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Stereoselective synthesis of (1′*S*,3*R*,4*R*)-4-acetoxy-3-(2′-fluoro-1′-trimethylsilyloxyethyl)-2-azetidinone

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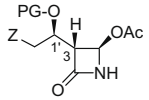
ABSTRACT

A stereoselective synthesis of (1′*S*,3*R*,4*R*)-4-acetoxy-3-(2′-fluoro-1′-trimethylsilyloxyethyl)-2-azetidinone as a new fluorine-containing intermediate towards β-lactams, is described. The synthetic key step relies upon the dynamic kinetic resolution (DKR) of ethyl 2-benzamidomethyl-4-fluoro-3-oxo-butanoate via asymmetric transfer hydrogenation catalyzed by [Ru(η^6-arene)(*S*,*S*)-R_2NSO_2DPEN].

The 2-azetidinone moiety is present in a large number of important biologically active compounds of which β-lactam antibiotics are representative. Despite the rapid increase in the resistance of microorganisms to current antibiotics, β-lactam antibiotics still represent more than half of available antibacterial agents.[1] Moreover, owing to the unique properties attributed to the fluorine atom, selectively fluorinated organic intermediates constitute challenging targets which are useful towards the synthesis of biologically active substances with modified properties.[2]

The use of asymmetric catalysis has led to several industrial processes on a multi-ton scale. One of the earliest and most referred to being the process for the synthesis of the precursor to carbapenems by the Takasago Co. Relying upon the Ru-(BINAP)-catalyzed asymmetric hydrogenation of a β-keto ester derivative via dynamic kinetic resolution (DKR), the optically pure (3*R*,4*R*)-4-acetoxy-3-[(*R*)-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**1**) precursor was prepared.[3] In the subsequent step, the acetoxy group was displaced readily by nucleophiles with high stereocontrol aided by the presence of the bulky *O*-TBDMS protecting group.[4]

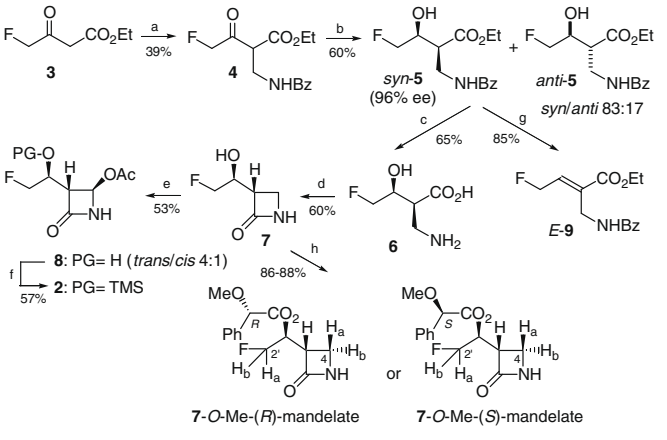


1: Z= H, PG= TBDMS
2: Z= F, PG= TMS

In our ongoing research on trinems (i.e., tricyclic β-lactams) with improved biological properties,[5] we devised a synthetic strategy towards the preparation of highly optically active fluorine-containing reactive 4-acetoxy-azetidinones.[6] A literature survey revealed only a few cases of the preparation of such intermediates.[7]

Herein, we present our synthesis of the new fluoroalkyl acetoxy azetidinone **2** (Scheme 1) via a modified procedure to that developed by the Takasago Co. for the synthesis of **1**.

Thus, ethyl 2-benzamidomethyl-4-fluoro-3-oxo-butanoate (**4**), prepared by alkylation of commercially available ethyl γ-fluoroacetoacetate (**3**),[8] was subjected to asymmetric transfer hydrogenation[9] using the Mohar–Stephan [Ru(η^6-arene)(*S*,*S*)-R_2NSO_2DPEN] catalyst (R_2NSO_2DPEN = *N*-sulfamoyl-1,2-diphenylethylenediamine). Asymmetric hydrogenation of **4** using Ru-BINAP as catalyst gave poorer results than using the latter asymmetric transfer hydrogenation.[10]



Scheme 1. Reagents and conditions: (a) LiH, $BzNHCH_2Cl$, THF, 0 °C→rt; (b) [Ru(1,3,5-$Et_3C_6H_3$)(*S*,*S*)-Me_2NSO_2DPEN], HCO_2H–Et_3N (5:2), DMF, rt; (c) (i) 10% aq HCl, reflux; (ii) Et_3N, MeOH, rt; (d) $(2\text{-PyS})_2$, PPh_3, DMSO, 90 °C; (e) $RuCl_3{\cdot}xH_2O$, NaOAc, AcOOH, PrOAc, −40 °C→−10 °C; (f) (i) TMSCN, DMF, rt; (ii) Buffered silica gel (pH 8), CH_2Cl_2, rt, (>99% dr, 96% ee); (g) DEAD, PPh_3, CH_2Cl_2, rt; (h) (*R*)- or (*S*)-$PhCH(OMe)CO_2H$, DCC, DMAP, CH_2Cl_2, rt.

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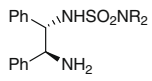
Table 1
[Ru(η^6-arene)(*S*,*S*)-R_2NSO_2DPEN]-catalyzed transfer hydrogenation of 4[a]

Ligand: 

a-c

a: R= Me
b: RR= -$(CH_2)_5$-
c: RR= -$(CH_2)_2O(CH_2)_2$-

Entry	[$RuCl_2$(η^6-arene)]$_2$ arene=	Ligand	*syn*/*anti*[b]	ee (*syn*, %)[c]
1	1,3,5-Triethylbenzene	**a**	83:17	96
2	Hexamethylbenzene	**a**	71:29	96
3	Benzene	**b**	76:24	74
4	Mesitylene	**b**	71:29	93
5	1,3,5-Triethylbenzene	**b**	75:25	95
6	Hexamethylbenzene	**b**	83:17	95
7	Hexamethylbenzene	**c**	74:26	94

[a] HCO_2H–Et_3N (5:2, 250 μL) was added to a mixture of **4** (1 mmol) and preformed [RuCl(η^6-arene)(*S*,*S*)-R_2NSO_2DPEN] (0.5 mol %) in DMF (1 mL), and the reaction was stirred at rt for 1 d to attain 100% conversion.
[b] Determined by ^{19}F NMR spectroscopy: $\delta(syn) = -231$, $\delta(anti) = -228$.
[c] Determined by HPLC analysis on a chiralcel OD column with hexane/2-PrOH/CF_3CO_2H 97:3:0.2 (1 mL/min) and UV (λ = 222 nm) detection: $t(R,R)$ = 44 min, $t(S,S)$ = 58 min.

Asymmetric transfer hydrogenation of **4** in the presence of HCO_2H–Et_3N (5:2) was performed at rt using 0.5% of the in situ generated catalyst which was prepared from [$RuCl_2$(η^6-arene)]$_2$ and (*S*,*S*)-R_2NSO_2DPEN ligand in DMF at 80 °C. Screening various catalysts (Table 1) led to the optimum result using [$RuCl_2$(1,3,5-$Et_3C_6H_3$)]$_2$ and (*S*,*S*)-Me_2NSO_2DPEN. The efficiency of this transformation resides in the highly stereoselective DKR leading to the formation of **5** in 83:17 dr (*syn*/*anti*) and in quantitative yield. Pure *syn*-**5** was easily isolated in 60% yield after a single column chromatography eluting with CH_2Cl_2/Et_2O (4:1) and chiral HPLC analysis revealed an ee of 96%.

The *syn*-(2*S*,3*S*) configuration of the major diastereomer **5** was confirmed by a combination of ^1H NMR NOE analysis of its dehydrated derivative **9** (prepared under Mitsunobu conditions[11]-Scheme 1, step g) which showed *E*-geometry, and in the subsequent synthetic steps, by ^1H NMR analysis using an improved Mosher method[12] involving the *O*-methyl-(*R*)- and *O*-methyl-(*S*)-mandelates of **7**.

In the following step, *syn*-**5** was subjected to hydrolysis in boiling 10% aq HCl to give the corresponding hydrochloride salt of ß-amino acid **6**. After treatment of the residue with Et_3N in MeOH, ß-amino acid **6** was isolated in 65% yield. Azetidinone formation employing 2,2′-dipyridyl disulfide and PPh_3 in DMSO at 90 °C and crucial slow addition of **6** in DMSO, resulted in the formation of **7** in 60% isolated yield. We utilized the modified Ohno conditions[13] as we previously noted a partial loss of fluorine while monitoring the reaction progress by ^{19}F NMR (α,α,α-trifluorotoluene was used as the internal standard). HPLC analysis of the **7**-*O*-Me-(*R*)-mandelate revealed a diastereomeric ratio of 98:2, and 96% ee for **7**. This result indicates the retention of the stereochemistry during the transformation sequence of *syn*-**5** having 96% ee.

Protection of **7** using TBDMSCl/Et_3N led to the preferential formation of the *N*-TBDMS-protected compound. Due to this unexpected result, the preparation of **2** was carried out by direct peracetic acid oxidation of **7** catalyzed by $RuCl_3{\cdot}xH_2O$ followed by *O*-TMS-protection. Under these conditions, the acetoxylation proceeded smoothly furnishing **8** in a 4:1 trans/cis ratio as confirmed by ^1H and ^{19}F NMR. This mixture was subjected to treatment with trimethylsilyl cyanide in DMF under mild conditions affording the crude *N*,*O*-bis-TMS-protected derivative of **8**, which yielded in turn the desired *O*-TMS-protected compound **2** via selective *N*-desilylation using buffered silica gel (pH 8).[14] Column chromatography on buffered silica gel (pH 8) with gradient elution (hexane/CH_2Cl_2) allowed the isolation of **2** as a single diastereomer in 57% yield and with high chemical purity.

In summary, (1′*S*,3*R*,4*R*)-4-acetoxy-3-(2′-fluoro-1′-trimethylsilyloxyethyl)-2-azetidinone (**2**) was prepared in 96% ee relying upon asymmetric transfer hydrogenation as the key step using HCO_2H–Et_3N (5:2) and catalyzed with 0.5% [Ru(1,3,5-$Et_3C_6H_3$)(*S*,*S*)-Me_2NSO_2DPEN]. The application of this reactive intermediate in the synthesis of fluorine-containing trinems is under study and the results will be communicated shortly.

Supplementary data

Supplementary data (experimental procedures and characterization data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.111.

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