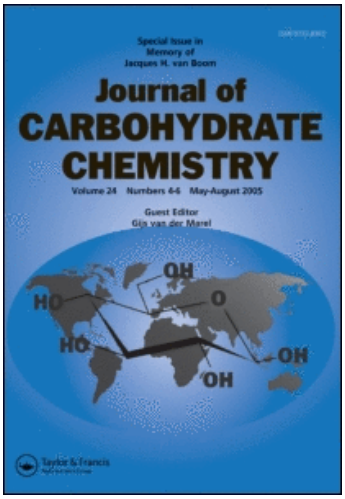

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Synthesis of the Eight Configurational Isomers of N-Trifluoroacetyl-2-C-Methyl-2,3,6-Trideoxy-3-Amino-L-Hexcse from Non-Carbohydrate Precursors

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SYNTHESIS OF THE EIGHT CONFIGURATIONAL ISOMERS OF N-TRIFLUOROACETYL-2-C-METHYL-2,3,6-TRIDEOXY-3-AMINO-L-HEXOSE FROM NON-CARBOHYDRATE PRECURSORS

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ABSTRACT

The erythro and threo chiral C_4-N, phenylsulfenimines (3) and (4), prepared from the (2S,3R)-methyl diol obtained in fermenting baker's yeast from cinnamaldehyde, were converted via reaction with $BrMgCH_2CH=CHCH_3$ and $BrMgCH_2CH=CHCH_3$ / $ZnCl_2$, respectively, into the isomeric C_8-N adducts (5), bearing relative stereochemistry at position 4 and 5 depending upon the reagent used. Ozonolysis of the terminal vinyl group of the N-trifluoroacetyl derivatives yielded, through the different addition experiments, the eight isomeric 2-C-methyl-2,3,6-trideoxy-3-amino-L-hexose derivatives (6) - (13).

INTRODUCTION

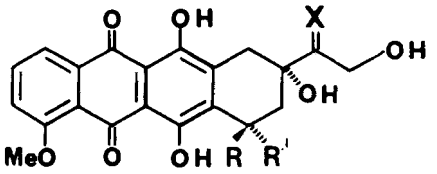
One of the main operations in the metabolism of the anticancer agent adriamycin[1] (1) in mammals is the reductive deglycosidation giving rise to the 7-deoxyaglycone (2).[2] It seemed of interest to evaluate the activity profile of analogs of (1), modified in the

neighborhood of the glycoside linkage, by introduction of a methyl group in position 2'. In this context we present now the synthesis of the eight configurational isomers of the N-trifluoroacetyl-2,3,6-trideoxy-2-C-methyl-L-amino-hexose (6) - (13), which are the required intermediates in the convergent synthesis of such anthracycline glycosides. Our approach to the above 2-C-methyl aminodeoxy sugars starts from the chiral phenylsulfenimines (3) and (4), prepared from (2S,3R)-5-phenylpent-4-en-2,3-diol,[3] obtained in fermenting baker's yeast from cinnamaldehyde. These C_4-N materials have recently been incorporated[4] into the C_6-N framework of the four configurational isomers of the 2,3,6-trideoxy-3-amino-L-hexose through reaction with allylmetals and ozonolysis of the terminal vinyl group of the C_7-N adducts. We thought to have access to the 2-C-methyl analogs of L-daunosamine and its configurational isomers substituting crotyl metals for allyl metals in the above sequence . However, the addition of crotyl metals onto the sp^2 carbon of chiral carbonyl compounds or their nitrogen equivalents (3) and (4) raises the problem of control of the relative stereochemistry around the newly formed C-C bond. Facial selectivity in the present case will dictate the stereochemistry of the nitrogen bearing carbon atom in the adduct. Ongoing experiments[5] in this field are demonstrating that stereochemically defined crotyl metals (e.g. crotyl boronates) react with chiral α,β -dialkoxyaldehydes with high allylic-homoallylic diastereoselectivity. However, the degree of facial selectivity with the same metal strongly depends upon the double bond

geometry. Conversely, configurationally unstable crotylmagnesium bromide gives rise, with a similar substrate, to the four possible isomers in comparable ratios.[6]

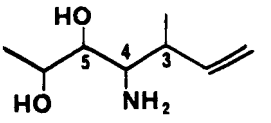
RESULTS AND DISCUSSION

With the configurational isomers of 2-C-methyl-2,3,6-trideoxy-3-amino-L-hexose as target materials, the phenylsulfenimines (3) and (4) were reacted with $BrMgCH_2CH=CHCH_3$ (reagent A) and with $BrMgCH_2CH=CHCH_3/ZnCl_2$ (reagent B), respectively, in ethyl ether at room temperature. Acid work up, N-trifluoroacetylation, ozonolysis in MeOH at -40 °C and Me_2S treatment, afforded the required N-trifluoroacetyl amino sugars, 6 - 13. Products 6 - 12 were isolated in pure form by silica gel chromatography (Table 1), whereas 13 was in mixture with 12. The relative percentages of the various isomers (Table 2) in the four experiments was determined from the weight of the isolated products and from ^1H NMR data (see below). From the product distribution (Table 2) it appears that addition of crotyl magnesium bromide onto (3) and (4) proceeds with ca. 6:4 syn/anti facial selectivity and with ca. 2:1 syn/anti allylic/homoallylic selectivity. A prevalent anti facial selectivity (anti/syn = ca. 4:1), according to the operation of a Felkin model,[7] and a similar 2:1 allylic/homoallylic selectivity, was observed when the addition was performed in the presence of $ZnCl_2$. Entries 3 and 4 in Table 2 illustrate these selectivities.



(1) X= O; R= H; R' = L-daunosaminyl

(2) X= H, OH; R=R' = H



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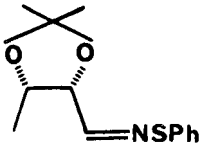

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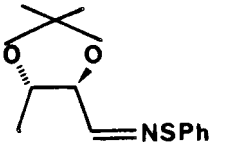

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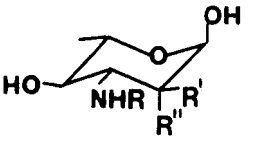
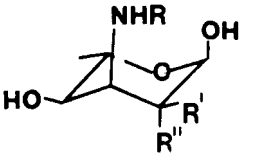


(6) R' = H; R'' = Me

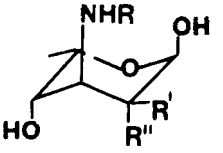
(7) R' = Me; R'' = H



(8) R' = H; R'' = Me

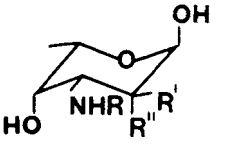
(9) R' = Me; R'' = H

$R=COCF_3$



(10) R' = H; R'' = Me

(11) R' = Me; R'' = H



(12) R' = Me; R'' = H

(13) R' = H; R'' = Me

$R=COCF_3$

TABLE 1. Physical properties of products (6) - (12)[a]

Compd.	(6)	(7)	(8)[c]	(9)[c]	(10)	(11)	(12)
m.p.[b]	218-220	116	174	95	168	142-143	117
$[\alpha]_D^{20}$	-40.5[d]	-45[d]			-27[e]	+21[e]	-15[e]

a. Satisfactory elemental analysis were obtained for all compounds, see Table 5 in the experimental part. b. °C, uncorrected. c. Racemic material. Prepared from racemic (3) in a parallel experiment.
d. (c 0.5, EtOH); e. (c 1, MeOH).

TABLE 2. Relative percentages of products (6)-(13) obtained from the addition of reagents A and B onto (3) and (4)

			Products							
Entry	Substrate	Reagent	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
1	(3)	A	40	20	30	10				
2	(4)	A					40	20	25	15
3	(3)	B	10	5	60	25				
4	(4)	B					10	10	55	25

DISCUSSION OF THE NMR SPECTRA

The structures of the N-trifluoroacetyl-2,3,6-trideoxy-2-C-methyl-3-amino-L-hexoses (6) - (13) have been determined through analysis of the ^{1}H 300 MHz spectra (Tables 3 and 4). The compounds 7, 9, 11 and 12 bearing a 2S oriented 2-C-methyl group are detected, just after the dissolution of the sample, as α-anomers of the six-membered ring form. The structures of these compounds were assigned from the values of the vicinal coupling constants, which are in reasonable agreement with those predicted for substituted pyranose rings with $^{1}C_{4}(L)$ conformation on the basis of the electronegativity and orientation of the substituents.[8] In particular, the stereochemistry at C-2 carbon can be determined from the value of J (1e,2a) (3.1-3.4 Hz), which differs from J (1e,2e), J (1a,2e) and J (1a,2a) (predicted values 1.3, 2.1 and 9.3 Hz respectively) for 2-deoxypyranoses. In addition, compounds 7, 11 and 12 display a four-bond coupling constant of 1.3 - 1.6 Hz between OH-1 and H-2a, a coupling which is specific for a trans-diaxial relationship of the anomeric hydroxy group and H-2 proton.[9] For the L-ribo isomer (9) this long-range coupling constant was not detected since the OH signal is broad owing to exchange with water. The L-ribo and L-lyxo compounds (8) and (13), bearing a (2R)-2-C-methyl group, exist in solution essentially as five-membered rings. The relative stereochemistry at C-2 and C-3 carbons has been determined from a set of NOE experiments with the assumption that the configuration of the C-4 and C-5 carbons is carried over from the starting materials, the

TABLE 3. ^{1}H NMR Chemical Shifts of 3-N-trifluoroacetyl-2,3,6-trideoxy-2-C-methyl-3-amino-L-hexoses[a]

Compd.	(6)	(7)	(8)[b,e]	(9)	(10)	(10)[c]	(11)	(12)	(13)[e]
H-1	4.94	5.00	4.90	5.03	4.90	4.84	5.07	5.03	5.11
H-2	2.29	1.94	1.97	2.08	1.78	1.76	2.41	2.18	2.41
H-3	4.39	4.05	3.95	4.32	3.92	3.89	4.00	4.22	4.69
H-4	3.41	3.19	3.84	3.42	3.67	3.71	3.48	3.55	3.95
H-5	3.96	3.96	3.64	3.90	4.23	4.21	4.21	4.22	3.73
Me-2	0.99	0.91	0.96	0.98	1.11	1.04	0.97	0.93	0.96
Me-5	1.21	1.19	0.98	1.20	1.20	1.22	1.15	1.14	1.14
OH-1	5.33	5.20	6.38	6.07	5.58	--	6.04	5.17	5.50
OH-4	4.35	4.20	--	d	4.33	--	4.30	4.01	--
OH-5	--	--	4.68	--	--	--	--	--	d
NH-3	8.20	8.10	9.47	8.02	8.34	--	8.35	7.98	8.52

a. Chemical shifts (in ppm) from internal Me_4Si. Solvent $(CD_3)_2CO$-d_6 except otherwise indicated. All the reported data are for the α-(L)-isomers.
b. Solvent $(CD_3)_2SO$-d_6.
c. Solvent $(CD_3)_2CO$-d_6 + D_2O.
d. Not detected.
e. Furanose form.

TABLE 4. ^{1}H NMR Coupling Constants of 3-N-trifluoroacetyl-2,3,6-trideoxy-2-C-methyl-3-amino-L-hexoses[a]

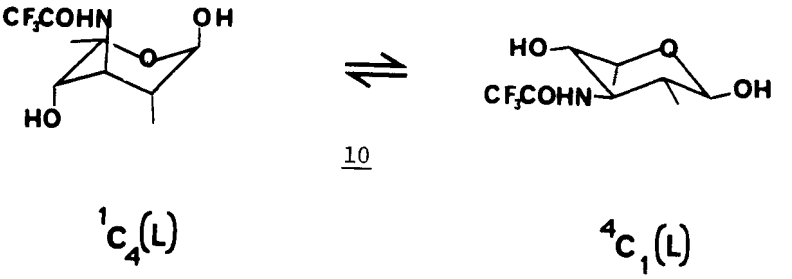
Compd	(6)	(7)	(8)[b,e]	(9)	(10)	(10)[c]	(11)	(12)	(13)[e]
J(1,2)	1.5	3.3	5.1	3.3	4.8	6.2	3.4	3.1	2.1
J(2,3)	5.0	11.7	8.0	3.2	7.0	9.0	3.6	12.0	7.2
J(3,4)	10.5	9.6	7.5	4.1	6.4	7.5	3.6	2.8	6.8
J(4,5)	9.4	9.4	4.1	9.9	3.8	4.4	1.8	1.5	3.8
J(2,Me)	7.2	6.9	6.9	7.0	7.0	6.9	7.2	6.7	7.2
J(5,Me)	6.1	6.3	6.4	6.1	6.7	6.7	6.6	6.5	6.6
J(1,OH-1)	3.6	3.9	5.5	d	4.6	-	3.3	3.8	5.4
J(4,OH-4)	6.2	6.4	-	d	5.0	-	5.8	6.8	-
J(5,OH-5)	-	-	4.5	-	-	-	-	-	d
J(2,OH-1)	-	1.3	-	d	-	-	1.6	1.3	-
J(3,NH)	8.0	9.6	8.5	9.4	9.0	-	8.5	9.0	7.5

a. Coupling Constants in Hz. Solvent $(CD_3)_2CO$-d_6 except otherwise indicated. All the reported data re for α-(L)-isomer
b. Solvent $(CD_3)_2SO$-d_6.
c. Solvent $(CD_3)_2CO$-d_6 + D_2O.
d. Not detected.
e. Furanose form

erythro or threo phenylsulfenimines 3 and 4. The most significant experiments involved the selective irradiation of H-2 and 2-C-methyl hydrogens. Thus, for the L-ribo isomer (8) the saturation of H-2 produced an enhancement for the signals of H-4 (2.8%) and NH-3 (3%), while irradiation of the 2-C-methyl group produced enhancement of H-3 (7%) with no variation of the intensity of H-4 and NH-3 signals. These experiments clearly indicate the 1,3-syn-relationship of H-2 and H-4 protons and the trans-relationship between the 2-C-methyl and 3-$NHCOCF_3$ groups. In the case of the L-lyxo isomer (13) irradiation of H-2 produced enhancement of the H-3 signal (10%) but had no effect on the H-4 and NH-3 signals. Irradiation of Me-2 protons produced enhancements for H-4 (2%) and NH-3 (3.5%) with no variation for H-3. Finally the L-arabino and L-xylo compounds (6) and (10) exist, just after dissolution, as α-pyranoses. The values of the vicinal coupling constants for (6) are consistent with the $^1C_4$(L) conformation, while for compound (10) they are completely out of the expected range for such a conformation and are similar to the values normally displayed by a five-membered ring. On the other hand the six-membered ring structure is unequivocally proved by the existence of a coupling constant of 5.0 Hz between OH-4 and H-4 hydrogens. Moreover the ^3J values are extremely sensitive to the nature of the solvent. For instance the addition of a drop of D_2O causes strong variations of ^3J's (see Table 4), which are not usual for conformationally stable pyranose rings. These data strongly suggest that a rapid equilibrium

exists between the possible two $^{1}C_{4}(L)$ and $^{4}C_{1}(L)$ chair conformations for compound 10 (Scheme 1).

SCHEME 1



10

$^{1}C_{4}(L)$ $^{4}C_{1}(L)$

In order to estimate the population P_1 and P_2 of each conformer of 10, the well known[8] time average equation $J(av) = P_1J_1 + P_2J_2$ can be applied, where J_1 and J_2 are the predicted values for the coupling constants of the two chair conformations. The values of J_1 and J_2 have been calculated from the reported[9] additivity constants $\Delta J(X)$ for a substituent X. The calculated amount of $^{1}C_{4}(L)$ conformer is 50 ± 10% in acetone solution and 30 ± 10% for an acetone solution containing D_2O. Usually the $^{1}C_{4}(L)$ conformation is highly preferred by pyranose rings bearing a substituent at C-5.[8] It is apparent in the case of the L-xylo isomer (10) that the $^{1}C_{4}(L)$ conformation is strongly destabilized by significant 1,3-diaxial interactions.

CONCLUSIONS

Formation of the eight isomeric 2-C-methyl-2,3,6-trideoxy-3-amino-L-hexose derivatives (6) - (13) from the phenylsulfenimines (3) and (4), is a further example of the significance of the synthesis of enantiomerically pure natural products and analogs of potential pharmacological interest. The method used here is based on chiral starting materials prepared by microbial transformations of unconventional substrates. Preliminary data,[10] indicate that the glycoside derived from daunomycinone and the (2S)-2C-methyl-2,3,6-trideoxy-3-amino-L-arabino-hexose derivative (7) shows biological activity similar to that of the compound devoid of the 2-C-methyl group (i.e.: 4'-epi-daunomycine).

EXPERIMENTAL

Phenylsulfenimines (3) and (4). To a solution of 13 g (0.076 mol) of $AgNO_3$ in 1200 mL of dry MeOH in a three necked flask, equipped with a mechanical stirrer and an inlet tube were added at 0 °C 16.6 g (0.076 mol) of phenyldisulfide, and then dry ammonia was passed through for 30 min at 0 °C. To the above mixture were added 10.9 g (0.076 mol) of the appropriate erythro or threo aldehyde, prepared as reported,[11] and the reaction mixture was stirred overnight at room temperature. Silver mercaptide was removed by filtration, and the solvent was evaporated under reduced pressure to give a residue which was redissolved in ethyl ether and filtered. The ethereal solution was washed with water

and dried. Silica gel column chromatography with hexane:ethyl acetate (95:5) gave 13.3 g (0.053 mol, 70%) of a red oil: (3) $[\alpha]_D^{20}$ = -30.4 (c 0.5, $CHCl_3$). Anal. calcd for $C_{13}H_{17}NO_2S$: C, 62.14; H, 6.82; N, 5.57; S, 12.73. Found: C, 62.16; H, 6.83; N, 5.53; S, 12.75. (4) $[\alpha]_D^{20}$ = +9.5 (c 1, $CHCl_3$). Anal. found: C, 62.15; H, 6.82; N, 5.58; S, 12.76.

Addition of crotylmagnesium bromide to the isomeric phenylsulfenimines (3) and (4). (REAGENT A). The appropriate phenylsulfenimine (3) or (4) 13.3 g (0.053 mol) in 40 mL of anhydrous ethyl ether was added at room temperature to a solution of crotylmagnesium bromide obtained from 3.6 g (0.15 mol) of Mg and 12.1 mL (0.12 mol) of crotyl bromide in ether at room temperature. The reaction mixture was left at room temperature under stirring for 3 h, 50 mL of saturated solution of NH_4Cl was added, and the separated ethereal phase was washed with 3x30 mL of 6N HCl. The combined acid solution was taken to dryness at reduced pressure to leave 7.25 g (0.037 mol) of a thick oily residue (70%). The latter crude material was taken up in 20 mL of dry CH_2Cl_2 and treated at 0 °C under stirring with a large excess (20 mL, 0.14 mol) of trifluoroacetic anhydride. The reaction mixture was stirred at room temperature for 6 h and then concentrated to dryness under reduced pressure. The oily residue was taken up in 100 mL of MeOH, 50 mg of MeONa was added to the solution,and the solution was boiled for 6 h at reflux. The crude oily residue, obtained upon concentration in vacuum, was purified by silica gel column chromatography (eluent hexane : ethyl acetate, 1:1) to give 5 g (0.02 mol, 60%) of a mixture

TABLE 5. Elemental analysis for compounds 6 - 13

Anal. calcd for $C_9F_3H_{14}NO_4$: C, 42.02; H, 5.49; N, 5.45.

	C	H	N
6	42.04	5.50	5.47
7	42.04	5.47	5.48
8	41.98	5.49	5.45
9	42.05	5.45	5.43
10	41.99	5.48	5.42
11	42.01	5.51	5.42
12	42.00	5.46	5.47
13[a]	42.07	5.46	5.48

a. In mixture with 12.

of diastereoisomers. Ozonized oxygen was passed through a solution of the above material in 70 mL of MeOH at -40 °C for 20 min (our apparatus produces ca. 150 mmol of ozone per hour; flowing gas oxygen). The solution was purged with nitrogen to remove the excess of ozone, and 1.85 mL (0.025 mol) of Me_2S was added. The reaction mixture was kept at room temperature for 1 h, and heated at 50 °C for 3 h. Concentration in vacuum, careful silica gel flash chromatography (eluent hexane : ethyl acetate, 3:7) and subsequent crystallization of the various fractions from ethyl acetate gave the amino deoxysugars (6) - (13) in the ratios reported in Table 2. Total recovery 2 g (60%).

Addition of crotyl zinc to the isomeric phenylsulfenimines (3) and (4). (REAGENT B). To a solution of crotylzinc, prepared by addition of 13.6 g (0.1 mol) of anhydrous zinc chloride in 150 mL of ether at 0° C to crotylmagnesium bromide was added at room temperature 13 g

(0.05 mol) of the appropriate isomeric phenylsulfenimines (3) or (4) under nitrogen. The crotylmagnesium bromide was prepared from 12 mL (0.12 mol) of crotyl bromide and 3.6 g (0.15 mol) of Mg in 150 mL of dry ether. The reaction mixture was stirred at the same temperature for 3 h and then quenched with 50 mL of a satd soln of NH_4Cl. The ethereal solution was separated and the mixture of the trideoxy-amino sugars (6) - (13), in the percentages reported in Table 2, was isolated following the sequence reported for reagent A. Total recovery 1.8 g (53%).

ACKNOWLEDGMENTS

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