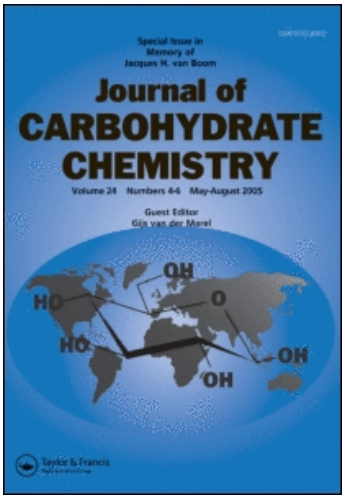

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SYNTHESES OF 3-DEOXY-3-FLUOROGLUCOSAMINE DERIVATIVES

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ABSTRACT

Methyl 2-acetamido-4,6-di-O-acetyl-2,3-dideoxy-3-fluoro-α-D-glucopyranoside (5) and methyl 2-diallylamino-2,3,6-trideoxy-3,6-di-fluoro-4-O-methanesulfonyl-α-D-glucopyranoside (10) were prepared from methyl 4,6-O-benzylidene-α-D-glucopyranoside. Fluorination at C-3 was carried out by ring opening of an aziridinium ion. Two fluorinating reagents were used depending on the starting material.

INTRODUCTION

Substitution of fluorine into natural products such as carbohydrates has been studied for several years.[1-3] The biological activity of these compounds can be dramatically enhanced because of the greater electronegativity of fluorine, which affects the acidity or basicity of neighbouring groups, and the ability of fluorine to accept a hydrogen bond like oxygen. These properties led to many syntheses of fluorinated

analogues of sugars such as D-glucose or D-galactose[2] for biochemical studies.

Because of the wide distribution of D-glucosamine in the animal kingdom, the synthesis of fluorinated analogues was investigated, especially by Hough and co-workers[4] but their method was inefficient for the synthesis of 3-fluoro derivatives. To our knowledge no synthesis of such products has been described.

RESULTS AND DISCUSSION

Hexopyranosides generally adopt the $^4C_1$(D) conformation ; nevertheless we have found that some altropyranosides exist preferentially in the $^1C_4$(D) conformation[5] because of 1,3-diaxial steric hindrance. This characteristic is very important because the key step of our synthesis involves an aziridinium ion formation which requires diallylamino and methanesulfonyloxy groups in a trans diaxial relationship.

Our starting compound was methyl 3-diallylamino-4,6-O-benzylidene-3-deoxy-2-O-methanesulfonyl-α-D-altropyranoside; [6] acidic deprotection gave methyl 3-diallylamino-3-deoxy-2-O-methanesulfonyl-α-D-altropyranoside (1) which was acetylated to give compound 2. Fluorination (using $Et_3N.3HF/Et_3N$ in acetonitrile) took place via an aziridinium ion (two conformations, A and B, in equilibrium cf. Fig.1) which was opened axially to give the two isomers methyl 4,6-di-O-acetyl-2-diallylamino-2,3-dideoxy-3-fluoro-α-D-glucopyranoside (3) and methyl 4,6-di-O-acetyl-3-diallylamino-2,3-dideoxy-2-fluoro-α-D-altropyranoside (4) as an unseparated mixture (by NMR spectroscopy 3/4 = 7/1). After N,N-dideallylation[7] and N-acetylation, methyl 2-acetamido-4,6-di-O-acetyl-2,3-dideoxy-3-fluoro-α-D-glucopyranoside (5) was isolated by crystallization (path A, Scheme 1). The yield was 46 % in four steps (*altro* isomer was not isolated).

In the same way (path B, Scheme 1) it was possible to synthesize methyl 2-diallylamino-2,3,6-trideoxy-3,6-difluoro-4-O-methanesulfonyl-α-D-glucopyranoside (10) starting from methyl 3-diallylamino-4,6-O-

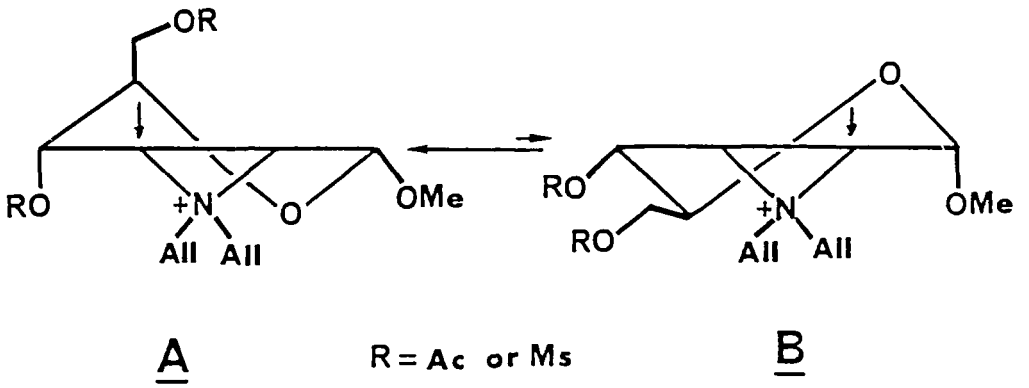
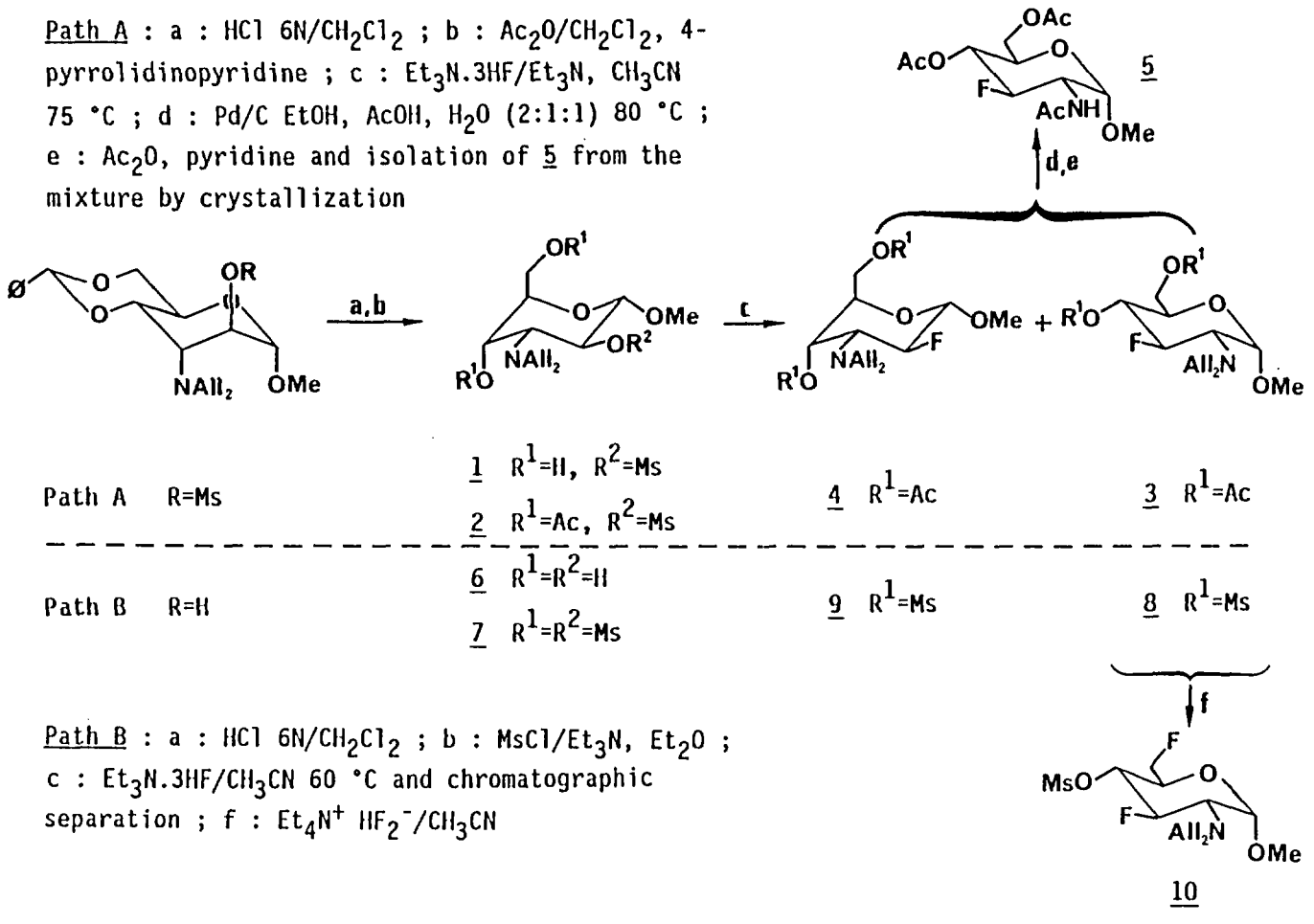


Figure 1

benzylidene-3-deoxy-α-D-altropyranoside.[6] Acidic deprotection followed by trimesylation lead to methyl 3-diallylamino-3-deoxy-2,4,6-tri-O-methanesulfonyl-α-D-altropyranoside (7) in 99 % yield. The fluorination step was very surprisingly dependent on the fluorinating reagent. If we used a basic reagent, such as $Et_4N^+HF_2^-$ (which has given good results in such an assisted fluorination[8]) only tars were formed. Probably the axial 4-OMs underwent elimination to give very unstable enamines. When $Et_3N.3HF/Et_3N$ was used we obtained four products, the monofluoro and difluoro *altro* 8, 11 and *gluco* 9, 10 (^{19}F NMR shifts and coupling constants are given in Table 1). With $Et_3N.3HF$ as the reagent, compounds 8 and 9 were obtained in a 7/3 ratio in 56 % yield and separated by chromatography to give the desired product 8. Methyl 2-diallylamino-2,3-dideoxy-3-fluoro-4,6-di-O-methanesulfonyl-α-D-glucopyranoside (8) which has no axial OMs was reacted with $Et_4N^+HF_2^-$ to give methyl 2-diallylamino-2,3,6-trideoxy-3,6-difluoro-4-O-methanesulfonyl-α-D-glucopyranoside (10) in 74 % yield after purification. A study of these different fluorinating reagents is reported elsewhere.[9]

EXPERIMENTAL

General procedures. Melting points were determined with a Kofler apparatus and were reported uncorrected. Specific rotations were deter-



Scheme 1

Table 1 - ^{19}F NMR Spectral Data[a]

	$J_{1,F}$	$J_{2,F}$	$J_{3,F}$	$J_{4,F}$	$J_{5,F}$	$J_{6,F}$	$\delta_{F(CH)}$	$\delta_{F(CH2)}$
altro								
4	10.5[b]	51.5	12[b]	4	-	-	-194.1	-
9	14	51	20	3	-	-	-190.5	-
11	14	51	14	3	27.8	47	-192.2	-234.8
gluco								
3	3.5	10.5	56.5	10.5	-	-	-195.7	
8	3	10.5	53	10.5	-	-	-191.1	
10	3	10.7	52	10.7	24.9	47	-191.2	-231.5

a Chemical shifts are relative to $CFCl_3$ and coupling constants are given in Hz.

b Assignments may be interchanged.

mined with a Perkin Elmer 141 polarimeter. ^1H NMR spectra were recorded with a Cameca (350 MHz) spectrometer. ^{19}F NMR spectra were recorded with a Brucker WP 80 spectrometer ; internal reference compounds used were tetramethylsilane (δ = 0.00 p.p.m.) and trichlorofluoromethane (δ = 0.00 p.p.m.).

Methyl 3-Diallylamino-3-deoxy-2-O-methanesulfonyl-α-D-altropyranoside (1). Hydrochloric acid (6N, 33 mL) was added to a solution of methyl 3-diallylamino-4,6-O-benzylidene-3-deoxy-2-O-methanesulfonyl-α-D-altropyranoside[6] (4.88 g, 11.12 mmol) in dichloromethane (17 mL) . The mixture was stirred for 2 h (TLC light petroleum-ethyl acetate 2:1), benzaldehyde was removed by extraction (3 x 20 mL dichloromethane) and sodium chloride, sodium hydrogen carbonate and ice were

added; the mixture was extracted with ether (3 x 40 mL) and the extracts dried (sodium sulfate) and concentrated to give 3.76 g (96 %) of a yellow syrup which was used without further purification.

Methyl 4,6-Di-O-acetyl-3-diallylamino-3-deoxy-2-O-methanesulfonyl-α-D-altropyranoside (2). Acetic anhydride (2 mL, 40 mmol) was added dropwise to a stirred solution of 1 (2.81 g, 8 mmol) and 4-pyrrolidinopyridine (0.15 g) in triethylamine (3.45 mL) and dichloromethane (15 mL) cooled to 0 °C. After 30 min (TLC light petroleum-acetone 2:1), 300 mL of ether was added and the mixture was washed twice with water, dried (sodium sulfate) and the solvents were evaporated to give a yellow solid which was chromatographed on a column of silica gel (light petroleum-acetone 3:1) and the product crystallized from cyclohexane : mp 63 °C, 2.7 g, 77 % ; ^{1}H NMR ($CDCl_3$) δ 5.76 (m, 2H, CH=), 5.17 (q, 1H, H-4, $J_{4,5}$ = 1.5 Hz), 5.16 (m, 4H, CH_2=), 4.95 (q, 1H, H-2, $J_{1,2}$ = 4.6 Hz, $J_{2,3}$ = 11.1 Hz), 4.82 (d, 1H, H-1), 4.36 (q, 1H, H-6a, $J_{5,6a}$ = 6.7 Hz, $J_{6a,6b}$ = 12 Hz), 4.15 (q, 1H, H-6b, $J_{5,6b}$ = 4.3 Hz), 3.96 (m, 1H, H-5), 3.44 (s, 3H, OCH_3), 3.33 (q, 1H, H-3, $J_{3,4}$ = 3.2 Hz), 3.13 (s, 3H, CH_3SO_2), 2.11 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO).

Anal. Calcd for $C_{18}H_{29}NO_9S$: C, 49.65 ; H, 6.67 ; N, 3.22 ; S, 7.36. Found: C, 49.53 ; H, 6.74 ; N, 3.32 ; S, 7.41.

Methyl 4,6-Di-O-acetyl-2-diallylamino-2,3-dideoxy-3-fluoro-α-D-glucopyranoside (3) and Methyl 4,6-Di-O-acetyl-3-diallylamino-2,3-dideoxy-2-fluoro-α-D-altropyranoside (4). Compound 2 (2.8 g, 6.44 mmol) was dissolved in acetonitrile (10 mL) containing triethylamine (6.8 mL, 64.4 mmol) and triethylamine tris-hydrofluoride (13.6 mL, 64.4 mmol). The solution was heated at 75 °C for 8 h (TLC light petroleum-acetone 2:1) then poured into ether (180 mL), and 200 mL of an aqueous solution of 5 % sodium hydrogen carbonate was added. The organic layer was dried (sodium sulfate) and the solvents were evaporated to give a yellow syrup (2.3 g, 100 %) of an unseparated mixture of 3 and 4 in a ratio 7/1 (determined by ^{19}F NMR).

Methyl 2-Acetamido-4,6-di-O-acetyl-2,3-dideoxy-3-fluoro-α-D-glucopyranoside (5). To a solution of crude 3 + 4 (1 g, 2.78 mmol) in water (4 mL), acetic acid (4 mL) and ethanol (8 mL) was added palladium

10 % on carbon (0.2 g) and the mixture was refluxed under nitrogen with a water condenser at 55 °C to strip off propanal. After 6h (TLC light petroleum-acetone 1:2), a solution of 5 % sodium hydrogen carbonate in water was added. The solution was saturated with sodium chloride, extracted with ether, dried (sodium sulfate) and the solvents were evaporated *in vacuo*. Pyridine (8 mL) and acetic anhydride (16 mL) were added and the solution was kept at room temperature for 24 h. Ether (35 mL) and a solution of sodium hydrogen carbonate (5 %) in water (175 mL) were added. The water layer was extracted twice with ether (35 mL) and the organic layers were dried (sodium sulfate). After solvent evaporation the residue was crystallized as a white solid from cyclohexane-ethyl acetate : mp 141 °C, 550 mg, 62 % ; $[\alpha]_D$ +105 ° (c 1.44, chloroform) ; ^{1}H NMR ($CDCl_3$) δ 5.72 (d, NH, $J_{NH,2}$ = 9 Hz), 5.21 (m, 1H, H-4, $J_{3,4}$ = 8.9 Hz, $J_{4,5}$ = 10.2 Hz, $J_{4,F}$ = 12.6 Hz), 4.62 (t, 1H, H-1, $J_{1,2} = J_{1,F}$ = 3.2 Hz), 4.54 (m, 1H, H-3, $J_{3,F}$ = 55 Hz, $J_{2,3}$ = 10.5 Hz), 4.49 (m, 1H, H-2), 4.24 (sext, 1H, H-6a, $J_{6a,6b}$ = 12.2 Hz), 4.13 (q, 1H, H_{6b}), 3.86 (oct, 1H, H-5, $J_{5,6a}$ = 4.5 Hz, $J_{5,6b}$ = 2.3 Hz), 3.39 (s, 3H, OCH_3), 2.11 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3CO) 2.05 (s, 3H, CH_3CO).

Anal. Calcd for $C_{13}H_{20}NO_7F$: C, 48.60 ; H, 6.23 ; N, 4.36 ; F, 5.92. Found : C, 48.62 ; H, 6.46 ; N, 4.25 ; F, 5.90.

Methyl 3-Diallylamino-3-deoxy-α-D-altropyranoside (6). We used the same procedure as for 1 but starting from methyl 3-diallylamino-4,6-O-benzylidene-3-deoxy-α-D-altropyranoside[6] (TLC light petroleum-acetone 2:1). Compound 6 was obtained as an orange syrup (yield 99 %) used in crude form in the next step.

Methyl 3-Diallylamino-3-deoxy-2,4,6-tri-O-methanesulfonyl-α-D-altropyranoside (7). This compound was obtained according to Picq and Anker.[10] The product was crystallized from ether : mp 94 °C, $[\alpha]_D$ +8 ° (c 4.9, chloroform).

Methyl 2-Diallylamino-2,3-dideoxy-3-fluoro-4,6-di-O-methanesulfonyl-α-D-glucopyranoside (8). A solution of 7 (13.3 g, 26.2 mmol) in triethylamine tris-hydrofluoride (26 mL, 5 eq.) and acetonitrile (15 mL) was heated at 60 °C for 18 h (TLC light petroleum-ether 1:4). The mixture was poured slowly into a solution of sodium hydrogen

carbonate (5 %) in water (400 mL) and ether (200 mL). The water layer was extracted twice with ether (100 mL) and the organic layers were dried (sodium sulfate) and the solvents were evaporated to give an orange syrup which was chromatographed on a column of silica gel (light petroleum-ether 1:2). The first eluted product was the *altro* compound 9 and the second the *gluco* one 8 (4.5 g, 40 % from 6) : $[\alpha]_D$ +84 ° (c 1.32, chloroform) ; ^1H NMR ($CDCl_3$) δ 5.79 (m, 2H, CH=), 5.16 (m, 4H, CH_2=), 5.08 (oct, 1H, H-3, $J_{3,F}$ = 53.5 Hz, $J_{3,4}$ = 8.5 Hz, $J_{2,3}$ = 10.5 Hz), 4.7 (oct, 1H, H-4, $J_{4,F}$ = 13.5 Hz, $J_{4,5}$ = 10 Hz), 4.69 (t, 1H, H-1, $J_{1,F}$ = $J_{1,2}$ = 3.7 Hz), 4.49 (m, 1H, H-6a), 4.39 (q, 1H, H-6b, $J_{6a,6b}$ = 11 Hz, $J_{5,6b}$ = 4.5 Hz), 3.95 (oct, 1H, H-5, $J_{5,6a}$ = 2 Hz), 3.5 (m, 2H, N-CH_2), 3.39 (s, 3H, OCH_3), 3.20 (m, 2H, N-CH_2), 3.15 (s, 3H, CH_3SO_2), 3.12 sext, 1H, H-2, $J_{2,F}$ = 10.5 Hz), 3.08 (s, 3H, CH_3SO_2).

Anal. Calcd for $C_{15}H_{26}NO_8S_2F$: C, 41.76 ; H, 6.03 ; N, 3.25 ; S, 14.85 ; F, 4.41. Found : C, 42.05 ; H, 6.04 ; N, 3.08 ; S, 15.01 ; F, 4.29.

Methyl 3-Diallylamino-2,3-dideoxy-2-fluoro-4,6-di-O-methanesulfonyl-α-D-altropyranoside (9). This compound was the faster eluted product from above (1.8 g, 16 % from 6), $[\alpha]_D$ +44 ° (c 1.01, chloroform).

Methyl 2-Diallylamino-2,3,6-trideoxy-3,6-difluoro-4-O-methanesulfonyl-α-D-glucopyranoside (10). $Et_4N^+HF_2^-$ (obtained from 2.4 g of $Et_4N^+F^-.2H_2O$ dried overnight at 65 °C *in vacuo*[11]) was added to a solution of 8 (0.51 g, 1.18 mmol) in acetonitrile (17 mL) . The mixture was heated at 60 °C for 45 min (TLC light petroleum-acetone 2:1), then a solution of sodium hydrogen carbonate 5 % in water (150 mL) was added and the mixture was extracted twice with ether (50 mL), dried (sodium sulfate) and the solvents were evaporated. Compound 10 was purified on a column of silica gel (light petroleum-acetone 2:1). A colourless syrup was obtained (310 mg, 74 %) : $[\alpha]_D$ +8,6 ° ; ^1H NMR ($CDCl_3$) δ 5.78 (m, 2H, CH=), 5.17 (oct, 4H, CH_2=), 5.13 (oct, 1H, H-3, $J_{3,F}$ = 53 Hz, $J_{2,3}$ = 10.8 Hz, $J_{3,4}$ = 8.3 Hz), 4.72 (oct, 1H, H-4, $J_{4,5}$ = 9.5 Hz, $J_{4,F}$ = 14.4 Hz), 4.7 (t, 1H, H-1, $J_{1,2}$ = $J_{1,F}$ = 3.6 Hz), 4.67 (q, 2H, H-6, $J_{5,6}$ = 3.1 Hz, $J_{6,F}$ = 47 Hz), 3.85 (m, 1H, H-5, $J_{5,F}$ = 24.9 Hz),

3.38 (s, 3H, OCH_3), 3.32 (m, 2H, N-CH_2), 3.2 (q, 2H, N-CH_2), 3.14 (s, 3H, CH_3SO_2).

Anal. Calcd for $C_{14}H_{23}NO_5SF_2$: C, 47.32 ; H, 6.48 ; N, 3.94 ; S, 9.01 ; F, 10.70. Found : C, 47.66 ; H, 6.59 ; N, 3.59 ; S, 8.69 ; F, 10.79.

Methyl 3-Diallylamino-2,3,6-trideoxy-2,6-difluoro-4-O-methanesulfonyl-α-D-altropyranoside (11). A mixture of 7 (0.5 g), Et_3N (1 mL) and $Et_3N.3HF$ (2 mL) was heated at 75 °C for 26 h. When starting material had disappeared, TLC showed four products which were then separated by chromatography (light petroleum-ether 1:1). The order of elution was 10, 11, 9 and 8. 11 : ^1H NMR ($CDCl_3$) δ 5.81 (m, 2H, CH=), 5.21 (m, 4H, CH_2=) 4.91 (t, 1H, H-1, $J_{1,2} = J_{1,F} = 3.5$ Hz) 4.86 (q, 1H, H-4, $J_{3,4} = 4$ Hz, $J_{4,5} = 3$Hz) 4.79 (oct, 1H, H-2, $J_{2,F} = 54$ Hz, $J_{2,3} = 9.4$ Hz) 4.69 (oct, 1H, H-6a, $J_{6a,F} = 46.4$ Hz, $J_{6a,6b} = 10$ Hz, $J_{5,6a} = 3.4$ Hz) 4.62 (oct, 1H, H-6b, $J_{6b,F} = 47.8$ Hz, $J_{5,6b} = 2.4$ Hz) 4.13 (oct, 1H, H-5, $J_{5,F} = 27.8$ Hz) 3.47 (s, 3H, OCH_3) 3.37 (oct, 1H, H-3, $J_{3,F} = 13.3$ Hz) 3.10 (s, 3H, CH_3SO_3).

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