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SYNTHESIS OF 3,3-DIFLUORO-2-AZETIDINONES AND 2,3-DIDEOXY-2,2-DIFLUORO-3-AMINO-SUGARS THROUGH THE REFORMATSKY REACTION OF DIFLUOROACETATE WITH IMINE

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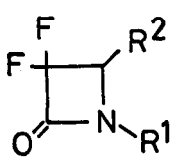
Summary: The Reformatsky reaction of iodo- or bromodifluoroacetate with imine(5) gave the corresponding 3,3-difluoro-2-azetidinone derivative(1). Reaction of 2,2-difluoroketene silyl acetal(4) with the imine(5a) or N,O-acetal derivatives(8, 9) gave the 3-amino-2,2-difluoro esters. 2,2-Difluoro analogs of 2,3-dideoxy-3-aminosugars(2) including daunosamine derivative (2a) were efficiently prepared through the reaction of 3 or 4 with N-benzylimine of 4-deoxy-L-threose acetonide(5a) and (R)-glyceraldehyde acetonide(5b).

In a previous paper we reported aldol reaction of iododifluoroacetate(3a)-Zn and 2,2-difluoroketene silyl acetal(4), which could be carried out under mild conditions.[1] High anti-(erythro)selectivity was observed in the reaction of the ketenesilyl acetal(4) with glyceraldehyde acetonide and 4-deoxy-L-threose acetonide(6). The aldol products were converted to 2-deoxy-2,2-difluorosugars. Fluorinated sugars[2] and amino acids[3] have been attracting much attention in recent years due to dramatic changes in biological responses. Typical examples are incorporation of fluorine into 2' position of sugar moiety, resulting in stabilization of the glycosidic bond.[2,4]

In this context, we report the Reformatsky reaction of difluoroacetate with aldimine(5) leading to 3,3-difluoro-2-azetidinones(1) and their conversion to 2,3-dideoxy-2,2-difluoro-3-aminosugars(2). The related reactions of 2,2-difluoroketene silyl acetal(4) with the imine (5a) and N,O-acetal(8, 9) leading to 3-amino-2,2-difluoro esters are also reported.



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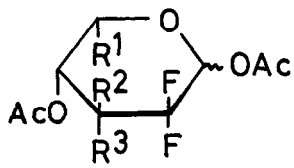
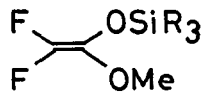


2a R^1=Me R^2=H R^3=NHBn
2b R^1=Me R^2=NHBn R^3=H
2c R^1=R^2=H R^3=NHBn
2d R^1=R^3=H R^2=NHBn

XCF_2COOR
3a X=I R=Me
3b X=Br R=Et



4a R=Et
4b R=Me

Reaction of the Zn reagent, formed by treating methyl iododifluoroacetate(3a, 6 mmol) with Zn powder(6.3 mg-atm) in THF at 0°C for 20 min, with N-benzylimine of (R)-glyceraldehyde acetonide(5b, 3 mmol, 0°C-rt, 20 h; Method A) gave a diastereomeric mixture of the difluoro-β-lactam (1b), which was easily separated by silica gel column chromatography[syn-1b, 49%, mp 75-76°C, $[\alpha]_D$ -8.48°(c=1.02 $CHCl_3$); anti-1b, 16%, colorless oil, $[\alpha]_D$ 5.72°(c=1.03 $CHCl_3$)]. Since relatively high temperature is required for generation of Zn reagent from bromodifluoroacetate (3b) and this reagent is thermally unstable,[1,5] the lactam(1) was obtained by slowly adding a mixture of the bromide(3b) and imine(5) to Zn powder in boiling THF(Method B). The results are summarized in Table 1. Syn-selectivity(sny/anti=3.1-4.7/1) was observed with 5a and 5b(Run 1-3). Imines derived from aromatic aldehydes afforded the lactam(1) in good yields(Run 4-6), as compared with crotonaldehyde imine(Run 7).

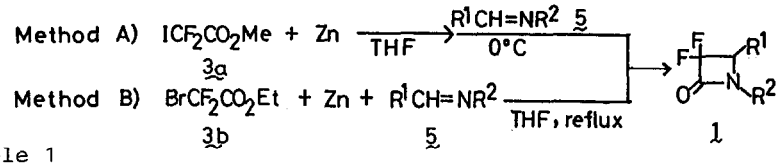
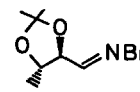
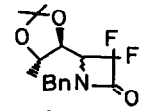
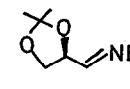
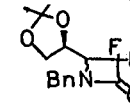
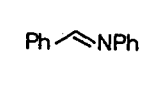
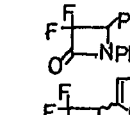
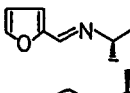
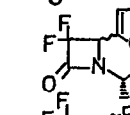
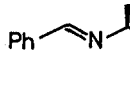
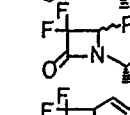
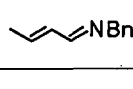
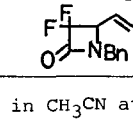


Table 1

Run	Imine (5)	Method	Product (1)	Yield (%)
1	 5a	A[a]	 1a	71[b] (syn/anti = 4.3/1)[c]
2	 5b	A	 1b	65 (syn/anti = 3.1/1)
3	5b	B	1b	67 (syn/anti 4.7/1)
4	 5c	B	 1c	87
5	 5d	A	 1d	66
6	 5e	B	 1e	79
7	 5f	B	 1f	35

a) The reaction was carried out in CH_3CN at room temperature. b) 3,4-Syn 7a was also isolated in 13% yield. c) The ratio is based on isolated 1a and 7a.

Although the stereochemistry of 1a and 1b was determined by converting to the sugar derivatives(2), X-ray analysis of anti-1a(mp 84.5°C, see Fig.) and syn-1b was carried out for unequivocal confirmation.

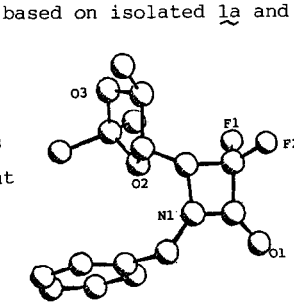
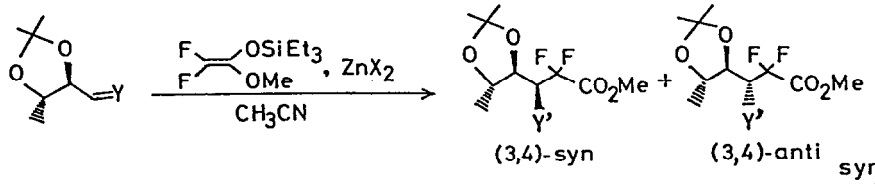
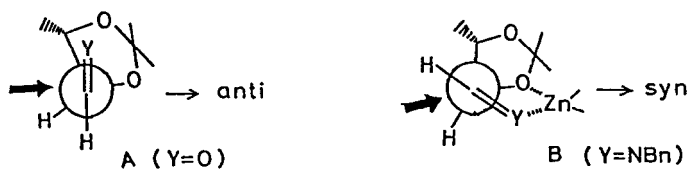


Fig. Molecular Structure of anti-1a

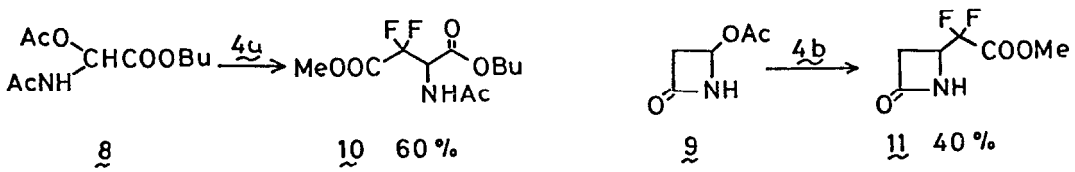
Reaction of 5a with the ketene silyl acetal(4a) in CH_3CN gave the β-amino ester(7) with moderate syn-selectivity(syn/anti=3.7/1), while similar reaction with the aldehyde(6) proceeded in a highly anti-selective manner(syn/anti=1/17).[1] The observed diastereoselectivity for the aldehyde(6, Y=O) is probably brought about from the si face attack through a Felkin-Anh transition state(A).[7,8] The presence of zinc halide in the reaction mixture may result in the enhancement of the anti-selectivity by a chelate with β-oxygen in the transition state.[8] However, in the case of the imine(5a, Y=NBn), increased Lewis basicity of the nitrogen compared with that of the aldehyde oxygen and the stereoelectronic effect of the imine group(anti-favoured structure of the C=N bond)[9] may facilitate the co-ordination of zinc halide to contribute to a greater extent to the α-chelated transition state(B), which results in the diastereoselectivity in syn-favoured manner.[8,10]



			(3,4)-syn	(3,4)-anti	syn/anti
6 Y=O	Y'=OTES		5%	84%	1/17
5a Y=NBn	7a Y'=NHBn		55%	15%	3.7/1



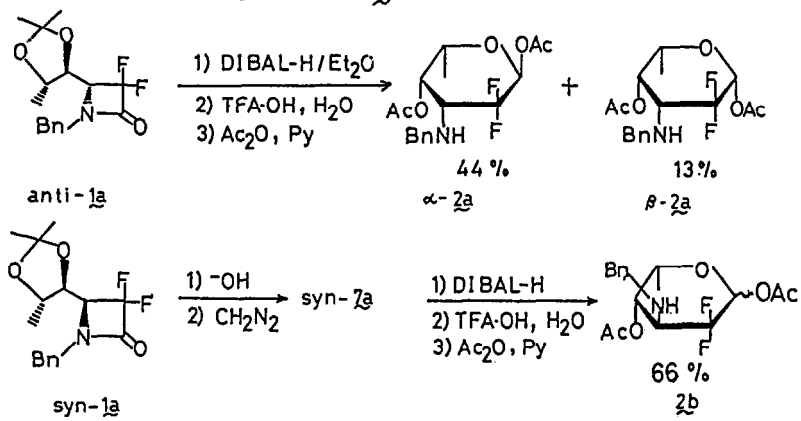
The ketene silyl acetal(4) was reacted with the N,O-acetal compounds(8 and 9) to give the corresponding adducts(10 and 11). Thus, reaction of 4a, formed from 2 equiv. of 3a in CH_3CN, with 1 equiv. of 8 for 2 h gave the difluoro derivative of aspartic acid(10)[3a] in 60% yield, while the Reformatsky-type reaction of 3 with 8 produced a complex mixture. Introduction of the difluoroacetate moiety into the 4 position of the 2-azetidinone was successfully carried out by the reaction of the ketene silyl acetal(4b) with 9 to give 11 in 40 % yield.[11]



8 10 60% 9 11 40%

Conversion of each of the adducts(1a, 1b and 7) to the diacetate form of 2,3-dideoxy-3-amino-2,2-difluorosugars(2) was achieved by the following procedure. Reduction of anti-1a with DIBAL(Et_2O, -78°C) followed by deprotection(CF_3COOH, rt) and acetylation(Ac_2O, Py) gave the 1,4-O-diacetyl-N-benzyldaunosamine(2a) in 57% yield(α/β ratio=3.4/1).[12] After being converted from syn-1a(1.1equiv. KOH, EtOH-H_2O, rt, 1 h then acidified with 1N-HCl, followed by CH_2N_2, Et_2O-EtOH), syn-7a was converted to the diacetate form of L-2,3,6-trideoxy-3-N-benzylamino-2,2-

difluorogulopyranoside(2b, 66%, α/β ratio=2.3/1). In a similar manner, anti-1b was converted to 2c(45%, α/β ratio=3/1) and syn-1b to α-2d(45%).



References and Notes

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10) Anti-selective addition of lithium enolate of acetamide derivative with N-benzylimine of 2,3-O-cyclohexylidene-4-deoxy-L-threose in THF in the presence of zinc halide[a] and ketene silyl acetal with the Z-nitrone derived from 6[b,c] has been reported. a) T. Mukaiyama, Y. Goto, and S. Shoda, Chem. Lett., 671(1983); b) Y. Kita, F. Itoh, O. Tamura, Y. Y. Ke, and Y. Tamura, Tetrahedron Lett., 28, 1431(1987); c) Y. Kita, O. Tamura, F. Itoh, H.Kishino, T. Miki, M. Kohno, and Y. Tamura, J. Chem. Soc., Chem. Commun., 761(1988).

11) N. V. Shah and L. D. Cama, Heterocycles, 25, 221(1987).

12) The major α-anomer was isolated in crystalline form, mp 128°C. $[\alpha]_D$ -129°(c=0.68, $CHCl_3$), ^{1}H-nmr(400 MHz, $CDCl_3$)δ: 1.15(3H, d, J=6.5 Hz, 6-H), 1.70(1H, brs, NH), 2.12(3H, s, acetyl), 2.18(3H, s, acetyl), 3.30(1H, ddd, J=4, 5.9 and 23.9 Hz, 3-H), 3.93(1H, d, J=13 Hz, NCHPh), 3.97(1H, d, J=13 Hz, NCHPh), 4.16(1H, dq, J=1.4 and 6.5 Hz, 5-H), 5.33(1H, m, 4-H), 6.15 (1H, d, J=7 Hz, 1-H), 7.22-7.40(5H, m, phenyl); ^{19}F-nmr($CDCl_3$, relative to internal benzotrifluoride)δ: -55.0(m).

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