Synthesis of Derivatives of 3-Amino-2,2-difluoro-2,3,6-trideoxy-L-lyxopyranose (2,2-Difluorodaunosamine)

Aimée Dessinges,† Francisca Cabrera Escribano,† Gabor Lukacs,*† Alain Olesker,† and Ton That Thang†

Institut de Chimie des Substances Naturelles du CNRS, 91190 Gif-sur-Yvette, France, and Equipe de Recherche ERA 948, CNRS, USTL, 34060 Montpellier Cedex, France

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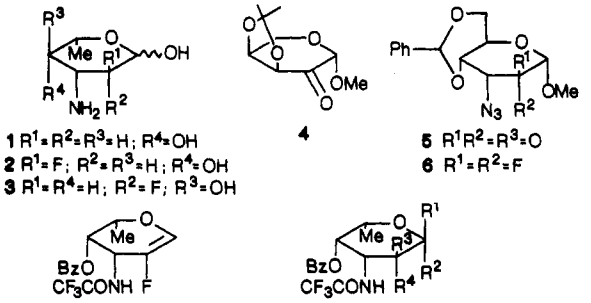
In view of the considerable continuing interest in the synthesis of daunosamine (**1**), the carbohydrate constituent of the antitumor antibiotics daunomycin and adriamycin, and its analogues, four different research groups have recently reported the preparation of this amino sugar with an equatorial fluorine atom at C-2 (**2**).[1-5] The interest in C-2 fluoro analogues of 2-deoxy antibiotic sugars is justified by the expectation that the glycosidic bond of the corresponding antibiotics should exhibit increased resistance to hydrolysis. We have also published a stereospecific access to 4-epidaunosamine, the carbohydrate component of the anticancer drug epirubicin, in which the fluorine atom is axially attached to C-2 (**3**).[6] At this time we report the synthesis of protected daunosamines in which both C-2 hydrogen atoms have been replaced by fluorine.

Diethylaminosulfur trifluoride (DAST) treatment of methyl 3,4-*O*-isopropylidene-β-L-*erythro*-pentopyranosid-2-ulose (**4**) was shown to afford,[7] although with a moderate



yield, an anomeric mixture of the corresponding C-2 difluoro sugar. Such reactions were also attempted on a number of 2-uloses in our laboratory. Results appear to be extremely sensitive to the steric environment of the carbonyl group since in some cases gem difluoro sugars were obtained in 75% yield while in others rearranged products or complex mixtures were produced. In the reaction mixture produced from DAST treatment of methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-*ribo*-hexopyranosid-2-ulose (**5**) no C-2 gem difluoro sugar (**6**) was detected.

Therefore, another obvious approach to the synthesis of protected 2,2-difluorodaunosamine appeared to be by way of the addition of trifluorofluoroxymethane[8] to 4-*O*-benzoyl-3,6-dideoxy-2-fluoro-3-trifluoroacetamido-L-galactal (**8**). The latter was prepared from the known 4-*O*-benzoyl-2-fluoro-2,3,6-trideoxy-3-trifluoroacetamido-α-L-galactopyranosyl bromide (**7**)[5] by dehydrobromination according to the method of Lemieux and Lineback.[9]

Trifluorofluoroxymethane addition to the double bond of L-galactal derivative **8** afforded a mixture from which careful chromatography allowed the isolation of four different protected 2,2-difluorodaunosamine derivatives, **9**, **10**, **11**, and **12**, in an overall yield of 50%. Specific yield of each constituent of the reaction mixture was respectively 6%, 10%, 15%, and 20%. Their structures were easily determined by high-field proton NMR spectroscopy. Compounds **10** and **12** are ready for glycosylation since their anomeric center is activated by fluorine. It is of interest to note that (a) galactosyl fluorides predominate in the reaction mixture over trifluoromethyl galactosides and (b) β-anomers were produced in significantly higher proportion than α-anomers.

Experimental Section

General Methods. The melting point was determined with a Buchi apparatus and is uncorrected. A Perkin-Elmer Model 141 MC polarimeter and 1-dm tubes were used for measurement of specific rotations. ^{1}H NMR spectra were recorded in chloroform-*d* solution at 400 MHz. The ^{13}C NMR spectrum was measured in chloroform-*d* solution at 50.31 MHz with a Bruker WP-200 spectrometer. Chemical shifts are given in parts per million, and tetramethylsilane was the internal standard (δ 0.000). Carbon-13 chemical shifts for aromatic carbons are not given. Microanalyses were performed by the Service Central de Microanalyse du CNRS. Silica gel 60 PF_{254} (Merck) activated at 120 °C was the support for TLC and for column chromatography. The term "standard workup" means that the organic layer was washed with water, dried over Na_2SO_4, and filtered and the solvent was removed at reduced pressure.

4-*O*-Benzoyl-3,6-dideoxy-2-fluoro-3-trifluoroacetamido-L-galactal (8). To a solution of **7** (45 mg, 0.1 mmol) in acetonitrile (6 mL) were added at −20 °C diethylamine (0.2 mL, 0.3 mmol) and tetra-*n*-butylammonium bromide (32 mg, 0.1 mmol). The mixture was stirred at −20 °C for 2 h. After dilution of the reaction mixture with methylene chloride (20 mL) and water (20 mL), the solution was brought to pH 7 by dropwise addition of cold hydrochloric acid (0.1 N). After neutralization with a saturated solution of aqueous sodium hydrogen carbonate, standard workup furnished a residue which was chromatographed (4:1 hexane–ethyl acetate), giving pure crystalline **8** (25 mg, 70%): mp 92–95 °C; $[\alpha]^{22}_D$ −79° (*c* 0.9, chloroform); mass spectrum *m/z* 347 ($M^{+\cdot}$); ^{1}H NMR δ 8.20 and 7.50 (m, 5 H, Ph), 6.92 (dd, 1 H, $J_{1,F}$ = 5 Hz, $J_{1,3}$ = 1 Hz, H-1), 6.30 (d, 1 H, $J_{3,NH}$ = 7 Hz, NH), 5.67 (bs, 1 H, H-4), 5.38 (m, 1 H, H-3), 4.25 (q, 1 H, $J_{5,6}$ = 7 Hz, H-5), 1.33 (d, 3 H, $J_{5,6}$ = 7 Hz, Me); ^{13}C NMR δ 142.5 (d, $J_{2,F}$ = 240 Hz, C-2), 133.5 (d, $J_{1,F}$ = 40 Hz, C-1), 73.0 (C-4), 67.6 (d, $J_{5,F}$ = 5 Hz, C-5), 46.2 (d, $J_{3,F}$ = 20 Hz, C-3), 16.3 (Me).

Trifluoromethyl 4-*O*-Benzoyl-2,2-difluoro-2,3,6-trideoxy-3-trifluoroacetamido-α-L-lyxopyranoside (9); 4-*O*-Benzoyl-2,2-difluoro-2,3,6-trideoxy-3-trifluoroacetamido-α-L-lyxopyranosyl Fluoride (10); Trifluoromethyl 4-*O*-Benzoyl-2,2-difluoro-2,3,6-trideoxy-3-trifluoroacetamido-β-L-lyxopyranoside (11); and 4-*O*-Benzoyl-2,2-difluoro-2,3,6-trideoxy-3-trifluoroacetamido-β-L-lyxopyranosyl Fluoride (12). To a solution of **8** (145 mg, 0.42 mmol) in dry trichlorofluoromethane (20 mL) containing calcium oxide (10 mg) in an argon atmosphere at −70 °C was added trifluorofluoroxymethane gas

† Institut de Chimie des Substances Naturelles du CNRS.
‡ Equipe de Recherche, ERA 948.

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(25 mmol) in argon (mixture ratio: trifluorofluoroxymethane/argon = 1:9) in about 10 min. The course of the reaction was monitored until test samples no longer reacted with alkaline $KMnO_4$. After filtration and concentration to dryness, the residue was chromatographed (4:1 hexane–ethyl acetate), giving pure syrupy **9** (R_f 0.68), (7 mg, 6%), $[\alpha]^{22}_D$ −237° (*c* 0.7, chloroform); mass spectrum *m/z* 451 ($M^{+\cdot}$); ^1H NMR δ 8.05 and 7.50 (m, 5 H, Ph), 6.51 (d, 1 H, $J_{3,NH}$ = 7 Hz, NH), 5.65 (d, 1 H, $J_{1,F_{2ax}}$ = 6 Hz, H-1), 5.60 (bs, 1 H, H-4), 4.92 (ddd, 1 H, $J_{3,F_{2ax}}$ = 24 Hz, $J_{3,F_{2eq}}$ = 6 Hz, $J_{3,NH}$ = 7 Hz, H-3), 4.50 (q, 1 H, $J_{5,6}$ = 7 Hz, H-5), 1.25 (d, 3 H, $J_{5,6}$ = 7 Hz, Me). Anal. Calcd for $C_{16}H_{13}F_8NO_5$: C, 42.57; H, 2.88; F, 33.70; N, 3.10. Found: C, 42.71; H, 2.84; F, 33.55; N, 3.17.

Following the elution a mixture (R_f 0.55) consisting of **10** and **11** and then pure syrupy **12** (R_f 0.40) (25 mg, 20%) was obbtained: **12** $[\alpha]^{22}_D$ −137° (*c* 0.6, chloroform); chemical ionization mass spectrum *m/z* 386 ($M^{+\cdot}$ + 1) and 366 ($M^{+\cdot}$ + 1 − HF); ^1H NMR δ 8.05 and 7.50 (m, 5 H, Ph), 6.60 (d, 1 H, $J_{NH,3}$ = 7 Hz, NH), 5.57 (bs, 1 H, H-4), 5.46 (dd, 1 H, J_{1,F_1} = 52 Hz, $J_{1,F_{2ax}}$ = 14 Hz, H-1), 4.78 (ddd, $J_{3,F_{2ax}}$ = 23 Hz, $J_{3,F_{2eq}}$ = 6 Hz, $J_{3,NH}$ = 7 Hz, H-3), 4.17 (q, 1 H, $J_{5,6}$ = 7 Hz, H-5), 1.37 (d, 3 H, $J_{5,6}$ = 7 Hz, Me). Anal. Calcd for $C_{15}H_{13}F_6NO_4$: C, 46.75; H, 3.38; F, 29.61; N, 3.63. Found: C, 46.51; H, 3.50; F, 29.70; N, 3.23.

The mixture of R_f 0.55 was rechromatographed (3:1 toluene–methylene chloride), giving pure syrupy **10** (R_f 0.60) (12 mg, 10%): $[\alpha]^{22}_D$ −232° (*c* 0.4, chloroform); chemical ionization mass spectrum *m/z* 386 ($M^{+\cdot}$ + 1) and 366 ($M^{+\cdot}$ + 1 − HF); ^1H NMR δ 8.05 and 7.50 (m, 5 H, Ph), 6.53 (d, 1 H, $J_{3,NH}$ = 7 Hz, NH), 5.66 (dd, 1 H, J_{1,F_1} = 50 Hz, $J_{1,F_{2ax}}$ = 4 Hz, H-1), 5.60 (bs, 1 H, H-4), 4.98 (ddd, 1 H, $J_{3,F_{2ax}}$ = 23 Hz, $J_{3,F_{2eq}}$ = 6 Hz, $J_{3,NH}$ = 7 Hz, H-3), 4.52 (q, 1 H, $J_{5,6}$ = 7 Hz, H-5), 1.30 (d, 3 H, $J_{5,6}$ = 7 Hz, Me). Anal. Calcd for $C_{15}H_{13}F_6NO_4$: C, 46.75; H, 3.38; F, 29.61; N, 3.63. Found: C, 46.56; H, 3.42; F, 29.80; N, 3.60.

Pure syrupy **11** was also isolated (R_f 0.45) (18 mg, 15%): $[\alpha]^{22}_D$ −88° (*c* 0.7, chloroform); chemical ionization mass spectrum *m/z* 452 ($M^{+\cdot}$ + 1), 3.66 ($M^{+\cdot}$ + 1 − CF_3OH) and 348 ($M^{+\cdot}$ + 1 − CF_3OF); ^1H NMR δ 8.05 and 7.50 (m, 5 H, Ph), 6.63 (d, 1 H, $J_{3,NH}$ = 7 Hz, NH), 5.57 (bs, 1 H, H-4), 5.30 (d, 1 H, $J_{1,F_{2ax}}$ = 14 Hz, H-1), 4.68 (ddd, 1 H, $J_{3,F_{2ax}}$ = 24 Hz, $J_{3,F_{2eq}}$ = 6 Hz, $J_{3,NH}$ = 7 Hz, H-3), 4.15 (q, 1 H, $J_{5,6}$ = 7 Hz, H-5), 1.35 (d, 3 H, $J_{5,6}$ = 7 Hz, Me). Anal. Calcd for $C_{16}H_{13}F_8NO_5$: C, 42.57; H, 2.88; F, 33.70; N, 3.10. Found: C, 42.60; H, 2.71; F, 33.85; N, 2.99.

Communications

An Example of Spontaneous Resolution by Sublimation

Summary: The unprecedented discovery has been made that it is possible to separate the racemic *anti*-7-norbornenol **2** into its enantiomorphs merely by sublimation at reduced pressure.

Sir: The separation of enantiomers by direct crystallization, first demonstrated by Pasteur,[1] takes advantage of the spontaneous resolution that occurs when a conglomerate (a racemic substance that exists as a mechanical mixture of antipodal forms) crystallizes. Although hemihedrism (dissymmetry in the crystal) is relatively uncommon, the distinctive crystal faces are often too poorly developed when it does occur to be useful.[2] The sodium ammonium salt of tartaric acid is a notable exception.

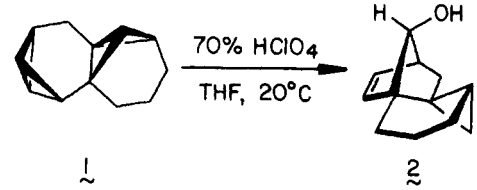
To our knowledge, no other purely mechanical, nonassociative technique has been utilized to bring about the spontaneous separation of enantiomers. *Herein we describe the successful resolution of a racemate merely by sublimation at reduced pressure.* Several groups have previously demonstrated that partially resolved substances can be optically enriched by sublimation.[3] This quite different phenomenon arises by virtue of the nonidentical vapor pressures of an enantiomer and the corresponding racemic compound.[4] In the present case, the sample is initially racemic and the rates of sublimation of the dextro- and levorotatory forms must therefore be equal. Consequently, independent nucleation of the enantiomorphs on the cooler walls of the vessel and individual crystal growth in homochiral fashion by preferential assimilation of like molecules must operate.

Table I. Typical Optical Rotation Data Obtaind on Part-Clusters of Sublimed Lots of Racemic 2 ($[\alpha]^{20}_D$ Values in C_2H_5OH Solution)

	expt A, deg	expt B/C, deg
solid prior to sublimation	0.0	0.0
crystals from cluster I	−9.5	+5.2
crystals from cluster II[a]	+0.8	+2.8
crystals from cluster III[a]	−1.6	−0.8
unsublimed material	0.0	−0.1
percent of original sample recovered	95	92

[a] Mechanical admixing of crystals from various clusters was unavoidable after removal of some crystals from cluster I.

The *anti*-7-norbornenol **2**, available by acid-catalyzed hydration of the bis(bicyclo[1.1.0]butane) **1**,[5] was placed



1 **2**

in a round-bottomed flask and evacuated to 20 Torr. The flask was allowed to stand at 20 °C for several days with occasional reevacuation. Produced by this procedure were crystals of **2** suitable for x-ray analysis. The selected trigonal crystal, which proved to be that of a single enantiomer, was found to belong to the $P3_1$ space group.[6]

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