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Addition of lithium ethyl fluoroacetate to *cis* and *trans* α,β-epoxyaldehydes. Access to C_2 fluorinated butyrolactones

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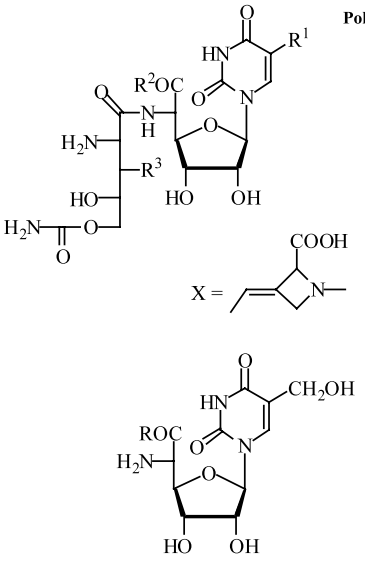
Abstract—The aldolisation reaction of lithium ethyl fluoroacetate with *cis* and *trans* α,β-epoxyaldehydes in their racemic forms proceeds with good C_3-OH diastereoselectivity and much less at the C_2-F carbon atom. A two-step reaction on the major aldol compounds (iodination, lactonisation) led to racemic functionalised C_2 fluorinated lactones, possessing a C_2/C_3 *cis* relationship between the fluorine and hydroxyl groups. © 2003 Elsevier Science Ltd. All rights reserved.

Polyoxins form an important class of peptidyl nucleosidic antibiotics (Fig. 1) that selectively and competitively inhibit membrane bound enzyme chitin synthase, a linear β-1,4-*N*-acetylglucosamine polymer. This constitutes one of the major structural components of the fungal cell wall[1] that is absent from the mammalian host and can thus represent an attractive target for pharmaceutical but also for agricultural pathogen management.[2]

However most polyoxins are weakly active against whole cells of pathogenic fungi such as *Candida albicans*, presumably due to their hydrolytic instability or to insufficient affinity for chitin synthase(s) or to insufficient transport by the peptide transport system.[3] In this respect, synthetic research has evolved on methodologies to provide polyoxins in an efficient fashion[4] and on the search for more potent and safer analogues.[5]

A convergent total synthesis of polyoxin J has been elaborated in our group starting from achiral compounds. This strategy has been applied to the synthesis of thymine polyoxin C,[6a] its C_2' deoxy analogue[6b] and the preparation of the aminoacid moiety of polyoxin J, known as 5-*O*-carbamoylpolyoxamic acid.[6c] In order to synthesise compounds that might contribute to a better in vivo activity of polyoxins, we have also attempted an approach toward the C_2' deoxy fluoro analogue of thymine polyoxin C.[6a] After different unsuccessful attempts to introduce the fluorine atom on the nucleosidic part of polyoxin, electrophilic fluorination of an azidolactone with NFSI (*N*-fluorobenzenesulfonimide) was achieved with a moderate yield affording a C_2 fluoro azido lactone, interesting intermediate for the preparation of the epimeric C_2' deoxy fluoro analogue of polyoxin C (Scheme 1).

Here in, we would like to report our study on an alternative approach towards the C_2 fluoro butyrolactone synthons, where the fluorine atom is introduced at the beginning during the aldolisation reaction with a suitable fluoroester.



Polyoxins	R^1	R^2	R^3
A	CH_2OH	X	OH
B	CH_2OH	HO	OH
D	COOH	HO	OH
E	COOH	HO	H
F	COOH	X	OH
G	CH_2OH	HO	H
H	CH_3	X	OH
J	CH_3	HO	OH
K	H	X	OH
L	H	HO	OH

	R
C	HO
I	X

Figure 1.

Keywords: epoxyaldehydes; aldolisation; 2-fluorobutyrolactones.

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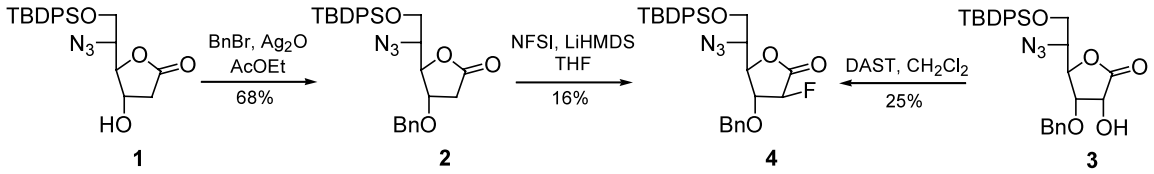


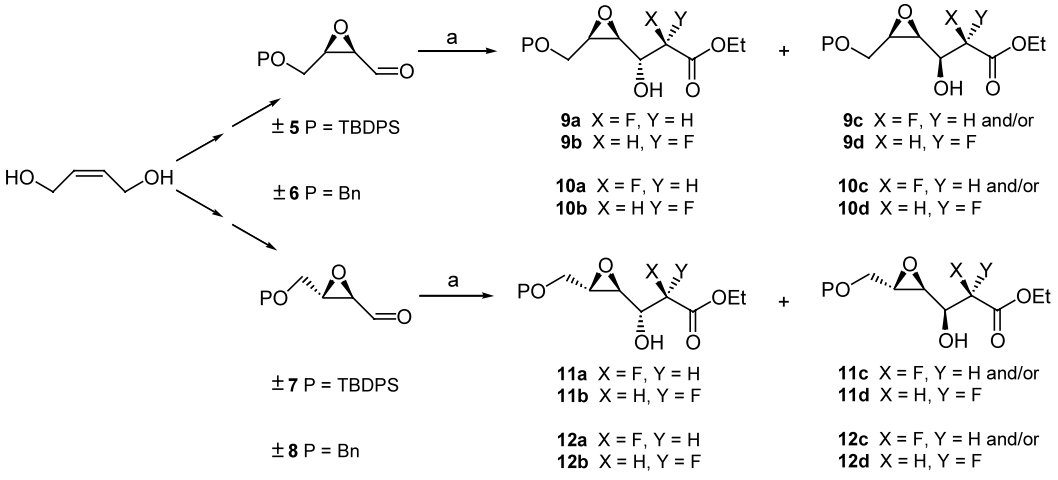
Scheme 1. (Ref. 12).

Racemic *cis* and *trans* α,β-epoxyaldehydes **5**–**8** were obtained as previously described.[7] *cis* α,β-Epoxyaldehydes **5**, **6** were obtained in 57% and 48% yield, and *trans* α,β-epoxyaldehydes **7**, **8** in 56% and 28% yield respectively. The α,β-epoxyaldehydes were subjected to the aldolisation reaction with ethyl fluoroacetate. First a Welch aldolisation reaction[8] was attempted. To a solution of lithium hexamethyldisilazane and HMPA in ether was added at −78°C ethyl fluoroacetate and the aldehyde **5**. This reaction led to a complicated mixture of compounds, where the four diastereoisomeric aldol adducts could be partially purified in a 20% total yield (no starting material recovered). No diastereoisomeric preference was observed. The dissociation effect of HMPA may render an open chain transition state in the aldolisation process more probable, enhancing thus the *syn* C_3/C_4 selectivity. On the other hand, the aldolate formed, less stabilised by Li^+, may react intra- or intermolecularly (on the epoxide ring for example), lowering considerably the yield of the reaction by affording degradation products. *cis* α,β-epoxyaldehyde **5** behave thus differently in terms of reactivity when compared with glyceraldehyde acetonide or cyclohexylidene compounds.[9]

We then tried the aldolisation reaction in the presence of LDA[10] (Scheme 2). When racemic *cis* α,β-epoxyaldehyde **5** was condensed with ethyl fluoroacetate at −78°C in the presence of LDA, fairly good yields of condensation products were obtained. After partial purification of the mixture ^{19}F NMR spectroscopy shows four group of peaks (doublet, doublet) in the range δ: −120 to −135 ppm (CF_3COOH as internal reference). They are attributed to the four diastereoisomers **9a**–**d** (racemic forms) of the aldolisation reaction (total yield 50%) obtained in the ratio 46/42/9/3 (a/b/c and/or d). Major compounds can be separated or isolated together from the mixture of minor diastereoisomers. All adducts were identified by ^1H, ^{13}C, ^{19}F NMR spectroscopy and mass spectrometry.

While the stereochemistry of the C_2, C_3 carbon atoms for the major compounds was confirmed at the final lactone stage, that of the C_3 was less in doubt when considering the aldolisation reaction. Condensation of different α,β-epoxyaldehydes with esters have been extensively studied in our group.[11] The *anti* diastereofacial preference of the resulting γ,δ-epoxy-β-hydroxyesters has been rationalised. On the other hand, reactions of α,β-cycloalkoxy aldehydes with ethyl fluoroacetate is known to afford adducts with the same *anti* diastereofacial preference on the C_3 carbon atom.[8,9] The C_2/C_3 relative stereochemistry for the major *anti* aldol adducts **9a**,**b** was assigned according to the literature,[9] where the ^{19}F chemical shift for an anti C_2/C_3 relationship is higher than that of a *syn* one.

In Table 1 we have reported ^{19}F NMR data of the compounds issued from the aldolisation reactions with racemic *cis* and *trans* α,β-epoxyaldehydes along with the ratio calculated by integration of the fluorine peaks of the diastereoisomers. We can notice first that in relation to the C_3 stereochemistry, the global ratio of the major versus minor aldol compounds is ∼90/10 and ∼75/25 for reactions with *cis* and *trans* α,β-epoxyaldehydes respectively. This is in accordance with our results concerning the diastereofacial preference during the aldolisation reaction of *cis* and *trans* α,β-



Scheme 2. *Reagents and conditions*: (a) LDA (2 equiv.), FCH_2CO_2Et (2 equiv.), anhydrous diethyl ether, −78°C, 3 h, 40%.

Table 1.

Aldol adducts	^{19}F NMR characteristics of the diastereoisomeric mixtures of the aldol adducts (δ ppm, J Hz)	Ratio[a]
9	**a** (−126.57, dd, J=47.1 and 20.7 Hz), **b** (−133.84, dd, J=48.9 and 26.4 Hz), **c** and **d** (−122.06 and −131.66, dd, J=47.1 and 16.9 Hz, and J=48.9 and 26.4 Hz)	9/46/3/42
10	**a** (−126.43, dd, J=47.1 and 20.7 Hz), **b** (−133.77, dd, J=48.9 and 26.4 Hz), **c** and **d** (−122.32 and −131.35, dd, J=48.9 and 18.8 Hz, and J=48.9 and 22.6 Hz)	3/50/7/40
11	**a** (−124.18, dd, J=48.9 and 18.8 Hz), **b** (−132.19, dd, J=39.2 and 24.5 Hz), **c** and **d** (−124.26 and −129.22, dd, J=48.9 and 18.8 Hz, and J=48.9 and 22.6 Hz)	35/17/8/40
12	**a** (−124.29, dd, J=43.3 and 16.9 Hz), **b** (−132.08, dd, J=47.1 and 24.5 Hz), **c** and **d** (−124.45 and −129.08, dd, J=48.9 and 18.8 Hz, and J=45.2 and 22.6 Hz)	40/12/11/37

[a] Ratio numbers are ordered in relation to ^{19}F chemical shifts of the aldol compounds **a**–**d**.

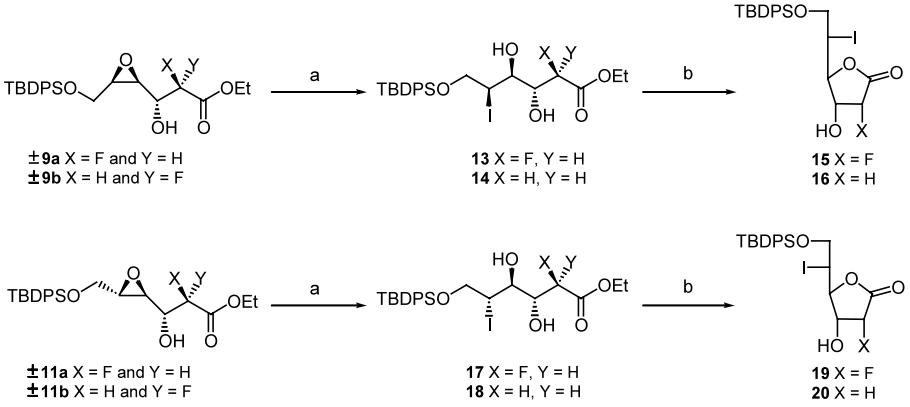
epoxyaldehydes with ethyl, methyl or *tert*-butyl acetates.[10] On the contrary, no increase in diastereoselectivity was observed with fluoroacetates when changing the reaction conditions (2 equiv. of enolate; −78°C ↗ 0°C) as is the case for the reaction of *cis* α,β-epoxyaldehyde with the aforementioned esters.

The regio- and stereospecific opening of the epoxide ring was then attempted in order to introduce the azido functionality. Compounds **9a** and **9b** issued from *cis* epoxyalcohols were allowed to react under standard non-chelating conditions[6b] i.e. in the presence of 5 equiv. of sodium azide and 2.5 equiv. of NH_4Cl in $MeOH/H_2O$ (8/1).

While opening of the epoxide ring and formation of azidolactone was observed with non fluorinated γ,δ-epoxy-β-hydroxyesters issued from *cis* epoxyalcohols,[12] the fluorinated aldol adducts were either inert or after prolonged heating were degraded. ^1H NMR spectroscopy of the reaction mixture showed absence of fluorine atom and IR spectroscopy, no incorporation of the azido group. Opening of the epoxide ring was also attempted in the presence of magnesium iodide.[13] When a mixture of major aldol compounds **9a**,**b** (1:1 ratio) was treated with MgI_2 in toluene, two major products **13**, **14** were purified in 40% total yield as an inseparable mixture and 1:1 ratio (Scheme 3). Spectroscopic analysis of the products showed that one was fluorinated (**13**) while the other had lost its C_2 fluorine atom. Defluorinated ester was identified as compound **14**. In fact, ^1H, ^{13}C NMR spectra of compound **14** were identical (except for the ester groups) with those obtained after MgI_2 opening of the epoxide ring of the non-fluorinated γ,δ-epoxy-β-hydroxy methyl ester analogue.[6b] While the pathway for the selective defluorination observed is yet unclear, a similar one has been recently reported in the literature. In fact, Uneyama et al.[14] gain efficient access to the interesting synthons 2,2-difluoroenolsilylethers through Mg^0 promoted defluorination of trifluoromethylketones.

NMR analysis of the fluorinated iodoester revealed also a C_5 opening of the epoxide ring. ^1H and ^{13}C chemical shifts and coupling constants of H_2 revealed the presence of geminal fluorine atom (δ_{H2}=5.25 ppm, d.d. J=47.5 and 1.8 Hz and δ_{C2}=88.8 ppm, d. J=186 Hz), while for H_5 atom revealed the presence of a geminal iodine atom (δ_{H5}=4.38 ppm, t.d. J=5.5 and 1.1 Hz and δ_{C5}=40.6 ppm).

In order to establish an unambiguous C_2 absolute configuration of the fluoro iodinated ester, compounds **13**,**14** were allowed to react in the presence of trifluoroacetic acid in toluene. After 30 minutes of reflux under Dean–Stark conditions two products were obtained (Scheme 3), purified and identified as lactones (±)-**15** and (±)-**16** (90% total yield).[15] The stereochemistry of the fluorine label of the lactone was confirmed by comparison of ^1H and ^{19}F NMR spectra[15] with the one reported by us[6a] and those by Goekjian et al.[9] Lactone **15** thus possesses a C_2/C_3 *cis* relationship



Scheme 3. *Reagents and conditions*: (a) MgI_2 (1.2 equiv.), anhydrous toluene, rt, 3 h, 40%; (b) CF_3CO_2H (excess), toluene, reflux, Dean–Stark, 30 min, 90%.

between the fluorine and hydroxyl groups confirming its affiliation with epoxyfluoroester **9a**.

trans Epoxyesters **11a**,**b** behave similarly (Scheme 3) affording lactones (±)-**19** and (±)-**20** in 35% total yield.

In conclusion, the diastereofacial preference of the aldolisation reaction of *cis* and *trans* α,β-epoxyaldehydes with lithium ethyl fluoroacetate is *anti* for the C_3 hydroxy carbon atom, in agreement with our previous results. Compounds **15** and **19** issued from epoxyfluoroesters **9a** and **11a** in a two-step sequence (iodination and lactonisation), represent a successful attempt in this series of C_2 fluorinated butyrolactones possessing a C_2/C_3 *cis* relationship between the fluorine and hydroxyl groups.

Further studies are in progress in order to optimise the synthesis of functionalised fluorobutyrolactones and to apply them in the elaboration of the nucleosidic part of the polyoxin and nikkomycin families.

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15. Synthesis of lactone **15** from aldehyde **5**:
(a) Aldolisation. At −78°C, to a solution of LDA (5.3 mmol) in anhydrous ether (11 mL), was added ethyl fluoroacetate (562 mg, 5.3 mmol). The mixture was stirred for 30 min at −78°C. Then, was added slowly a solution of aldehyde **5** (900 mg, 2.65 mmol) in anhydrous ether (4 mL). The mixture was stirred for 30 min at −78°C and 2 h at 0°C. It was then hydrolysed with satd NH_4Cl, and the aqueous phase was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with petroleum ether/Et_2O, 6/4, to give 434 mg of compounds **9a**–**b** (37%) (R_f = 0.32) and 58 mg of compounds **9c**–**d** (5%) (R_f = 0.29).
(b) Iodination. At 0°C, to a mixture of compounds **9a**–**b** (434 mg, 1 mmol) in anhydrous toluene (25 mL) was added magnesium iodide (324 mg, 1.2 mmol). The mixture was stirred for 3 h at rt. After dilution with Et_2O, it was decolorated with satd Na_2SO_3, and the aqueous phase was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (eluant: petroleum ether/Et_2O, 65/35), affording 223 mg of compounds **13** and **14** (39%, R_f = 0.30).
(c) Lactonisation. A mixture of compounds **13** and **14** (223 mg) and TFA (1 mL) in toluene (20 mL) was refluxed for 1 h under Dean–Stark conditions. Toluene and TFA were then evaporated. The residue was chromatographed on silica gel (eluant petroleum ether/CH_2Cl_2/AcOEt, 65:28:7), to give 103 mg of compound **15** (51%) (R_f = 0.13) and 80 mg of compound **16** (39%) (R_f = 0.10).
(d) Characteristics. ^{13}C NMR data for different 2-fluorobutyrolactones: Lactone **15** (200 MHz, $CDCl_3$) δ ppm: 168.5 (d, J = 21.0 Hz, C=O); 135.6, 135.5, 130.2, 128.0 (CH arom.); 85.0 (d, J = 168.8 Hz, C2); 83.4 (d, J = 25.5 Hz, C3); 70.8 (d, J = 15.3 Hz, C4); 66.0 (C6); 31.8 (C5); 26.8 (CH_3 $tBuPh_2Si$). Lactone **16** (400 MHz, $CDCl_3$) δ ppm: 168.9 (d, J = 22.3 Hz, C=O); 136.0, 135.8, 130.3, 128.1 (CH arom.); 85.6 (d, J = 169.7 Hz, C2); 78.0 (d, J = 5.6 Hz, C4); 69.8 (d, J = 15.9 Hz, C3); 64.5 (C6); 28.0 (C5); 27.0 (CH_3 $^tBuPh_2Si$); 19.6 (Cq $^tBuPh_2Si$). Compound **13a** from Ref. 9; C_2-F/C_3-OH *cis* relationship, (100 MHz, D_2O) δ ppm: 174.8 (d, J = 22 Hz); 88.0 (d, J = 15 Hz); 86.7 (d, J = 188 Hz); 69.2 (d, J = 15 Hz); 60.9. Compounds **13b** and **22** from Ref. 9 and 6a respectively; C_2-F/C_3-OH *trans* relationship; compound **13b** (100 MHz, D_2O) δ ppm: 172.5 (d, J = 23 Hz); 92.7 (d, J = 195 Hz); 81.7 (d, J = 9 Hz); 71.6 (d, J = 20 Hz); 60.0. compound **22** (63 MHz, $CDCl_3$) δ ppm: 168.0 (d, J = 22.8 Hz); 135.9, 135.7; 132.6; 130.2, 128.8, 128.6, 128.3, 128.1; 91.6 (d, J = 199.0 Hz); 78.1 (d, J = 20.2 Hz); 76.7 (d, J = 7.5 Hz); 73.2; 63.8; 63.3; 26.8; 19.2.