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Stereoselective synthesis of fluorine-containing analogues of *anti*-bacterial sanfetrinem and LK-157

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ABSTRACT

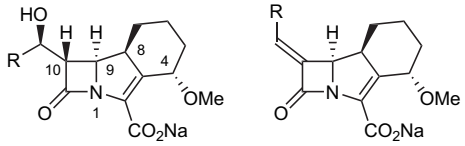
The synthesis of (1′*S*,3*R*,4*R*)-4-acetoxy-3-(1′-trimethylsilyloxy-2′,2′,2′-trifluoroethyl)-2-azetidinone (**10**) precursor of modified carbapenems is described relying upon [Ru(C_6Me_6)(*S*,*S*)–$(CH_2)_5NSO_2DPEN$]-catalyzed asymmetric transfer hydrogenation under dynamic kinetic resolution using HCO_2H–Et_3N. This fluorine-containing precursor yielded the targeted trinems **1** and **2** via a stereoselective key step condensation with lithium (*S*)-6-methoxy-cyclohexenolate.

1. Introduction

β-Lactam antibiotics encompassing penicillins, cephalosporins, monobactams, and carbapenems, are the major class of antibacterial agents used in modern health care. Nonetheless, the resistance to them by some bacterial strains incited the search for further modified analogues.[1] Following the discovery of the highly active sanfetrinem (a tricyclic carbapenem referred to as trinem) by the Glaxo Co.,[2] several of its derivatives have been prepared and tested.[3] In particular, the (4*S*,8*S*,9*R*)-10*E*-ethylidene-4-methoxy-trinem (LK-157) proved to be effective against both gram-positive and gram-negative bacteria.[4] Furthermore, the increased interest in fluorine-containing antibiotics stems from the potential to favorably alter the original pharmacological properties,[5] and such fluorine-incorporated compounds are of great value in drug design.

As part of our ongoing research program aimed to studying the structure–activity relationship of β-lactam antibiotics through modification of sanfetrinem substituents at C-4 and C-10,[6] we devised the synthesis of the new fluorine-containing trinems **1** and **2**.

The synthesis of sanfetrinem and LK-157 has been reported relying on a highly stereoselective $SnCl_4$-catalyzed condensation of enantiomerically pure (*S*)-2-methoxy-cyclohexanone with (1′*R*,3*R*,4*R*)-4-acetoxy-3-[1′-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone.[7] In addition, the synthesis of the related (1′*R*,3*R*,4*R*)-diastereomer of (1′*S*,3*R*,4*R*)-4-acetoxy-3-(1′-hydroxy-2′,2′,2′-trifluoroethyl)-2-azetidinone (**8**) has been reported by Prati's group based upon the condensation of the optically enriched ethyl (*R*)-3-hydroxy-4,4,4-trifluorobutanoate with *N*-(trimethylsilyl)cinnamylidenimine.[8]



Sanfetrinem: R= CH_3
1: R= CF_3

LK-157: R= CH_3
2: R= CF_3

Hereafter, we describe a stereoselective synthesis of enantiopure (1′*S*,3*R*,4*R*)-4-acetoxy-3-(1′-trimethylsilyloxy-2′,2′,2′-trifluoroethyl)--2-azetidinone (**10**) precursor and its transformation into the new trinems **1** and **2**.

2. Results and discussion

2.1. Synthesis of (1′*S*,3*R*,4*R*)-4-acetoxy-3-(1′-trimethylsilyloxy-2′,2′,2′-trifluoroethyl)-2-azetidinone (10)

Among the several synthetic approaches described in the literature toward (1′*R*,3*R*,4*R*)-4-acetoxy-3-[1′-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone, the Takasago Co. synthetic pathway

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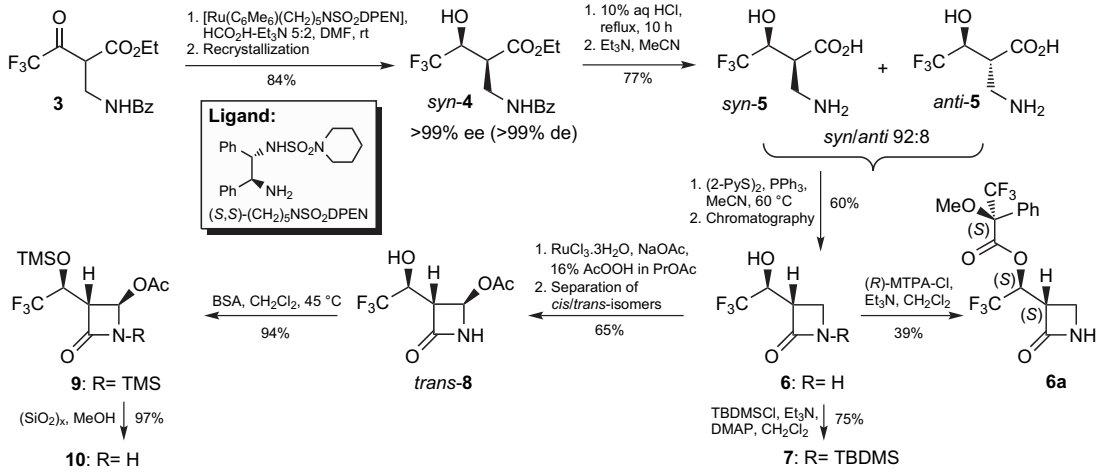
proved to be highly efficient. It relies upon a stereoselective dynamic kinetic resolution (DKR) via the [$RuCl_2$(*R*)-BINAP]$_2\cdot Et_3N$-catalyzed asymmetric hydrogenation at 100 atm of H_2 of methyl 2-benzamidomethyl-3-oxobutanoate leading to a dr of 94:6 and 98% ee for the *syn*-stereoisomer.[9,10] Following a similar general outlined strategy (Scheme 1), we have prepared the ethyl 2-benzamidomethyl-3-oxo-4,4,4-trifluorobutanoate (**3**) from the commercially available ethyl 4,4,4-trifluoroacetoacetate and subjected it to asymmetric transfer hydrogenation. The reduction was carried out at room temperature in DMF using HCO_2H–Et_3N 5:2 in the presence of our[11] in situ-generated catalyst derived from [$RuCl_2(C_6Me_6)]_2$ and (1*S*,2*S*)-*N*-(piperidyl-*N*-sulfonyl)-1,2-diphenylethylenediamine ((*S*,*S*)-$(CH_2)_5NSO_2$DPEN). The reaction parameters were varied in order to attain optimum results. During this study, it turned out that the substrate concentration and the η^6-arene of the catalyst were detrimental for high diastereoselectivity. Thus, operating at different concentrations of substrate **3**, *syn*/*anti*-**4** ratios of 94:6 (>99% ee *syn*, 52% ee *anti*) and 83:17 were obtained for 0.25 M and 1 M solutions, respectively.[12] Also, using C_6Me_6 as the η^6-arene yielded the best result compared to employing benzene, *p*-cymene, mesitylene or 1,3,5-triethylbenzene.[13] After a single recrystallization from *i*-Pr_2O/hexane, pure alcohol *syn*-**4** was obtained in >99% de. Note that the [$RuCl_2$(*R*)-BINAP]$_2\cdot Et_3N$-catalyzed hydrogenation of **3** under 90 atm of H_2 resulted in our hands in the formation of *syn*-**4** in a dr of 96:4 in 22% ee. Thus, the transfer hydrogenation methodology using our [Ru(η^6-arene)$(CH_2)_5NSO_2$DPEN] catalyst proved to be highly efficient for the preparation of fluoroalkyl alcohols from the corresponding ketones.[14]

Facing these various synthetic challenges,[17] we pursued the synthesis with the unprotected azetidinone **6**. Thus, under the action of 16% peracetic acid in PrOAc in the presence of $RuCl_3\cdot 3H_2O$/NaOAc, the 4-acetoxy-azetidinone **8** was obtained in a dr of 9:1 (*trans*/*cis*) accompanied with up to 4% of the product resulting from the oxidation of the hydroxy group as shown by ^{1}H NMR.[18] The pure stereoisomer *trans*-**8** was isolated in 65% yield after column chromatography. Treatment of *trans*-**8** with *N*,*O*-bis(trimethylsilyl)-acetamide (BSA, >2 equiv) in CH_2Cl_2 led to the *N*,*O*-bisTMS-protected azetidinone **9** (94% yield), which by regioselective deprotection upon treatment with silica gel slurry in MeOH afforded the *O*-TMS-protected compound **10**. Note that azetidinones **9** and **10** were conveniently purified by distillation under high vacuum.

2.2. Determination of the absolute configuration of *syn*-4

Attempts to esterify alcohol *syn*-**4** with (*R*)-Mosher's acid chloride led to its dehydration into ethyl (*E*)-2-benzamidomethyl-4,4,4-trifluorobut-2-enoate as shown by ^{1}H NMR (see Supplementary data). In parallel, (*S*)-1-(phenyl)ethyl and (*S*)-1-(1-naphthyl)ethyl carbamates of alcohol *syn*-**4** were prepared, but unfortunately we were unable to obtain suitable crystals for X-ray diffraction analysis. Finally, the esterification of azetidinone **6** to its (*S*)-Mosher's acid ester **6a** ((*R*)-Mosher's acid chloride used) followed by crystallization was successful and the X-ray analysis[19] revealed a (1′*S*,3*S*) configuration. This corresponds consequently to a (2*S*,3*S*) configuration for *syn*-**4**.



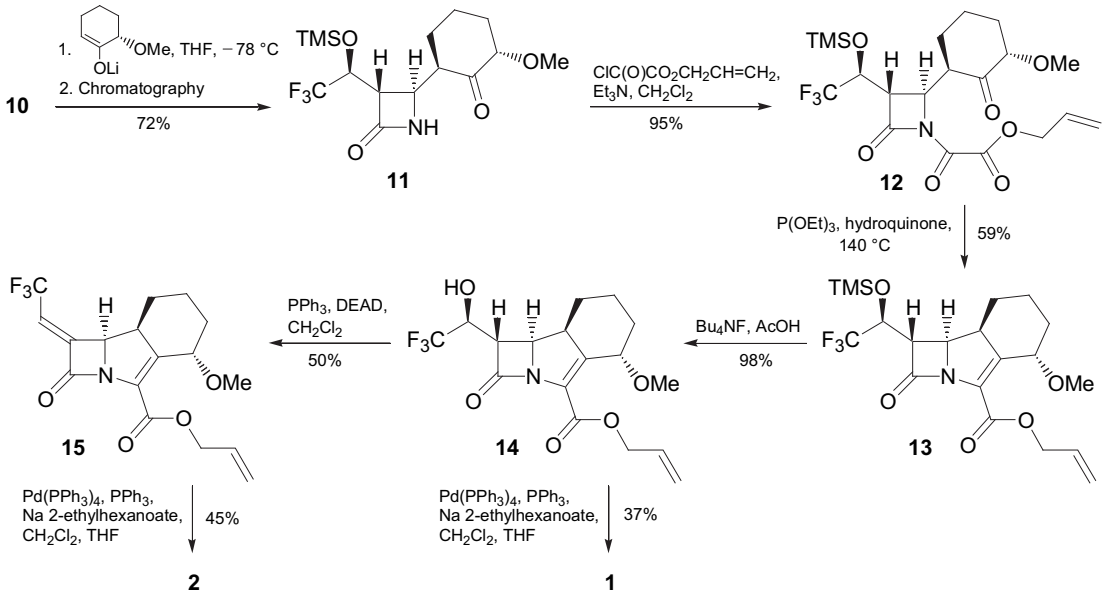
Scheme 1.

Subsequent hydrolysis of *syn*-**4** in boiling 10% aq HCl furnished the hydroxytrifluoroethyl β-amino acid **5**. A prolonged hydrolysis period (10 h) was necessary for complete conversion, which is the double of the required time for the hydrolysis of the non-fluorine-containing analogue methyl (2*S*,3*S*)-2-benzamidomethyl-3-hydroxybutanoate.[9] However, a certain degree of epimerization at the α-position concomitantly occurred under these conditions, which was up to 8% after 10 h and 20% after 24 h. Subsequently, the *syn*/*anti*-**5** (92:8) mixture was used directly in the following cyclization step. This latter transformation was carried out according to Ohno's conditions,[15] which call upon 2,2′-dipyridyl disulfide and PPh_3. Interestingly, the azetidinone **6** was isolated as a single stereoisomer in 60% combined yield after recrystallization of the crude and column chromatography of the filtrate. Attempts to *O*-TBDMS-protect azetidinone **6** under various conditions[16] led to the *N*-TBDMS-protected product **7**, in contrast to the literature result for the non-fluorine-containing analogue.[9]

2.3. Synthesis of fluorine-containing trinems 1 and 2

Adopting a comparable literature synthetic strategy for building trinem skeletons from 4-acetoxy-2-azetidinones,[20] the introduction of the (*S*)-methoxy-cyclohexanone moiety was accomplished by reacting lithium (*S*)-6-methoxy-cyclohexenolate (2 equiv) with the *O*-TMS-protected azetidinone **10** in THF at −78 °C (Scheme 2). The resulting bicyclic *O*-TMS-protected product was formed in a dr of 82:18 as determined by ^{1}H and ^{19}F NMR analyses. The pure stereoisomer (3*S*,4*R*)-4-[(1*R*,3*S*)-3-methoxy-2-oxo-cyclohexyl]-3-[1-(*S*)-trimethylsilyloxy-2,2,2-trifluoroethyl]-2-azetidinone (**11**) was isolated in 72% yield after column chromatography. Note, the condensation of the *N*,*O*-bisTMS-protected azetidinone **9** under the same reaction conditions led to an identical dr, albeit in 50% yield.

Progressing toward the synthesis of **1** and **2**, intermediate **11** was treated with allyl oxalyl chloride affording product **12** (95% yield), which was cyclized into trinem **13** with triethyl phosphite/



Scheme 2.

hydroquinone at 140 °C (59% yield).[21] Removal of the TMS-protecting group of **13** with Bu_4NF/AcOH furnished alcohol **14**, which afforded pure sodium salt **1** in 37% yield following Pd-catalyzed deallylation[22] in the presence of sodium 2-ethylhexanoate. The pure sodium salt **2** was obtained from **14** following dehydration into **15** by PPh_3/DEAD treatment (50% yield) and Pd-catalyzed deallylation (45% yield).

3. Conclusion

Though the synthesis of (1′*R*,3*R*,4*R*)-4-acetoxy-3-[1′-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone was straightforward, unexpected synthetic difficulties were encountered in the preparation of a CF_3-containing analogue. Resorting to a different synthetic approach, we have achieved the stereoselective synthesis of enantiopure (1′*S*,3*R*,4*R*)-4-acetoxy-3-(1′-trimethylsilyloxy-2′,2′,2′-trifluoroethyl)-2-azetidinone (**10**), which proved to be a useful precursor for the preparation of modified trinems bearing a CF_3 group. This new fluorine-containing intermediate was prepared relying upon an asymmetric transfer hydrogenation key step under DKR of ethyl 2-benzamidomethyl-3-oxo-4,4,4-trifluorobutanoate (**3**) catalyzed by [Ru(C_6Me_6)(*S*,*S*)–$(CH_2)_5NSO_2$DPEN]. This latter transformation proceeded effectively as the corresponding alcohol *syn*-**4** was obtained in 84% yield with >99% ee (>99% de). The intermediate (1′*S*,3*R*,4*R*)-**10** was further efficiently transformed into the new trinems **1** and **2** following a novel stereocontrolled approach via its condensation with lithium (*S*)-6-methoxy-cyclohexenolate. These trinems are under biological testing and the results will be communicated in due course.

4. Experimental section

4.1. General considerations

Reactions were carried out under an inert atmosphere using dry solvents when required. ^1H (300 MHz, internal Me_4Si), ^{13}C (75 MHz, internal $CDCl_3$), and ^{19}F NMR (282 MHz, internal CCl_3F) were recorded as solutions in $CDCl_3$ if not stated otherwise.

*4.1.1. Ethyl 2-benzamidomethyl-3-oxo-4,4,4-trifluorobutanoate (**3**).* To powdered sodium (10.0 g, 0.435 atm g) under Et_2O (350 mL) was added at 0 °C a solution of ethyl 4,4,4-trifluoroacetoacetate (63 mL, 0.43 mol) in Et_2O (100 mL) over 30 min. The mixture was stirred at rt until all sodium had disappeared (~6 h). Subsequently, solid *N*-(chloromethyl)benzamide[23] (72.8 g, 0.43 mol) was added portionwise and the mixture was left to stir at rt. After 30 min, the yellow colored suspension was diluted with EtOAc (250 mL) and filtered through a short pad of silica gel (20 g) washing with EtOAc (2×100 mL). The concentrated filtrate was recrystallized from cold (0 °C) toluene (130 mL). The crystals were filtered, rinsed successively with cold toluene (100 mL), toluene/*i*-Pr_2O (1:1, 100 mL) and finally with *i*-Pr_2O (100 mL). After drying, **3** (70.99 g) was obtained as white crystals. An additional crop (18.3 g) was obtained after concentration of the filtrate and recrystallization from toluene (50 mL) (total yield 72%). Mp 85–88 °C; ν_{max}(KBr) 3328, 1772, 1721, 1640, 1526, 1294, 1206, 1182, 1155 cm^{-1}; δ_H (mixture of rotamers) 1.27 and 1.30 (3H, 2 t, *J* 7.2 Hz), 3.16 (0.2H, t, *J* 4.3 Hz), 3.85–4.41 (4.6H, m), 5.19 (0.1H, s), 6.00 (0.1H, s), 6.69 (1H, m), 7.41–7.53 (3H, m), 7.72–7.76 (2H, m); δ_C (mixture of rotamers) 13.8, 37.2, 37.8, 46.8, 52.5, 62.4, 62.8, 93.6 (q, *J* 33 Hz), 115.1 (q, *J* 293 Hz), 126.9 (q, *J* 291 Hz), 128.6, 131.9, 133.5, 133.6, 166.1, 167.9, 168.6, 172.9, 186.5 (q, *J* 38 Hz); δ_F (mixture of rotamers) −66.9 (s), −78.3 (s), −85.3 (s). *m*/*z* (FAB) 318 (85, MH^+); HRMS (EI): M^+, found 317.0877. $C_{14}H_{14}F_3NO_4$ requires 317.0875.

*4.1.2. Ethyl (2S,3S)-2-benzamidomethyl-3-hydroxy-4,4,4-trifluorobutanoate (syn-**4**). Catalyst preparation*: A mixture of [$RuCl_2(C_6Me_6)]_2$ (248 mg, 0.37 mmol) and (1*S*,2*S*)-*N*-(piperidyl-*N*-sulfonyl)-1,2-diphenylethylenediamine[11] (292 mg, 0.81 mmol) in DMF (50 mL) was heated progressively to 80 °C, stirred at this temperature for 30 min then cooled to rt. Reduction of **3**: to a solution of **3** (62.77 g, 198 mmol) in DMF (800 mL) was added the above catalyst solution followed by HCO_2H–Et_3N 5:2 (50 mL). The mixture was left to stir at rt for 12 h. H_2O (1 L) was added and the product was extracted with Et_2O (5×250 mL). The combined organic extracts were washed with H_2O (300 mL) and the aqueous layer was reextracted with Et_2O (3×500 mL). The combined Et_2O layers were again washed with H_2O (300 mL), dried (Na_2SO_4), and partially concentrated. The precipitated product was filtered and washed with Et_2O affording white crystals. An additional crop was obtained after concentration of the filtrate and washing with *i*-Pr_2O (53.1 g, total yield: 84%). ^{19}F NMR analysis revealed a de >99%. Ee (>99%) was determined by HPLC on Chiralcel OD column eluting with hexane/*i*-PrOH 98:2 at 1 mL/min flow rate and UV (λ 227 nm) detection: *t*(*R*,*R*)=52 min, *t*(*S*,*S*)=56 min. Mp 108–110 °C; [Found: C, 52.52; H,

5.11; N, 4.23. $C_{14}H_{16}F_3NO_4$ requires C, 52.67; H, 5.05; N, 4.39]; $[\alpha]_D^{25}$ +33.8 (*c* 1.0, $CHCl_3$); ν_{max}(KBr) 3417, 3402, 1724, 1651, 1543, 1281, 1177, 1131, 1104 cm^{-1}; δ_H 1.28 (3H, t, *J* 7.1 Hz), 2.96 (1H, dt, *J* 9.3, 3.7 Hz), 3.56 (1H, dt, *J* 14.7, 3.4 Hz), 4.11–4.34 (4H, m), 5.56 (1H, br d, *J* 5.4 Hz), 6.90 (1H, m), 7.42–7.57 (3H, m), 7.76–7.80 (2H, m); δ_C 14.0, 37.8, 45.9, 61.6, 68.5 (q, *J* 31 Hz), 124.6 (q, *J* 281 Hz), 127.1, 128.8, 132.3, 133.2, 169.5, 171.6; δ_F −77.5 (d, *J* 7.1 Hz). *m*/*z* (FAB) 320 (80, MH^+). HRMS (EI): M^+, found 319.1033. $C_{14}H_{16}F_3NO_4$ requires 319.1031.

*4.1.3. (2S,3S)-2-Aminomethyl-3-hydroxy-4,4,4-trifluorobutanoic acid (syn-**5**).* A suspension of alcohol *syn*-**4** (85.5 g, 0.268 mol) in 10% aq HCl (1.7 L) was refluxed under vigorous stirring for 10 h. The reaction mixture was cooled down on an ice-bath and the precipitate filtered. The filtrate was washed with CH_2Cl_2 (3×200 mL) and the aqueous phase concentrated to dryness. The syrupy residue was dissolved in MeCN (150 mL), concentrated, and dried under high vacuum. The yellowish viscous residue (66.2 g) was redissolved in MeCN (450 mL) and Et_3N (36.5 mL, 0.267 mol) was added. This mixture was stirred at rt overnight and the precipitate filtered. The filter cake was suspended in CH_2Cl_2 (300 mL), refluxed for 0.5 h then passed hot through a sintered glass filter. This latter treatment was repeated in order to eliminate the $Et_3N{\cdot}HCl$. Product *syn*-**5** was obtained as a white powder accompanied with 8% of *anti*-(2*S*,3*R*)-**5** (38.4 g, 76.6%). ν_{max}(KBr) 3138 (br), 1646, 1577, 1372, 1277, 1179, 1160, 1132, 1080 cm^{-1}; *m*/*z* (FAB) 188 (100, MH^+). Characteristics of *syn*-**5**: δ_H (D_2O) 2.85 (1H, app. q, *J* 6.1 Hz), 3.30 (2H, d, *J* 6.1 Hz), 4.58 (1H, m); δ_C (D_2O) 35.8, 45.5, 70.5 (q, *J* 31 Hz), 125.4 (q, *J* 282 Hz), 176.6; δ_F (D_2O) −77.0 (d, *J* 7.6 Hz).

*4.1.4. (1′S,3S)-3-(1′-Hydroxy-2′,2′,2′-trifluoroethyl)-2-azetidinone ((1′S,3S)-**6**).* To product **5** (31.2 g, 0.167 mol; containing 8% of *anti*-**5**) in MeCN (3 L), PPh_3 (48.8 g, 0.168 mol) and 2,2′-dipyridyl disulfide (37.0 g, 0.168 mol) were successively added and the mixture was heated at 60 °C for 12 h. The clear yellow solution was cooled down to rt and $Cu(OAc)_2{\cdot}H_2O$ (33.5 g, 0.168 mol) was added. The orange precipitate was filtered off and the filtrate concentrated. The residue was suspended in toluene (300 mL) and the product was extracted with H_2O (7×250 mL). The combined aqueous layers were washed with toluene (100 mL) and NaCl was added till saturation. The product was extracted with EtOAc (4×1 L), filtered through a short pad of silica gel surmounted with Na_2SO_4 and concentrated. The solid residue (22.9 g) was triturated with Et_2O and the pure crystalline **6** (15.65 g, 55.5%) was collected by filtration. The filtrate was concentrated and the residue was purified by column chromatography on silica gel eluting with *n*-BuOAc to afford an additional amount of **6** (1.38 g, 4.9%; R_f (EtOAc) 0.5). Further elution with EtOAc afforded the diastereomer (1′*S*,3*R*)-**6** (0.90 g, 3.2%; R_f (EtOAc) 0.3) as a white powder. (1′*S*,3*S*)-**6**: mp 166–167 °C; [Found: C, 35.51; H, 3.58; N, 8.28. $C_5H_6F_3NO_2$ requires C, 35.65; H, 3.68; N, 8.02]; $[\alpha]_D^{25}$ −42.1 (*c* 1.0, MeOH); ν_{max}(KBr) 3268, 1736, 1704, 1264, 1192, 1176, 1148, 1124 cm^{-1}; δ_H (CD_3OD) 3.29 (1H, app. t, *J* 5.5 Hz), 3.50 (1H, m), 3.57 (1H, dt, *J* 5.5, 2.3 Hz), 3.34 (1H, dq, *J* 7.6, 2.3 Hz); δ_C (CD_3OD) 36.9, 51.8, 66.6 (q, *J* 32 Hz), 126.6 (q, *J* 290 Hz), 170.0; δ_F (CD_3OD) −76.2 (d, *J* 7.3 Hz), HRMS (ESI): MH^+, found 170.0430. $C_5H_7F_3NO_2$ requires 170.0429.

*4.1.5. (1′S,3R)-3-(1′-Hydroxy-2′,2′,2′-trifluoroethyl)-2-azetidinone ((1′S,3R)-**6**).* Mp 125.5–127 °C; $[\alpha]_D^{25}$ −19.4 (*c* 1.0, MeOH); ν_{max}(KBr) 3334, 1732, 1716, 1280, 1184, 1161, 1154, 1132 cm^{-1}; δ_H (CD_3OD) 3.22 (1H, dd, *J* 5.6, 2.4 Hz), 3.41 (1H, t, *J* 5.6 Hz), 3.55 (1H, dt, *J* 5.6, 2.7 Hz), 4.26 (1H, dq, *J* 7.6, 5.9 Hz); δ_C (CD_3OD) 38.9, 51.9, 69.1 (q, *J* 33 Hz), 126.4 (q, *J* 290 Hz), 169.1; δ_F (CD_3OD) −74.5 (d, *J* 7.3 Hz). HRMS (ESI): MH^+, found 170.0423. $C_5H_7F_3NO_2$ requires 170.0429.

*4.1.6. (1′S,3S)-3-(1′-Hydroxy-2′,2′,2′-trifluoroethyl)-1-(tert-butyldimethylsilyl)-2-azetidinone (**7**).* To a solution of (1′*S*,3*S*)-**6** (338 mg, 2 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (290 μL, 2.1 mmol), DMAP (49 mg, 0.4 mmol), and *tert*-butyldimethylsilyl chloride (317 mg, 2.1 mmol). After stirring at rt for one day, the reaction mixture was washed with 1 M HCl (10 mL), H_2O (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated. Column chromatography of the residue on silica gel eluting first with CH_2Cl_2 then with Et_2O afforded pure **7** (426 mg, 75%). ν_{max}(KBr) 3294 (br), 2962, 2934, 2862, 1724, 1364, 1272, 1224, 1169, 1123, 1039 cm^{-1}; δ_H 0.22 (3H, s), 0.27 (3H, s), 0.96 (9H, s), 3.03, (1H, app. t, *J* 4.8 Hz), 3.25 (1H, t, *J* 6.0 Hz), 3.53 (1H, m), 3.63 (1H, m), 4.47 (1H, m); δ_C −6.3, −6.2, 18.4, 25.8, 37.8, 51.1, 65.7 (q, *J* 32 Hz), 124.7 (q, *J* 282 Hz), 172.6; δ_F −78.7 (d, *J* 7.7 Hz); *m*/*z* (FAB) 284 (100, MH^+).

*4.1.7. (1′S,3S)-3-{1′-[(S)-α-Methoxy-α-(trifluoromethyl)phenylacetoxy]-2′,2′,2′-trifluoroethyl}-2-azetidinone (**6a**).* To a solution of (1′*S*,3*S*)-**6** (17 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (17 μL, 0.12 mmol), DMAP (a crystal), and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (22.4 μL, 0.12 mmol). After stirring for 16 h at rt, the mixture was concentrated, suspended in CH_2Cl_2 and washed with diluted HCl then satd aq $NaHCO_3$, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel eluting with CH_2Cl_2/Et_2O 95:5. The product was recrystallized from CH_2Cl_2/heptane to obtain colorless crystals (15 mg, 39%); mp 69–71 °C; δ_H 3.33 (2H, m), 3.59 (3H, s), 3.73 (1H, m), 5.24 (1H, br s), 5.99 (1H, m), 7.40–7.54 (5H, m); δ_F −72.14 (s), −75.85 (d, *J* 6.1 Hz). For its X-ray structure analysis, see Supplementary data.

*4.1.8. (1′S,3R,4R)-4-Acetoxy-3-(1′-hydroxy-2′,2′,2′-trifluoroethyl)-2-azetidinone (trans-**8**).* To a cold mixture (−10 °C) of (1′*S*,3*S*)-**6** (18.09 g, 0.107 mol), AcONa (8.78 g, 0.107 mol), and $RuCl_3{\cdot}3H_2O$ (675 mg, 2.58 mmol) in a mixture of AcOH (110 mL) and PrOAc (110 mL), a 16% solution of peracetic acid in PrOAc[24] (167 g, 0.35 mol) was added dropwise at −10 to 0 °C within 2 h. The reaction mixture was poured onto 10% aq Na_2SO_3 (300 mL) followed by addition of Et_2O (250 mL). The aqueous phase was extracted with Et_2O (2×250 mL) and the combined organic extracts were washed with satd aq $NaHCO_3$ (3×50 mL), filtered through a short pad of silica gel surmounted with Na_2SO_4 and concentrated. Crude **8** (*trans*/*cis* 9:1) was purified by column chromatography on silica gel eluting with petroleum ether 40–60/Et_2O 3:2. Pure crystalline *trans*-**8** (15.9 g, 65.4%) was obtained after rinsing the crystals with EtOAc/hexane. [Found: C, 37.29; H, 3.70; N, 5.90. $C_7H_8F_3NO_4$ requires C, 37.01; H, 3.55; N, 6.17]; R_f (Et_2O) 0.67; mp 112–114 °C; $[\alpha]_D^{25}$ +104.0 (*c* 1.0, $CHCl_3$); ν_{max}(KBr) 3366, 3231, 1768, 1732, 1275, 1221, 1190, 1167, 1127, 1047 cm^{-1}; δ_H 2.14 (3H, s), 3.56 (1H, app. t, *J* 1.5 Hz), 4.17 (1H, br s), 4.43 (1H, q, *J* 6.3 Hz), 6.00 (1H, s), 7.15 (1H, s); δ_C 20.7, 56.8, 65.2 (q, *J* 33 Hz), 73.3, 124.1 (q, *J* 282 Hz), 164.9, 171.5; δ_F −78.9 (d, *J* 6.9 Hz). *m*/*z* (FAB) 228 (60, MH^+); HRMS (ESI): MH^+, found 228.0488. $C_7H_9F_3NO_4$ requires 228.0484.

*4.1.9. (1′S,3R,4R)-4-Acetoxy-3-(1′-trimethylsilyloxy-2′,2′,2′-trifluoroethyl)-1-(trimethylsilyl)-2-azetidinone (**9**).* To a solution of **8** (11.3 g, 49.7 mmol) in CH_2Cl_2 (20 mL) was added *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 30 mL, 122.7 mmol). After stirring at 45 °C for 2 h, the reaction mixture was distilled on a Kugelrohr: after removal of the first fraction (50 °C/0.1 mbar) containing BSA and trimethylsilylacetamide, the product **9** distilled at 60 °C/0.1 mbar as colorless oil (17.37 g, 94%). δ_H 0.17 (9H, s), 0.29 (9H, s), 2.10 (3H, s), 3.53 (1H, t, *J* 1.3 Hz), 4.32 (1H, dq, *J* 7.0, 1.2 Hz), 6.33 (1H, s); δ_C 1.2, 1.9, 20.7, 57.6, 66.5 (q, *J* 33 Hz), 73.5, 124.1 (q, *J* 283 Hz), 164.1, 171.3; δ_F −78.4 (d, *J* 6.2 Hz); *m*/*z* (LC-MS) 372 (30, MH^+).

*4.1.10. (1′S,3R,4R)-4-Acetoxy-3-(1′-trimethylsilyloxy-2′,2′,2′-trifluoroethyl)-2-azetidinone (**10**).* *N*,*O*-bisTMS-protected **9** (3.20 g,

8.6 mmol) was stirred with silica gel (1 g) in MeOH (20 mL) overnight. The mixture was concentrated and filtered through a short pad of silica gel eluting with EtOAc. The residue was distilled on a Kugelrohr at 100 °C/0.1 mbar affording **10** as colorless oil (2.50 g, 97%). [Found: C, 40.38; H, 5.48; N, 4.51. $C_{10}H_{16}F_3NO_4Si$ requires C, 40.13; H, 5.39; N, 4.68]; δ_H 0.17 (9H, s), 2.13 (3H, s), 3.52 (1H, t, *J* 1.4 Hz), 4.37 (1H, qd, *J* 6.7, 1.4 Hz), 5.94 (1H, s), 6.56 (1H, br s); δ_F −78.6 (d, *J* 7.0 Hz).

4.1.11. (S)-6-Methoxy-1-(trimethylsilyloxy)cyclohex-1-ene[20b]. To a cold (0 °C) solution of *i*-Pr_2NH (62 mL, 0.44 mmol) in THF (400 mL) was added dropwise *t*-BuMgCl (2.0 M in Et_2O, 210 mL). After stirring at 0 °C for 1 h, a solution of (*S*)-2-methoxy-cyclohexanone (50 mL, 0.40 mol) was added over 2.5 h. The mixture was left to stir for 1 h then TMSCl (60 mL, 0.47 mol) was added. The mixture was left to warm up to rt and stirred for an additional hour. The precipitate was filtered off, rinsed with Et_2O and the filtrate partitioned between Et_2O (500 mL) and H_2O (500 mL). The organic layer was washed with H_2O (200 mL), dried (Na_2SO_4), and concentrated on rotary evaporator at 200 mbar. The residue was distilled at 75–77 °C/12 mbar affording colorless oil (65.88 g, 82.6%). δ_H 0.19 (9H, s), 1.47–1.64 (3H, m), 1.87–2.09 (3H, m), 3.41 (3H, s), 3.50 (1H, t, *J* 3.0 Hz), 4.98 (1H, t, *J* 4.2 Hz); *m*/*z* (EI) 200 (55, M^+).

*4.1.12. (3S,4R)-4-[(1R,3S)-3-Methoxy-2-oxo-cyclohexyl]-3-[1-(S)-trimethylsilyloxy-2,2,2-trifluoroethyl]-2-azetidinone (**11**).* To a cold (−60 °C) solution of (*S*)-6-methoxy-1-(trimethylsilyloxy)cyclohex-1-ene (2.70 g, 13.5 mmol) in THF (30 mL) was added dropwise MeLi (1.5 M in Et_2O, 8.5 mL) over 20 min. After stirring for 30 min at 0 °C, the lithium enolate was transferred via a cannula to a cold (−78 °C) solution of **10** (2.40 g, 8.0 mmol) in THF (15 mL). The reaction mixture was left to stir at this temperature for 1 h then quenched with satd aq NH_4Cl (15 mL). The mixture was partitioned between EtOAc (30 mL) and H_2O (30 mL), and the organic layer was dried (Na_2SO_4) and concentrated. The excess of (*S*)-2-methoxy-cyclohexanone was distilled off on Kugelrohr (70 °C/0.1 mbar). The crude containing the diastereomers in a ratio of 82:18 was purified by column chromatography on silica gel (EtOAc/hexane 1:1) affording pure product **11** as white crystals (2.12 g, 72%). δ_H 0.19 (9H, s), 1.53–1.71 (3H, m), 1.97–2.10 (2H, m), 2.25 (1H, m), 3.10 (1H, m), 3.25 (1H, t, *J* 2.4 Hz), 3.29 (3H, s), 3.59 (1H, t, *J* 3.0 Hz), 4.34 (1H, m), 4.40 (1H, dq, *J* 7.3, 1.5 Hz), 5.81 (1H, br s); δ_C −0.2, 18.9, 27.2, 33.6, 46.6, 46.7, 52.3, 56.9, 67.2 (q, *J* 33 Hz), 83.9, 124.4 (q, *J* 283 Hz), 166.0, 213.4; δ_F −78.3 (d, *J* 8.0 Hz); HRMS (ESI): MH^+, found 368.1514. $C_{15}H_{25}F_3NO_4Si$ requires 368.1505.

*4.1.13. (3S,4R)-1-Allyl oxalyl-4-[(1R,3S)-3-methoxy-2-oxo-cyclohexyl]-3-[1-(S)-trimethylsilyloxy-2,2,2-trifluoroethyl]-2-azetidinone (**12**).* To a cold (0 °C) solution of **11** (1.85 g, 5.08 mmol) in CH_2Cl_2 (15 mL) was added allyl oxalyl chloride (0.86 mL, 7.1 mmol) followed by Et_3N (1 mL, 7.6 mmol) over 10 min. The mixture was stirred at 0–5 °C for 30 min, then partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL). The organic layer was washed with satd aq $NaHCO_3$ (30 mL), brine (30 mL), dried (Na_2SO_4), and concentrated. The residue was rapidly purified by column chromatography on silica gel (hexane/EtOAc 4:1) affording **12** as light yellowish crystals (2.30 g, 94.6%); mp 44–50 °C; δ_H 0.16 (9H, s), 1.39 (1H, m), 1.70 (2H, m), 2.06 (2H, m), 2.23 (1H, m), 3.22 (3H, s), 3.53 (1H, m), 3.86 (1H, m), 3.97 (1H, dt, *J* 13.2, 4.4 Hz), 4.48 (2H, m), 4.79 (2H, m), 5.31 (1H, m), 5.40 (1H, m), 5.95 (1H, m); δ_C −0.5, 19.4, 31.0, 33.7, 43.7, 52.1, 53.6, 56.9, 67.1, 67.3 (q, *J* 33 Hz), 84.1, 119.8, 122.9 (q, *J* 283 Hz), 130.3, 155.7, 159.4, 163.1, 212.2; δ_F −77.5 (d, *J* 6.1 Hz). HRMS (ESI): MH^+, found 480.1657. $C_{20}H_{29}F_3NO_7Si$ requires 480.1665.

*4.1.14. Allyl (4S,8S,9R,10S)-4-methoxy-10-[1-(S)-trimethylsilyloxy-2,2,2-trifluoroethyl]-11-oxo-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (**13**).* A solution of **12** (2.30 g, 4.80 mmol) and hydroquinone (250 mg, 2.27 mmol) in $P(OEt)_3$ (15 mL) was heated at 140 °C for 2 h. The mixture was cooled to rt and the excess of $P(OEt)_3$ was distilled off on Kugelrohr (40 °C/0.1 mbar). The residue was purified by column chromatography on silica gel (hexane/EtOAc 9:1) affording **13** as yellowish crystals (1.77 g, 58.8%). δ_H 0.20 (9H, s), 1.22–1.59 (2H, m), 1.63 (1H, m), 1.86 (2H, m), 2.08 (1H, m), 3.25 (1H, m), 3.20–3.62 (4H, m), 4.44 (2H, m), 4.70 (1H, dd, *J* 12.9, 4.8 Hz,), 4.79 (1H, dd, *J* 12.6, 4.5 Hz), 4.96 (1H, m), 5.27 (1H, d, *J* 10.2 Hz), 5.44 (1H, d, *J* 17.1 Hz), 5.96 (1H, m); δ_C −0.3, 20.1, 30.2, 32.6, 43.4, 52.4, 53.3, 56.1, 65.6, 66.9 (q, *J* 33 Hz), 72.2, 118.3, 124.2 (q, *J* 282 Hz), 126.0, 131.3, 148.8, 160.6, 172.8; δ_F −78.5 (d, *J* 8.2 Hz); HRMS (ESI): MH^+, found 448.1760. $C_{20}H_{29}F_3NO_5Si$ requires 448.1767.

*4.1.15. Allyl (4S,8S,9R,10S)-4-methoxy-10-[1-(S)-hydroxy-2,2,2-trifluoroethyl]-11-oxo-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (**14**).* To a solution of **13** (1.63 g, 3.6 mmol) in THF (30 mL) was added AcOH (830 μL) followed by Bu_4NF (1 M in THF, 11 mL). After stirring at rt for 30 min, the reaction mixture was partitioned between EtOAc (100 mL) and satd aq $NaHCO_3$ (50 mL). The organic layer was washed with satd aq NH_4Cl (50 mL), dried (Na_2SO_4), and concentrated affording **14** as white crystals (1.34 g, 98%); mp 78–85 °C; δ_H 1.27–1.51 (2H, m), 1.63–1.90 (3H, m), 2.09 (1H, m), 3.23–3.32 (4H, m), 3.58 (1H, m), 3.83 (1H, m), 4.51 (1H, m), 4.60 (1H, m), 4.70 (1H, m), 4.82 (1H, m), 4.95 (1H, m), 5.29 (1H, dq, *J* 10.5, 1.4 Hz,), 5.41 (1H, dq, *J* 17.1, 1.5 Hz), 5.97 (1H, m); δ_C 20.0, 30.1, 32.4, 43.5, 52.4, 52.6, 56.0, 65.5 (q, *J* 32 Hz), 66.0, 72.3, 119.0, 124.5 (q, *J* 282 Hz), 125.8, 131.3, 149.0, 160.7, 173.5; δ_F −78.8 (d, *J* 6.7 Hz); *m*/*z* (FAB) 376 (75, MH^+).

*4.1.16. Sodium (4S,8S,9R,10S)-4-methoxy-10-[1-(S)-hydroxy-2,2,2-trifluoroethyl]-11-oxo-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (**1**).* To a solution of **14** (940 mg, 2.5 mmol) in THF (8 mL) was added a solution of $Pd(PPh_3)_4$ (72 mg, 0.06 mmol) and PPh_3 (65 mg, 0.25 mmol) in THF (8 mL) followed by sodium 2-ethylhexanoate (0.21 M, 11.9 mL, 2.5 mmol). The reaction mixture was left to stir at rt for 2 h. The precipitate was filtered using a Durapore® HV filter (0.22 μ) and washed with THF (10 mL) to afford pure **1** as an off white powder (410 mg, 37%). ν_{max}(KBr) 3388 (br), 2938, 1768, 1606, 1406, 1273, 1256, 1178, 1162, 1126, 1089 cm^{-1}; δ_H (DMSO-d_6) 1.14–1.39 (2H, m), 1.47–1.74 (3H, m), 1.84 (1H, m), 2.89 (1H, m), 3.10 (3H, s), 3.41 (1H, t, *J* 3.3 Hz), 4.11 (1H, dd, *J* 10.3, 3.1 Hz), 4.40 (1H, m), 5.11 (1H, t, *J* 2.8 Hz), 7.05 (1H, br s); δ_C (DMSO-d_6) 21.2, 30.5, 32.6, 42.8, 52.5, 52.6, 55.7, 66.0 (q, *J* 30.4 Hz), 72.7, 126.2 (q, *J* 283 Hz), 135.6, 135.7, 165.0, 173.5; δ_F (DMSO-d_6) −76.2 (d, *J* 7.5 Hz). HRMS (ESI): MH^+, found 358.0854. $C_{14}H_{16}F_3NNaO_5$ requires 358.0878.

*4.1.17. Allyl (4S,8S,9R)-4-methoxy-10-(E)-2,2,2-trifluoroethylidene-11-oxo-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (**15**).* To a cold (0 °C) solution of **14** (250 mg, 0.67 mmol) in CH_2Cl_2 (10 mL) was added PPh_3 (175 mg, 0.67 mmol) and diethyl azodicarboxylate (DEAD, 117 mg, 0.67 mmol). After stirring at rt for 30 min, the reaction mixture was concentrated and the residue was purified by column chromatography on silica gel eluting with CH_2Cl_2 affording **15** as light yellowish oil (120 mg, 50%), which crystallized upon standing. δ_H 1.16 (1H, m), 1.39–1.44 (2H, m), 1.84 (2H, m), 2.08 (1H, m), 3.27 (3H, s), 3.37 (1H, m), 4.72 (1H, m), 4.83 (1H, m), 4.89 (1H, m), 4.99 (1H, m), 5.29 (1H, m), 5.44 (1H, m), 5.97 (1H, m), 6.35 (1H, dq, *J* 7.6, 1.7 Hz); δ_C 19.9, 30.5, 32.8, 45.4, 56.2, 62.0, 65.9, 72.5, 115.6 (q, *J* 36 Hz), 119.0, 121.8 (q, *J* 271 Hz), 126.2, 131.2, 147.7 (q, *J* 5 Hz), 149.8, 160.3, 166.8; δ_F −62.3 (d, *J* 7.9 Hz); HRMS (ESI): MH^+, found 358.1273. $C_{17}H_{19}F_3NO_4$ requires 358.1266.

*4.1.18. Sodium (4S,8S,9R)-4-methoxy-10-(E)-2,2,2-trifluoroethylidene-11-oxo-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (**2**).* To a solution of **15** (100 mg, 0.28 mmol) in THF (2 mL) was added a solution of

$Pd(PPh_3)_4$ (8 mg, 0.007 mmol) and PPh_3 (7 mg, 0.028 mmol) in CH_2Cl_2 (8 mL) followed by sodium 2-ethylhexanoate (46 mg, 0.28 mmol) in THF (1 mL). The reaction mixture was left to stir at rt for 3 h. The precipitate was filtered using a Durapore® HV filter (0.22 μ) and recrystallized from THF to afford pure **2** as yellowish crystals (43 mg, 45%). δ_H (D_2O) 1.16 (1H, m), 1.48–1.69 (3H, m), 1.85 (1H, m), 2.02 (1H, m), 3.25–3.34 (4H, m), 4.96–5.03 (2H, m), 6.58 (1H, dq, *J* 7.5, 1.5 Hz); δ_C (D_2O) 22.8, 33.0, 34.8, 47.5, 58.2, 65.0, 76.4, 118.9 (q, *J* 35 Hz), 125.0 (q, *J* 266 Hz), 135.0, 143.8, 149.6 (q, *J* 5 Hz), 170.8, 173.4; δ_F (DMSO-d_6) −56.1 (d, *J* 8.2 Hz). HRMS (ESI): MH^+, found 340.0766. $C_{14}H_{14}F_3NNaO_4$ requires 340.0773.

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Supplementary data

Experimental procedures, ^1H, ^{13}C NMR spectra of the new compounds and X-ray crystallographic data (cif file) are provided. Supplementary data associated with this article can be found in the online version, doi:10.1016/j.tet.2010.03.104. These data include MOL files and InChIKeys of the most important compounds described in this article.

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12. The *syn*/*anti* configurations for **4** were assigned based on the separate transformation of the stereoisomers into their corresponding (*E*)- and (*Z*)-olefins by stereoselective dehydration under Mitsunobu's conditions. For this, see Supporting data.
13. A series of [Ru(η^6-arene)(*S,S*)-$(CH_2)_5NSO_2$DPEN] was screened with a [substrate **3**]=1 M leading to the following *syn*/*anti* ratios: η^6-arene= benzene (68:32), *p*-cymene (43:57), mesitylene (68:32), 1,3,5-$Et_3C_6H_3$ (74:26). Noteworthy, $NaBH_4$ in MeOH at 0 °C led to *syn*/*anti* ratio of 13:87. For this, see Supporting data.
14. Asymmetric transfer hydrogenation under DKR of ethyl 2-benzamidomethyl-4-fluoro-3-oxo-butanoate using [Ru(1,3,5-$Et_3C_6H_3$)(S,S)-Me_2NSO_2DPEN] afforded the corresponding *syn*-β-hydroxy ester with 96% ee and a dr of 83:17. For this, see: (a) Plantan, I.; Stephan, M.; Urleb, U.; Mohar, B. *Tetrahedron Lett.* **2009**, *50*, 2676–2677; (b) Plantan, I.; Preželj, A.; Urleb, U.; Mohar, B.; Stephan, M. EP158454, 2008.
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17. We also failed to acetoxylate the new *N*-TBDMS-protected azetidinone **7** following standard literature procedures. For adopted conditions, see: (a) Murahashi, S.-I.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1990**, *112*, 7820–7822; (b) Murahashi, S.-I.; Saito, T.; Naota, T.; Kumobayashi, H.; Akutagawa, S. *Tetrahedron Lett.* **1991**, *32*, 5991–5994.
18. According to literature, the acetoxylation of 3-(1-hydroxyethyl)-2-azetidinone using AcOOH/$OsCl_3$/AcONa led to the corresponding *trans*/*cis*-4-acetoxy-azetidinone in a dr of ca. 4:1, while the $RuCl_3$-catalyzed oxidation gave a complex mixture. For this, see: Murahashi, S.-I.; Saito, T.; Naota, T.; Kumobayashi, H.; Akutagawa, S. *Tetrahedron Lett.* **1991**, *32*, 2145–2148.
19. CCDC 751242 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre (12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033, or deposit@ccdc.cam.ac.uk).
20. The displacement of the acetoxy group from (1′*R*,3*R*,4*R*)-4-acetoxy-3-[1′-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone using *O*-TMS-enol ether or metal (Mg, Zn, Zr, Sn) enolates of (*S*)-2-methoxycyclohexanone has been shown to be a reasonably stereoselective C–C coupling reaction. For examples of this, see: (a) Ref. 7; (b) Matsumoto, T.; Murayama, T.; Mitsuhashi, S.; Miura, T. *Tetrahedron Lett.* **1999**, *40*, 5043–5046; (c) Ghiron, C.; Piga, E.; Rossi, T.; Tamburini, B.; Thomas, R. J. *Tetrahedron Lett.* **1996**, *37*, 3891–3894; (d) Kennedy, G.; Rossi, T.; Tamburini, B. *Tetrahedron Lett.* **1996**, *37*, 7441–7444; (e) Giacobbe, S. A.; Rossi, T. *Tetrahedron: Asymmetry* **1996**, *7*, 3079–3082.
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