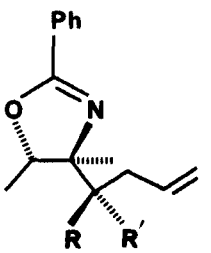
13 R = H ; R′ = OCH_2Ph ; R″ = COC_6H_5

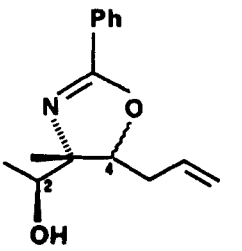
14 R = OCH_2Ph ; R′ = H ; R″ = COC_6H_5



15 R = OCH_2Ph ; R′ = H ; R″ = COC_6H_5

16 R = H ; R′ = OCH_2Ph ; R″ = COC_6H_5

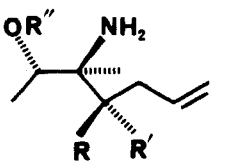




17 R = OCH_2Ph ; R' = H

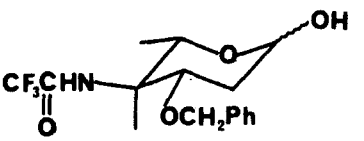
18 R = H ; R' = OCH_2Ph

29



19 R = OCH_2Ph ; R' = H ; R'' = COC_6H_5

20 R = H ; R' = OCH_2Ph ; R'' = COC_6H_5



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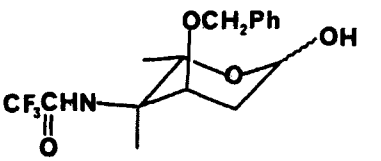

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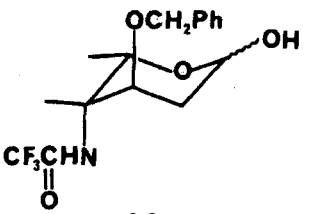

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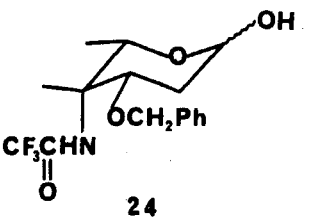

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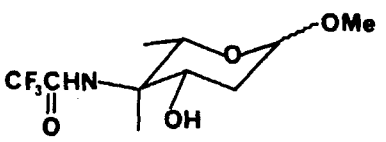

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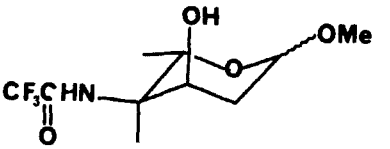

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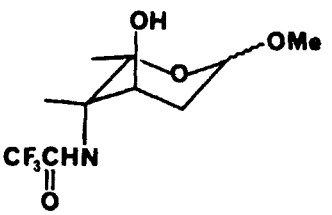

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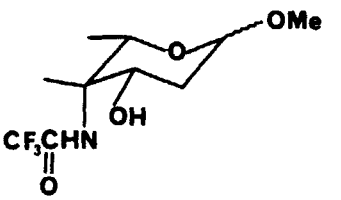

28

DISCUSSION OF THE NMR SPECTRA

The chemical shifts and coupling constants of the 3-O-benzyl derivatives (**21-24**) and of the methyl glycosides (**25-28**) of the N-trifluoroacetyl-2,4,6-trideoxy-4-C-methyl-4-amino-L-hexoses are reported in Tables 1 and 2 respectively. All compounds were isolated as a mixture of α and β pyranose forms and the NMR data have been reported for both anomers. The conformation of the pyranose ring and the configuration of C-1 and C-3 carbons were deduced from the values of the vicinal coupling constants. These values for conformationally pure pyranoses can be predicted on the basis of a set of additivity constants reported by Altona et al.[8] The calculated values ofJ(3e,2a), J(3a,2e), J(3a,2a) and J(3e,2e) for the $^1C_4$(L) conformation are 2.6, 4.9, 11.8 and 3.1 Hz respectively. The experimental coupling constants for compounds **21-28** are reasonably in agreement with the predicted values allowing the determination of the configuration at the C-1 and C-3 carbons. A remarkable deviation is observed for J(3e,2a) for **26**α, **27**α and **27**β glycosides, for which the observed values are 0.6-1.1 Hz greater than the predicted value (2.6 Hz). These data are difficult to rationalize. Calculation of the spectra has been performed where the difference between the chemical shift of H-2e and H-2a protons was

TABLE 1. ^{1}**H Chemical shifts of the N-trifluoroacetyl-2,4,6-trideoxy-4-C-methyl-4-amino-L-hexoses.**[a]

Compound	H-1	H-2a	H-2e	H-3	H-5	Me-4	Me-5	CHaHb-3		OH-1	OH-3	NH-4	OMe-1
21 α	5.32	1.69	2.21	4.69	5.00	1.27	1.11	4.59	4.44	2.44	-	5.90	-
21 β	4.90	1.55	2.33	4.41	4.47	1.31	1.15	4.59	4.43	2.95	-	5.90	-
22 α	5.12	1.95	2.14	4.09	4.19	1.55	1.19	4.70	4.46	4.79	-	6.37	-
22 β	5.13	1.74	2.25	3.83	3.92	1.62	1.20	4.68	4.40	2.98	-	6.64	-
23 α	5.13	1.88	1.98	4.31	4.36	1.52	1.19	4.69	4.63	4.95	-	6.48	-
23 β	5.12	1.60	2.13	4.21	4.05	1.49	1.19	4.64	4.54	3.05	-	6.60	-
24 α	5.36	1.68	2.12	3.67	4.05	1.63	1.16	4.67	4.55	2.51	-	6.33	-
24 β	4.73	1.48	2.29	3.31	3.29	1.61	1.23	4.69	4.55	3.07	-	6.33	-
25 α	4.71	1.73	2.04	4.66	4.37	1.28	1.16	-	-	-	2.82	5.91	3.32
25 β	4.47	1.64	2.13	4.55	4.18	1.29	1.20	-	-	-	2.53	5.91	3.50
26 α	4.77	2.09	2.00	3.66	3.92	1.56	1.27	-	-	-	3.83	7.18	3.36
26 β	4.75	1.91	1.91	4.21	3.97	1.55	1.26	-	-	-	2.44	6.55	3.48
26 β[b]	4.45	1.64	1.38	3.35	3.54	1.37	1.06	-	-	-	c	6.37	3.25
27 α	4.78	2.00	1.89	4.24	4.15	1.51	1.19	-	-	-	3.33	6.38	3.38
27 β	4.72	1.73	1.88	4.44	3.98	1.48	1.20	-	-	-	2.07	6.59	3.50
28 α	4.75	1.67	2.04	3.91	3.83	1.56	1.18	-	-	-	3.52	6.56	3.32
28 β	4.39	1.55	2.14	3.64	3.37	1.57	1.25	-	-	-	3.62	6.56	3.49

a. chemical shifts in ppm from internal TMS. Solvent $CDCl_3$ except otherwise indicated.

b. solvent C_6D_6. c. not detected.

Table 2. ^{1}H Coupling constants of the N-trifluoroacetyl-2,4,6-trideoxy-4-C-methyl-4-amino-L-hexoses.[a]

Compound	J(1,2e)	J(1,2a)	J(2e,2a)	J(3,2e)	J(3,2a)	J(5,Me)	J(CH_2Ph)	J(1,OH-1)	J(3,OH-3)	J(2a,OH-1)
21 α	1.2	3.9	13.2	5.1	11.5	6.5	11.4	2.6	-	1.6
21 β	2.5	9.7	12.6	5.0	11.6	6.4	11.4	5.7	-	-
22 α	1.2	4.0	15.0	3.3	2.6	6.4	10.6	10.4	-	-
22 β	2.3	9.8	14.4	3.2	2.6	6.6	11.0	b	-	-
23 α	1.2	3.8	15.0	2.9	2.8	6.6	11.0	10.6	-	-
23 β	2.5	9.9	14.1	2.8	2.7	6.6	11.2	b	-	-
24 α	1.4	4.0	13.7	4.8	11.3	6.3	12.0	3.0	-	1.9
24 β	2.5	9.8	13.1	4.9	11.6	6.3	12.0	b	-	-
25 α	1.0	4.0	13.4	5.3	11.6	6.4	-	-	b	-
25 β	2.4	9.9	12.8	5.2	11.9	6.6	-	-	b	-
26 α	1.4	3.6	15.0	3.0	3.4	6.3	-	-	9.9	-
26 β[c]	2.5	9.2	14.2	3.6	2.8	6.5	-	-	b	-
27 α	1.2	3.7	14.9	2.7	3.7	6.4	-	-	9.2	-
27 β	2.5	9.8	14.0	2.7	3.2	6.4	-	-	b	-
28 α	1.1	4.0	13.6	4.8	11.8	6.6	-	-	6.8	-
28 β	2.5	9.7	13.0	4.6	11.8	6.4	-	-	b	-

a. Coupling constants in Hz; solvent $CDCl_3$. b. broad signal. c. solvent C_6D_6.

less then 40 Hz to avoid possible errors due to second order effects. An equilibrium between the $^1C_4$(L) and $^4C_1$(L) conformations can be invoked to account for the increase of J(3e,2a), but a concomitant increase of J(3e,2e) should be observed. In addition the vicinal coupling constants J(1,2) are rather consistent within the whole series of compounds, supporting that no conformational equilibria occur. Thus the observed anomalies are probably due to local changes of the ring geometry or to long range substituent effects. The configuration at C-4 carbon was determined through a set of NOE experiments by irradiation of the Me-4 group. The saturation of axial methyls causes the enhancement of the H-2a protons (ca. 4%), while for the equatorial methyls no perturbation of the intensity of H-2a protons is observed. Finally, the chemical shifts and coupling constants of the hydroxyl groups are rather scattered throughout the series of compounds and their behavior can be rationalized with the existence of internal hydrogen bonding. Thus, within the series of the 3-O-benzyl derivatives, the anomeric hydroxyl proton of the β isomers resonates at ca. 3 ppm in diluted solutions. For the α isomers two distinct patterns exist: the OH-1 proton resonates at ca. 2.5 ppm for compounds with the **L**-arabino (**21**α) and **L**-lyxo (**24**α) configuration and displays a vicinal coupling J(OH-1,H-1) of ca. 3 Hz and a long range coupling J(OH-1,H-2a) of 1.6 and 1.9 Hz respectively. These data indicate that the O-H bond forms a planar W pattern with the C-H-2a bond and a torsion angle of about 60° with the C-H-1 bond.[9] The anomeric hydroxyls of the **L**-ribo and **L**-xylo isomers resonate at 4.79 and 4.75 ppm and show a coupling constant of 10.4 and 10.6 Hz respectively. These values are consistent with the existence of an internal hydrogen bonding between OH-1 and the oxygen atom of the $PhCH_2O$-3 group, forcing the OH-1 and CH-1 bonds in an anti relationship. No appreciable long-range couplings with H-2a are observed since the favorable W arrangement is lost. Within the series of the methyl glycosides the OH-3 group of the α anomers of the **L**-ribo (**26**α) and **L**-xylo (**27**α) compounds resonates at 3.83 and 3.33 ppm and displays a coupling constant of 9.9 and 9.2 Hz respectively with the H-3 proton, indicating that hydrogen bonding occurs between the OH-3 and OCH_3 groups. Comparable low field shifts are shown by OH-3 of the **L**-lyxo anomers

(28α) and (28β), suggesting the formation of hydrogen bonding between the equatorial OH-3 and the axial amide group. For the L-ribo (26β) and the L-arabino (25α) and (25β) isomers the chemical shift of the OH-3 ranges from 2.4 to 2.8 ppm indicating that for an arrangement with an equatorial amide group and an axial or equatorial OH group no strong hydrogen bonding occurs.

CONCLUSIONS

The present work represents a completely stereospecific synthesis of the L-ribo and L-lyxo derivatives 22 and 24 from the amino acid L-threonin. This synthesis takes advantage of: (i) the stereospecific conversion of L-threonin into the oxazolines 1 and 2, depending upon the procedure used; (ii) the Felkin-type addition of allylmagnesium bromide at -90 °C onto the chiral aldehydes 3 and 4 to afford the L and D-ribo adducts 7 and 11 as almost exclusive reaction products; (iii) the complete stereospecificity of oxazoline formation in going from D-ribo (16) to L-lyxo (20), the precursor of 24. The minor L and D-arabino adducts 5 and 9, obtained from 3 and 4 on reaction with allylmagnesium bromide at 20 °C, are similarly convertible into the L-arabino and L-xylo isomers 21 and 23. Interestingly, the major difficulty in the present synthetic work has been with the hydrolysis of the oxazoline ring. Apart from this, the availability of the four configurational isomers of the 2,4,6-trideoxy-4-C-methyl-4-amino-L-hexose from L-threonin as a chiral synthetic precursor is significant.

EXPERIMENTAL

General methods. ^1H NMR were determined on a Varian EM 390 (90 Mhz) and on a Bruker CXP (300 MHz) spectrometer, chemical shifts are expressed in ppm (δ) relative to internal TMS. All NMR spectra were recorded in $CDCl_3$ unless otherwise stated. GC analysis were performed on a DANI apparatus, model 6500. Optical rotations value were recorded on a JASCO DIP 181 digital polarimeter. Specific rotation values refer to 20 °C and c 1 $CHCl_3$. All the $[\alpha]_D$ are reported in Table 3. Purification of the products was performed by silica gel column chromatography (Merck 60, 0.04-0.063 mm) eluting with mixtures of n-hexane and ethyl acetate. Analytical samples were prepared, when possible, by

TABLE 3. Optical rotation values for compounds 1 - 28.

20 °C; c=1 ($CHCl_3$)

1	-9.51	**13**	+75.17	**21**[a]	+46.63
2	+9.42	**14**	+12.84	**22**[a]	-92.14
3	+178.44	**15**	-3.71	**23**[a]	-21.51
4	-175.34	**16**	+39.58	**24**[a]	-2.93
6	-26.50	**17**	+24.91	**25**	-56.55
8	-55.80	**18**	+42.98	**26**	-21.35
10	+24.30	**19**	+1.39	**27**	+7.26
12	+54.50	**20**	+62.12	**28**	-39.30

a. measured after 24 h.

bulb to bulb distillation at reduced pressure. Elemental analysis of compounds **21-28** are reported in Table 4.

Preparation of the aldehyde 3 or 4. 28 g (0.12 mole) of the oxazoline ester **1** or **2**, prepared as reported,[4] were added dropwise to a solution of 2.3 g (0.06 mole) of $LiAlH_4$ in 200 mL of dry ethyl ether at room temperature. At the end of the addition the reaction mixture was heated at reflux for 1 h, cooled, and 20 mL of ethyl acetate added. The organic phase was poured into ice water, washed with brine, dried and concentrated to dryness under vacuum. Purification of the oily residue by silica gel column chromatography (eluent hexane: ethyl acetate 1:1) gave 23 g (0.11 mole, 90%) of oil which solified on standing. $[\alpha]_D$ +14.86 for the (2S,3S) enantiomer, $[\alpha]_D$ -13.96 for the (2R,3R) enantiomer. ^1H NMR (δ) 1.38 (3H, CH_3, s), 1.58 (3H, CH_3, d), 3.28 (1H, OH, broad), 3.74 (2H, CH_2, s), 4.49 (1H, CH, q), 7.27-7.53 (3H, Ph, m) and 7.82-8.08 (2H, Ph, m). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.75; H, 7.04; N, 6.80. To a solution of oxalyl chloride, 10 mL (0.11 mole) in 500 mL of dry CH_2Cl_2, cooled at -70 °C, 18 mL (0.22 mole) of dry DMSO, diluted in 100 mL of dry CH_2Cl_2, were added during 30 min. The reaction mixture was stirred for an additional 20 min at the same temperature and 23 g (0.11 mole) of the above alcohol, dissolved in dry dichloromethane,

TABLE 4. Elemental analysis for compounds 21-28.

21 - 24. Anal. Calcd for $C_{16}H_{20}F_3NO_4$: C, 55.36; H, 5.80; N, 4.03.
25 - 28. Anal. Calcd for $C_{10}H_{16}F_3NO_4$: C, 44.28; H, 5.94; N, 5.16.

Found:	C	H	N		C	H	N
21	55.40	5.78	4.05	**25**	44.23	5.94	5.18
22	55.32	5.75	3.98	**26**	44.27	6.00	5.12
23	55.41	5.77	4.00	**27**	44.32	5.91	5.14
24	55.38	5.84	4.09	**28**	44.25	5.93	5.21

were added dropwise. After an additional hour of stirring at the same temperature, 80 mL (0.55 mole) of Et_3N were added and the reaction left to warm to room temperature. An equal amount of ethyl ether was added and the organic phase washed twice with water. The solvent was dried, evaporated at 35° C under vacuum to give a thick oil. Purification on silica gel (eluent hexane: ethyl acetate 8:2) gave **3** 17.3 g (0.085 mole, 75%), oil. ^1H NMR (δ) 1.39 (3H, CH_3,d), 1.48 (3H, CH_3, s), 4.58 (1H, CH, q), 7.32-8.20 (5H, Ph, m) and 9.83 (1H, CHO, s). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.87; H, 6.51; N, 6.95.

Addition of allyl Grignard reagent onto 3. The aldehyde **3**, (10.1 g, 0.05 mole) in 40 mL of anhydrous ethyl ether was added at 20° C to a solution of allylmagnesium bromide, prepared from 2.4 g (0.1 mole) of Mg and 10.9 g (0.09 mole) of allyl bromide in ethyl ether at room temperature. Performing the Grignard reaction in a Dewar flask carefully thermostated at -90 °C, gave only the 3,4-anti adduct **7**. After stirring the reaction mixture for 3 h at the same temperature, a saturated aqueous solution of NH_4Cl (100 mL) was added dropwise and the organic phase separated and washed twice with water. Concentration in vacuum gave a thick oil (13 g) which was not further purified. Attempts to purifie the crude oil by silica gel column chromatography led to **29**, 7 g, $[\alpha]_D$ -40.79. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H,

7.81; N, 5.71. Found: C, 73.38; H, 7.79; N, 5.74. ^{1}H NMR (DMSO-d_6) (δ) 1.09 (3H, CH_3, s), 1.12 (3H, CH_3, d), 2.30-2.40 (2H, CH_2, m), 3.56 (1H, CH, dq), 4.57 (1H, CH, dd), 4.80 (1H, OH, d), 5.08-5.28 (2H, CH_2, m), 5.95 (1H, CH, m), 7.18-7.48 (3H, Ph, m) and 7.74-7.88 (2H, Ph, m). The above crude material was added at room temperature to a suspension of NaH, 1.2 g (0.05 mole) in 50 mL of dry DMF. The reaction mixture was heated at 50 °C for 1 h, cooled at 25 °C, and 6.3 g (0.05 mole) of benzyl chloride added dropwise. After stirring overnight at 25° C the solution was poured into ice water and extracted three times with a mixture of hexane: ethyl ether (1:2). The combined organic layer was dried and concentrated at reduced pressure to give an oil, which was carefully purified on silica gel column chromatography (eluent hexane: ethyl acetate 9:1) to give first **8**, 6.4 g (0.019 mole), ^{1}H NMR (δ) 1.4 (3H, CH_3, s), 1.44 (3H, CH_3, d), 2.32-3.13 (2H, CH_2, m) 3.67 (1H, CH, dd), 4.33 and 4.90 (2H, CH_2, AB system), 4.56 (1H, CH, m), 4.95-5.32 (2H, CH_2, m), 5.88-6.35 (1H, CH, m) 7.23-7.54 (8H, 2 Ph, m) and 7.90-8.09 (2H, Ph, m); and then **6**, 5.36 g (0.016 mole), ^{1} H NMR (δ) 1.42 (3H, CH_3, s), 1.50 (3H, CH_3, d), 2.32-2.57 (2H, CH_2, m), 3.60 (1H, CH, dd), 4.46 (1H, CH, q), 4.80 (2H, CH_2, s), 4.90-5.22 (2H, CH_2, m), 5.70-6.23 (1H, CH, m), 7.23-7.58 (8H, 2 Ph, m) and 7.91-8.14 (2H, Ph, m). Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: **8**, C, 78.71; H, 7.47; N, 4.20; **6**, C, 78.75; H, 7.53; N, 4.21.

Hydrolysis of the oxazoline ring. Product **8**, 5 g (0.015 mole), was diluted in 50 mL of MeOH and a mixture of 15 mL of water and 10 mL of concd HCl was added. The reaction was heated at reflux for 2 h, cooled at 20 °C, concentrated to reduced volume and carefully neutralized with a saturated solution of $NaHCO_3$. Extraction with ethyl acetate, concetration in vacuum and silica gel column chromatography (eluent hexane: ethyl acetate 1:1) gave the pure product **14**, 3.5 g (0.01 mole,70%). In the case of the threo oxazolines **17** and **18**, the acidic hydrolysis was less efficient and the yield decreased to less than 30%. Anal. Calcd for $C_{22}H_{27}O_3N$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.74; H, 7.55; N, 4.02. **14**, ^{1}H NMR (δ) 1.26 (3H, CH_3, s), 1.35 (3H, CH_3, d), 1.41 (2H, NH_2, s broad), 2.31-2.67 (2H, CH_2, m), 3.50 (1H, CH, dd), 4.52 and 4.80 (2H, CH_2, AB system), 5.09 (1H, CH, m), 5.28 (2H, CH_2, m), 5.76-6.27 (1H, CH, m), 7.26-7.53 (8H, 2 Ph, m) and 8.00-8.20 (2H, Ph, m); **13**, ^{1}H NMR (δ) 1.14 (3H, CH_3, s), 1.28 (2H, NH_2, s

broad), 1.34 (3H, CH_3, d), 2.30-2.52 (2H, CH_2, m), 3.50 (1H, CH, dd), 4.31 and 4.60 (2H, CH_2, AB system), 4.92-5.12 (1H, CH, m), 5.15-5.42 (2H, CH_2, m), 5.74-6.26 (1H, CH, m), 7.20-7.57 (8H, 2 Ph, m) and 7.97-8.15 (2H, Ph, m).

General procedure for the preparation of the Ribo and Arabino isomers. To a solution of compound **14** or **13**, 4 g (0.012 mole), in 10 mL of dry CH_2Cl_2, 25 g (0.12 mole) of trifluoroacetic anhydride and 100 mg of dimethylaminopyridine were added at 0 °C and the reaction mixture stirred overnight at 25 °C. Concentration at reduced pressure and purification on silica gel gave 4 g (9 mmole, 75%) of pure product showing $[\alpha]_D$ -7.42 for the product derived from **14** and $[\alpha]_D$ +32.97 for the other isomer derived from **13.** To the above material, dissolved in 20 mL of EtOH, 10 mL of 10% NaOH aqueous solution were added at 25° C and the mixture stirred at the same temperature for 2 h. Concentration to dryness at reduced pressure and extraction with boiling ethyl acetate, gave an oil (2 g) which was not further purified. To the above crude material, suspended in 10 mL of dry CH_2Cl_2, 30 g (0.14 mole) of trifluoroaceticanhydride were added at 0 °C and the reaction stirred at 25 °C for 16 h. Concentration in vacuum gave an oil which was immediately redissolved in 20 mL of dry MeOH and 50 mg of MeONa were added. The reaction was refluxed for 8 h, cooled, and 2 drops of CH_3COOH added. Concentration under reduced pressure gave an oil which was purified on silica gel chromatography to give 2.2 g (6.3 mmole) of pure (2S, 3S, 4R)-2-hydroxy-3-methyl-3(N-trifluoroacetylamino)-4-benzyloxy-hept-6-ene: ^1H NMR (δ) 1.23 (3H, CH_3, d), 1.41 (3H, CH_3, s), 2.40-2.62 (2H, CH_2, m), 3.38 (1H, OH, d), 4.10-4.33 (2H, 2 CH, m), 4.48 and 4.77 (2H, CH_2, AB system), 5.03-5.30 (2H, CH_2, m), 5.70-6.20 (1H, CH, m), 6.67 (1H, NH, broad) and 7.38 (5H, Ph, s), $[\alpha]_D$ -33.53; or the (2S, 3S, 4S) isomer, ^1H NMR (δ) 1.19 (3H, CH_3, d), 1.30 (3H, CH_3, s), 2.38 (2H, CH_2, m), 3.77 (2H, 2 CH, m), 4.54 and 4.74 (2H, CH_2, AB system), 5.05-5.32 (2H, CH_2, m), 5.60-6.35 (3H, CH, OH, NH, m) and 7.36 (5H, Ph, s), $[\alpha]_D$ +6.83. Ozone was passed through a solution of the above material in 50 mL of dry MeOH at -70° C for 20 min (our apparatus produce ca. 150 mmole per h using oxygen as flowing gas). The solution was purged with N_2, 0.4 g (7 mmole) of Me_2S were added and the reaction mixture was subsequently kept at room temperature for 1 h and heated at 50 °C for 3 h. Concentration in vacuum and silica

gel column chromatography (eluent hexane: ethyl acetate 1:1) gave the amino deoxy sugars (**22**) or (**21**), 2 g (5.7 mmole, 90%). To the above compounds, dissolved in 20 mL of dry MeOH, 2 mL of MeOH saturated with HCl gas were added and the reaction mixture left at 25° C for 16 h. To the same solution 200 mg of 10% Pd on charcoal were added and the reaction was stirred at 25 °C in an atmosphere of H_2 until the absorption was completed (1 h). The mixture was filtered over a pad of celite, the solvent evaporated in vacuum, and the residue purified by silica gel chromatography (eluent hexane: ethyl acetate 7:3) to give 1.4 g (5.1 mmole, 90 %) of **26** or **25**.

General procedure for the preparation of the Lyxo and Xylo compound. To 4 g (12 mmole) of the enantiomers of **14** or **13** dissolved in 40 mL of EtOH, 15 mL of 10% aqueous NaOH were added at 25 °C and the reaction stirred for 2 h. Concentration to dryness and extraction with boiling ethyl acetate gave an oil which solified on standing and was purified by silica gel chromatography (eluent hexane: ethyl acetate 8:2) to give 3.6 g (11 mmole, 90 %) of **16**: ^{1}H NMR (δ) 1.23 (3H, CH_3, d), 1.45 (3H, CH_3, s), 1.70 (1H, OH, broad), 2.54 (2H, CH_2, m), 4.23-4.71 (2H, 2 CH, m), 4.55 and 4.84 (2H, CH_2, AB system), 5.00-5.32 (2H, CH_2, m), 5.78-6.28 (1H, CH, m), 6.46 (1H, NH, broad) and 7.25-7.80 (10H, 2 Ph, m); or **15**, ^{1}H NMR (δ) 1.21 (3H, CH_3, d), 1.49 (3H, CH_3, s), 1.77 (1H, OH, broad), 2.54 (2H, CH_2, m), 3.50-3.92 (2H, 2 CH, m), 4.48 and 4.90 (2H, CH_2, AB system), 5.08-5.37 (2H, CH_2, m), 5.78-6.28 (1H, CH, m), 7.07 (1H, NH, broad) and 7.21-7.68 (10H, 2 Ph, m). Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.75; H, 7.70; N, 3.96. Found: **16**, C, 74.78; H, 7.68; N, 4.02; **15**, C,74.69; H,7.72; N, 3.96. The above products **16** or **15**, 3.5 g (10 mmole) dissolved in 10 mL of $CHCl_3$, were added dropwise at 0 °C to 30 mL of $SOCl_2$ and the reaction stirred at the same temperature for 16 h. Work up as reported,[10] gave 2.7 g (8 mmole, 80 %) of **18** or **17**. From this point ahead the procedure follows exactly that reported for the preparation of the ribo and arabino isomers, and compounds **24**, **23**, **28** and **27** were obtained. The intermediates in the synthesis of compounds **28** and **27** had the following ^{1}H NMR; **18**, (δ) 1.28 (3H, CH_3, s), 1.37 (3H, CH_3, d), 2.13-3.75 (2H, CH_2, m), 3.58 (1H, CH, dd), 4.64 (2H, CH_2, s), 4.79 (1H, CH, q), 4.93-5.30 (2H, CH_2, m), 5.78-6.24 (1H, CH, m), 7.27 (5H, Ph, s), 7.30-7.51 (3H, Ph, m) and 7.87-8.03 (2H, Ph, m); **17**, (δ) 1.38 (3H, CH_3, s), 1.39 (3H, CH_3, d),

2.22-2.49 (2H, CH_2, m), 3.65 (1H, CH, dd), 4.73 (2H, CH_2, s), 4.81 (1H, CH, q), 4.90-5.23 (2H, CH_2, m), 5.72-6.20 (1H, CH, m), 7.21-7.52 (8H, 2 Ph, m) and 7.87-8.04 (2H, Ph, m); **20**, (δ) 1.13 (3H, CH_3, s), 1.38 (3H, CH_3, d), 1.68-2.10 (2H, NH_2, broad), 2.33-2.70 (2H, CH_2, m), 3.47 (1H, CH, dd), 4.32 and 4.60 (2H, CH_2, AB system), 4.98-5.32 (2H, CH_2, m), 5.39 (1H, CH, q), 5.76- 6.27 (1H, CH, m), 7.20-7.60 (8H, 2 Ph, m) and 7.96-8.14 (2H, Ph, m); **19**, (δ) 1.14 (3H, CH_3, s), 1.32 (3H, CH_3, d), 1.52 (2H, NH_2, s broad), 2.27-2.63 (2H, CH_2, m), 3.48 (1H, CH, dd), 4.51 and 4.79 (2H, CH_2, AB system), 4.92-5.28 (2H, CH_2, m), 5.29 (1H, CH, q), 5.63-6.23 (1H, CH, m), 7.28-7.64 (8H, 2 Ph, m) and 8.00-8.18 (2H, Ph, m); (2S, 3R, 4S)-2-hydroxy-3-methyl-3(N-trifluoroacetylamino)-4-benzyloxy-hept-6-ene, (δ) 1.10 (3H, CH_3, d), 1.37 (3H, CH_3, s), 2.30-2.53 (2H, CH_2, m), 4.03-4.37 (2H, 2 CH, m), 4.52 and 4.68 (2H, CH_2, AB system), 5.02-5.33 (2H, CH_2, m), 5.70-6.12 (1H, CH, m) and 7.05-7.40 (6H, NH, Ph, m), $[\alpha]_D$ +91.24; (2S, 3R, 4R)-2-hydroxy-3-methyl-3(N-trifluoroacetylamino)-4-benzyloxy-hept-6-ene, (δ) 1.16 (3H, CH_3, d), 1.37 (3H, CH_3, s), 2.20-2.85 (2H, CH_2, m), 3.87 (1H, CH, q), 4.02 (1H, CH, dd), 4.40 and 4.77 (2H, CH_2, AB system), 5.03-5.32 (2H, CH_2, m), 5.78-6.22 (1H, CH, m), 6.64 (1H, NH, broad) and 7.39 (5H, Ph, s), $[\alpha]_D$ -51.14.

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